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

Optical Rotatory Dispersion Studies. VII.[1] Application to Problems of Absolute Configurations[2]

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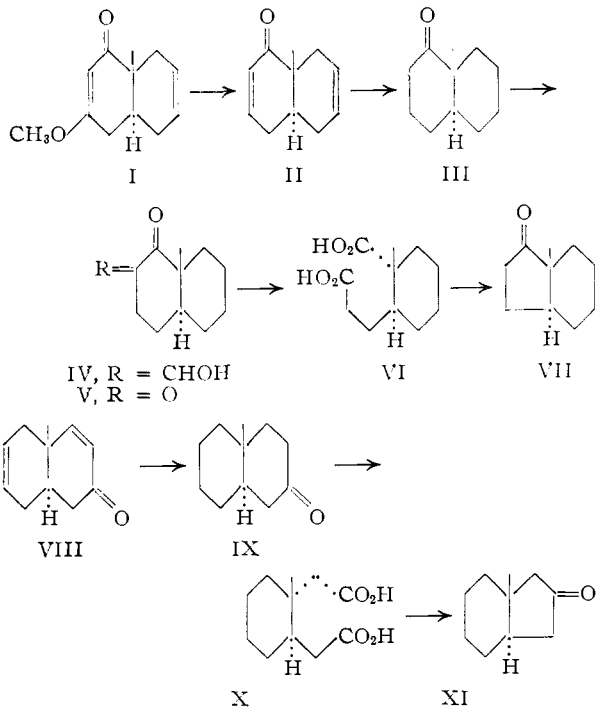
The earlier observed, characteristic features of rotatory dispersion curves of saturated and unsaturated steroid ketones have now been found to be a reflection of the appropriate bicyclic nucleus. This permits an enormous extension of the rotatory dispersion method to many other alicyclic ketones and absolute configurations can be assigned on the basis of coincidence of rotatory dispersion curves with those of known reference compounds. The method has been applied to carissone, α- and β-cyperone, santonin, ψ-santonin, eremophilone, cafestol, phyllocladene, yohimbone, friedelin, etc., and the large effect of certain axial alkyl substituents upon the rotatory dispersion curve has also been noted.

In the last two papers[1,3] of this series, it was pointed out that rotatory dispersion curves of steroidal ketones can be used to striking advantage in localizing such functional groups and that frequently the characteristic shape of the dispersion curve would provide also stereochemical information[1] which might otherwise have to be secured by more circuitous means. If one takes into additional consideration the results with α,β-unsaturated ketones[4,5] and certain analytical applications[6] then it becomes clear that the rotatory dispersion method represents an important and powerful adjunct to steroid methodology.[7]

The fact that the shape of the rotatory dispersion curve of a given keto steroid (*e.g.*, 3-keto steroid) is not changed to any appreciable extent by additional substitution (of optically weak chromophores) in the rest of the molecule, provided the stereochemical environment in the immediate neighborhood remains unaltered,[1] encouraged us to undertake the present investigation, namely, the applicability of the data from the steroid work[1,3-6] to simpler alicyclic ketones. The results, to be described below, have been sufficiently striking so that it can be predicted safely that the scope of the rotatory dispersion method[8] will be applicable to a wide variety of optically active substances, particularly in the field of natural products. Preliminary work has also indicated that certain subtle conformational features (see below for discussion of XXIV *vs.* XXV; XXXI *vs.* XXXII; XXXIV *vs.* XXXV) may be amenable to correlation with rotatory dispersion curves and we expect to cover this subject in greater detail in a future paper.

Since the absolute configuration of the steroids with respect to D-glyceraldehyde[9] has been established,[10] it follows that if our earlier results in the steroid series[1,3-6] should also be applicable to other non-steroidal ketones, then the coincidence (in shape) of their respective rotatory dispersion curves would afford strong evidence in so far as their absolute configurations are concerned. This, in short, is the thesis which will be presented in this paper and which will be supported by a variety of examples.

Of considerable help was the work of the Monsanto group[11] since they succeeded in obtaining certain optically active bicyclic ketones (*e.g.*, I, VIII) to which absolute configurations could be assigned on the basis of their eventual incorporation into rings C and D of natural cortisone (the absolute configuration of which is known[10]).



