Removal of catalyst and solvent gave 0.15 g. of a 9-methyldecalin mixture, the infrared spectrum of which showed it to contain 55% of the *cis* and 45% of the *trans* isomer. Exactly the same result was obtained when the hydrogenation was carried out in glacial acetic acid solution.

REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Optical Rotatory Dispersion Studies. XVII.[1] Detection of Conformational Alterations. Effects of Alkyl Groups and Double Bonds in Polycyclic Systems[2]

BY CARL DJERASSI, O. HALPERN, V. HALPERN AND B. RINIKER

RECEIVED FEBRUARY 5, 1958

Since alterations in conformation in a cyclic system incorporating a carbonyl group change the asymmetric environment, it can be expected that this would be reflected in the rotatory dispersion curve of such ketones. This supposition has now been verified by measurements on a large group of related polycyclic ketones. In particular, it was found that introduction of alkyl groups and double bonds in certain locations have a pronounced effect upon the rotatory dispersion curve of the corresponding unsubstituted ketone and this must be due to conformational distortion of the system. The subtlety of the conformational effects uncovered by the rotatory dispersion approach is illustrated by the pronounced dispersion change accompanying 4,4-dimethylation in 3-keto-5α-steroids which is not due to interactions with the angular methyl group at C-10 nor produced by a sole axial substituent located at C-4. The utility of these observations for stereochemical assignments is exemplified in the santonin and butyrospermol series and attention is called to the fact that determination of the rotatory dispersion curve or the rate of condensation with benzaldehyde seems to be a measurement of the same conformational factor operating in polycyclic ketones.

Most of the rotatory dispersion work carried out in this Laboratory[3] has dealt with carbonyl compounds since this chromophore exhibits rather low ultraviolet absorption in a suitable spectral range which permits rotatory dispersion measurements through the region of maximal absorption.[4] The resulting ketonic wave, represented either by a single (saturated ketone or aldehyde) or multiple (usually α,β-unsaturated ketone) Cotton effect curve,[5] is a consequence of the asymmetric environment in which the carbonyl chromophore has been placed. It is not surprising, therefore, that in cyclic systems, changes in conformation should reflect themselves in the rotatory dispersion curve and isolated examples of this phenomenon have been recorded in some of our past publications.[1,4b,6,7] A sufficient number of measurements on diverse polycyclic compounds have now been carried out so that a detailed discussion is in order and the present paper is concerned with an examination of the effect of alkyl (chiefly methyl) substituents and of double bonds upon the conformation of cyclic ketones and its detection by rotatory dispersion. As will become apparent in the sequel, under certain circumstances the optical rotatory dispersion curve will yield information on conformational distortion which at the present time cannot be secured readily by any other physical tool.

The most notable rotatory dispersion changes attributable to conformational distortion have so far been observed in α,β-unsaturated ketones. Particularly striking examples are the pair[6] α-cyperone (I) and *epi*-α-cyperone (II), where the axial isopropenyl grouping of the latter inverts the multiple Cotton effect of the Δ^4-3-ketone, or 8-iso-Δ^4-3-ketosteroids[4b] such as 8-isotestosterone (III) where this same dispersion change is due to the fact that rings B or C must assume a boat conformation in contrast to the all-chair situation obtaining in the usual steroids. Another interesting case is represented by the 6-halo-Δ^4-3-ketosteroids[8] where the axial 6β-bromine or chlorine atom produces an inversion of the Cotton effect of the unsubstituted Δ^4-3-ketone, while axial fluorine affects the amplitude and resolution of the curve but does not invert it. In order to determine whether steric or electronic factors were primarily responsible for this markedly different behavior between fluorine on the one hand and chlorine or bromine on the other, it was of very considerable interest to measure the rotatory dispersion curves of the recently synthesized[9] epimeric 6-methyltestosterones (IV, V). As shown in Fig. 1, the equatorial 6α-methyl group had no effect since the dispersion curve of 6α-methyltestosterone (IV) closely follows that of testosterone.[4b] On the other hand, a completely different curve is observed with the axial 6β-methyl isomer V, its most characteristic feature being the appearance of fine structure in the 370 mμ region with positive rather than negative rotation values. To that extent, the curve resembles[10] that of 8-isotestosterone (III) and 6β-chloro- and -bromotestosterone thus suggesting a common con-

(1) Paper XVI, C. Djerassi and D. Marshall, THIS JOURNAL, **80**, 3986 (1958).

(2) Supported by a research grant (No. CY-2919) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) For review see C. Djerassi, *Bull. soc. chim. France*, 741 (1957), and Abstracts, 15th National Org. Chem. Symposium, Rochester, N. Y., 1957, pp. 12-20.

(4) For details see (a) C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4354 (1955); (b) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6377 (1956).

(5) For nomenclature see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

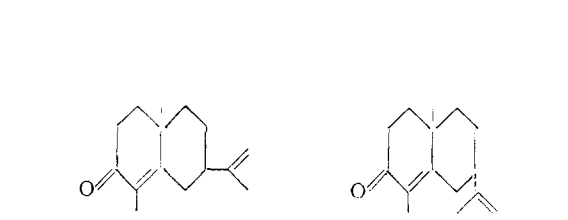
(6) C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956).

(7) C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

(8) C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, THIS JOURNAL, **80**, 1216 (1958).

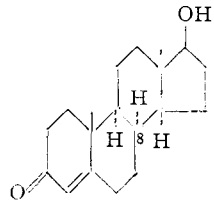
(9) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(10) There are changes below 330 mμ where the 6β-methyl derivative again moves toward positive rotation values while the two 6β-halo ketones continue in a negative direction without exhibiting important fine structure. These differences would suggest that the steric factor alone is not the only one entering into the picture.



I

II



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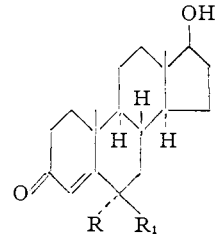

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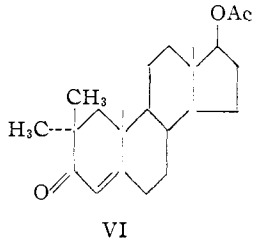
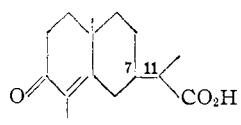
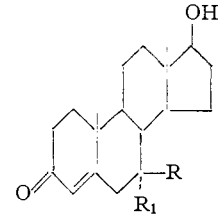
V, R = H; R_1 = CH_3



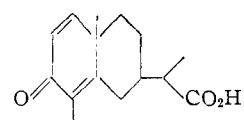
VI



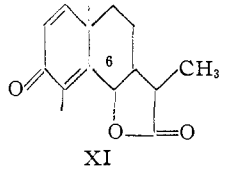
VII



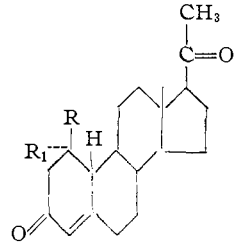
VIII, R = CH_3; R_1 = H
IX, R = H; R_1 = CH_3



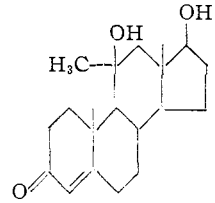
X



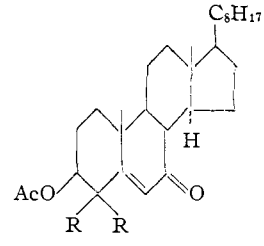
XI



XII, R = CH_3; R_1 = H
XIII, R = H; R_1 = CH_3



XIV



XV, R = H
XVI, R = CH_3

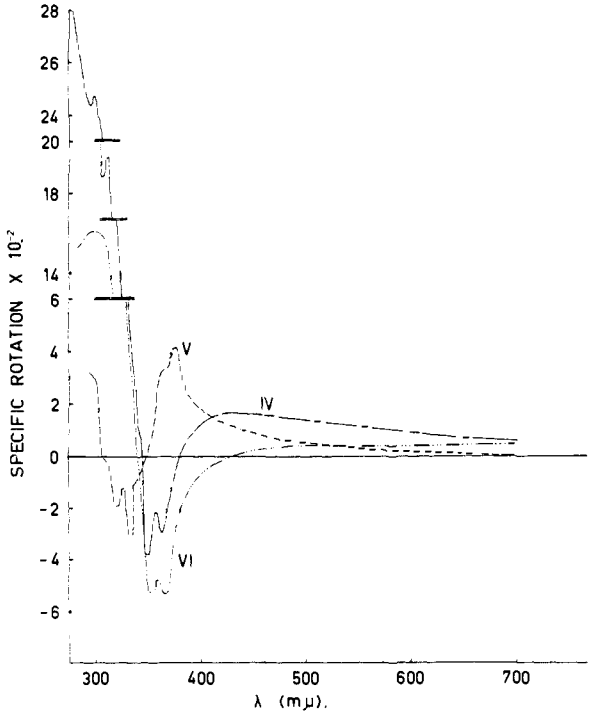
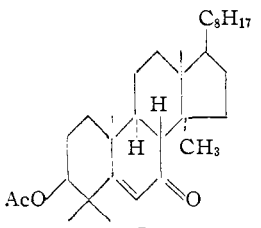


Fig. 1.—Optical rotatory dispersion curves (dioxane solution) of 6α-methyltestosterone (IV), 6β-methyltestosterone (V) and 2,2-dimethyltestosterone acetate (VI).

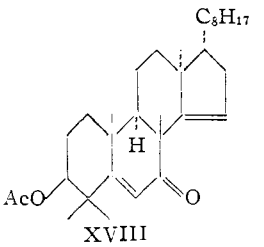
formational alteration due to axial interactions involving the 6β-substituent and possibly resulting in partial conversion toward a boat conformation in ring B, known to exist in III. It is interesting to note that no such change is produced in the epimeric 6-hydroxy-Δ^4-3-ketones[4b]—the only differences being recognized below 310 mμ—from which we conclude that steric factors (OH, F < CH_3, Cl, Br) appear to play the dominant, though not exclusive,[10] role. The nature of this steric effect is rather subtle since it must either involve interaction of the 6β-methyl function with the axial methyl group at C-10 *and* the axial hydrogen atom at C-8 or it must mean that conformational distortions in the *adjacent* rather than in the *same* ring are more readily reflected in the dispersion picture. The basis for this statement is the dispersion curve (Fig. 1) of 2,2-dimethyltestosterone acetate (VI),[11] where the presence of a single diaxial methyl interaction (2β *vs.* 10) does not affect the shape of the curve to any marked extent. Further evidence for the absence of major conformational distortion due to such interaction will be presented below in a discussion of saturated ketones.

One conformational change, which would not have been detected by any other available physical tool, is that observed[6] between α-cyperone (I) and *epi*-α-cyperone (II). It already has been shown that the isolated double bond plays no role since the corresponding dihydro derivative (II with isopropyl group) exhibits the same type of anomalous dispersion. A further example is now offered in Fig. 2 with (−)-Δ^4-3-keto-11-*epi*-(7)-isoeusanton-

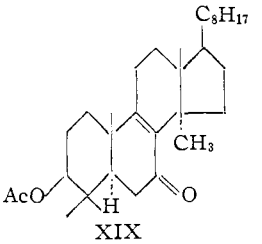
(11) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).



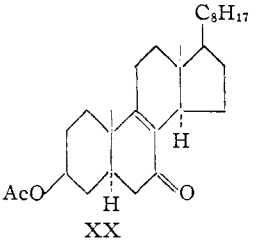
XVII



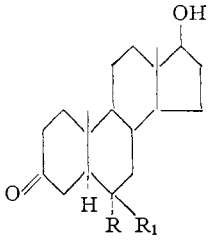
XVIII



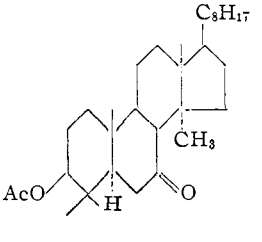
XIX



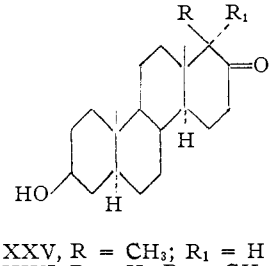
XX



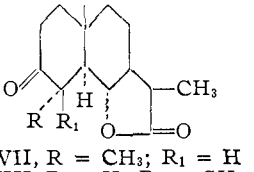
XXI, R = CH_3; R_1 = H
XXII, R = H; R_1 = CH_3
XXIII, R = R_1 = H



XXIV



XXV, R = CH_3; R_1 = H
XXVI, R = H; R_1 = CH_3



XXVII, R = CH_3; R_1 = H
XXVIII, R = H; R_1 = CH_3

enic acid (VII)[12] whose rotatory dispersion curve is very similar[13] to that of *epi*-α-cyperone (II) and which again demonstrates that a bulky axial substituent in that position produces a marked conformational aberration. It was of considerable interest to determine the effect of size upon this remarkable conformational and dispersion change and since the analog of VII (or II) with a methyl group at C-7 is unknown, the corresponding steroids were selected. As was to be anticipated, the rotatory dispersion curve (see Experimental) of the equatorially substituted 7β-methyltestosterone (VIII)[14] was identical to that[4b] of testosterone. On the other hand, the axial epimer 7α-methyltestosterone (IX)[14] exhibited an altered dispersion curve (Fig. 2) and while it does not reach the extreme change observed in *epi*-α-cyperone (II) or the acid VII, it nevertheless does demonstrate the operation of a conformational factor which in this instance can only be due to non-bonded interactions involving the axial 7α-methyl group. Whether the difference in the rotatory dispersion curves of *epi*-α-cyperone (II) and 7α-methyltestosterone (IX) is solely an expression of the difference in effective size of the axial C-7 substituent or whether it also reflects an additional interaction[15] between the 4-methyl group (in II and VII) and the axial three-carbon fragment at C-7 cannot be decided at this time and would require the synthesis and rotatory dispersion measurement of appropriate, bicyclic model compounds.

