Basel, for preparing a fresh sample of methyl 3β,16β-diacetoxyetianate from gitoxin to permit direct comparison; to Professor T. Reichstein for a sample of methyl 3β-acetoxyetianate; to Dr. J. J. Pfiffner of Parke, Davis and Company for supplying the starting material, 3β-acetoxy-Δ[16]-pregnen-20-one; and to Dr. E. W. D. Huffman for the microanalyses reported in this paper.

CLEVELAND, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Optical Rotatory Dispersion Studies. VI.[1] The Bile Acid Series. Polycarbonyl Compounds and Stereochemical Differentiations[2]

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RECEIVED MARCH 1, 1956

Rotatory dispersion curves for various bile acid derivatives with carbonyl groups at carbon atoms 3, 6, 7, 11 and 12 are presented, thus illustrating further the utility of the rotatory dispersion method for the localization of isolated ketonic functions. More subtle differentiations are also possible and in the case of 3-, 6- or 7-ketosteroids the stereochemistry of the A/B ring juncture can be determined readily by this procedure. The additive nature of individual rotatory contributions of carbonyl groups in steroidal diketones has been investigated by examining the degree of coincidence between observed and calculated rotatory dispersion curves.

Our earlier investigations in the androstane,[3] cholestane[1,4] and sapogenin[5] series have clearly demonstrated that isolated ketone functions are strongly optically active and that the resulting rotatory dispersion curves are typical of that particular carbonyl group and its stereochemical environment and rather independent of additional weak chromophores such as hydroxyl and acyloxyl substituents or isolated double bonds. As pointed out in our last paper,[1] the characteristic shapes of certain dispersion curves permit in many instances the precise localization of isolated carbonyl groups which is often not possible by infrared or ultraviolet spectroscopic procedures. The scope and precision of the rotatory dispersion method—for identification purposes,[1] analytical applications[5,6] and for the assignment of absolute configurations to various alicyclic ketones[7]—requires the accumulation of dispersion curves for a variety of structural systems and the present paper is concerned with bile acids. This series is particularly useful since it affords a great number of representatives with the 5β (A/B *cis*) stereochemistry (most of the earlier examples[1,3,5] possessed the 5α (A/B *trans*) configuration) and, furthermore, there are available various diketones which permit an evaluation of the additive effects of individual optically active chromophores.

As in the earlier studies,[3,5] it was first necessary

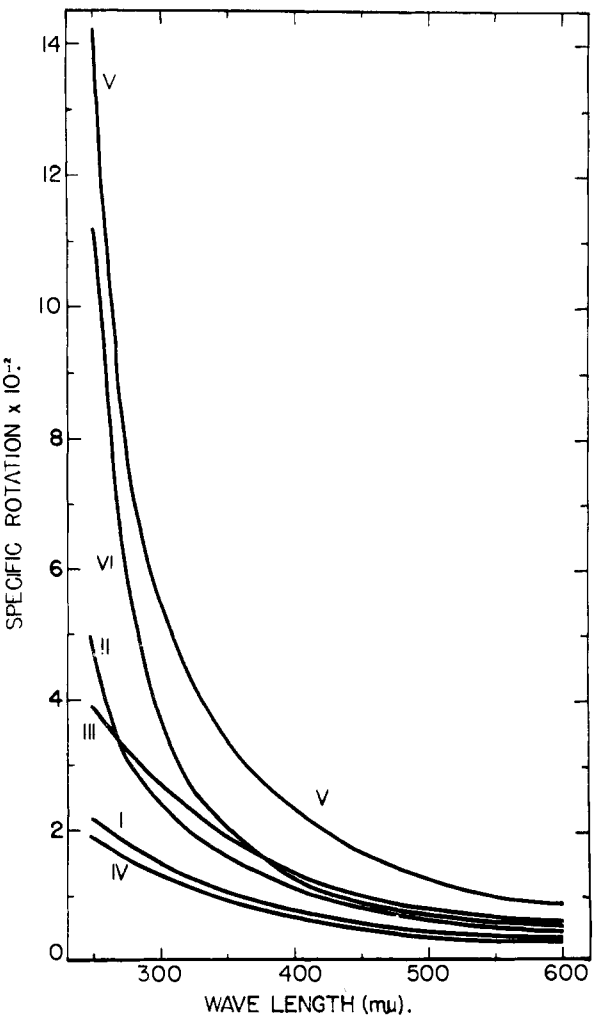


Fig. 1.—Rotatory dispersion curves of: methyl cholanate (I), desoxycholic acid (II), 3α,12α-dihydroxynorcholanic acid (III), 3α,12α-dihydroxybisnorcholanic acid (IV), 3α,12α-dihydroxyetianic acid (V) and methyl 3β-hydroxy-5α-etianate (VI).

(1) Paper V, C. Djerassi, W. Closson and A. E. Lippman, THIS JOURNAL, **78**, 3163 (1956).

(2) Supported by a research grant from the Damon Runyon Memorial Fund for Cancer Research.

(3) C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4350 (1955).

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

(5) C. Djerassi and R. Ehrlich, *ibid.*, **78**, 440 (1956).

(6) As illustrated in this and earlier papers, the characteristic features of the rotatory dispersion curves of carbonyl-containing steroids and related substances (ref. 7) become noticeable only below 400 mμ. The magnitude of the rotations in those regions often permits the determination of dispersion curves with 0.1–0.2 mg. of material (1–2 cc. of solvent), thus making it possible to utilize this procedure on a micro scale.

(7) This application in the field of terpenes, alkaloids and certain miscellaneous ketones will be reported in a forthcoming paper of this series (part VII).

to determine the "background" rotation of a few non-ketonic bile acids[8] in order to interpret correctly the effects of carbonyl substituents in that system and the appropriate information is collected in Fig. 1. Methyl cholanate (I)[9] represents the fundamental substance of this series and demonstrates that the carbomethoxy group at the end of the side chain has only a minor effect which results in a gradual increase of the rotation in a positive direction in going to shorter wave length. Introduction of hydroxyl groups in positions 3 and 12 (II) and shortening the side chain by one (III) or two (IV) carbon atoms produces no major changes other than altering the slope of the curve to a relatively minor extent. This change of slope

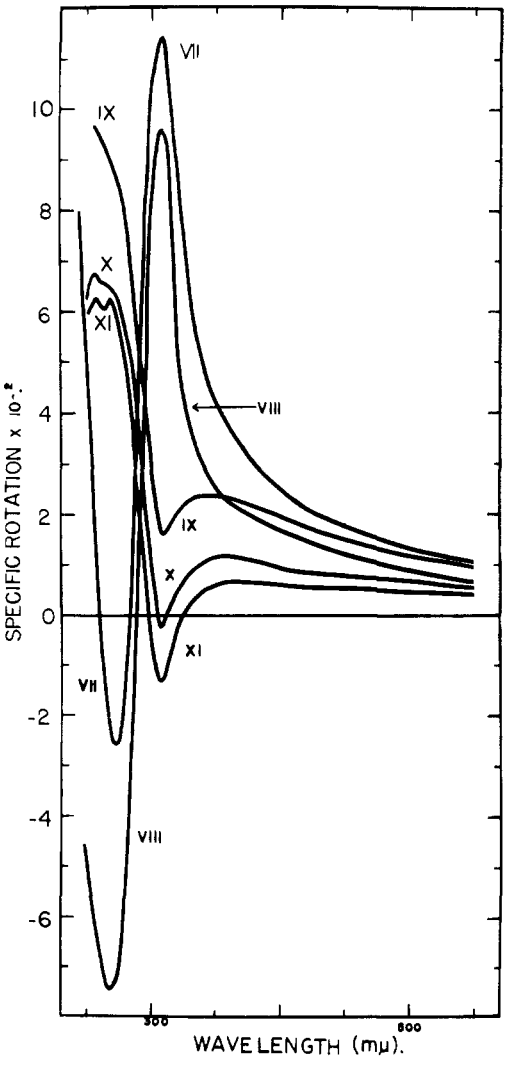


Fig. 2.—Rotatory dispersion curves of: methyl 3-keto-5α-etianate (VII), cholestan-3-one (VIII), methyl 3-keto-12α-acetoxycholanate (IX), coprostan-3-one (X), etiocholan-17β-ol-3-one (XI).