I II III

IV, R = CHOH
V, R = O

VI VII

VIII IX

X XI

(1) Paper VI, C. Djerassi and W. Closson, THIS JOURNAL, **78**, 3761 (1956).

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

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

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

(5) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6377 (1956).

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

(7) Our results with triterpenoid ketones will be reported in a future publication.

(8) By "rotatory dispersion method," we mean the empirical correlation of characteristic shapes of dispersion curves with certain structural and stereochemical features. This will be chiefly applicable to compounds with strong, optically active chromophores (*e.g.*, ketones) and we have limited our studies for the time being to carbonyl-containing substances.

(9) J. M. Bijvoet, A. F. Peerdeman and A. J. v. Bommel, *Nature*, **168**, 271 (1951); J. M. Bijvoet, *Endeavour*, **14**, 71 (1955).

(10) For leading references see J. Kalvoda, P. Buchschacher and O. Jeger, *Helv. Chim. Acta*, **38**, 1847 (1955).

(11) (a) A. J. Speziale, J. A. Stephens and Q. E. Thompson, THIS JOURNAL, **76**, 5011 (1954); (b) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Tompson, *ibid.*, **76**, 5014 (1954); (c) L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, *ibid.*, **76**, 5017 (1954).

Through the kind coöperation of these authors[12] we secured generous amounts of the ketones I, II and VIII which served as starting materials for the synthesis of simple, bicyclic model compounds of certain keto-steroids. Thus by the sequence I → VII it was possible to prepare bicyclic analogs of 1-keto (III) and 17-keto (VII)[13] steroids while from VIII[11a] there became available *trans*-9-methyldecalone-3 (IX)[14] and *via* the dicarboxylic acid X[14] the important *trans*-8-methylhydrindan-2-one (XI). It was felt that some of these ketones would represent test cases to see whether the earlier correlations in the steroid series are also applicable to the simpler bicyclic analogs and as will be shown below, this proved to be the case.

In Fig. 1 are repeated the earlier reported rotatory dispersion curves of cholestan-3-one (XIIa)[4c] and coprostan-3-one (XIIb)[1] since they illustrate

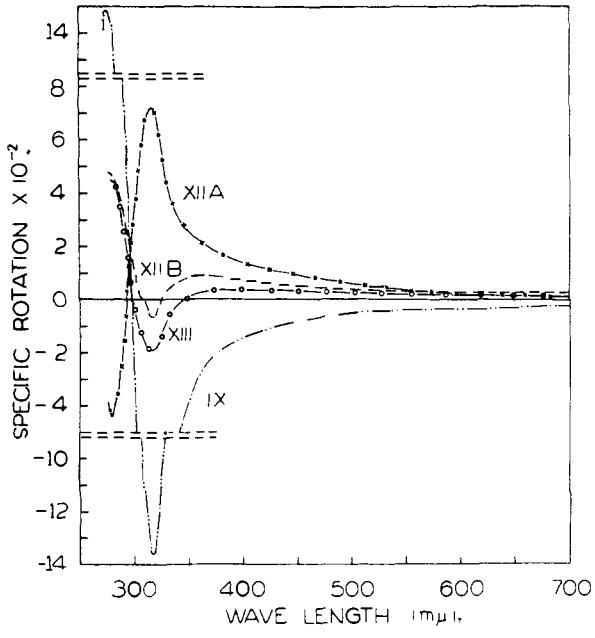


Fig. 1.—Rotatory dispersion curves (dioxane solution) of (−)-*trans*-9-methyldecalone-3 (IX), cholestan-3-one (XIIa), coprostan-3-one (XIIb) and (+)-*cis*-8-methylhydrindan-5-one (XIII).

the typical curves of a 3-keto-steroid of the A/B *trans*, respectively, A/B *cis* series. Since the (−)-*trans*-9-methyldecalone-3 (IX) belongs to the enantiomeric series (derived from (+)-VIII[11a]), its rotatory dispersion curve should be roughly the mirror image of that of cholestan-3-one (XIIa), which in fact it is. It follows that the rotatory dispersion curve considered typical of 3-keto-5α-steroids is actually typical of *trans*-3-ketodecalins. In fact, even the size of the adjacent ring does not appear to be crucial, the important factor being the stereochemistry of the ring juncture, since (+)-*cis*-8-methyl-hydrindan-5-one (XIII)[15] exhibits a rotatory dispersion curve which is very similar in shape to that of coprostan-3-one (XIIb).