The absolute configuration of (−)-α-santonin (XI with 6α-orientation) had to be determined[6] by comparison of certain tetrahydrosantonins with appropriate 3-keto steroids of the 5α- and 5β-series since the dispersion curve of santonin itself was quite distinct from that of steroidal 1,4-dien-3-ones. That this was not due to the lactone ring fusion could now be demonstrated (Fig. 2) by the rotatory dispersion curve of (−)-$\Delta^{1,4}$-3-ketoeusantonadienic acid (X)[16] which strongly resembles that[6] of (−)-α-santonin from which it was derived. Unless the 4-methyl group of X plays an unexpectedly important role, the difference between the rotatory

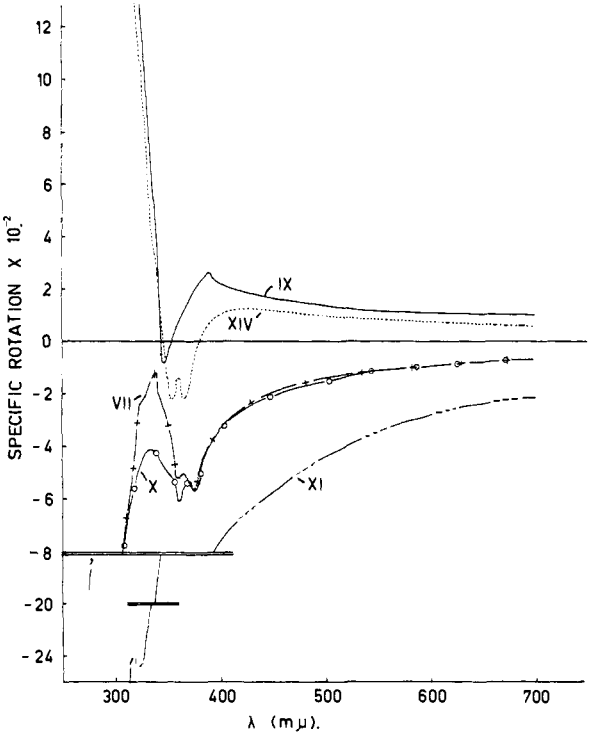


Fig. 2.—Optical rotatory dispersion curves (dioxane solution) of (−)-Δ^4-3-keto-11-epi-(7)-isoeusantonenic acid (VII), 7α-methyltestosterone (IX), (−)-$\Delta^{1,4}$-3-ketoeusantonadienic acid (X), (−)-$\Delta^{1,4}$-6β-hydroxy-3-ketoeusantonadienic acid lactone (XI) and 11α-methyl-11β-hydroxytestosterone (XIV).

dispersion of santonin and the acid X on the one hand and of steroidal 1,4-dienones[4b,6] on the other must be due to the additional ring fusion in the lat-

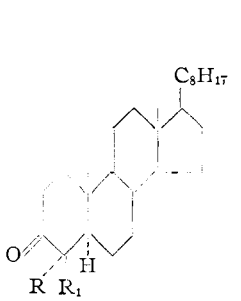
(12) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, THIS JOURNAL, **78**, 1416 (1956), refer to this substance as "(−)-A acid."

(13) The curves are of mirror image types since the two substances belong to antipodal series.

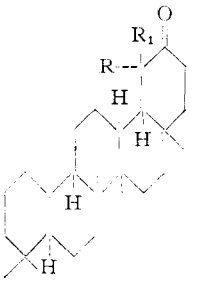
(14) J. A. Zderic and H. J. Ringold, to be published.

(15) As pointed out in ref. 6, construction of models suggests that such an interference should be taken into consideration.

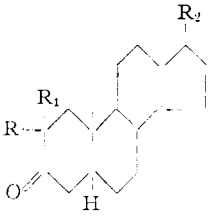
(16) Y. Abe, T. Miki, M. Sumi and T. Toga, *Chemistry & Industry*, 953 (1956); T. Miki, *J. Pharm. Soc. Japan*, **75**, 412 (1955).



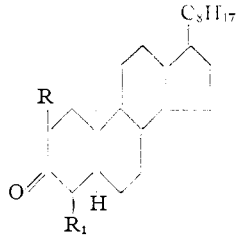
XXIX, R = CH_3; R_1 = H
XXX, R = H; R_1 = CH_3
XXXI, R = C_2H_5; R_1 = H
XXXII, R = R_1 = H



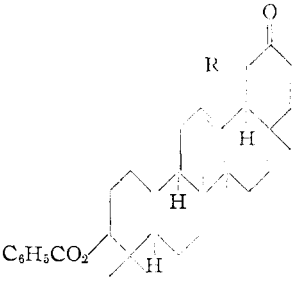
XXXIII, R = CH_3; R_1 = H
XXXIV, R = H; R_1 = CH_3



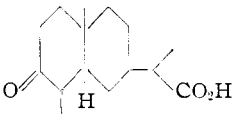
XXXV, R = CH_3; R_1 = H; R_2 = C_8H_{17}
XXXVI, R = H; R_1 = CH_3; R_2 = C_8H_{17}
XXXVII, R = CH_3; R_1 = H; R_2 = OH
XXXVIII, R = R_1 = CH_3; R_2 = OH
XXXIX, R = $(CH_3)_2NCH_2$; R_1 = H; R_2 = OH



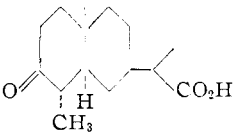
XL, R = CH_3; R_1 = H
XLI, R = H; R_1 = CH_3



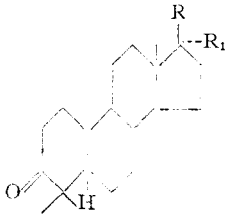
XLII, R = H
XLIII, R = CH_3



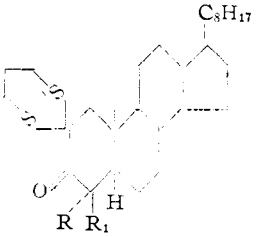
XLIV



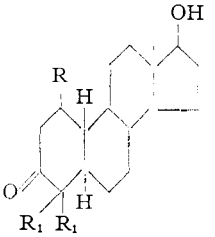
XLV



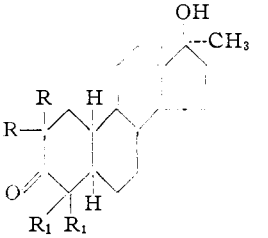
XLVI, R = C_8H_{17}; R_1 = H
XLVII, R = OH; R_1 = H
XLVIII, R = OH; R_1 = CH_3



XLIX, R = R_1 = H
L, R = CH_3; R_1 = H
LI, R = H; R_1 = CH_3
LII, R = R_1 = CH_3



LIII, R = R_1 = H
LIV, R = CH_3; R_1 = H
LV, R = H; R_1 = CH_3



LVI, R = CH_3; R_1 = H
LVII, R = H; R_1 = CH_3

ter, but a more precise definition of this effect requires further dispersion measurements on model compounds which are as yet unavailable.

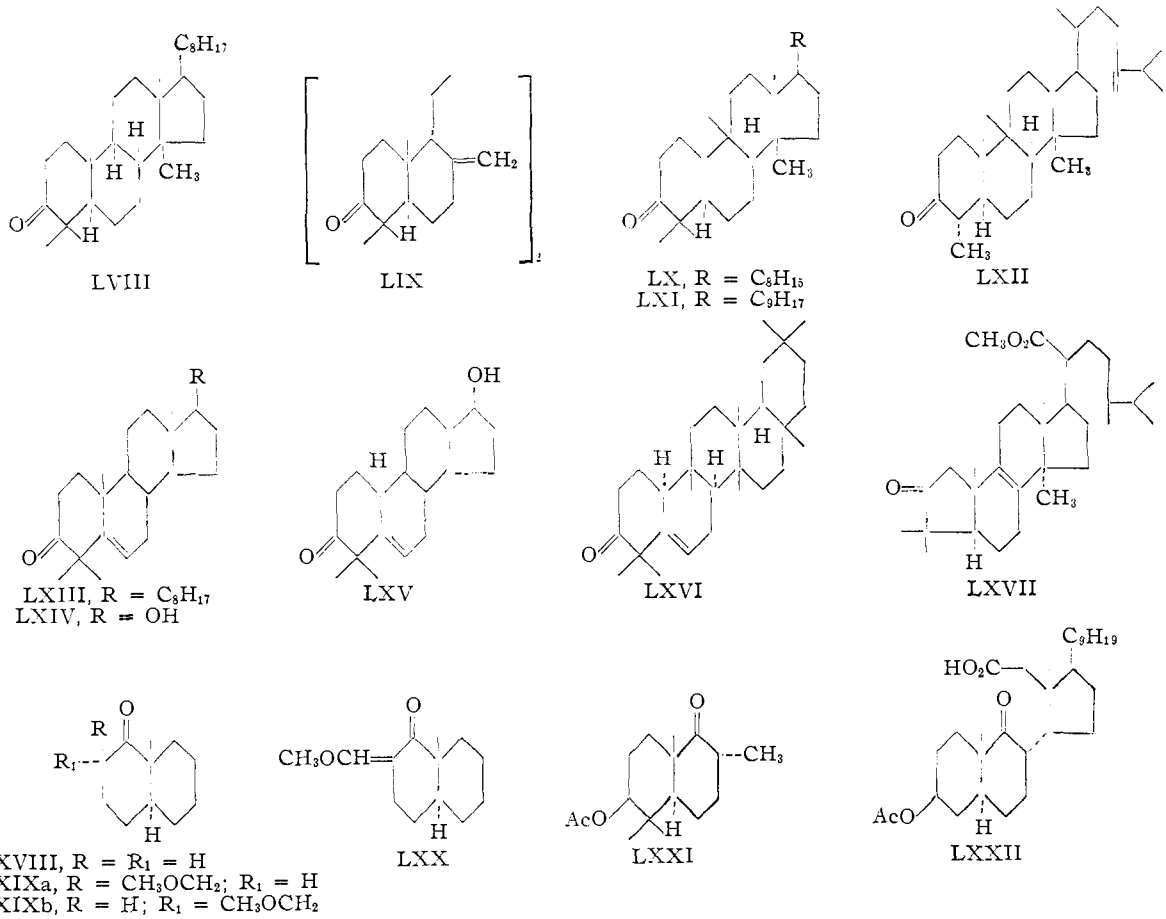
Since the 6α-attachment of the lactone ring in (−)-α-santonin does not contribute to the rotatory dispersion picture, the corresponding 6β-isomer XI[16] also was examined. This stereochemical change led to a pronounced negative drift (Fig. 2) and considerable loss of fine structure, thus indicating that axial–equatorial fusion of the lactone ring produces some distortion not present in the diequatorially fused α-santonin.

The rotatory dispersion curves of two 1-methyl-19-norprogesterones (XII, XIII), epimeric at C-1, were reproduced in an earlier paper[4b] and it was noted that the biologically active[17] epimer exhibited a curve which was nearly indistinguishable from that of progesterone, while that of the inactive isomer[17] was completely different from progesterone and rather similar to that of 8-isoprogesterone (where ring B exists in a boat form). This suggested a major deformation in conformation in the biologically inactive isomer due to nonbonded interaction with one of the methyl groups and since it was felt that this would be most pronounced with the equatorial methyl group and the methylene group at C-11 (for a similar example see discussion below with respect to the pair XXXIII and XXXIV), the inactive isomer was assigned[4b] the 1β-orientation (XII). It has now been possible to measure the rotatory dispersion of 11α-methyl-11β-hydroxytestosterone (XIV)[18] where a somewhat similar type of interaction (C-1 methylene hydrogen atoms and equatorial 11α-methyl group) should exist. It is noteworthy that the curve (Fig. 2) of XIV is essentially that of a typical Δ^4-3-keto steroid, which would mean that any steric strain is relieved by distortion of ring C rather than rings A or B. If the latter had been involved then this would almost certainly have shown up in the rotatory dispersion curve.

The sensitivity of the α,β-unsaturated ketone chromophore to steric changes in the adjacent ring is further illustrated in Fig. 3 by considering the effect of methylation in ring A upon the carbonyl moiety in ring B. As already has been pointed out earlier,[4b] the dispersion curve (Fig. 3) of 7-keto cholesteryl acetate (XV) is approximately the

(17) C. Djerassi, A. E. Lippman and J. Grossman, THIS JOURNAL, **78**, 2479 (1956).

(18) H. J. Ringold, E. Batres and J. A. Zderic, *Tetrahedron*, **2**, 164 (1957).



mirror image of that of a Δ^4-3-keto steroid and the two systems can, therefore, be considered as enantiomeric in the sense defined by Klyne.[19] With this in mind, it is instructive to note that the rotatory dispersion curve (Fig. 3) of 3β-acetoxy-Δ^5-lanosten-7-one (XVII), though possessing a Δ^5-7-keto moiety, is characterized by a multiple Cotton effect curve which is opposite in sign to that of 7-ketocholesteryl acetate (XV). In order to localize this striking dispersion effect, we have synthesized 4,4-dimethyl-7-ketocholesteryl acetate (XVI) by allylic oxidation of 4,4-dimethylcholesteryl acetate[20] and its rotatory dispersion curve (Fig. 3) shows the same type of inverted Cotton effect as XVII. It follows, therefore, that the 14α-methyl group in the lanostenone derivative XVII is not the chief factor and that this remarkable rotatory dispersion behavior is due largely to the introduction of a *gem*-dimethyl grouping at C-4. Some conformational distortion is, however, attributable to the 14α-methyl function as shown by the differences between XVI and XVII below 350 mμ. This inversion of the Cotton effect (with respect to the unmethylated precursor) already has been commented on above with 6β-methyltestosterone (V) and it would appear, therefore, that in each case a conformational distortion of the adjacent ring is caused by interaction of an axial methyl group with other axial substituents in the same ring.