(8) The rotations of a few simple bile acids (*e.g.*, cholic acid) and their conjugates (*e.g.*, taurocholic acid) have been measured at a number of wave lengths down to 439 mμ by B. Josephson, *Biochem. J.*, **29**, 1484 (1935); *cf.* F. Hoppe-Seyler, *J. Prakt. Chem.*, **89**, 257 (1863).

(9) As demonstrated in the Experimental section, the rotatory dispersion curves of methyl or ethyl esters differ only insignificantly from those of the corresponding acids.

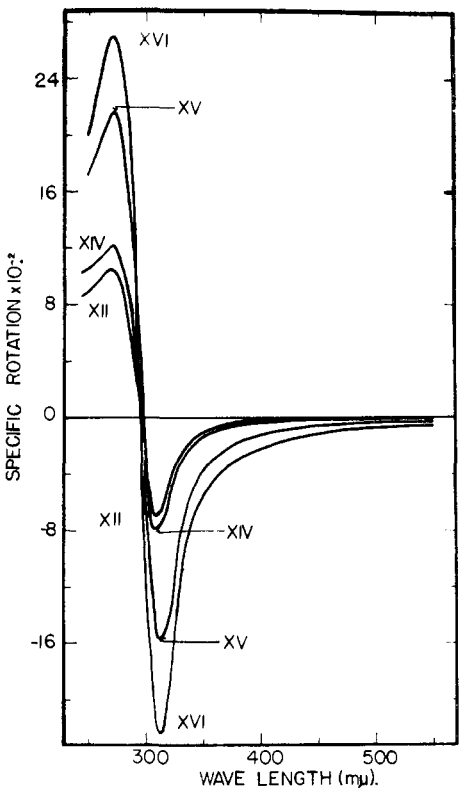


Fig. 3.—Rotatory dispersion curves of: methyl 3α-acetoxy-6-ketoallocholanate (XII), cholestan-6-one (XIV), methyl-3α-acetoxy-6-ketocholanate (XV) and coprostan-6-one (XVI).

is very marked in the etianic acid series (V, VI), the specific rotations ranging considerably beyond 1000° at 250 mμ and consequently the corresponding carbonyl-containing etianic acids (*e.g.*, VII, XXVII) will tend to have higher "maxima"[10] without, however, affecting the characteristic shapes of the respective curves.

Bile Acids with One Ketonic Group

The dispersion curves of 3-ketoallosteroids (A/B ring juncture *trans*) are characterized[1,3-5] by a "maximum" at 307–315 mμ,[11] the height of the peak being somewhat dependent upon the "background" rotation of the particular system under investigation.[12] Cholestan-3-one (VIII) (Fig. 2) represents a typical example and it can be seen that methyl 3-keto-5α-etianate (VII) possesses essentially the same type of curve. On the other hand, when the configuration at C-5 is altered a radical change is observed (Fig. 2) and a "minimum" is now noticed in the 307 mμ region. This is typical of a 3-keto-5β-steroid (A/B ring juncture *cis*)

(10) See ref. 3 for general definition of terms.

(11) The exact position will depend upon the choice of solvent. In methanol, the "maximum" occurs at 307 mμ (*cf.* ref. 1) while the higher value will be observed in dioxane (refs. 3-5). This rather characteristic solvent effect becomes very noticeable in unsaturated ketones and will be discussed in detail in a future paper.

(12) In sapogenins (ref. 5) because of the strongly negative influence of the spiroketal side chain, this 315 mμ "maximum" occurs at $[\alpha]$ +326° but the characteristic shape of the curve is still retained. In those examples where the "background" rotation is very low (*e.g.*, androstane) or positive, the rotation at the "maximum" will be in the neighborhood of 1000°.

irrespective of the nature of the side chain at C-17 (*e.g.*, IX, X, XI) since the latter affects only the "intensity" but not the shape of the curve. It thus seems possible to determine the configuration at C-5 of an unknown steroid by determining the rotatory dispersion of its derived 3-mono-ketone.[13]

The earlier determination of the rotatory dispersion curves of two 6-keto-5α-steroids, 3β-acetoxycholestan-6-one (XIII)[1] and cyclocholestan-6-one[4] suggested that the strong "minimum" in the 310 mμ region serves as a ready means of differentiation between 3-keto and 6-keto steroids of the 5α-series. This could now be confirmed (Fig. 3) with two additional examples and a further difference was noted which can be associated with the configuration at C-5. The negligible effect of a 3-acyloxy substituent is demonstrated by the dispersion curve of cholestan-6-one (XIV) which

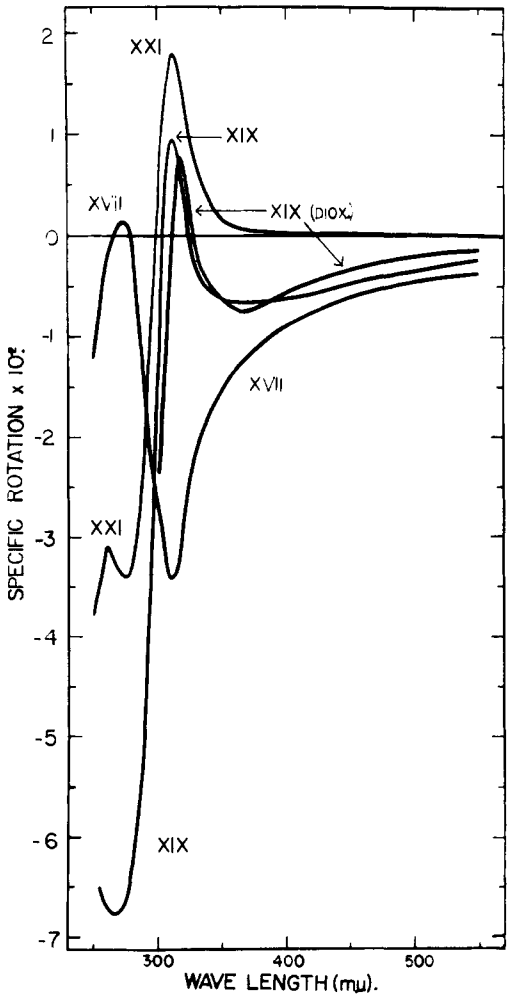


Fig. 4.—Rotatory dispersion curves of: 3β-acetoxycholestan-7-one (XVII), 3α-hydroxy-7-ketocholanic acid (XIX) and ethyl 3α,12α-dihydroxy-7-ketocholanate (XXI).

(13) It should be remembered that this applies only to monoketones since other carbonyl groups, particularly if they are strongly active, will completely alter the picture. As demonstrated earlier (ref. 3), androstane-3,17-dione and etiocholane-3,17-dione exhibit very similar curves by virtue of the very strong influence of the 17-keto function. Other examples of such interferences in diketones are considered in the present paper.