A similar reduction to the simplest common structural basis is demonstrated in Fig. 2 where it is shown that the characteristic rotatory dispersion curve[4a] of a typical 17-ketosteroid (androstan-17-one (XV)) is practically identical with that of *trans*-8-methylhydrindanone-1 (VII).[16] For future reference purposes, there is also included in Fig. 2 the rotatory dispersion curve of a 14β,17-keto-steroid (XVI) which presumably will be typical of *cis*-8-methylhydrindanone-1.

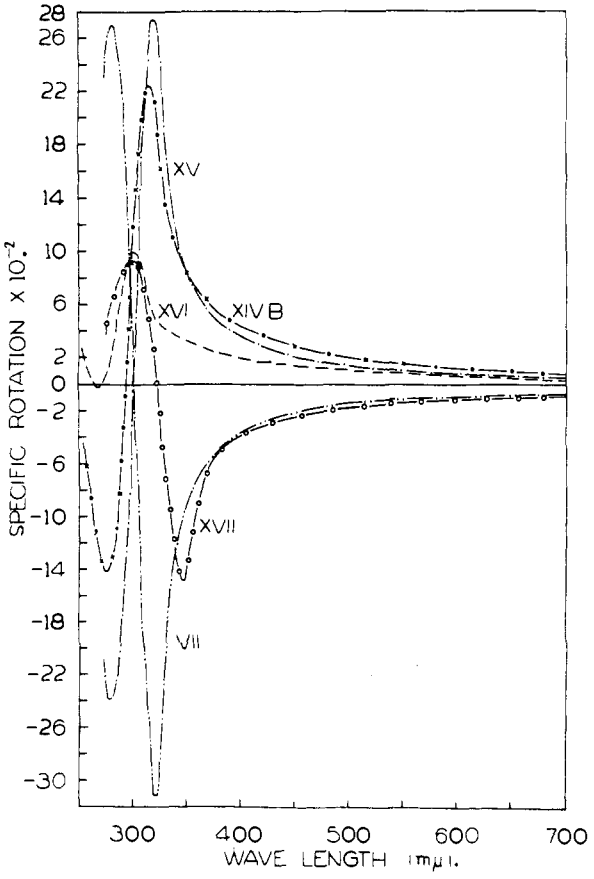


Fig. 2.—Rotatory dispersion curves of (−)-*trans*-8-methylhydrindan-1-one (VII, dioxane), 3-keto-A-norcholanic acid (XIVb, methanol), androstan-17-one (XV, dioxane), 14β-androstan-3β-ol-17-one acetate (XVI, methanol) and 14β,22a,25a,5α-spirostane-2α,3β-diol-15-one (XVII, dioxane).

It seems appropriate at this stage to bring up briefly a stereochemical point pertaining to 15-ketosteroids. It has been shown recently[17] that 15-ketosteroidal sapogenins with the 14α (C/D *trans*) juncture are readily isomerized to the 14β (C/D *cis*) isomers (XVII). In an important

(12) We should like to express our appreciation to Drs. W. S. Knowles, Q. E. Thompson and O. Weinkauff (Monsanto Chemical Co., St. Louis, Mo.) for this valuable gift.

(13) As the optical antipode.

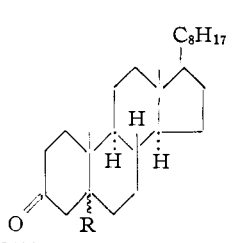
(14) B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, THIS JOURNAL, **76**, 312 (1954).

(15) Kindly provided by Prof. Gilbert Stork (Columbia University). See E. Cohen, Ph.D. Thesis, Columbia University, 1956. Since the *cis*-juncture had not been proved rigorously and since it is important to establish the effect of the size of the adjacent ring, we are currently undertaking the synthesis of *trans*-8-methylhydrindan-5-one and of *cis*-9-methyldecalone-3 in optically active form.