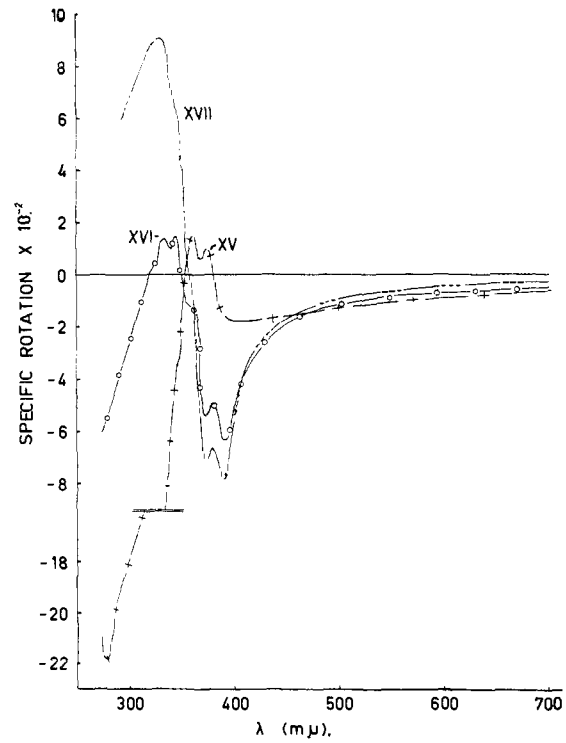
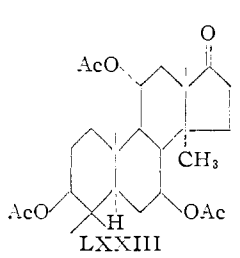
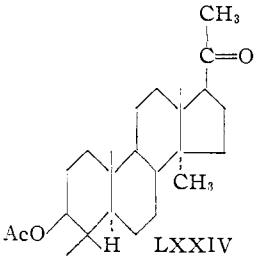


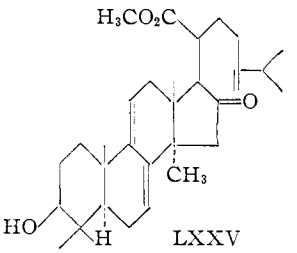
Fig. 3.—Optical rotatory dispersion curves (dioxane solution) of 7-ketocholesteryl acetate (XV), 4,4-dimethyl-7-ketocholesteryl acetate (XVI) and 3β-acetoxy-Δ^5-lanosten-7-one (XVII).

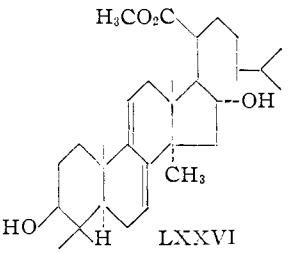
(19) W. Klyne, *J. Chem. Soc.*, 2916 (1952).

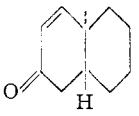
(20) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *ibid.*, 1131 (1957).

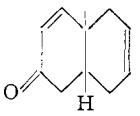

LXXIII

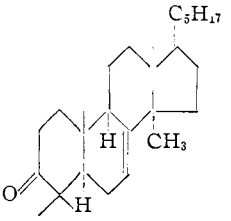

LXXIV

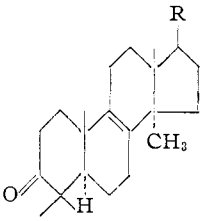

LXXV

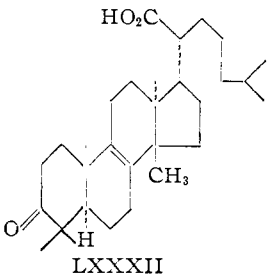

LXXVI

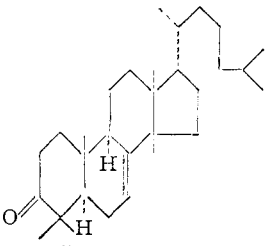

LXXVII

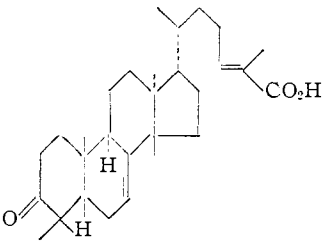

LXXVIII

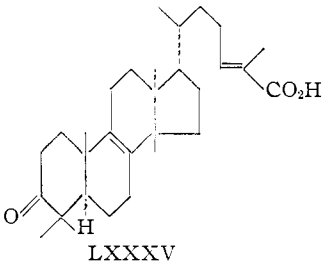

LXXIX

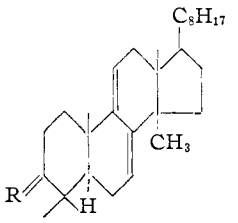

LXXX, R = C_8H_{17}
LXXXI, R = $C_8H_{16}\cdot CO_2H$

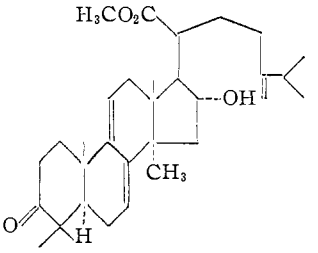

LXXXII

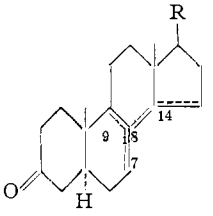

LXXXIII

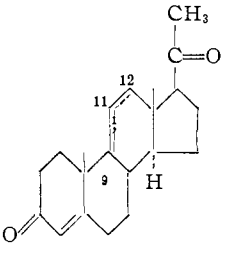

LXXXIV

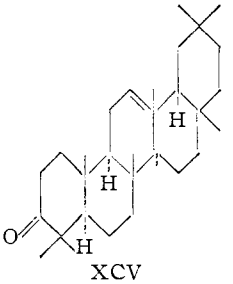

LXXXV


LXXXVI, R = O
LXXXVII, R = 


LXXXVIII


LXXXIX, R = C_9H_{19}; 7–8 double bond
XC, R = C_8H_{17}; 8–9 double bond
XCI, R = C_9H_{19}; 8–14 double bond
XCII, R = C_9H_{19}; 14–15 double bond


XCIII, double bond at 9–11
XCIV, double bond at 11–12


XCV

The extent to which this effect is insulated from the rest of the molecule is demonstrated in Fig. 4 by the dispersion curve of $\Delta^{5,14}$-7-ketoapoeuphadienyl acetate (XVIII)[21] which is very similar in shape to that of 4,4-dimethyl-7-ketocholesteryl acetate (XVI) in spite of marked chemical and stereochemical changes in rings C and D.

(21) W. Lawrie, W. Hamilton, F. S. Spring and H. S. Watson, *J. Chem. Soc.*, 3272 (1956).

The sensitivity of the dispersion curve of an α,β-unsaturated ketone toward conformational changes in the adjacent ring is only noticeable when this chromophore is involved in the juncture connecting it to that ring (*e.g.*, II, III, V, XVI, XVII). This is best illustrated by comparing the dispersion curve (Fig. 3) of 3β-acetoxy-Δ^5-lanosten-7-one (XVII)—exhibiting the strong *gem*-dimethyl effect—with that (Fig. 4) of 3β-benzoyloxy-Δ^8-

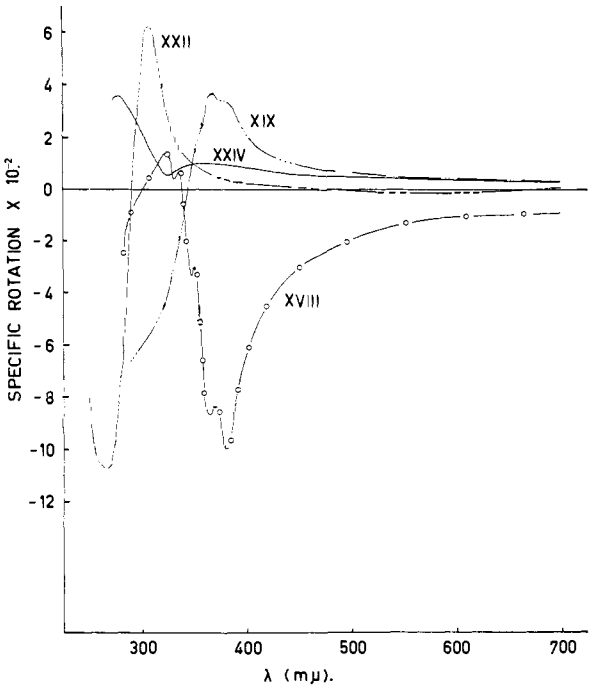


Fig. 4.—Optical rotatory dispersion curves of $\Delta^{5,14}$-7-ketoapoeuphadienyl acetate (XVIII) (dioxane), 3β-benzoyloxy-Δ^{8}-lanosten-7-one (XIX) (dioxane), 6β-methyldihydrotestosterone (XXII) (methanol) and 3β-acetoxylanostan-7-one (XXIV) (dioxane).

lanosten-7-one (XIX),[22] which shows a Cotton effect typical[4b] of Δ^{8}-7-ketones such as 3β-acetoxy-Δ^{8}-cholesten-7-one (XX). Here neither the 4,4-dimethyl grouping nor the 14α-methyl substituent plays any particular role other than to affect the amplitude of the curve to a certain extent. This result implies that once the conjugation of the optically active chromophore with the conformationally disturbing center is broken, the dispersion changes will be of a minor character and will demonstrate themselves chiefly by amplitude variations. Two further examples collected in Fig. 4 support the correctness of this assumption. Thus while the axial 6β-methyl group in 6β-methyltestosterone (V) has a pronounced effect on the rotatory dispersion (Fig. 1) as compared to the equatorial 6α-isomer IV, hydrogenation of the double bond leads to the corresponding dihydrotestosterones XXI and XXII (Fig. 4) whose dispersion curves are of exactly the same type as that of dihydrotestosterone (XXIII) except for some amplitude variations. It is interesting to note that the smallest amplitude is shown by 6α-methyldihydrotestosterone (XXI) as has already been observed[1] with its bicyclic analog *trans*-5,9-dimethyl-3-decalone where it was suggested that this might be an indication of some intramolecular crowding between the equatorial 6α-methyl group and the hydrogen atoms at C-4.

The other example in Fig. 4 is represented by the hydrogenation product of 3β-acetoxy-Δ^{5}-lanosten-7-one (XVII), 3β-acetoxylanostan-7-one (XXIV), and while its rotatory dispersion curve has now been shifted completely to the positive side as compared to steroidal 5α-7-ketones,[23] both the characteristic shape and amplitude are retained and no inversion in the Cotton effect is observed as is the case in the unsaturated precursor XVII (Fig. 3).

The effect of methyl groups next to a saturated carbonyl group (rather than in the adjoining ring as in XXII *vs.* XXIII) has been noted earlier[6] in two examples—the pair of 17a-methyl-D-homo-17-ketones XXV and XXVI and the two C-4 epimeric tetrahydrosantonins XXVII and XXVIII—and in each instance axial methylation produced a marked reduction in amplitude, without, however, inverting the sign of the single Cotton effect curve. A large number of methylated 3-ketosteroids have recently become available and this has made possible a much more precise evaluation of the effect of methyl groups adjacent to a saturated ketone function as demonstrated in Figs. 5–8.

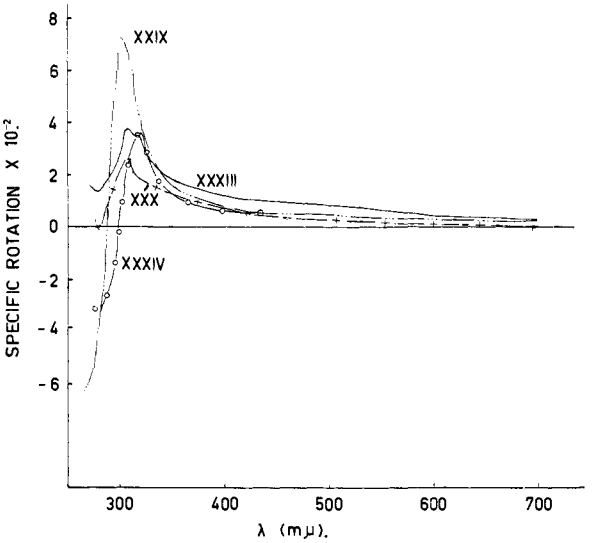


Fig. 5.—Optical rotatory dispersion curves of 4α-methylcholestan-3-one (XXIX) (methanol), 4β-methylcholestan-3-one (XXX) (methanol), 30-nortaraxastan-20-one (XXXIII) (dioxane) and 30-nor-19α(H)-taraxastan-20-one (XXIV) (dioxane).

The reduction in amplitude in the thermodynamically less stable isomer is demonstrated in Fig. 5 by a comparison of the dispersion curves of 4α-methylcholestan-3-one (XXIX)[24] and 4β-methylcholestan-3-one (XXX),[24,25] while an increase in the size of an equatorial alkyl group as in 4α-ethylcholestanone (XXXI)[26] plays no important role (see Experimental). It is noteworthy that in the triterpene series, the equatorially substituted ketone 30-nortaraxastan-20-one (XXXIII) shows (Fig. 5) the reduced amplitude as compared to the axial isomer 30-nor-19α(H)-taraxastan-20-one (X-

(22) Changes in the ester function such as the suhstitution of a benzoate for an acetate grouping at C-3 has no effect upon the rotatory dispersion curve as has already been demonstrated by C. Djerassi and W. Closson, THIS JOURNAL, **78**, 3761 (1956).

(23) C. Djerassi, W. Closson and A. E. Lippman, *ibid.*, **78**, 3163 (1956).

(24) J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips, *J. Chem. Soc.*, 753 (1957); G. D. Meakins and O. R. Rodig, *ibid.*, 4679 (1956).

(25) F. Sondheimer, *et al.*, to be published.

(26) C. Djerassi, M. Cais and L. A. Mitscher, THIS JOURNAL, **80**, 247 (1958).

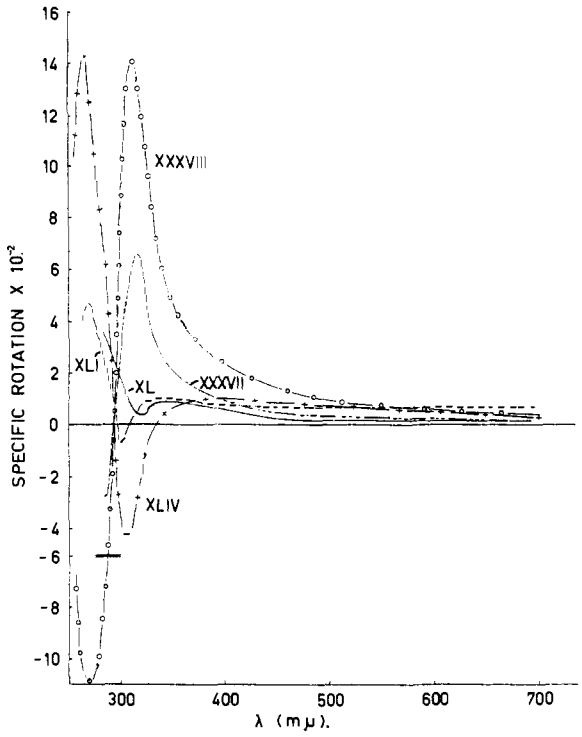


Fig. 6.—Optical rotatory dispersion curves of 2α-methyldihydrotestosterone (XXXVII) (dioxane), 2,2-dimethyldihydrotestosterone (XXXVIII) (methanol), 2β-methylcoprostan-3-one (XL) (dioxane), 4β-methylcoprostan-3-one (XLI) (methanol) and *cis*-3-ketoeusantonanic acid (XLIV) (methanol).