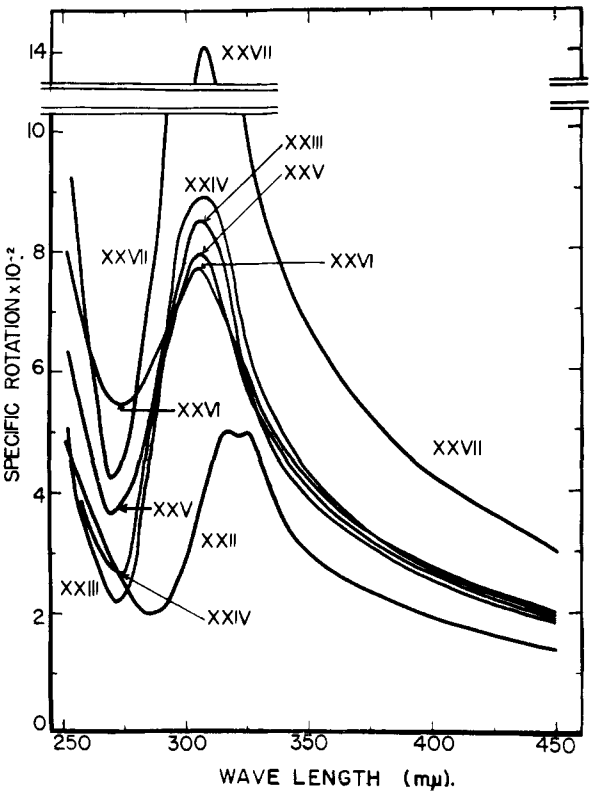
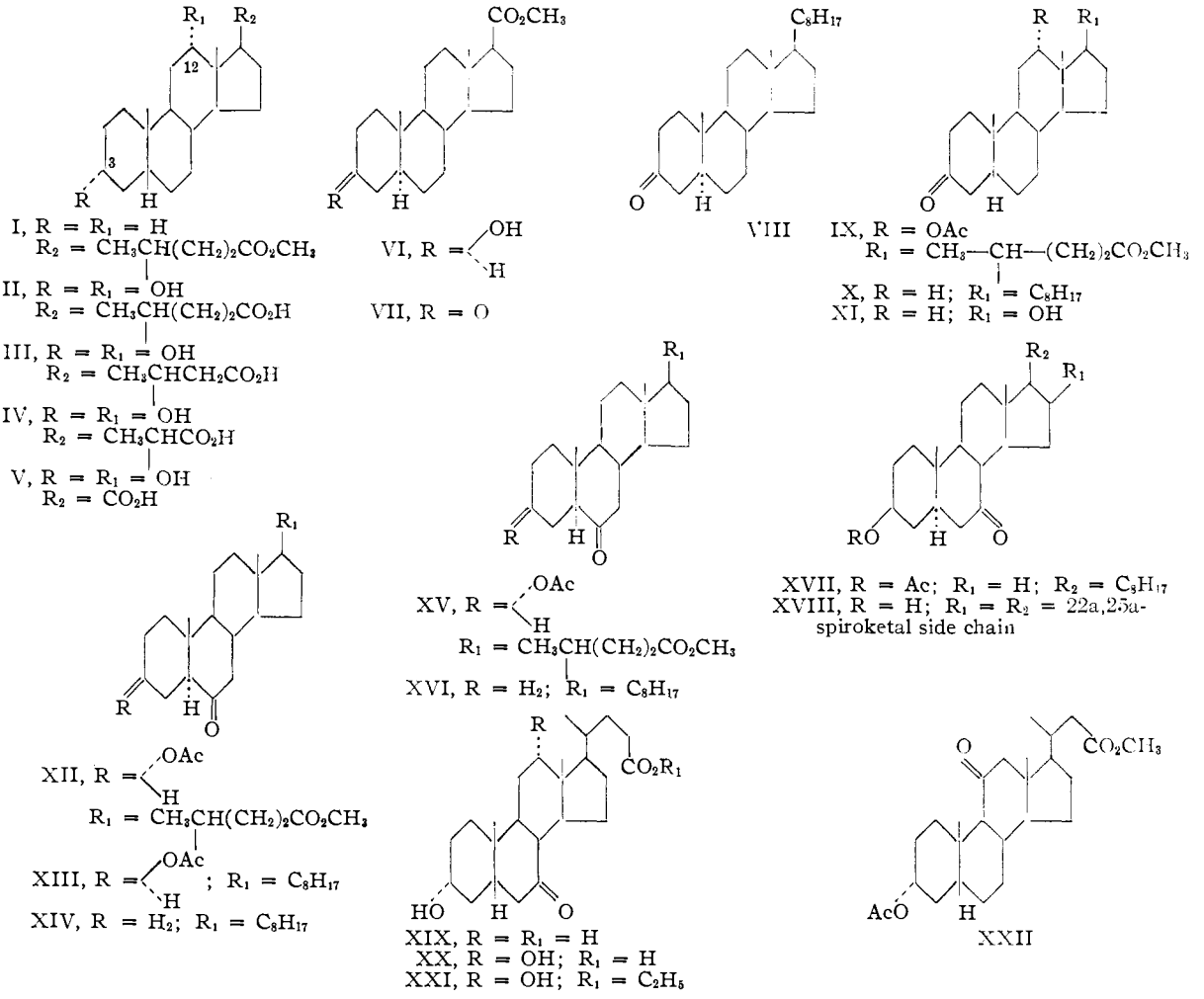


Fig. 5.—Rotatory dispersion curves of: methyl 3α-acetoxy-11-ketocholanate (XXII), 12-ketocholanic acid (XXIII), methyl 12-ketocholanate (XXIV), methyl 3α-hydroxy-12-ketocholanate (XXV), methyl 3α-acetoxy-12-ketocholanate (XXVI) and methyl 3α-acetoxy-12-keto-etianate (XXVII).

is very similar to that of its 3β-acetoxy analog (XIII)[1] as well as to methyl 3α-acetoxy-6-ketoallocholanate (XII). All three substances exhibit "minima" at 307 mμ (methanol solution) with rotations between 700–800°. On the other hand, inversion of the C-5 ring juncture as in coprostan-6-one (XVI) or methyl 3α-acetoxy-6-ketocholanate (XV) not only results in a small bathochromic shift to 312 mμ (Fig. 3), but more strikingly produces a large increase in the "intensity" of the "minimum." This is again an illustration where the rotatory dispersion curve will not only give stereochemical information but where it can be of considerable analytical utility. The difference in the *specific* rotation between cholestan-6-one (XIV) and coprostan-6-one (XVI) is only about 40° at the sodium D line but over 1400° at 310 mμ. The composition of a mixture of these two substances could, therefore, be determined very readily by simply measuring the specific rotation at 310 mμ and this could also be used to study kinetically the rate of the base-catalyzed inversion of coprostan-6-one (XVI) to the more stable 5α-isomer XIV. The same statement, of course, applies also to the pair of isomeric bile acids (XII, XV).