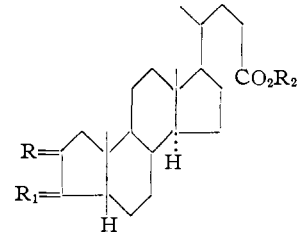
(16) The curves, of course, are mirror images around the zero axis since the two compounds are of enantiomeric types.

(17) C. Djerassi, T. T. Grossnickle and L. B. High, THIS JOURNAL, **78**, 3166 (1956); see also C. Djerassi, L. B. High, J. Fried and E. F. Sabo, *ibid.*, **77**, 3673 (1955).

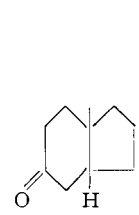
paper, which will be shown below to be of direct applicability to rotatory dispersion studies, Klyne[18] has pointed out that 17-keto- and 15-ketosteroids with the 14α-configuration are of the same enantiomeric type. This is fully substantiated by a comparison of the rotatory dispersion curves of androstan-17-one (XV, Fig. 2) and 22a,25a,5α-spirostane-2α,3β-diol-15-one diacetate[6,19] both of them entering their optical absorption bands from the positive side. We have now measured the rotatory dispersion of an authentic 14β,15-ketone (XVII)[17] and its dispersion curve (Fig. 2) is completely different from that of its 14α-isomer since it is characterized by an initial strong "minimum," which furthermore exhibits a remarkable bathochromic shift. The dispersion curve of 3β-acetoxycholestan-15-one[3] is clearly of the 14α,15-keto type[20]; *trans*-hydrindanones in the 15-ketocholestane series are, therefore, more stable than the *cis* isomers while the reverse relationship exists in the spirostan and presumably also 15,20-diketopregnane series.[17] In Fig. 2 is also shown the dispersion curve of 3-keto-A-norcholanic acid (XIVb) and in accordance with expectation it is roughly opposite in sign to that of the 14β,15-ketone XVII.



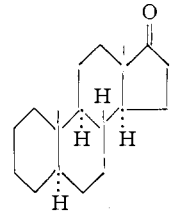
XIIa, R = ...H
b, R = —H



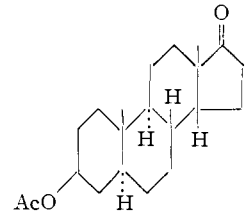
XIVa, R = O; R_1 = H_2; R_2 = CH_3
b, R = H_2; R_1 = O; R_2 = H



XIII

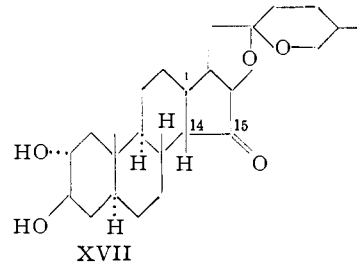


XV

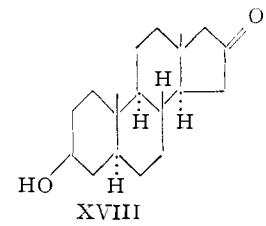


XVI

We have already commented[3,6] on the rotatory dispersion curves of 16-ketosteroids which are characterized by tremendous optical activity and by the fact that the optically active absorption band is entered from a very negative "minimum." Both these features greatly facilitate the recognition of a 16-keto function in a steroid and as additional examples, there are now presented (Fig. 3) androstan-3β-ol-16-one (XVIII), the 3,20-bis-ketal of 16-ketoprogesterone (XIX)[21] and 2-keto-A-norcholestane (XX).[16,22] It has been shown earlier[4b] that a phenolic ring does not interfere with the recognition of a 17-keto group and as demonstrated in the Experimental section with 3-hydroxy-16-keto-1,3,5-estratriene, this also applies to the 16-keto function. The dispersion curve of the bicyclic analog, *trans*-8-methylhydrindan-2-one