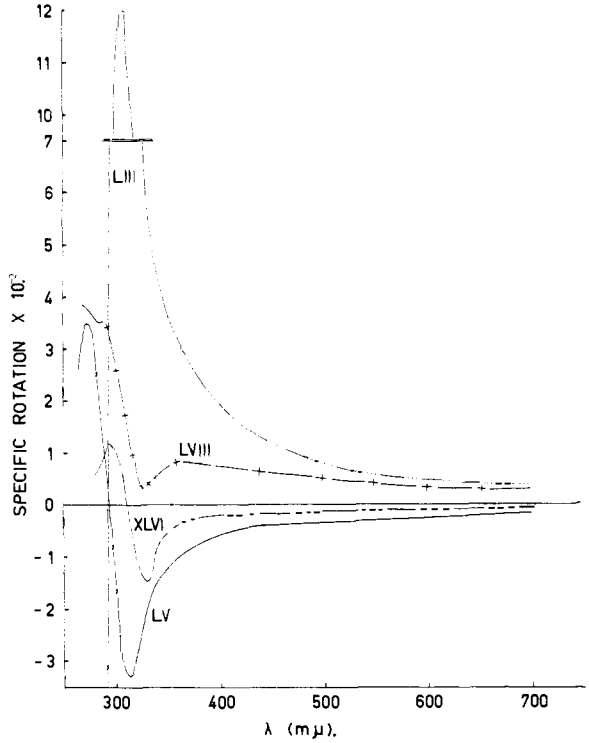


Fig. 7.—Optical rotatory dispersion curves of 4,4-dimethylcholestan-3-one (XLVI) (dioxane), 19-nordihydrotestosterone (LIII) (methanol), 4,4-dimethyl-19-nordihydrotestosterone (LV) (methanol) and lanostan-3-one (LVIII) (methanol).

XXIV) and this is precisely a pair of epimers where the usual stability order is reversed,[27] the equatorial isomer being less stable because of interference with the C-12 methylene function.

This reduction in amplitude by the less stable isomer apparently applies only to those ketones where methyl substitution occurs at the carbon atom (C-4 in the steroids) next to the ring fusion. In the pair 2α-methylcholestan-3-one (XXXV)[25] and 2β-methylcholestan-3-one (XXXVI)[25] the amplitude of the respective dispersion curves is virtually the same (see Experimental) and an even more striking illustration (Fig. 6) is provided by a comparison of dihydrotestosterone (XXIII), 2α-methyldihydrotestosterone (XXXVII)[11] and 2,2-dimethyldihydrotestosterone (XXXVIII),[11] where the latter exhibits markedly increased amplitude in spite of the presence of an axial methyl substituent. That this is not a general property inherent in *gem*-dialkylated ketones (irrespective of the site of substitution) is shown below with 4,4-dimethyl-3-keto steroids and triterpenes. Here again, the size of an equatorial substituent does not have a large influence upon the amplitude of the single Cotton effect curve and this is illustrated in the Experimental section with 2α-(dimethylaminomethyl)-dihydrotestosterone (XXXIX).

The above data in the A/B *trans* series of 3-keto steroids show that equatorial methylation on either side of the 3-keto function does not affect greatly

(27) T. R. Ames, J. L. Beton, A. Bowers, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 1905 (1954).

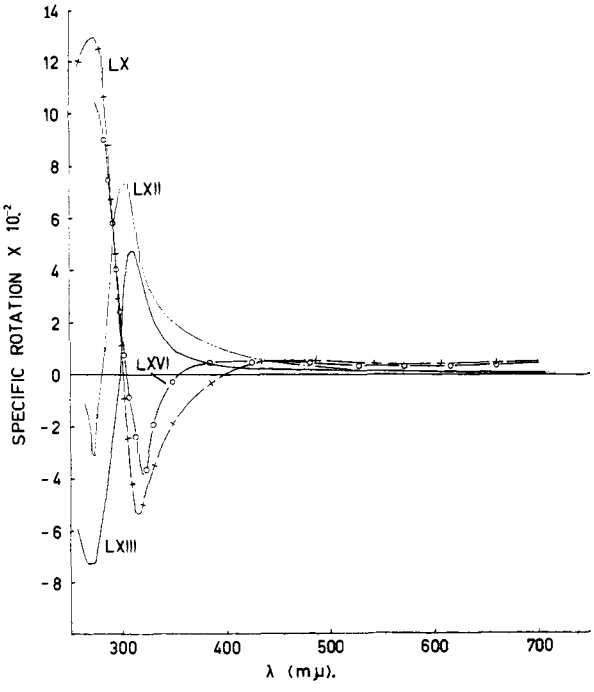


Fig. 8.—Optical rotatory dispersion curves of cycloartenone (LX) (methanol), cycloeucalenone (LXII) (methanol), 4,4-dimethyl-Δ⁵-cholesten-3-one (LXIII) (methanol) and alnusenone (LXVI) (dioxane).

the amplitude of the dispersion curve (XXIX *vs.* XXXV) and this statement also applies to the *cis*

series as supported by the dispersion curves (Fig. 6) of 2β-methylcoprostan-3-one (XL)[25] and 4β-methylcoprostan-3-one (XLI).[25] Indeed this situation obtains even in the triterpene series in the pair 29,30-bisnor-20-keto-β-amyrin benzoate (XLII)[28] and 30-nor-20-keto-α-amyrin benzoate (XLIII),[28] whose pertinent data are listed in the Experimental portion.

The utility of these observations in stereochemical assignments is illustrated in the bicyclic series where Abe, *et al.*,[16] examined the hydrogenation of the dienone X and isolated several tetrahydro acids of unknown stereochemistry. The rotatory dispersion curves of two of these acids have now been measured and the curve (Fig. 6) of the tetrahydro acid m.p. 133–135°[16] is typical of an A/B *cis*-steroid and consequently the substance should be represented by the stereoformula XLIV. Another isomer, m.p. 111°, exhibited a curve (see Experimental) which in sign and amplitude of the single positive Cotton effect suggests strongly that the stereochemistry is depicted correctly in XLV with a *trans* ring juncture and an equatorial methyl group.

It already has been pointed out above (see Fig. 6) that a 2,2-dimethyl grouping in a 3-keto-5α-steroid (XXXVIII) does not affect the sign of the Cotton effect curve but increases its amplitude. A completely different picture is obtained when the dispersion of 4,4-dimethyl-3-keto-5α-steroids is examined. Whereas 3-keto-5α-steroids such as cholestan-3-one (XXXII) or dihydrotestosterone (XXIII) exhibits a single positive Cotton effect curve with an amplitude of *ca.* 1500–1800°, the corresponding 4,4-dimethylated derivatives (XLVI,[24] XLVII,[29] XLVIII[29]) show an inversion of the sign of the Cotton effect and a large reduction in amplitude (less than 500°). This inversion (see Fig. 7 and Experimental section) is so pronounced that it is carried over into the visible region of the spectrum and the characteristically positive sodium D line rotations of 3-keto-5α-steroids[30] are now negative in their 4,4-dimethyl analogs. This inversion appears to be so typical that substitution at the 2-position does not affect it and this is shown in the Experimental section by the rotatory dispersion data of a series of methylated derivatives (L, LI, LII) of cholestan-3-one-2-spiro-2′-(1′,3′-dithiane) (XLIX).[24,31]

In order to define more clearly the steric factors necessary to produce the type of dispersion effects noted above upon methylation, a series of 19-nor-steroids were examined since the removal of the angular methyl group should result in marked reduction of steric strain involving diaxial interactions with that angular substituent. The parent compound of this series is 19-nordihydrotestosterone (LIII)[32] and its rotatory dispersion curve, characterized by a strong, positive single Cotton effect, is depicted in Fig. 7. Introduction of a 1α-methyl group[33] (LIV) results in some reduction in amplitude which may be an indication of the operation of a "3-alkyl ketone effect"[34] while 2,2-dimethylation (LVI)[35] increases the amplitude (see Experimental) as already has been observed above in a similar compound (XXXVIII) possessing the C-19 angular methyl group. Of particular interest were the 4,4-dimethyl-3-ketones LV and LVII of the 19-nor series[35] in order to see whether the inversion of the Cotton effect, noted above with steroids possessing an angular methyl group, would also be found here. While interaction between an axial methyl group at C-10 and at C-4 could, *per se*, hardly have been responsible in view of the fact that a single diaxial dimethyl interaction (as in the 2,2-dimethyl-3-ketone XXXVIII) did not show this effect, the possibility existed that "triangular" interference between the axial methyl groups at C-4 and C-10 as well as the interaction of the C-4 substituents with C-6 was responsible. Since the dispersion curves (Fig. 7) of 4,4-dimethyl-19-nordihydrotestosterone (LV) and of the corresponding 17α-methyl derivative LVII (see Experimental) show again the characteristic inversion of the Cotton effect, non-bonded interactions involving the angular substituent cannot be implicated. In summary, it can be stated that all of the rotatory dispersion effects noted in 3-keto-5α-steroids are also applicable to 19-nor-steroids except that the latter invariably show a considerably increased amplitude. This similarity in shape shows that the nature of the angular substituent is not critical[36] and that stereochemical assignments in the 19-nor series based on rotatory dispersion comparison with steroids possessing an angular methyl group are valid.

The generality of this inversion of the Cotton effect accompanying 4,4-dimethylation already has been demonstrated in the bicyclic series[1] and can now be supported further by several additional examples from the triterpene group. Thus lanostan-3-one (LVIII) shows such an inverted Cotton effect curve (Fig. 7) even though it is moved to positive rotation values; this inversion also applies to α-onoceradienedione (LIX)[37] which exhibits a considerable bathochromic shift (see Experimental) as far as the positions of the peak and trough are concerned. Even a 9,10-cyclopropane ring with its consequent distortion of ring B because of the 9β-orientation does not obliterate this effect which is perfectly noticeable in cycloartenone (LX)[38] (Fig. 8) and cyclolaudenone (LXI).[39] Both of these

(28) E. J. Corey and E. W. Cantrall, THIS JOURNAL, **80**, 499 (1958).

(29) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957).

(30) J. P. Mathieu and A. Petit, "Pouvoir Rotatoire Naturel. Vol. 1. Steroids," Masson & Cie., Paris, 1956.

(31) It should be noted that no amplitude reduction seemed to have occurred in the axial 4β-methyl derivative LI, but unfortunately dispersion measurements below 300 mμ were unsatisfactory in this series and the effect of the dithiane ring could not be determined precisely.

(32) A. Bowers, H. J. Ringold and R. I. Dorfman, THIS JOURNAL, **79**, 4556 (1957). The assignment of the A/B *trans* juncture is based on the mode of preparation (lithium-ammonia reduction of 19-nortestosterone) and the shape of the rotatory dispersion curve.

(33) The assignment of the α-orientation to the C-1 substituent was made in the precursor (1α-methyl-19-nortestosterone) on rotatory dispersion grounds (see ref. 4b).

(34) W. Klyne, *Experientia*, **12**, 119 (1956).

(35) A. Bowers and H. J. Ringold, to be published.

(36) This statement does not have to apply, however, when the carbonyl group is adjacent to the ring juncture.

(37) D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 2639 (1955).

(38) D. H. R. Barton, *ibid.*, 1444 (1951); D. H. R. Barton, J. E. Page and E. W. Warnhoff, *ibid.*, 2715 (1954); D. S. Irvine, J. A. Henry and F. S. Spring, *ibid.*, 1316 (1955).

(39) J. A. Henry, D. S. Irvine and F. S. Spring, *ibid.*, 1607 (1955).

compounds show a single, negative Cotton effect curve while cycloeucalenone (LXII)[40] with only one methyl group at C-4 exhibits a positive Cotton effect (Fig. 8) which is in perfect agreement with the results in the steroid series. The "abnormal" molecular rotation calculations which have been commented upon in the past[29,38-40] and which will be discussed in more detail below in connection with dihydrobutyrospermone (LXXXIII) are largely due to the influence of the inverted Cotton effect farther in the ultraviolet which makes itself felt to a varying extent at the sodium D line.

The "4,4-dimethyl" effect disappears in the presence of a Δ^5-double bond as demonstrated (Fig. 8) with Δ^5-4,4-dimethylcholesten-3-one (LXIII),[20] 4,4-dimethyl-Δ^5-androsten-17β-ol-3-one (LXIV)[29] and its 19-nor analog LXV,[35] the latter again showing increased amplitude typical of 19-nor-steroids. Since the nature of the angular substituent is of no importance as far as the over-all shape of the rotatory dispersion curve is concerned, alnusenone (LXVI)[41] should show a Cotton effect opposite in sign to that of 19-nor-Δ^5-4,4-dimethyl-androsten-17β-ol-3-one (LXV) since their respective angular substituents bear an antipodal relationship and this was found to be the case (Fig. 8), thus supporting the earlier[41] stereochemical assignment at C-10.

In summary, the remarkable inversion of the Cotton effect accompanying 4,4-dimethylation does *not* involve the angular methyl group at C-10[42] and must be of a rather subtle, steric origin when contrasted to the absence of such inversion in 2,2-dimethylated (XXXVIII) or 4β-monomethyl (XXX) derivatives. The obliteration of this effect in the presence of a 5,6-double bond suggests that interference with the C-6 methylene function might be involved[43] in some manner, while similar strain in the 4-monomethyl derivatives XXIX and XXX can be relieved by slight distortion, which reflects itself only in the amplitude but not the sign of the Cotton effect. The "4,4-dimethyl" effect[44] may involve a combination of the "2-alkyl ketone effect"[34] and interference with the *peri*-substituent at C-6 and we hope to shed more light on this interesting point in an examination of the rotatory dispersion of appropriate optically-active, polyalkylated cyclohexanones which are currently being synthesized in our laboratory.