A similar situation exists with 7-keto steroids and this is illustrated in Fig. 4. Just as with 6-keto-5α-steroids, the chief feature of 7-keto-5α-steroids such as 3β-acetoxy-cholestan-7-one (XVII)[1] or the corresponding sapogenin XVIII[5] is the en-

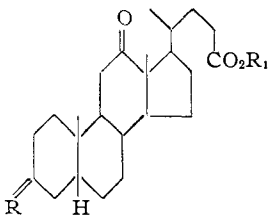


trance into the optically active absorption band from the negative side with an initial "minimum" at *ca.* 310 mμ. The 6- and 7-keto analogs, can, however, be separated from each other by virtue of the fact that the "minimum" of the 7-ketones (*e.g.*, XVII *vs.* XIII) is much less intense and that the corresponding maximum occurs near zero rotation (*cf.* Fig. 4) while that of 6-ketones is highly positive (Fig. 3). We have now measured a series of 7-keto bile acids (XIX, XX, XXI) which possess the 5β-configuration and as illustrated in Fig. 4, they can again be differentiated very readily from 5α-isomers on the basis of their rotatory dispersion curves since their optically active absorption band is entered from the positive side thus resulting in an initial "maximum" at 312 mμ. The presence of an additional hydroxyl group at C-12 has no effect (XIX *vs.* XX), the two curves being superimposable throughout almost the entire spectral range, and esterification of the carboxyl group (XX *vs.* XXI) produces only rather small intensity changes. In order to illustrate the solvent effect in going from methanol to dioxane, rotatory dispersion curves for 3α-hydroxy-7-ketocholanic acid (XIX) are given in both solvents in Fig. 4.

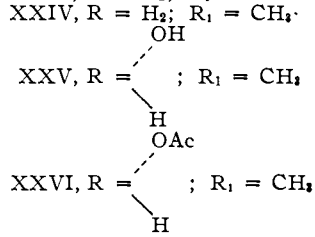
The rotatory dispersion curves of bile acids with ketonic substituents in ring C are collected in Fig. 5. The dispersion curve of methyl 3α-acetoxy-11-ketocholanate (XXII) shows all of the features which already have been associated earlier[5,14] with an 11-ketone, namely, rather low optical activity coupled with a bathochromic shift of the "maximum" by 10–15 mμ. The remaining curves in Fig. 5 are those of various 12-keto bile acids (XXIII–XXVII) which serve to illustrate again the important point that additional substitution due to weak or inactive chromophores does not alter the shape of the curves. Compounds XXIII–XXVI typify structural changes due to hydroxylation, acetylation or methylation and all four substances exhibit, with minor intensity variations, the characteristic 12-keto bile acid curves as reflected by a "maximum" at 306 mμ and a "minimum" at *ca.* 272 mμ. It is important to notice that the "minimum" still occurs on the positive side and does not involve a change of rotation, a feature which also applies to the 11-ketone XXII. The corresponding etianic acid XXVII possesses the same shape except that the "maximum" is more intense, which is probably due to the higher positive "background" rotation (Fig. 1) associated with etianic acids (*e.g.*, V).

In summary, it can be stated from the material

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

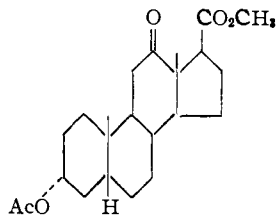


XXIII, R = H_2; R_1 = H
XXIV, R = H_2; R_1 = CH_3

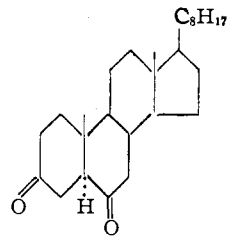


XXV, R = ; R_1 = CH_3

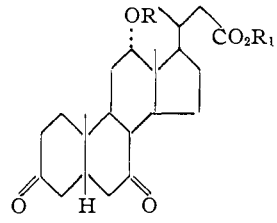
XXVI, R = ; R_1 = CH_3



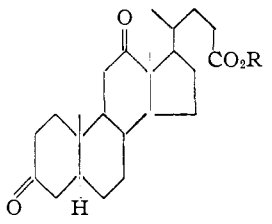
XXVII



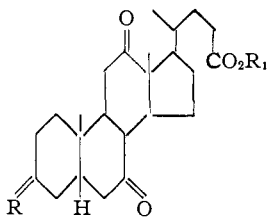
XXVIII

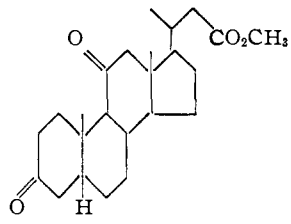


XXIX, R = H; R_1 = C_2H_5
XXX, R = Ac; R_1 = CH_3

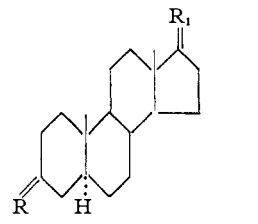


XXXI, R = CH_3
XXXII, R = H

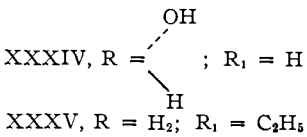




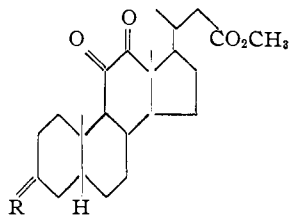
XXXIII



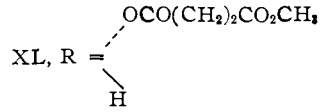
XXXVI, R = O; R_1 = H_2
XXXVII, R = H_2; R_1 = O
XXXVIII, R = R_1 = O



XXXIV, R = ; R_1 = H
XXXV, R = H_2; R_1 = C_2H_5



XXXIX, R = H_2



XL, R =

presented so far that it should be possible to define the location of a carbonyl substituent in a *monoketonic* bile acid strictly on the basis of the shape of the rotatory dispersion curve, provided the carbonyl group occurs at the common 3-, 6-, 7-, 11- or 12-positions. Judging from earlier experience in the cholestane series,[1] carbonyl groups in other portions of the molecule should also be recognizable, but standard dispersion curves of appropriate model bile acids (presently unknown) would first have to be measured. While the above statements apply to the usual bile acids and almost certainly the nor and bisnor derivatives (*cf.* Fig. 1), caution has to be exercised with etianic acids (V) where the high "background" rotation has to be taken into consideration. This should present no particular difficulty since the analytical figures will usually establish this fact. The present bile acid study further supports the statement[1] that *the rotatory dispersion curve of a ketosteroid will often afford information which is not available from infrared, ultraviolet or other means* and leads to the recommendation that the determination of the rotatory dispersion curve (rather than single determination of $[\alpha]_D$) of many steroids (as well as triterpenes and related compounds[7]) should be carried out as a routine operation provided the necessary spectropolarimeter is available.

Rotatory Dispersion of Diketones

As mentioned in the introduction to this paper, there are available various diketones in the bile acid series and it seemed important for two reasons to extend our rotatory dispersion measurements to such substances. It was of interest to determine whether any given diketone could be identified by means of its rotatory dispersion curve and even more importantly, whether the rotatory contribution of each carbonyl group is additive in a diketone. For this latter study—representing a graphic illustration of the presence or absence of vicinal effects in such systems—there have also been included examples from the cholestane and androstane series.

In Fig. 6 are collected rotatory dispersion curves of typical representatives of 3,7- (XXIX), 3,11- (XXXIII), 3,12- (XXXI) and 7,12- (XXXIV) diketo bile acids, while those of two 11,12-dike-

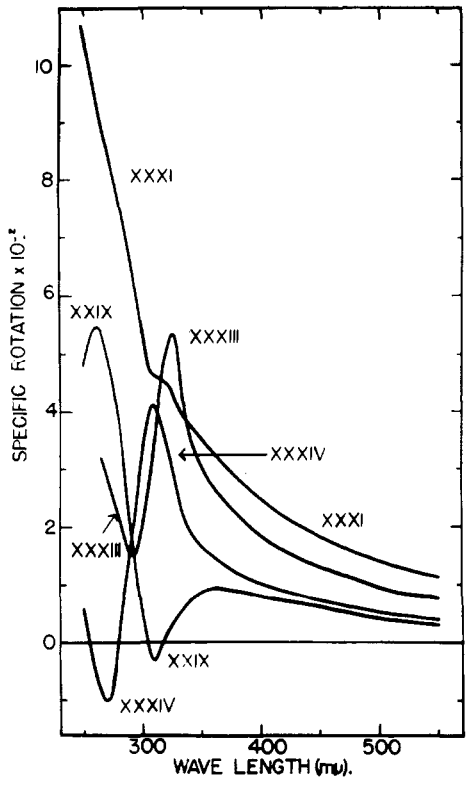


Fig. 6.—Rotatory dispersion curves of: ethyl 3,7-diketo-12α-hydroxycholanate (XXIX), methyl 3,12-diketocholanate (XXXI), methyl 3,11-diketocholanate (XXXIII) and 3α-hydroxy-7,12-diketocholanic acid (XXXIV).