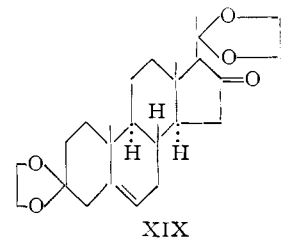


XVII

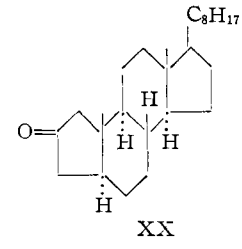


XVIII

(XI), exhibits all of the characteristic features of 16-ketosteroids as was to be anticipated in the light of the previously mentioned postulates. In Fig. 3 is also included the dispersion curve of methyl 2-keto-A-norcholanate (XIVa); except for its smaller optical "intensity" it is essentially the mirror image of the corresponding *trans*-A-nor-2-ketone XX.



XIX



XX

The above results with the ketones VII, IX, XI and XIII suggest strongly that the typical features of dispersion curves of alicyclic *mono*-ketones[23] are on the whole[24] only a reflection of the immediate structural and stereochemical environment around that particular carbonyl group. This, in turn, leads to the important conclusion that the general principles of Klyne[18] which have been used with such striking effectiveness in assigning absolute configurations to sesqui-,[25] di-[25] and triterpenoids[18] along molecular rotation lines are equally applicable to rotatory dispersion studies. The detailed arguments have already been presented by Klyne[18] and we should like to repeat only two of his statements which will form the guiding principles of the subsequent discussion, Klyne's use of "molecular rotation" now being replaced by "rotatory dispersion."

(a) Terminal ring units of the same type make contributions to the rotatory dispersion curve which are, very approximately, independent of the nature of the rest of the molecule.

(b) Each terminal unit can exist in two enantiomeric types which have rotatory dispersion contributions of opposite sign.

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

(19) The spiroketal system does not appear to have any pronounced effect (see ref. 6) except that all of the curves are shifted toward more negative values (*cf.* footnote 12 in ref. 1).

(20) The chemical evidence for the 14α-configuration presented by D. H. R. Barton and collaborators (*Chemistry and Industry*, 616 (1953); *J. Chem. Soc.*, 52 (1954)) is not unambiguous (*cf.* ref. 17) and even molecular rotation evidence could be misleading (see discussion below in connection with the absolute configuration of eremophilone).

(21) S. Bernstein, M. Heller and S. M. Stolar, THIS JOURNAL, **77**, 5327 (1955).

(22) B. B. Smith and H. R. Nace, *ibid.*, **76**, 6119 (1954).

(23) Strong vicinal effects may be observed in diketones (ref. 1).

(24) This implies that the presence of weak, optically active chromophores (double bonds, hydroxyl and carboxyl groups, etc.) will have no important effect. However, certain conformational factors may have a rather strong influence and the detection of such factors by the rotatory dispersion method may greatly increase its scope and precision. Detailed comment on this topic is reserved for a future paper.

(25) W. Klyne, *J. Chem. Soc.*, 3072 (1953).