Another instance of inversion of the Cotton effect attributable to conformational distortion has now been observed in the *trans*-9-methyl-1-decalone (LXVIII) series. The synthesis of the optically active decalone LXVIII already has been reported[6] and its rotatory dispersion curve[6] is again reproduced in Fig. 9 for comparison purposes. Its 2-hydroxymethylene derivative[6] was now methylated with diazomethane and the O-methyl ether LXX hydrogenated. The resulting product was clearly the axial *trans*-2β-methoxymethyl-9-methyl-1-decalone (LXIXa) since hydrogenation could be expected to proceed from the less hindered α-side. Furthermore, equilibration with alkali[45] led to an isomer, LXIXb, in which the interaction between the axial substituents at C-2 and C-9 is relieved by inversion to the equatorial (2α) orientation. That this type of interaction has resulted in rather serious conformational distortion can be judged from the rotatory dispersion curve (Fig. 9) of the axial isomer LXIXa, whose Cotton effect is inverted with respect to that of *trans*-9-methyl-1-decalone (LXVIII), while the original positive Cotton effect curve is again restored upon equilibration to LXIXb.

Two additional examples of equatorially substituted 1-decalones are listed in the Experimental section and these include the acetoxy ketone LXXI, derived[46] from α-amyrin and 3β-hydroxy-9-keto-9,11-secoergostan-11-oic acid (LXXII).[47] Both of them exhibit negative Cotton effect curves as would be expected since they bear an antipodal relationship to the reference ketone (+)-*trans*-9-methyl-1-decalone (LXVIII).

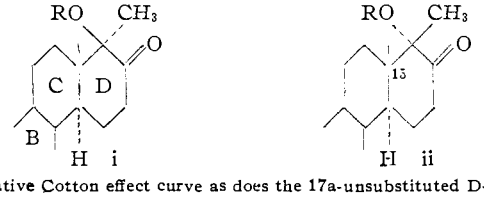
In the above discussion on the rotatory dispersion curves of various 19-nor-steroids, it was noted that removal of the C-19 angular methyl group resulted in an appreciable amplitude of the Cotton effect curve. The converse—addition of an extra angular substituent—has now been investigated in three triterpene transformation products with a 14α-methyl group (Fig. 10). When the carbonyl group is involved in the ring which bears the extra methyl group as in 3β,7β,11α-triacetoxylanan-17-one (LXXIII)[48] or methyl-$\Delta^{7,9(11),24(28)}$-3β-

(40) J. S. G. Cox, F. E. King and T. J. King, *J. Chem. Soc*, 1384 (1956); *Proc. Chem. Soc.*, 290 (1957).

(41) F. S. Spring, J. M. Beaton, R. Stevenson and J. L. Stewart, *Chemistry & Industry*, 1054 (1956); see also J. L. Courtney, R. M. Gascoigne and A. Z. Szumer, *ibid.*, 1479 (1956).

(42) The suggestion has been made (see ref. 60, p. 939) on the basis of work in the triterpene series that the 1,3-diaxial interaction between the methyl groups at C-4 and C-10 is of considerable conformational significance.

(43) The very subtle nature of this effect is shown by the observation (see Table 2 in ref. 7) that D-homosteroids of type i and ii *both* exhibit



a negative Cotton effect curve as does the 17a-unsubstituted D-homo-17-ketone. By analogy to the "4,4-dimethyl" effect discussed above, both i and ii should exhibit a positive Cotton effect curve and if the C-13 methyl group is responsible for this different behavior, its role is obscure.

(44) The ideal model—a 2-keto-3,3-dimethyl-A-nor-steroid—is not available, but the similarity of the rotatory dispersion (see Experimental) of methyl Δ^8-A-nor-2-ketoeburicen-21-oate (LXVII) with that of 2-keto-A-norcholestane (Fig. 3 in ref. 6) suggests that such an effect does not operate in a cyclopentanone; an element of uncertainty is, however, introduced by the presence of the 8-9 double bond in LXVII.

(45) As recorded in the Experimental section, this alkaline treatment is accompanied to a small extent (ultraviolet spectrum) by elimination to the 2-methylene derivative. That this contamination did not affect the rotatory dispersion is shown by the position of the peak and trough of the single, positive Cotton effect curve which is typical of saturated ketones. For comparison, the multiple Cotton effect curves (with fine structure above 350 mμ) of 16-methylene-17-keto steroids (Fig. 16 in ref. 4b) or of the methoxymethylene ketone LXX (Fig. 9) should be inspected.

(46) See O. Jeger in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Springer, Vienna, 1950, Vol. VII, p. 53; R. Rüegg, J. Dreiding, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **33**, 889 (1950).

(47) W. G. Dauben and T. W. Hutton, THIS JOURNAL, **78**, 2647 (1956).

(48) C. S. Barnes, D. H. R. Barton, A. R. H. Cole, J. S. Fawcett and B. R. Thomas, *J. Chem. Soc.*, 571 (1953).

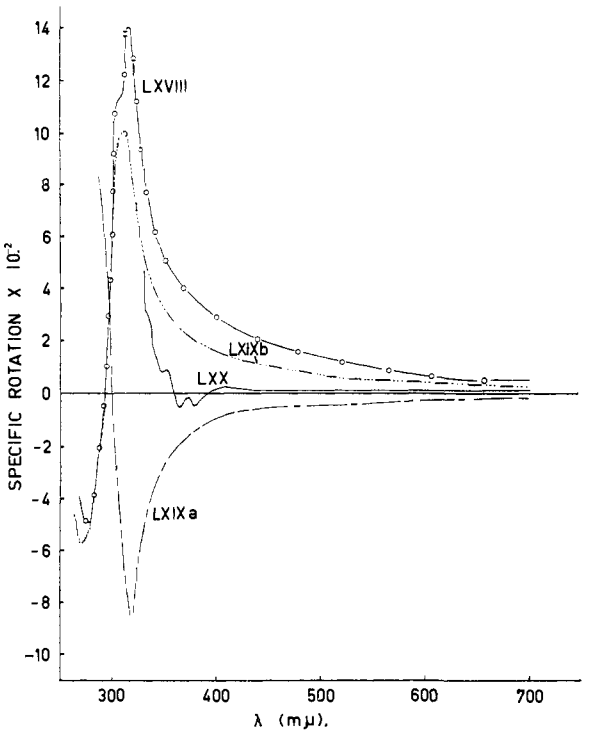


Fig. 9.—Optical rotatory dispersion curves of (+)-*trans*-9-methyl-1-decalone (LXVIII) (dioxane), (−)-*trans*-2β-methoxymethyl-9-methyl-1-decalone (LXIXa) (methanol), (+)-*trans*-2α-methoxymethyl-9-methyl-1-decalone (LXIXb) (methanol) and (+)-*trans*-2-methoxymethylene-9-methyl-1-decalone (LXX) (dioxane).

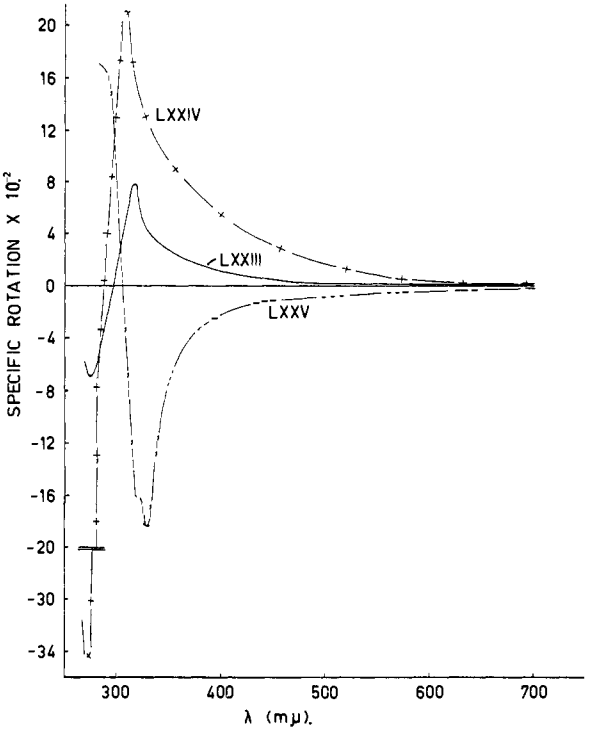


Fig. 10.—Optical rotatory dispersion curves of 3β,7β,11α-triacetoxylanan-17-one (LXXIII) (methanol), 4,4,14α-trimethylallopregnan-3β-ol-20-one acetate (LXXIV) (dioxane) and methyl $\Delta^{7,9(11),24(28)}$-3β-hydroxy-16-ketoeburicotrien-21-oate (LXXV) (dioxane).

hydroxy-16-keto-eburicotrien-21-oate (LXXV)[49,50] the amplitude is considerably reduced,[51] but this does not apply to 4,4,14α-trimethylallopregnan-3β-ol-20-one acetate (LXXIV)[52] where the carbonyl group does not form part of ring D.

One of the basic assumptions[4a] in our rotatory dispersion studies—that minor changes in the ring system can affect the dispersion curve to a marked extent—has been borne out in the above discussion of the effect of introduction of methyl groups and this is unquestionably ascribable to conformational distortion of the bicyclic environment[1] around the carbonyl chromophore. Suitably placed non-conjugated double bonds can also affect the conformation to such an extent that this might be noticeable by the rotatory dispersion technique and one such example already has been given in the bicyclic series[1] in a comparison of the rotatory dispersion curves of the octalone LXXVII and its Δ^6-unsaturated analog LXXVIII. Particularly suitable examples for a more detailed examination of this effect are available in the steroid and triterpene series[53] and these are illustrated below in Figs. 11 and 12.

Δ^7-Lanosten-3-one (LXXIX) exhibits (Fig. 11) the typical negative Cotton effect curve of a 4,4-dimethyl-3-keto-5α-steroid (see Fig. 7), but when this double bond is moved to the 8,9-position as in Δ^8-lanosten-3-one (LXXX) or Δ^8-3-ketoburicen-21-oic acid (LXXXI)[54] the Cotton effect curve becomes positive. This dramatic rotatory dispersion change accompanying migration of a double bond is independent of the nature of the C/D ring juncture, since the curve (Fig. 11) of elemenonic acid (LXXXII)[55] is very similar to that of the eburicoic acid derivative LXXXI. The virtual identity of the dispersion curve (see Experimental) of dihydrobutyrospermone (LXXXIII)[21,56] with that of Δ^7-lanosten-3-one (LXXIX) (see Fig. 11) seems to be excellent evidence in favor of 9α for the long debated[21,56] configuration of butyrospermol at C-9. The earlier arguments[21,38–40,56] are all based on supposed anomalies in calculations of molecular rotation differences utilizing specific rotations at the sodium D line, but these difficulties are easily resolved upon inspection of the rotatory dispersion curves. All of them show the typical negative Cotton effect, but in certain cases (the most marked

(49) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(50) Whether the changed conformation of ring C due to the extra unsaturation is in part or totally responsible for this effect cannot be determined with the information at hand, but the diene system itself shows only a plain positive dispersion curve as indicated in the experimental section for methyl $\Delta^{7,9(11)}$-3β,16α-dihydroxyeburicodien-21-oate (LXXVI).

(51) Compared to standard values (ref. 4a, 6, 23) for 17- or 16-keto steroids.

(52) C. S. Barnes, *Austral. J. Chem.*, **9**, 228 (1956).

(53) See also C. Djerassi, W. Closson and J. Osiecki, in preparation.

(54) J. S. E. Holker, A. D. G. Powell, A. Robertson, J. H. Simes, R. S. Wright and R. M. Gascoigne, *J. Chem. Soc.*, 2422 (1953), and earlier papers.

(55) P. Bilham and G. A. R. Kon, *ibid.*, 544 (1942); E. Menard, H. Wyler, A. Hiestand, D. Arigoni, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **38**, 1517 (1955).

(56) M. C. Dawson, T. G. Halsall, E. R. H. Jones, G. D. Meakins and P. C. Phillips, *J. Chem. Soc.*, 3172 (1956).

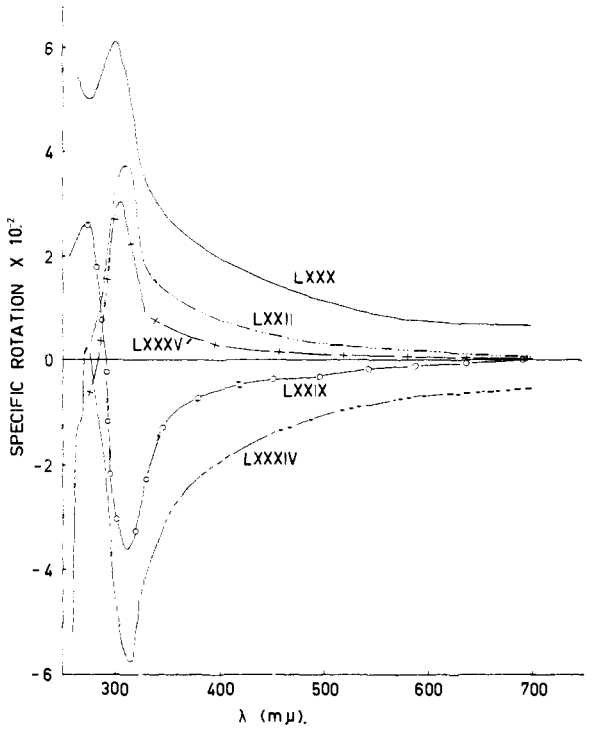


Fig. 11.—Optical rotatory dispersion curves of Δ^7-lanosten-3-one (LXXIX) (methanol), Δ^8-lanosten-3-one (LXXX) (methanol), elemenonic acid (LXXXIII, on the curve) (dioxane), masticadienonic acid (LXXXIV) (methanol) and isomasticadienonic acid (LXXXV) (methanol).

one being lanostan-3-one (LVIII)) the negative drift does not make itself noticeable in the 589 mμ region. Another instance where rotatory dispersion curves can provide stereochemical information is the pair masticadienonic acid (LXXXIV)[57] and isomasticadienonic acid (LXXXV)[58] whose constitution and stereochemistry has been elucidated[57] with the possible exception of C-9. The rotatory dispersion curves of these two acids are shown in Fig. 11 and they bear the same relation to each other as do those of Δ^7-(LXXIX) and Δ^8-lanosten-3-one (LXXX) except that the curves are moved somewhat to lower rotation values, possibly due to the presence of the α,β-unsaturated acid moiety. The general similarity in shape of the dispersion curves of masticadienonic acid (LXXXIV), Δ^7-lanosten-3-one (LXXIX) and dihydrobutyrospermone (LXXXIII) suggests that the former possesses the 9α-configuration.[59]

The introduction of a second double bond in Δ^7-lanosten-3-one (LXXIX) results in a strong positive shift of the rotatory dispersion curve as demonstrated in Fig. 12 with $\Delta^{7,9(11)}$-lanostadien-3-one (LXXXVI) and methyl polyporenate C (LXXXVIII).[49] While the 7,9(11)-diene system itself shows only a plain dispersion curve, that of the lanostane series (LXXXVII) exhibits a much steeper positive drift (see Experimental) than is observed in the polyporenic acid group (LXXVI) and this is

(57) D. H. R. Barton and E. Seoane, *J. Chem. Soc.*, 4150 (1956).
(58) E. Seoane, *ibid.*, 4158 (1956).
(59) The probable stereochemical identity of the C-9 center in LXXXIII and LXXXIV already has been inferred (ref. 57 and 60) on molecular rotation grounds.