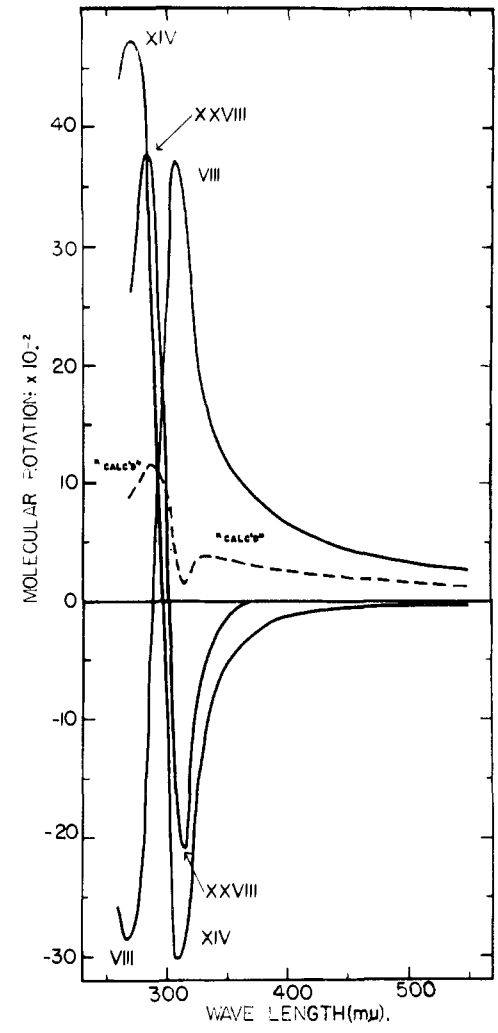


Fig. 7.—Rotatory dispersion curves of: cholestan-3-one (VIII), cholestan-6-one (XIV) and cholestane-3,6-dione (XXVIII); "calcd." curve of 3,6-dione based on VIII and XIV (ref. 15).

tones (XXXIX, XL) are given in Fig. 13, and it is clear that the curves differ from each other to such a marked extent that they can be used for characterization purposes. As was to be expected, minor changes involving methylation, acetoxylation, etc., do not affect the characteristic shapes (*cf.* Fig. 13) and the data for a few examples (XXX, XXXII, XXXV) are listed in the Experimental portion.

In order to determine the operation of vicinal effects in such diketones, it was necessary to construct "calculated" curves[15] using the dispersion data of the corresponding mono-ketones. Since in several instances, the exact counterpart was not available (*e.g.*, free acid in one case and methyl ester in the other), molecular rotations[15] were used in order to minimize as far as possible the effects of such minor structural alterations. The data are collected in Figs. 7–12 and in each case there are given the dispersion curves of the two mono-ketones as well as the observed and "calculated"[15] curves of the corresponding diketone. The degree of coincidence between the observed and calculated curves will then be a reflection of the vicinal effect exerted by two carbonyl groups separated over a certain distance in the steroid molecule.

Vicinal effects appear to be very strong in 3,6- (Fig. 7) and 3,7-diketones (Fig. 8) but are essentially absent in 3,12- (Fig. 9) and 7,12-diones (Fig. 11), since in the latter two instances the contributions of the individual carbonyl groups are additive. The 3,11-diketo system (Fig. 10) seems to be an intermediate case since there is some qualitative similarity between the observed and calculated curves. That the distance separating the two chromophores is not the only factor affecting vicinal interaction is shown in Fig. 12 where a 3,17-diketone is considered and where the individual contributions of the 3- and 17-keto groups are (in terms of intensity) not additive. It is obvious that the location of the chromophores around the contiguous chain of six asymmetric carbon atoms extending from C-5 to C-13 is a crucial factor, but no precise information concerning the actual cause (possibly also due to subtle conformational changes[16]) of such vicinal action in diketones is available at the present time.

Acknowledgment.—We are greatly indebted to the various investigators listed in the Experimental

(15) As an approximation this was done by taking the sum of the molecular rotations (at any given wave length) of the two appropriate mono-ketones and dividing by two; molecular rotation = (specific rotation × molecular weight)/100.

(16) *Cf.* D. H. R. Barton, *Experientia*, Suppl. **2**, 121 (1955).

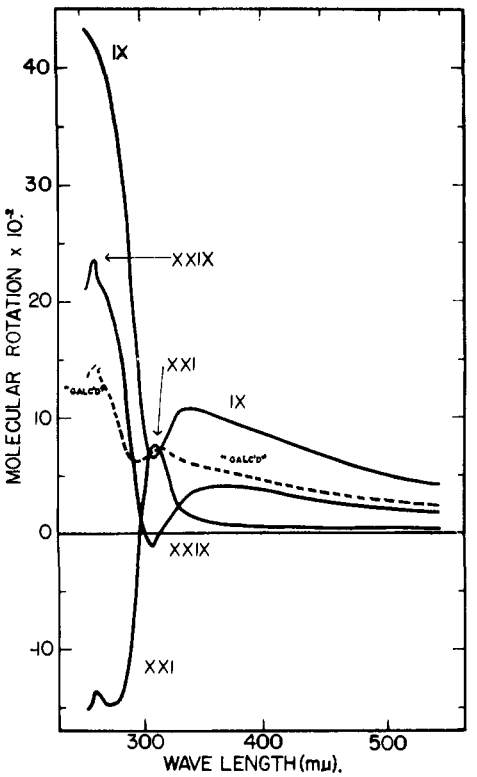


Fig. 8.—Rotatory dispersion curves of: methyl 3-keto-12α-acetoxycholanate (IX), ethyl 3α,12α-dihydroxy-7-ketocholanate (XXI) and ethyl 3,7-diketo-12α-hydroxycholanate (XXIX); "calcd." curve for 3,7-dione based on IX and XXI (ref. 15).

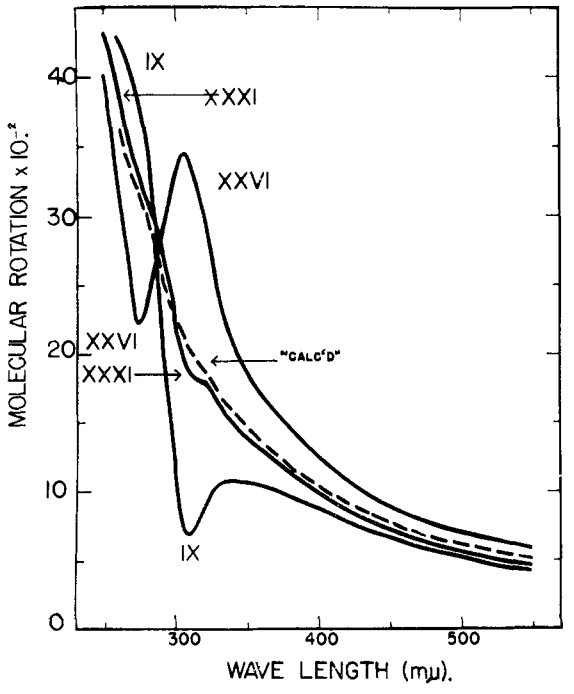


Fig. 9.—Rotatory dispersion curves of: methyl 3-keto-12α-acetoxycholanate (IX), methyl 3α-acetoxy-12-ketocholanate (XXVI) and methyl 3,12-diketocholanate (XXXI); "calcd." curve for 3,12-dione based on IX and XXVI (ref. 15).