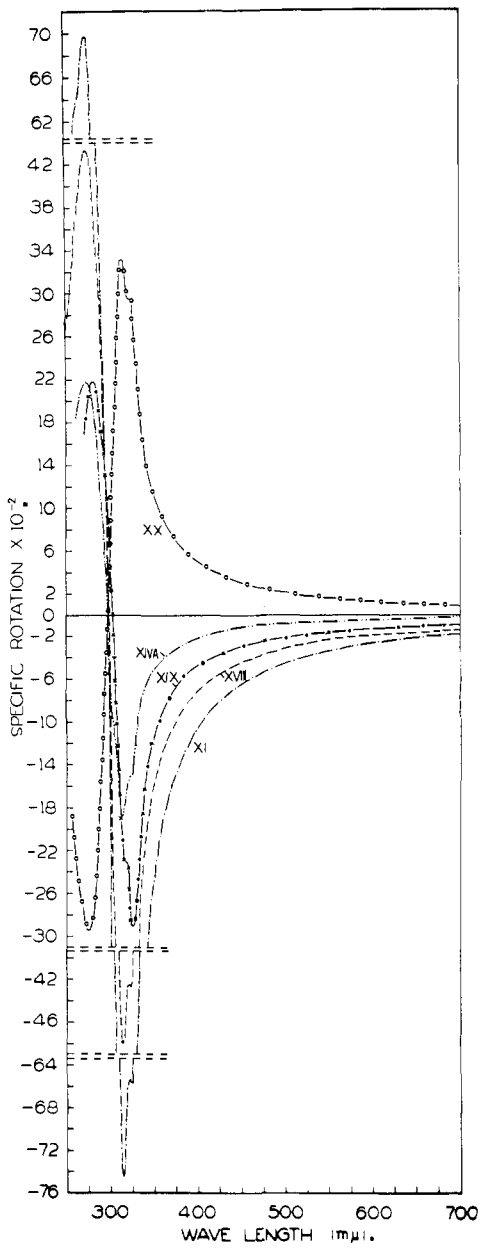


Fig. 3.—Rotatory dispersion curves (methanol solution) of (−)-*trans*-8-methylhydrindan-2-one (XI), methyl 2-keto-A-norcholanate (XIVa), androstan-3β-ol-16-one (XVIII), Δ^5-pregnene-3,16,20-trione 3,20-bis-ethylene ketal (XIX, dioxane) and 2-keto-A-norcholestane (XX).

It should be noted that while the principles underlying Klyne's "Generalized Method of Molecular Rotation Differences" are not altered, the use of rotatory dispersion curves (especially as they apply to carbonyl compounds) greatly increases the scope and precision of this type of approach. As will be apparent from a cursory inspection of the rotatory dispersion curves given in this and our preceding articles, important rotational effects of large magnitude usually occur only below 400 mμ and the 589 mμ region (sodium D line)—upon which nearly all molecular rotation work is based—represents a rather insensitive one. Consequently, arguments based on comparisons involving only a single optical rotation value at a given and quite "insensitive" region of the spectrum are much less valid than those which are derived from the similarity of shapes of rotatory dispersion curves ranging as far down into the ultraviolet as is experimentally possible. *In short, the rotatory dispersion method*[8] *represents an extension of the method of molecular rotation differences by carrying out comparisons at literally hundreds of points rather than just at one single wave length.* Examples to support this statement are given below.

One of the assumptions in this and Klyne's work[18,25] is that no significant changes in the rotational picture are produced when an angular methyl group is replaced by hydrogen with the reservation that the carbonyl group is not adjacent to the angular position (*cf.* difference in XIVb *vs.* XVI). Support for this assumption is presented in Fig. 4

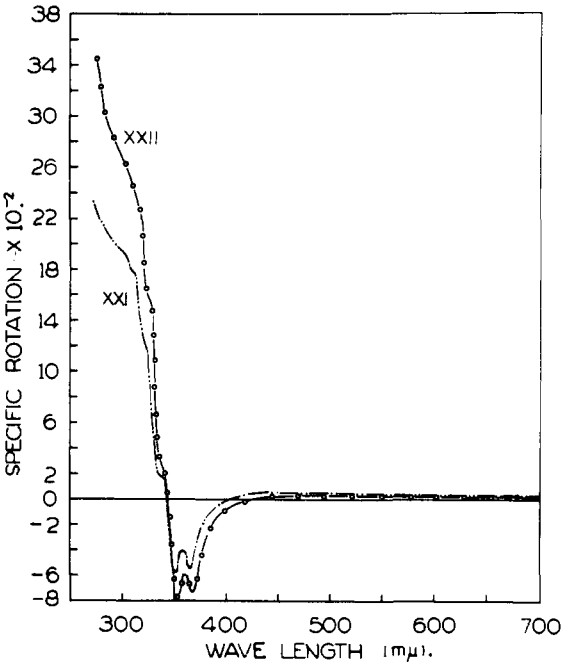
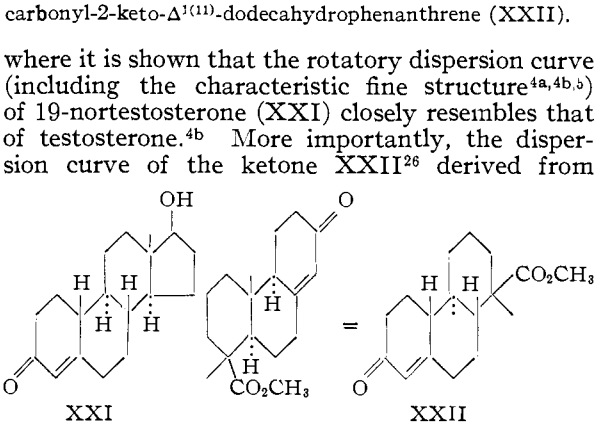