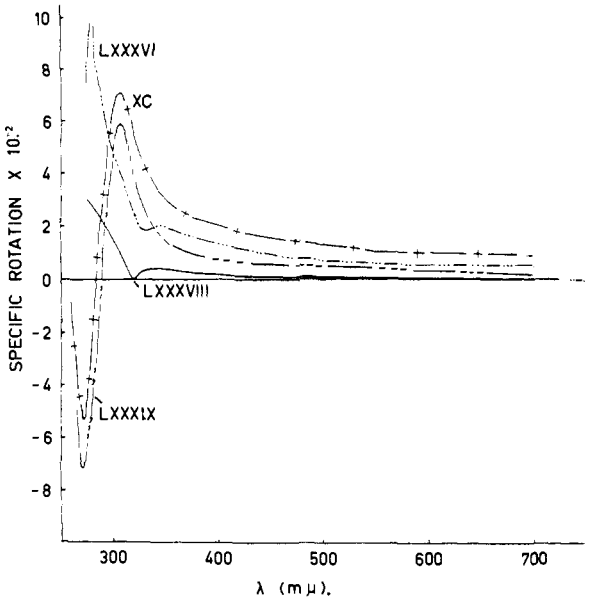


Fig. 12.—Optical rotatory dispersion curves of $\Delta^{7,9(11)}$-lanostadien-3-one (LXXXVI) (dioxane), methyl polyporenate C (LXXXVIII) (methanol), Δ^7-ergosten-3-one (LXXXIX) (methanol) and Δ^8-cholesten-3-one (XC) (methanol).

reflected in the position of the peaks of the respective 3-ketones (Fig. 12).

The question now arises as to the origin of the marked dispersion changes associated with the location of a double bond at 7–8 *vs.* 8–9 in the tetracyclic triterpene series. For that purpose, the rotatory dispersion curves of analogous steroidal ketones have been measured with double bonds in the 7–8 (LXXXIX), 8–9 (XC), 8–14 (XCI) and 14–15 (XCII) positions. Except for some amplitude differences, all of these ketones exhibited a single positive Cotton effect, characteristic of the saturated 5α-3-ketone, cholestan-3-one (XXXII) and the situation can be summarized by stating that unsaturation at these centers does not produce notable effects in steroids. This is particularly striking in the case of Δ^7-ergosten-3-one (LXXXIX) and Δ^8-cholesten-3-one (XC) whose dispersion curves (Fig. 12) should be compared with those (Fig. 11) of Δ^7-(LXXIX) and Δ^8-lanosten-3-one (LXXX). It is quite clear that in the latter compounds the *gem*-dimethyl grouping is implicated and the additional double bond in ring B could have one of two effects: (a) influence the "4,4-dimethyl" effect, which has been shown above not to involve the C-10 angular methyl group; or (b) cause a conformational distortion in which the 1,3-diaxial interaction between the methyl groups at C-4 and C-10 also enters into the picture. An answer could be provided by rotatory dispersion measurements of Δ^7- and Δ^8-unsaturated 4,4-dimethyl-19-nor-3-ketosteroids, but such compounds unfortunately are unknown at the present time.

In the beginning of this paper, it was pointed out that the rotatory dispersion curves of Δ^4-3-keto steroids are particularly sensitive to conformational changes in ring B. A detailed discussion of the effect of double bonds in that ring with and without

additional stereochemical alterations at C-9 and C-10 will be covered in a future paper in collaboration with Prof. E. R. H. Jones and co-workers of Oxford University, but as outlined in the Experimental section, introduction of unsaturation at positions 9–11 (XCIII) or 11–12 (XCIV) in the progesterone molecule produces no striking effects.

Barton, Head and May[60] have examined the rate of condensation of certain triterpenoid ketones with benzaldehyde and have noted rather wide variations in ketones differing only in the degree or site of unsaturation (*e.g.*, lanostan-3-one (LVIII) *vs.* Δ^7-lanosten-3-one (LXXIX) *vs.* Δ^8-lanosten-3-one (LXXX)). They have attributed these differences to conformational distortion produced by the double bond and have proposed the term "conformational transmission" for it. It is quite likely that the rotatory dispersion effects noted by us and which are clearly of a conformational character are of the same type as observed by Barton, *et al.*,[60] and that both approaches represent a measurement of the same factor. Our rotatory dispersion approach—though presently of a visual and qualitative rather than quantitative nature—has the advantage of great simplicity, of being applicable to a much greater variety of ketones and of utilizing only microquantities of recoverable substance. On the other hand, Barton's kinetic measurements[60] have quantitative significance and the two methods should serve to complement each other in a very desirable fashion. A good example is β-amyrone (XCV) and Δ^8-lanosten-3-one (LXXX) which appear quite dissimilar in structure but whose rotatory dispersion curves[53] as well as rate of condensation with benzaldehyde[60] suggest a common conformational effect upon the 3-keto group. We shall comment in greater detail upon the relation of Barton's measurements[60] and rotatory dispersion curves of pentacyclic triterpenes in a forthcoming paper,[53] but a correlation of the two methods would be strengthened greatly if predictions derived from one would prove to be applicable to the other. Thus our discovery of the "4,4-dimethyl" effect in the steroid and 19-norsteroid series by rotatory dispersion measurements and the similarity (see Figs. 7 and 11) of their rotatory dispersion curves to those of Δ^7-lanosten-3-one (LXXIX) and dihydrobutyrospermone (LXXXIII) suggests that the rate of condensation of such 4,4-dimethyl-3-keto-5α-steroids (XLVII, LV) with benzaldehyde should be of the same order of magnitude as observed[60] for Δ^7-lanosten-3-one (LXXIX). It will be interesting to see whether experimentation supports this prediction.

Experimental[61]

6α-Methyltestosterone (IV) (H. J. Ringold),[9] R.D. (Fig. 1) in dioxane (*c* 0.101): $[\alpha]_{700}$ +45°, $[\alpha]_{589}$ +84°, $[\alpha]_{420}$ +175° (broad peak), $[\alpha]_{365}$ −295°, $[\alpha]_{360}$ −213°, $[\alpha]_{352.5}$ −395°, $[\alpha]_{312.5}$ +1940°, $[\alpha]_{310}$ +1865°, $[\alpha]_{302.5}$ +2460°, $[\alpha]_{300}$ +2440°, $[\alpha]_{275}$ +3020°.

6β-Methyltestosterone (V) (H. J. Ringold),[9] R.D. (Fig. 1) in dioxane (*c* 0.069): $[\alpha]_{700}$ −27°, $[\alpha]_{589}$ +27°, $[\alpha]_{375}$ +422°, $[\alpha]_{360}$ +323° (sh), $[\alpha]_{335}$ −297°, $[\alpha]_{330}$ −105°, $[\alpha]_{325}$ −182°, $[\alpha]_{300}$ +321°.

2,2-Dimethyltestosterone acetate (VI) (H. J. Ringold),[11] R.D. (Fig. 1) in dioxane (*c* 0.050): $[\alpha]_{700}$ +28°, $[\alpha]_{589}$ +34°, $[\alpha]_{367.5}$ −530°, $[\alpha]_{360}$ −484°, $[\alpha]_{352.5}$ −526°, $[\alpha]_{280}$ +1560°.

(−)-Δ^4-3-Keto-11-epi-(7)-isoeusantonenic acid (VII) (Y. Abe),[12] R.D. (Fig. 2) in dioxane (*c* 0.082): $[\alpha]_{700}$ −70°, $[\alpha]_{589}$ −93°, $[\alpha]_{375}$ −566°, $[\alpha]_{365}$ −510°, $[\alpha]_{360}$ −528°, $[\alpha]_{340}$ −123°, $[\alpha]_{275}$ −1960°.

7β-Methyltestosterone (VIII) (J. A. Zderic),[14] R.D. in dioxane (*c* 0.094): $[\alpha]_{700}$ +49°, $[\alpha]_{589}$ +60°, $[\alpha]_{440}$ +100° (broad peak), $[\alpha]_{365}$ −411°, $[\alpha]_{360}$ −353°, $[\alpha]_{352.5}$ −458°, $[\alpha]_{290}$ +2420°.

7α-Methyltestosterone (IX) (J. A. Zderic),[14] R.D. in dioxane (*c* 0.051): $[\alpha]_{700}$ +102°, $[\alpha]_{589}$ +118°, $[\alpha]_{392.5}$ +258°, $[\alpha]_{352.5}$ −78°, $[\alpha]_{292.5}$ +2265°.

(−)-$\Delta^{1,4}$-3-Ketoeusantonadienic acid (X) (Y. Abe),[16] R.D. (Fig. 2) in dioxane (*c* 0.0905): $[\alpha]_{700}$ −63°, $[\alpha]_{589}$ −90°, $[\alpha]_{377.5}$ −565°, $[\alpha]_{370}$ −528°, $[\alpha]_{361.5}$ −601°, $[\alpha]_{337.5}$ −407°, $[\alpha]_{290}$ −1930°.

(−)-$\Delta^{1,4}$-6β-Hydroxy-3-ketoeusantonadienic acid lactone (XI) (Y. Abe),[16] R.D. (Fig. 2) in dioxane (*c* 0.088): $[\alpha]_{700}$ −207°, $[\alpha]_{589}$ −284°, $[\alpha]_{322.5}$ −2450°, $[\alpha]_{320}$ −2400°, $[\alpha]_{255}$ −5280°.

11α-Methyl-11β-hydroxytestosterone (XIV) (E. Batres),[18] R.D. (Fig. 2) in dioxane (*c* 0.100): $[\alpha]_{700}$ +56°, $[\alpha]_{589}$ +76°, $[\alpha]_{420}$ +128° (broad peak), $[\alpha]_{365}$ −214°, $[\alpha]_{360}$ −136°, $[\alpha]_{352.5}$ −206°, $[\alpha]_{290}$ +1775°.

4,4-Dimethyl-7-ketocholesteryl Acetate (XVI).—A solution of 330 mg. of chromium trioxide in 4 cc. of acetic acid and 0.5 cc. of water was added dropwise at 55° to 500 mg. of 4,4-dimethylcholesteryl acetate[20,62] in 8 cc. of acetic acid and 2 cc. of carbon tetrachloride. After stirring for 2 hr. at 55°, water was added and the product was isolated with ether. The neutral portion (470 mg.) after chromatography (9 g. of acid-washed alumina, benzene elution) and recrystallization from methanol afforded 240 mg. of the pure ketone, m.p. 154–156°; $\lambda_{max}^{CHCl_3}$ 5.76, 6.00 and 6.16 μ. R.D. (Fig. 3) in dioxane (*c* 0.090): $[\alpha]_{700}$ −45°, $[\alpha]_{589}$ −78°, $[\alpha]_{390}$ −637°, $[\alpha]_{377.5}$ −492°, $[\alpha]_{370}$ −541°, $[\alpha]_{357.5}$ −125° (sh), $[\alpha]_{342.5}$ +142°, $[\alpha]_{337.5}$ +101°, $[\alpha]_{332.5}$ +139°, $[\alpha]_{270}$ −604°.

Anal. Calcd. for $C_{31}H_{50}O_3$: C, 79.10; H, 10.71; O, 10.20. Found: C, 79.53; H, 10.69; O, 10.03.

3β-Acetoxy-Δ^5-lanosten-7-one (XVII) (R. C. Cookson), R.D. (Fig. 3) in dioxane (*c* 0.128): $[\alpha]_{700}$ −24°, $[\alpha]_{589}$ −44°, $[\alpha]_{387.5}$ −783°, $[\alpha]_{377.5}$ −663°, $[\alpha]_{372.5}$ −705°, $[\alpha]_{325}$ +909°, $[\alpha]_{275}$ +558°.

$\Delta^{5,14}$-7-Ketoapoeuphadienyl acetate (XVIII) (F. S. Spring),[21] R.D. (Fig. 4) in dioxane (*c* 0.082): $[\alpha]_{700}$ −79°, $[\alpha]_{589}$ −132°, $[\alpha]_{380}$ −1000°, $[\alpha]_{367.5}$ −833°, $[\alpha]_{365}$ −867°, $[\alpha]_{350}$ −304°, $[\alpha]_{347.5}$ −337°, $[\alpha]_{335}$ +78°, $[\alpha]_{302.5}$ +39°, $[\alpha]_{322.5}$ +141°, $[\alpha]_{280}$ −366°.

3β-Benzoyloxy-Δ^5-lanosten-7-one (XIX) (D. H. R. Barton), R.D. (Fig. 4) in dioxane (*c* 0.104): $[\alpha]_{700}$ +26°, $[\alpha]_{589}$ +35°, $[\alpha]_{382.5}$ +335° (sh), $[\alpha]_{367.5}$ +363°, $[\alpha]_{257.5}$ −676°.

6α-Methyldihydrotestosterone (XXI) (H. J. Ringold),[9] R.D. in methanol (*c* 0.0835): $[\alpha]_{700}$ +25°, $[\alpha]_{589}$ +35°, $[\alpha]_{310}$ +604°, $[\alpha]_{270}$ −503°, $[\alpha]_{250}$ −322°.