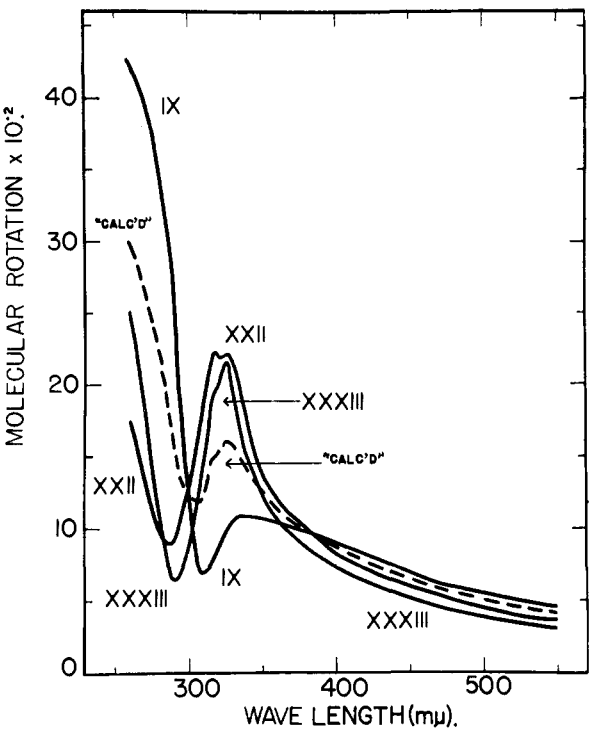


Fig. 10.—Rotatory dispersion curves of: methyl 3-keto-12α-acetoxycholanate (IX), methyl 3α-acetoxy-11-ketocholanate (XXII) and methyl 3,11-diketocholanate (XXXIII); "calcd." curve for 3,11-dione based on IX and XXII (ref. 15).

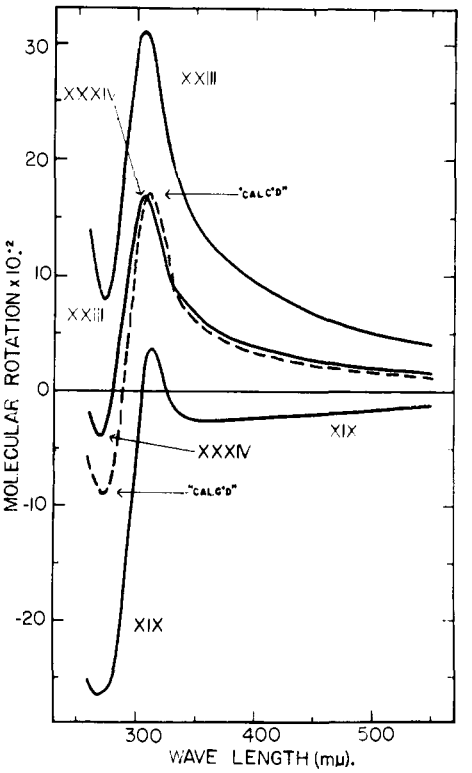


Fig. 11.—Rotatory dispersion curves of: 3α-hydroxy-7-ketocholanic acid (XIX), 12-ketocholanic acid (XXIII), and 3α-hydroxy-7,12-diketocholanic acid (XXXIV); "calcd." curve for 7,12-dione based on XIX and XXIII (ref. 15).

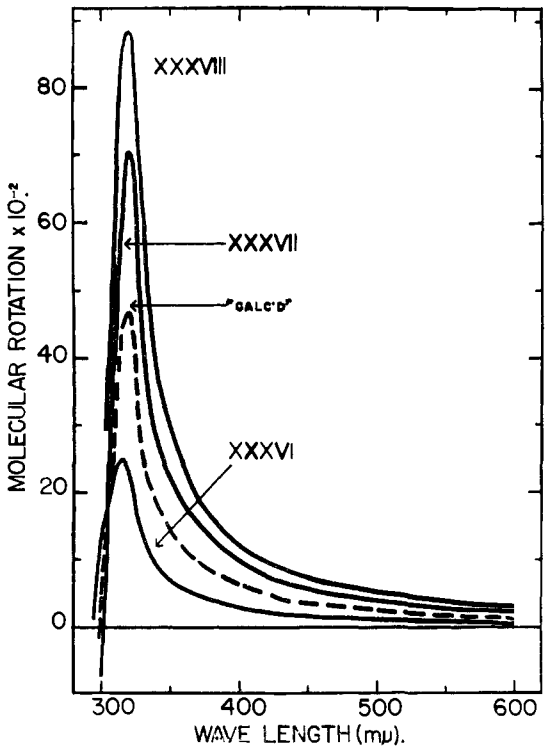


Fig. 12.—Rotatory dispersion curves (dioxane solution) of: androstan-3-one (XXXVI), androstan-17-one (XXXVII) and androstane-3,17-dione (XXXVIII); "calcd." curve of 3,17-dione based on XXXVI and XXXVII (ref. 15).

section for supplying us with samples and to the National Science Foundation for funds covering the purchase of the spectropolarimeter.

Experimental[17]

Methyl Cholanate (I) (T. Reichstein), R. D. (Fig. 1): $[\alpha]_{700}$ +25°, $[\alpha]_{589}$ +34°, $[\alpha]_{260}$ +238°, *c* 0.1, temp. 28–30°.

Desoxycholic Acid (II) (H. B. MacPhillamy), R. D. (Fig. 1): $[\alpha]_{700}$ +35°, $[\alpha]_{589}$ +50°, $[\alpha]_{250}$ +474°, *c* 0.1, temp. 24–30°.

3α,12α-Dihydroxynorcholanic Acid (III) (H. B. MacPhillamy), R. D. (Fig. 1): $[\alpha]_{700}$ +33°, $[\alpha]_{589}$ +54°, $[\alpha]_{250}$ +330°, *c* 0.1, temp. 25–27°.

3α,12α-Dihydroxybisnorcholanic Acid (IV) (H. B. MacPhillamy), R. D. (Fig. 1): $[\alpha]_{700}$ +26°, $[\alpha]_{589}$ +30°, $[\alpha]_{255}$ +177°, *c* 0.1, temp. 25–27.

3α,12α-Dihydroxyetianic Acid (V) (H. B. MacPhillamy), R. D. (Fig. 1): $[\alpha]_{700}$ +49°, $[\alpha]_{589}$ +90°, $[\alpha]_{250}$ +1410°, *c* 0.1, temp. 24–26°.

Methyl 3β-Hydroxy-5α-etianate (VI) R. D. (Fig. 1): $[\alpha]_{700}$ +33°, $[\alpha]_{589}$ +51°, $[\alpha]_{250}$ +1113°, *c* 0.1, temp. 23–25°.

Methyl 3-Keto-5α-etianate (VII) R. D. (Fig. 2): $[\alpha]_{700}$ +59°, $[\alpha]_{589}$ +90.6°, $[\alpha]_{240}$ +1077°, "max." $[\alpha]_{307.5}$ +1140°, "min." $[\alpha]_{272.5}$ −259°, *c* 0.1, temp. 24–26°.