6β-Methyldihydrotestosterone (XXII) (H. J. Ringold),[9] R.D. (Fig. 4) in methanol (*c* 0.0715): $[\alpha]_{700}$ + 4°, $[\alpha]_{589}$ −14°, $[\alpha]_{307.5}$ +619°, $[\alpha]_{267.5}$ −1075°, $[\alpha]_{250}$ −785°.

Dihydrotestosterone (XXIII) R.D. in dioxane (*c* 0.10): $[\alpha]_{700}$ +12°, $[\alpha]_{317.5}$ +801°, $[\alpha]_{275}$ −777°, $[\alpha]_{270}$ −478°.

3β-Acetoxylanostan-7-one (XXIV) (D. H. R. Barton), R.D. (Fig. 4) in dioxane (*c* 0.106): $[\alpha]_{700}$ +29°, $[\alpha]_{589}$ +37°, $[\alpha]_{362.5}$ +99° (broad peak), $[\alpha]_{325}$ +56°, $[\alpha]_{277.5}$ +359°, $[\alpha]_{272.5}$ +341°.

4α-Methylcholestan-3-one (XXIX) (T. G. Halsall),[24] R.D. (Fig. 5) in methanol (*c* 0.097): $[\alpha]_{700}$ −12°, $[\alpha]_{589}$ +25°, $[\alpha]_{302.5}$ +732°, $[\alpha]_{265}$ −624°.

4β-Methylcholestan-3-one (XXX) (F. Sondheimer),[25] R.D. (Fig. 5) in methanol (*c* 0.1285): $[\alpha]_{700}$ +6°, $[\alpha]_{589}$ +16°, $[\alpha]_{307.5}$ +247°, $[\alpha]_{280}$ −25°, $[\alpha]_{270}$ +40°.

(60) D. H. R. Barton, A. J. Head and P. J. May, *J. Chem. Soc.*, 935 (1957); see also D. H. R. Barton, *Experientia*, Suppl. II, 121 (1955).

(61) The experimental procedure, limits of error and method of reporting of experimental data have already been given in earlier papers (ref. 4, 5, 6). We are indebted to Mrs. T. Nakano, Mrs. J. Osiecki and Mr. W. Closson for certain of the dispersion measurements and to the various investigators listed in the Experimental section for gifts of samples.

(62) Kindly supplied by Prof. R. B. Woodward of Harvard University.

4α-Ethylcholestan-3-one (XXXI)[26] R.D. in dioxane (*c* 0.105): $[\alpha]_{700}$ +27°, $[\alpha]_{589}$ +44°, $[\alpha]_{317.5}$ +864°, $[\alpha]_{277.5}$ −633°, $[\alpha]_{275}$ −496°.

30-Nortaraxastan-20-one (XXXIII) (T. G. Halsall),[27] R.D. (Fig. 5) in dioxane (*c* 0.10): $[\alpha]_{700}$ +27°, $[\alpha]_{589}$ +39°, $[\alpha]_{317.5}$ +350° (sh), $[\alpha]_{310}$ +373°, $[\alpha]_{277.5}$ +130°, $[\alpha]_{272.5}$ +153°.

30-Nor-19α(H)-taraxastan-20-one (XXXIV) (T. G. Halsall),[27] R.D. (Fig. 5) in dioxane (*c* 0.10): $[\alpha]_{700}$ +14°, $[\alpha]_{589}$ +20°, $[\alpha]_{320}$ +356°, $[\alpha]_{280}$ −338°, $[\alpha]_{275}$ −307°.

2α-Methylcholestan-3-one (XXXV) (F. Sondheimer),[25] R.D. in methanol (*c* 0.062): $[\alpha]_{700}$ +47°, $[\alpha]_{589}$ +31°, $[\alpha]_{310}$ +853°, $[\alpha]_{265}$ −712°, $[\alpha]_{255}$ −604°.

2β-Methylcholestan-3-one (XXXVI) (F. Sondheimer),[25] R.D. in methanol (*c* 0.061): $[\alpha]_{700}$ +87°, $[\alpha]_{589}$ +67°, $[\alpha]_{310}$ +1179°, $[\alpha]_{265}$ −651°, $[\alpha]_{255}$ −546°.

2α-Methyldihydrotestosterone (XXXVII) (H. J. Ringold),[11] R.D. (Fig. 6) in dioxane (*c* 0.10): $[\alpha]_{700}$ +12°, $[\alpha]_{589}$ +29°, $[\alpha]_{315}$ +665°, $[\alpha]_{235}$ −311°.

2,2-Dimethyldihydrotestosterone (XXXVIII) (H. J. Ringold),[11] R.D. (Fig. 6) in methanol (*c* 0.10): $[\alpha]_{700}$ +48°, $[\alpha]_{589}$ +75°, $[\alpha]_{312.5}$ +1415°, $[\alpha]_{270}$ −1085°, $[\alpha]_{255}$ −675°.

2α-(Dimethylaminomethyl)-dihydrotestosterone (XXXIX) (H. J. Ringold), R.D. in methanol (*c* 0.102): $[\alpha]_{700}$ −2°, $[\alpha]_{589}$ −9°, $[\alpha]_{310}$ +383°, $[\alpha]_{267.5}$ −719°, $[\alpha]_{260}$ −642°.

2β-Methylcoprostan-3-one (XL) (F. Sondheimer),[25] R.D. (Fig. 6) in dioxane (*c* 0.386): $[\alpha]_{700}$ +19°, $[\alpha]_{589}$ +27°, $[\alpha]_{340-337.5}$ +81°, $[\alpha]_{317.5}$ +47°, $[\alpha]_{287.5}$ +291°.

4β-Methylcoprostan-3-one (XLI) (F. Sondheimer),[25] R.D. (Fig. 6) in methanol (*c* 0.118): $[\alpha]_{700}$ +38°, $[\alpha]_{589}$ +41°, $[\alpha]_{350-340}$ +107 to +102°, $[\alpha]_{305-302.5}$ −68°, $[\alpha]_{270}$ +455°, $[\alpha]_{267.5}$ +447°.

29,30-Bisnor-20-keto-β-amyrin benzoate (XLII) (E. J. Corey),[28] R.D. in dioxane (*c* 0.135): $[\alpha]_{700}$ +77°, $[\alpha]_{375}$ +257° (broad peak), $[\alpha]_{320}$ −330°, $[\alpha]_{295}$ +1080°, $[\alpha]_{285}$ +800°.

30-Nor-20-keto-α-amyrin benzoate (XLIII) (E. J. Corey),[28] R.D. in dioxane (*c* 0.096): $[\alpha]_{700}$ +88°, $[\alpha]_{362.5}$ +294° (broad peak), $[\alpha]_{315}$ −254°, $[\alpha]_{290}$ +1000°.

3-Ketoeusantonanic acid (m.p. 133–135°) (XLIV) (Y. Abe),[16] R.D. (Fig. 6) in methanol (*c* 0.095): $[\alpha]_{700}$ +29°, $[\alpha]_{400}$ +107° (broad peak), $[\alpha]_{302.5}$ −418°, $[\alpha]_{265}$ +1435°, $[\alpha]_{255}$ +1045°.

3-Ketoeusantonanic acid (m.p. 111°) (XLV) (Y. Abe),[16] R.D. in methanol (*c* 0.100): $[\alpha]_{700}$ −23°, $[\alpha]_{559}$ −15°, $[\alpha]_{310}$ +1087°, $[\alpha]_{265}$ −1696°, $[\alpha]_{255}$ −1456°.

4,4-Dimethylcholestan-3-one (XLVI) (E. R. H. Jones),[24] R.D. (Fig. 7) in dioxane (*c* 0.10): $[\alpha]_{700}$ −3°, $[\alpha]_{559}$ −14°, $[\alpha]_{330}$ −148°, $[\alpha]_{292.5}$ +117°, $[\alpha]_{280}$ +57°.

4,4-Dimethyldihydrotestosterone (XLVII) (H. J. Ringold),[29] R.D. in dioxane (*c* 0.10): $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −21°, $[\alpha]_{322.5}$ −255°, $[\alpha]_{287.5}$ +170°, $[\alpha]_{252.5}$ +138°.

4,4,17α-Trimethyldihydrotestosterone (XLVIII) (H. J. Ringold),[29] R.D. in dioxane (*c* 0.102): $[\alpha]_{700}$ −43°, $[\alpha]_{589}$ −39°, $[\alpha]_{325}$ −362°, $[\alpha]_{287.5}$ +12°, $[\alpha]_{252.5}$ +2°.

Cholestan-3-one-2-spiro-2′-(1′,3′-dithiane) (XLIX) (E. R. H. Jones),[24] R.D. in 1:1 methanol–dioxane (*c* 0.107): $[\alpha]_{700}$ +73°, $[\alpha]_{589}$ +121°, $[\alpha]_{330}$ +1805°, $[\alpha]_{300}$ +47°.

4α-Methylcholestan-3-one-2-spiro-2′-(1′,3′-dithiane) (L) (E. R. H. Jones),[24] R.D. in 1:1 methanol–dioxane (*c* 0.130): $[\alpha]_{700}$ +45°, $[\alpha]_{589}$ +70°, $[\alpha]_{320}$ +1665°, $[\alpha]_{290}$ −427°, $[\alpha]_{285}$ −277°.

4β-Methylcholestan-3-one-2-spiro-2′-(1′,3′-dithiane) (LI) (E. R. H. Jones),[24] R.D. in 1:1 methanol–dioxane (*c* 0.085): $[\alpha]_{700}$ +49°, $[\alpha]_{589}$ +86°, $[\alpha]_{325}$ +1800°, $[\alpha]_{285}$ −835°.

4,4-Dimethylcholestan-3-one-2-spiro-2′-(1′,3′-dithiane) (LII) (E. R. H. Jones),[24] R.D. in dioxane (*c* 0.096): $[\alpha]_{700}$ −8°, $[\alpha]_{589}$ −3°, $[\alpha]_{337.5}$ −1165°, $[\alpha]_{285}$ +323°.

19-Nordihydrotestosterone (LIII) (A. Bowers),[32] R.D. (Fig. 7) in methanol (*c* 0.162): $[\alpha]_{700}$ +38°, $[\alpha]_{589}$ +53°, $[\alpha]_{305}$ +1205°, $[\alpha]_{265}$ −2060°.

1α-Methyl-19-nordihydrotestosterone (LIV) (A. Bowers),[32] R.D. in methanol (*c* 0.108): $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +32°, $[\alpha]_{310}$ +1090°, $[\alpha]_{275}$ −1070°, $[\alpha]_{270}$ −972°.

4,4-Dimethyl-19-nordihydrotestosterone (LV) (A. Bowers),[35] R.D. (Fig. 7) in methanol (*c* 0.125): $[\alpha]_{700}$ −25°, $[\alpha]_{589}$ −26°, $[\alpha]_{310}$ −320°, $[\alpha]_{272.5}$ +350°, $[\alpha]_{265}$ +260°.

2,2,17α-Trimethyl-19-nordihydrotestosterone (LVI) (A. Bowers),[35] R.D. in methanol (*c* 0.107): $[\alpha]_{700}$ +56°, $[\alpha]_{589}$ +79°, $[\alpha]_{312.5}$ +2165°, $[\alpha]_{265}$ −2200°.

4,4,17α-Trimethyl-19-nordihydrotestosterone (LVII) (A. Bowers),[35] R.D. in methanol (*c* 0.090): $[\alpha]_{700}$ −30°, $[\alpha]_{589}$ −49°, $[\alpha]_{315}$ −412°, $[\alpha]_{277.5}$ +66°, $[\alpha]_{270}$ +21°.

Lanostan-3-one (LVIII) (D. H. R. Barton), R.D. (Fig. 7) in methanol (*c* 0.1125): $[\alpha]_{700}$ +13°, $[\alpha]_{589}$ +28°, $[\alpha]_{350}$ +81° (broad peak), $[\alpha]_{325}$ +31°, $[\alpha]_{285-275}$ +346°, $[\alpha]_{252.5}$ +382°.

α-Onoceradienedione (LIX) (D. H. R. Barton),[37] R.D. in methanol (*c* 0.0935): $[\alpha]_{700}$ +7°, $[\alpha]_{559}$ +1°, $[\alpha]_{325}$ −145°, $[\alpha]_{300}$ +274°, $[\alpha]_{250}$ −392°.

Cycloartenone (LX) (D. H. R. Barton),[38] R.D. (Fig. 8) in methanol (*c* 0.0975): $[\alpha]_{700}$ +21°, $[\alpha]_{559}$ +19°, $[\alpha]_{440}$ +44° (broad peak), $[\alpha]_{315}$ −270°, $[\alpha]_{272}$ +648°, $[\alpha]_{255}$ +541°.

Cyclolaudenone (LXI) (F. S. Spring),[39] R.D. in methanol (*c* 0.108): $[\alpha]_{700}$ +22°, $[\alpha]_{589}$ +21°, $[\alpha]_{317.5}$ −255°, $[\alpha]_{272.5}$ +494°, $[\alpha]_{260}$ +385°.

Cycloeucalenone (LXII) (F. E. King),[40] R.D. (Fig. 8) in methanol (*c* 0.10): $[\alpha]_{700}$ +16°, $[\alpha]_{589}$ +19°, $[\alpha]_{302.5}$ +732°, $[\alpha]_{272.5}$ −310°, $[\alpha]_{265}$ −110°.

4,4-Dimethyl-Δ⁵-cholesten-3-one (LXIII) (R. B. Woodward),[20] R.D. (Fig. 8) in methanol (*c* 0.042): $[\alpha]_{700}$ +33°, $[\alpha]_{589}$ +36°, $[\alpha]_{310}$ +474°, $[\alpha]_{272.5}$ −735°, $[\alpha]_{255}$ −534°.

4,4-Dimethyl-Δ⁵-androsten-3-one-17β-ol (LXIV) (H. J. Ringold),[29] R.D. in dioxane (*c* 0.10): $[\alpha]_{700}$ −13°, $[\alpha]_{589}$ −18°, $[\alpha]_{315}$ +673°, $[\alpha]_{280}$ −610°.

4,4-Dimethyl-Δ⁵-19-norandrosten-3-one-17β-ol-3-one (LXV) (A. Bowers),[35] R.D. in methanol (*c* 0.104): $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −10°, $[\alpha]_{315}$ +1600°, $[\alpha]_{267.5}$ −3280°, $[\alpha]_{265}$ −2580°.

Alnusenone (LXVI) (F. S. Spring),[41] R.D. (Fig. 8) in dioxane (*c* 0.02): $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +32°, $[\alpha]_{400}$ +50° (broad peak), $[\alpha]_{320}$ −420°, $[\alpha]_{275}$ +1050°.

Methyl Δ⁸-A-nor-2-ketoeburicen-21-oate (LXVII) (J. S. E. Holker),[54] R.D. in methanol (*c* 0.100): $[\alpha]_{700}$ +41°, $[\alpha]_{589}$ +78°, $[\alpha]_{317.5}$ +2187°, $[\alpha]_{272.5}$ −1735°, $[\alpha]_{265}$ −1210°.

(+)-*trans*-2-Methoxymethylene-9-methyl-1-decalone (LXX).—A solution of 600 mg. of (−)-*trans*-2-hydroxymethylene-9-methyl-1-decalone[6] in 20 cc. of ether and 1 cc. of methanol was left for 1 hr. at room temperature with an excess of ethereal diazomethane. The reagent was destroyed, the ether solution was washed with dilute alkali, water, dried, evaporated and the residue was distilled at a bath temperature of 175° and 10 mm.; yield 620 mg., $\lambda_{max}^{liquid\ film}$ 5.91, 6.20 and 8.0 μ; R.D. (Fig. 9) in dioxane (*c* 0.05): $[\alpha]_{700}$ +10°, $[\alpha]_{589}$ +10°, $[\alpha]_{405}$ +30° (broad peak), $[\alpha]_{380}$ −42°, $[\alpha]_{372.5}$ −14°, $[\alpha]_{365}$ −48°, $[\alpha]_{355}$ +104°, $[\alpha]_{350}$ +84°, $[\alpha]_{330}$ +470°.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.20; H, 9.38.

(−)-*trans*-2β-Methoxymethyl-9-methyl-1-decalone (LXIXa).—The hydrogenation of 560 mg. of the methyl ether LXX in 20 cc. of methanol in the presence of 200 mg. of 10% palladized charcoal catalyst was complete in less than 1 hr. and the product was distilled at a bath temperature of 60° and 0.05 mm.; $\lambda_{max}^{liquid\ film}$ 5.86 μ; R.D. (Fig. 9) in methanol (*c* 0.102): $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −32°, $[\alpha]_{320}$ −877°, $[\alpha]_{287.5}$ +833°.

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.09; H, 10.63.

(+)-*trans*-2α-Methoxymethyl-9-methyl-1-decalone (LXIXb).—The isomerization of 50 mg. of LXVIII was accomplished by heating under reflux for 5 min. with 5 cc. of 5% ethanolic potassium hydroxide solution and the product[45] was distilled at a bath temperature of 125–130° and 10 mm.; λ_{max}^{EtOH} 234 mμ (log ε 2.98), $\lambda_{max}^{liquid\ film}$ 5.83 μ; R.D. (Fig. 9) in methanol (*c* 0.083): $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +46°, $[\alpha]_{315}$ +1005°, $[\alpha]_{272.5}$ −575°, $[\alpha]_{265}$ −460°.

The 2,4-dinitrophenylhydrazone crystallized from methanol–methylene chloride as yellow needles. A pyrazoline formulation, produced by β-elimination of methanol and addition to the double bond, appears excluded by the analytical data.

Anal. Calcd. for $C_{19}H_{26}N_4O_5$: C, 58.45; H, 6.71. Found: C, 58.81; H, 6.64.

(−)-*trans*-2,5,5-Trimethyl-6-acetoxy-9-methyl-1-decalone (LXXI) (O. Jeger),[46] R.D. in methanol (*c* 0.070): $[\alpha]_{700}$ −9°, $[\alpha]_{589}$ −21°, $[\alpha]_{302.5}$ −353°, $[\alpha]_{270}$ +157°.

3β-Hydroxy-9-keto-9,11-secoergostan-11-oic acid (LXXII) (W. G. Dauben),[47] R.D. in methanol (*c* 0.102): $[\alpha]_{700}$ −32°, $[\alpha]_{589}$ −35°, $[\alpha]_{310}$ −752°, $[\alpha]_{275}$ +511°, $[\alpha]_{265}$ +282°.

3β,7β,11α-Triacetoxylanan-17-one (LXXIII) (D. H. R. Barton),[48] R.D. (Fig. 10) in methanol (*c* 0.0935): $[\alpha]_{700}$ +13°, $[\alpha]_{589}$ +27°, $[\alpha]_{315}$ +792°, $[\alpha]_{275}$ −686°, $[\alpha]_{260}$ −510°.

4,4,14α-Trimethylallopregnan-3β-ol-20-one acetate (LXXIV) (C. S. Barnes),[52] R.D. (Fig. 10) in methanol (*c* 0.103): $[\alpha]_{700}$ +40°, $[\alpha]_{589}$ +90°, $[\alpha]_{307.5}$ +2129°, $[\alpha]_{270}$ −3479°, $[\alpha]_{265}$ −2620°.

Methyl-$\Delta^{7,9(11),24(28)}$-3β-hydroxy-16-ketoeburicotrien-21-oate (LXXV) (T. G. Halsall),[49] R.D. (Fig. 10) in dioxane (*c* 0.052): $[\alpha]_{700}$ −10°, $[\alpha]_{589}$ −30°, $[\alpha]_{327.6}$ −1850°, $[\alpha]_{320}$ −1620° (sh), $[\alpha]_{280}$ +1750°.

Methyl-$\Delta^{7,9(11)}$-3β,16α-dihydroxyeburicodien-21-oate (LXXVI) (T. G. Halsall),[49] R.D. in dioxane (*c* 0.106): $[\alpha]_{700}$ +31°, $[\alpha]_{589}$ +40°, $[\alpha]_{275}$ +266°.

Δ^{7}-Lanosten-3-one (LXXIX) (D. H. R. Barton), R.D. (Fig. 11) in methanol (*c* 0.084): $[\alpha]_{700}$ +2°, $[\alpha]_{589}$ −10°, $[\alpha]_{315}$ −366°, $[\alpha]_{275}$ +260°, $[\alpha]_{260}$ +174°; in dioxane (*c* 0.10) (F. S. Spring): $[\alpha]_{700}$ −31°, $[\alpha]_{589}$ −30°, $[\alpha]_{320}$ −468°, $[\alpha]_{280}$ +268°.

Δ^{8}-Lanosten-3-one (LXXX) (D. H. R. Barton), R.D. (Fig. 11) in methanol (*c* 0.111): $[\alpha]_{700}$ +57°, $[\alpha]_{589}$ +74°, $[\alpha]_{300}$ +610°, $[\alpha]_{277.5}$ +498°, $[\alpha]_{270}$ +542°.

Δ^{8}-3-Ketoeburicen-21-oic acid (LXXXI) (J. S. E. Holker),[54] R.D. in methanol (*c* 0.10): $[\alpha]_{700}$ +29°, $[\alpha]_{589}$ +42°, $[\alpha]_{300}$ +437°, $[\alpha]_{260}$ −615°.

Elemenonic acid (LXXXII) (G. A. R. Kon[55] *via* T. G. Halsall), R.D. (Fig. 11) in dioxane (*c* 0.089): $[\alpha]_{700}$ −9°, $[\alpha]_{589}$ +17°, $[\alpha]_{315-312.5}$ +370°, $[\alpha]_{280}$ +37°.

Dihydrobutyrospermone (LXXXIII) (F. S. Spring),[21,56] R.D. in methanol (*c* 0.05): $[\alpha]_{700}$ −50°, $[\alpha]_{589}$ −50°, $[\alpha]_{310}$ −398°, $[\alpha]_{270}$ +312°.

Masticadienonic acid (LXXXIV) (D. H. R. Barton),[57] R.D. (Fig. 11) in methanol (*c* 0.1025): $[\alpha]_{700}$ −66°, $[\alpha]_{589}$ −75°, $[\alpha]_{317.5}$ −577°, $[\alpha]_{275}$ +22°, $[\alpha]_{270}$ −117° (infl.), $[\alpha]_{260}$ −606°.

Isomasticadienonic acid (LXXXV) (D. H. R. Barton),[58] R.D. (Fig. 11) in methanol (*c* 0.126): $[\alpha]_{700}$ 0°, $[\alpha]_{589}$ 0°, $[\alpha]_{305}$ +302°, $[\alpha]_{270}$ −310°, $[\alpha]_{260}$ −103°.

$\Delta^{7,9(11)}$-Lanostadien-3-one (LXXXVI) (D. H. R. Barton), R.D. (Fig. 12) in dioxane (*c* 0.116): $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +49°, $[\alpha]_{345-342.5}$ +203°, $[\alpha]_{330}$ +194°, $[\alpha]_{280}$ +978°, $[\alpha]_{277.5}$ +862°.

$\Delta^{7,9(11)}$-Lanostadien-3β-ol acetate (LXXXVII) (D. H. R. Barton), R.D. in dioxane (*c* 0.088): $[\alpha]_{700}$ +74°, $[\alpha]_{589}$ +100°, $[\alpha]_{250}$ +1015°.

Methyl polyporenate C (LXXXVIII) (E. R. H. Jones),[49] R.D. (Fig. 12) in methanol (*c* 0.104): $[\alpha]_{700}$ +9°, $[\alpha]_{589}$ +9°, $[\alpha]_{360}$ +38° (broad peak), $[\alpha]_{320}$ −2°, $[\alpha]_{270}$ +321°.

Δ^{7}-Ergosten-3-one (LXXXIX) (O. H. Wheeler, H. B. Henbest), R.D. (Fig. 12) in methanol (*c* 0.053): $[\alpha]_{700}$ +21°, $[\alpha]_{589}$ +51°, $[\alpha]_{307.5}$ +588°, $[\alpha]_{272.5}$ −721°, $[\alpha]_{265}$ −486°.

Δ^{8}-Cholesten-3-one (XC) (H. B. Henbest), R.D. (Fig. 12) in methanol (*c* 0.062): $[\alpha]_{700}$ +86°, $[\alpha]_{589}$ +103°, $[\alpha]_{307.5}$ +706°, $[\alpha]_{272.5}$ −540°, $[\alpha]_{260}$ −73°.

$\Delta^{8(14)}$-Ergosten-3-one (XCI) (O. H. Wheeler, H. B. Henbest), R.D. in methanol (*c* 0.086): $[\alpha]_{700}$ +15°, $[\alpha]_{589}$ +30°, $[\alpha]_{307.5}$ +635°, $[\alpha]_{270}$ −1175°, $[\alpha]_{260}$ −459°.

Δ^{14}-Ergosten-3-one (XCII) (O. H. Wheeler), R.D. in methanol (*c* 0.132): $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +58°, $[\alpha]_{305}$ +630°, $[\alpha]_{267.5}$ −743°, $[\alpha]_{255}$ −484°.

Δ^{9}-Dehydroprogesterone (XCIII) (J. Fried), R.D. in dioxane (*c* 0.184): $[\alpha]_{700}$ +100°, $[\alpha]_{589}$ +152°, $[\alpha]_{380}$ +473°, $[\alpha]_{367.5}$ +398°, $[\alpha]_{352.5}$ +463°, $[\alpha]_{350}$ +453°, $[\alpha]_{312.5}$ +3222°, $[\alpha]_{302.5}$ +1127°.

Δ^{11}-Dehydroprogesterone (XCIV) (J. Fried), R.D. in dioxane (*c* 0.060): $[\alpha]_{700}$ +100°, $[\alpha]_{589}$ +160°, $[\alpha]_{375}$ +566°, $[\alpha]_{365}$ +483°, $[\alpha]_{352.5}$ +573°, $[\alpha]_{350}$ +556°, $[\alpha]_{315}$ +2758°, $[\alpha]_{295}$ −3158°.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Synthesis of a Series of Substituted *trans*-2-Phenylcyclopropanecarboxylic Acids

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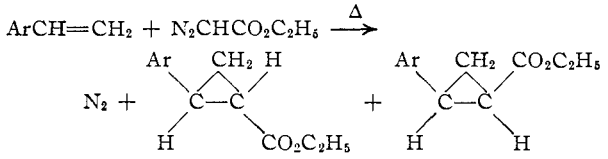
RECEIVED FEBRUARY 21, 1958

The syntheses, ultraviolet spectra and proofs of configuration of several *m*- and *p*-substituted *trans*-2-phenylcyclopropanecarboxylic acids are described. Further evidence is given in support of the stereochemical assignment to the isomers of 2-phenylcyclopropanecarboxylic acid melting at 106 and 93° of *cis* and *trans*, respectively.

For the purposes of the study reported in the accompanying paper,[2] it was necessary to prepare a series of *trans*-2-phenylcyclopropanecarboxylic acids substituted with *p*-nitro, *m*-nitro, *p*-chloro, *m*-chloro, *p*-acetamido, *p*-methyl and *p*-methoxy groups. In this paper are reported the syntheses, ultraviolet spectra and proofs of configuration of these compounds along with similar data for the unsubstituted acid in both the *cis* and *trans* modifications.

The method of synthesis generally employed consisted in the reaction of ethyl diazoacetate with an appropriately substituted styrene at an elevated temperature to give nitrogen and ethyl 2-arylcyclopropanecarboxylate. This led in several cases to a mixture of *cis* and *trans* isomers which was then subjected to one of the following procedures: (1) the ester mixture was saponified, the product acidified and the two isomeric acids separated by fractional crystallization; (2) the ester mixture was saponified, the product acidified, the acid mixture epimerized by refluxing with thionyl chloride in benzene and the more stable product isolated after hydrolyzing with water; (3) the ester mixture was epimerized to the more stable product by refluxing with ethanolic sodium ethoxide and the more stable isomer isolated after saponification and acidification.



In view of the fact that the various styrenes were generally made by decarboxylation of the corresponding cinnamic acids, it was held desirable to employ an alternate synthetic method involving reaction of diazomethane with a substituted cinnamic ester. However, preliminary experiments on ethyl cinnamate itself revealed that the reaction led predominantly, if not entirely, to ethyl β-methylcinnamate, isomeric with the desired product. That the diazoacetic ester reaction did not similarly yield this undesired olefinic product was tested for in all cases by use both of the permanganate test and of infrared spectroscopy.

(1) This paper is part of the work to be submitted by Mr. George Odian to the Graduate School of Columbia University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) E. N. Trachtenberg and G. Odian, THIS JOURNAL, **80**, 4018 (1958).