Methyl 3-Keto-12α-acetoxycholanate (IX) (T. Reichstein), R. D. (Fig. 2): $[\alpha]_{700}$ +57°, $[\alpha]_{589}$ +84°, $[\alpha]_{255}$ +967°, "min." $[\alpha]_{307}$ +154°, *c* 0.1, temp. 25–27°.

Coprostan-3-one (X) R. D. (Fig. 2): $[\alpha]_{700}$ +32°, $[\alpha]_{589}$ +48°, $[\alpha]_{260}$ +630°, "max." $[\alpha]_{255}$ +675°, "min." $[\alpha]_{307}$ −20.6°, *c* 0.1, temp. 24–26°.

Etiocholan-17β-ol-3-one (XI) R. D. (Fig. 2): $[\alpha]_{700}$ +24°, $[\alpha]_{589}$ +34°, $[\alpha]_{250}$ +601°, "min." $[\alpha]_{307.5}$ −133°, "max." $[\alpha]_{267.5}$ +625°, "min." $[\alpha]_{262.5}$ +607°, "max." $[\alpha]_{257.5}$ +630°, *c* 0.1, temp. 24–27°.

Methyl 3α-Acetoxy-6-ketoallocholanate (XII) (T. F. Gallagher), R. D. (Fig. 3): $[\alpha]_{700}$ 0°, $[\alpha]_{589}$ 0°, $[\alpha]_{240}$ +846°, "max." $[\alpha]_{270}$ +1055°, "min." $[\alpha]_{307}$ −695°, *c* 0.1, temp. 27–28°.

Cholestan-6-one (XIV) (C. W. Shoppee), R. D. (Fig. 3): $[\alpha]_{700}$ 0°, $[\alpha]_{589}$ −5°, $[\alpha]_{245}$ +1032°, "max." $[\alpha]_{270}$ +1223°, "min." $[\alpha]_{307.5}$ −781°, *c* 0.1, temp. 25–26°.

Methyl 3α-Acetoxy-6-ketocholanate (XV) (T. F. Gallagher), R. D. (Fig. 3): $[\alpha]_{700}$ −8°, $[\alpha]_{589}$ −14°, $[\alpha]_{245}$ +1628°, "max." $[\alpha]_{272}$ +2160°, "min." $[\alpha]_{312}$ −1558°, *c* 0.1, temp. 31–32°.

Coprostan-6-one (XVI) (C. W. Shoppee), R. D. (Fig. 3): $[\alpha]_{700}$ −21°, $[\alpha]_{589}$ −46°, $[\alpha]_{245}$ +1902°, "max." $[\alpha]_{270}$ +2695°, "min." $[\alpha]_{312.5}$ −224°, *c* 0.1, temp. 25–28°.

22a,25a,5α-Spirostan-3β-ol-7-one (XVIII).—The rotatory dispersion curve (in dioxane solution) down to 290 mμ has already been recorded[5] ("min." $[\alpha]_{315}$ −598°). In order to be able to define the "maximum," the measurements were now completed in methanol solution down to 245 mμ ($[\alpha]$ −548°): "max." $[\alpha]_{272}$ −257°.

3α-Hydroxy-7-ketocholanic Acid (XIX), (S. Bergstrom), R. D. (Fig. 4): $[\alpha]_{700}$ −15°, $[\alpha]_{589}$ −26°, $[\alpha]_{255}$ −656°, "max." $[\alpha]_{312}$ +95°, "min." $[\alpha]_{264}$ −676°, *c* 0.1, temp. 25–28°. Dioxane solution: $[\alpha]_{700}$ −20.4°, $[\alpha]_{589}$ −17°, $[\alpha]_{295}$ −326°, "max." $[\alpha]_{318}$ +74°, *c* 0.1, temp. 24–26°.

3α,12α-Dihydroxy-7-ketocholanic Acid (XX) (S. Bergstrom), R. D. (Fig. 4): $[\alpha]_{700}$ 0°, $[\alpha]_{589}$ +1°, $[\alpha]_{250}$ −432°, "max." $[\alpha]_{312}$ +171°, "min." $[\alpha]_{275}$ −432°, *c* 0.1, temp. 33–35°.

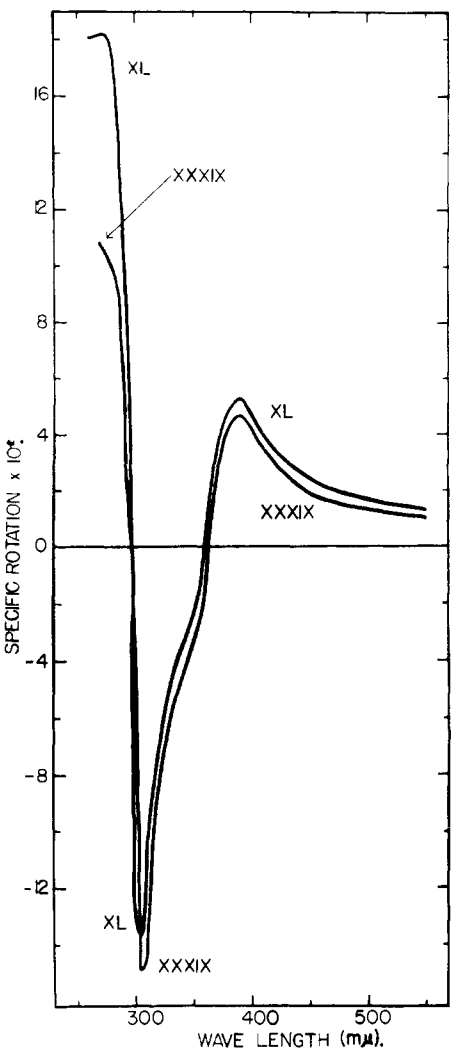


Fig. 13.—Rotatory dispersion curves of: methyl 11,12-diketocholanate (XXXIX) and 3α-succinoxy-11,12-diketocholanic acid dimethyl ester (XL).

(17) Unless noted otherwise, all rotations were measured in methanol solution. The experimental procedure described in ref. 3 was followed using the light source modification outlined in ref. 1.

Ethyl 3α,12α-Dihydroxy-7-ketocholanate (XXI) (H. B. MacPhillamy), R. D. (Fig. 4): $[\alpha]_{700}$ +4°, $[\alpha]_{589}$ +4°, $[\alpha]_{250}$ −374°, "max." $[\alpha]_{312}$ +176°, "min." $[\alpha]_{270}$ −340°, *c* 0.1, temp. 25–28°.

Methyl 3α-Acetoxy-11-ketocholanate (XXII) (T. F. Gallagher), R. D. (Fig. 5): $[\alpha]_{700}$ +42°, $[\alpha]_{589}$ +71°, $[\alpha]_{250}$ +514°, "max." $[\alpha]_{325}$ +495°, "min." $[\alpha]_{322.5}$ +491°, "max." $[\alpha]_{317.5}$ +499°, "min." $[\alpha]_{285}$ +198°, *c* 0.1, temp. 23–26.

12-Ketocholanic Acid (XXIII) (T. Reichstein), R. D. (Fig. 5): $[\alpha]_{700}$ +61°, $[\alpha]_{589}$ +95°, $[\alpha]_{245}$ +665°, "max." $[\alpha]_{305}$ +825°, "min." $[\alpha]_{272}$ +222°, *c* 0.1, temp. 28–29°.

Methyl 12-Ketocholanate (XXIV) (S. Bergstrom), R. D. (Fig. 5): $[\alpha]_{700}$ +62°, $[\alpha]_{589}$ +101°, $[\alpha]_{260}$ +374°, "max." $[\alpha]_{307}$ +887°, "min." $[\alpha]_{275}$ +264°, *c* 0.1, temp. 32–35°.

Methyl 3α-Hydroxy-12-Ketocholanate (XXV) (H. B. MacPhillamy), R. D. (Fig. 5): $[\alpha]_{700}$ +65°, $[\alpha]_{589}$ +101°, $[\alpha]_{250}$ +693°, "max." $[\alpha]_{306}$ +797°, "min." $[\alpha]_{270}$ +361°, *c* 0.1, temp. 24–27°.

Methyl 3α-Acetoxy-12-ketocholanate (XXVI) (T. Reichstein), R. D. (Fig. 5): $[\alpha]_{700}$ +83°, $[\alpha]_{589}$ +104°, $[\alpha]_{245}$ +958, "max." $[\alpha]_{305}$ +772°, "min." $[\alpha]_{272.5}$ +546°, *c*, 0.1, temp. 24–27°.

Methyl 3α-Acetoxy-12-ketoetianate (XXVII), R. D. (Fig. 5): $[\alpha]_{700}$ +111°, $[\alpha]_{589}$ +157°, $[\alpha]_{255}$ +841°, "max." $[\alpha]_{307.5}$ +1404; "min." $[\alpha]_{270}$ +422°, *c* 0.1, temp. 24–26°.

Ethyl 3,7-Diketo-12α-hydroxycholanete (XXIX) (H. B. MacPhillamy), R. D. (Figs. 6, 8): $[\alpha]_{700}$ +31°, $[\alpha]_{589}$ +37°, $[\alpha]_{250}$ +487°, "max." $[\alpha]_{260}$ +544°, "min." $[\alpha]_{310}$ −29°, *c* 0.1, temp. 25–27°.

Methyl 3,7-Diketo-12α-acetoxycholanate (XXX) (T. F. Gallagher), R. D.: $[\alpha]_{700}$ +28.6°, $[\alpha]_{589}$ +40.2°, $[\alpha]_{250}$ +376°, "max." $[\alpha]_{265}$ +519°, "min." $[\alpha]_{307.5}$ −50°, *c* 0.1, temp. 24–29°.

Methyl 3,12-Diketocholanate (XXXI) (T. Reichstein), R. D. (Figs. 6, 9): $[\alpha]_{700}$ +71°, $[\alpha]_{589}$ +95°, $[\alpha]_{250}$ +1060°, "inflection" $[\alpha]_{310\text{-}320}$ +450°, *c* 0.1, temp. 31–32°.

3,12-Diketocholanic Acid (XXXII) (S. Bergstrom), R. D.: $[\alpha]_{700}$ +63°, $[\alpha]_{589}$ +97°, $[\alpha]_{255}$ +920°, "inflection" $[\alpha]_{310\text{-}320}$ +451°, *c* 0.1, temp. 24–28°.

Methyl 3,11-Diketocholanate (XXXIII) (T. Reichstein), R. D. (Figs. 6, 10): $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ +71°, $[\alpha]_{260}$ +617°, "max." $[\alpha]_{325}$ +538°, "min." $[\alpha]_{290}$ +157°, *c* 0.1, temp. 25–28°.

3α-Hydroxy-7,12-diketocholanic Acid (XXXIV) (S. Bergstrom), R. D. (Figs. 6, 11): $[\alpha]_{700}$ +15°, $[\alpha]_{589}$ +37°, $[\alpha]_{250}$ +53°, "max." $[\alpha]_{307.5}$ +413°, "min." $[\alpha]_{270}$ −99°, *c* 0.1, temp. 24–28°.

Ethyl 7,12-Diketocholanate (XXXV) (T. Reichstein), R. D.: $[\alpha]_{700}$ +18°, $[\alpha]_{589}$ +23°, $[\alpha]_{250}$ −60°, "max." $[\alpha]_{305}$ +323°, "min." $[\alpha]_{267}$ −219°, *c* 0.1, temp. 31–34°.

Methyl 11,12-Diketocholanate (XXXIX) (T. Reichstein), R. D. (Fig. 13): $[\alpha]_{700}$ +50°, $[\alpha]_{589}$ +81°, $[\alpha]_{250}$ +1043°, "max." $[\alpha]_{290}$ +467°, "min." $[\alpha]_{305}$ −1489°, "inflection," $[\alpha]_{340}$ −453°, *c* 0.1, temp. 22–27°.

3α-Succinoxy-11,12-diketocholanic Acid Dimethyl Ester (XL) (O. Wintersteiner), R. D. (Fig. 13): $[\alpha]_{700}$ +75°, $[\alpha]_{589}$ +106°, $[\alpha]_{260}$ +1810°, "max." $[\alpha]_{390}$ +534°, "min." $[\alpha]_{305}$ −1368°, "inflection", $[\alpha]_{340}$ −368°, *c* 0.1, temp. 25–27°.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORY OF THE INDIAN INSTITUTE OF SCIENCE, BANGALORE AND COLLEGE OF ENGINEERING & TECHNOLOGY, BENGAL]

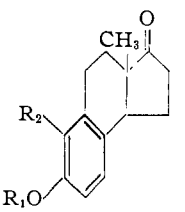
Stereospecific Syntheses of *trans*-1β-Hydroxy-8-methyl-4,5-(4′-methoxybenzo)-hydrindane, *trans*-1β-Hydroxy-8-methyl-4,5-(3′-methyl-4′-methoxybenzo)-hydrindane and *d,l*-Equilenin Methyl Ether

BY D. K. BANERJEE, S. CHATTERJEE, C. N. PILLAI AND M. V. BHATT

RECEIVED SEPTEMBER 30, 1955

By modification of Johnson, Peterson and Gutsche's synthesis of equilenin[5] it has been possible to realize stereospecific syntheses of *trans*-1β-hydroxy-8-methyl-4,5-(4′-methoxybenzo)-hydrindane, *trans*-1β-hydroxy-8-methyl-4,5-(3′-methyl-4′-methoxybenzo)-hydrindane and *d,l*-equilenin methyl ether.

The present paper describes stereospecific syntheses of *trans*-1β-hydroxy-8-methyl-4,5-(4′-methoxybenzo)-hydrindane (XIVa) and *trans*-1β-hydroxy-8-methyl-4,5-(3′-methyl-4′-methoxybenzo)-hydrindane (XIVb), which, in view of recent developments[1] in the technique of Birch reduction, are considered to be useful intermediates for the synthesis of steroids. Two isomers of each of the corresponding ketones Ia and Ib were previously prepared by Bachmann and Thomas,[2] and Martin and Robinson,[3] respectively, by following the classical procedure of Bachmann, Cole and Wilds[4] for the synthesis of equilenin. The American workers failed to assign definite configuration to the isomers of Ia, whereas the British workers indicated the probable structures of the isomers of Ib on the basis of solubility.



Ia, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

In Johnson's[5] synthesis of equilenin, the Stobbe condensation product (II) obtained from 1-keto-2-methyl-2-cyano-7-methoxy-1,2,3,4-tetrahydrophenanthrene on saponification followed by decarboxylation yielded two isomeric unsaturated ketones (III) and (IV). The latter on catalytic reduction furnished exclusively *d,l*-isoequilenin methyl ether, the hydrindene ring in IV assuming the more

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(2) W. E. Bachmann and D. G. Thomas, *ibid.*, **64**, 94 (1942).

(3) R. H. Martin and R. Robinson, *J. Chem. Soc.*, 491 (1943).

(4) W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

(5) W. S. Johnson, J. W. Petersen and C. D. Gutsche, *ibid.*, **69**, 2942 (1947).