Fig. 4.—Rotatory dispersion curves (dioxane solution) of 19-nortestosterone (XXI) and 8,13-dimethyl-8-methoxycarbonyl-2-keto-$\Delta^{1(11)}$-dodecahydrophenanthrene (XXII).

where it is shown that the rotatory dispersion curve (including the characteristic fine structure[4a,4b,5]) of 19-nortestosterone (XXI) closely resembles that of testosterone.[4b] More importantly, the dispersion curve of the ketone XXII[26] derived from



XXI XXII

neoabietic acid is also virtually superimposable upon that of 19-nortestosterone (XXI) from which

(26) G. C. Harris and T. F. Sanderson, THIS JOURNAL, **70**, 339 (1948); W. M. Hoehn, U.S. Patent 2,682,555 (C. A., **49**, 14033 (1955)).

it follows that the absolute configuration of XXII (and hence of many related resin acids) is correct as depicted.

Additional evidence that the characteristic features of the Δ^4-3-ketosteroid dispersion curves are in fact typical of most bicyclic ketones containing that particular structural grouping are presented in Figs. 5 and 6. An additional methyl group, as is

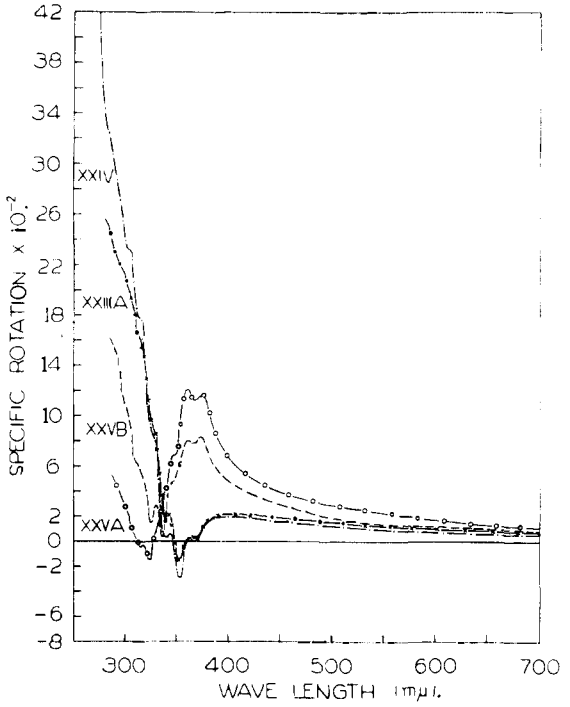


Fig. 5.—Rotatory dispersion curves (dioxane solution) of: 4-methyl-Δ^4-cholesten-3-one (XXIIIa), (+)-α-cyperone (XXIV), (+)-epi-α-cyperone (XXVa) and (+)-dihydro-epi-α-cyperone (XXVb).

found in so many sesquiterpenes, has no important influence as shown (Fig. 5) by the close similarity of the curves of 4-methyl-Δ^4-cholesten-3-one (XXIIIa)[27] and Δ^4-cholesten-3-one (XXIIIb).[4c] An interesting effect of a conformational nature is shown in Fig. 5 in the case of α-cyperone (XXIV). Its rotatory dispersion spectrum is practically superimposable upon that of 4-methyl-Δ^4-cholesten-3-one (XXIIIa), thus confirming its absolute configuration. On the other hand, the synthetic ketones XXV (a and b)[28] which are known to differ only in the orientation of the isopropenyl (XXVa) or isopropyl (XXVb) groups, exhibit a completely different dispersion curve. Inspection of models shows that in addition to the usual 1,3-interaction between the axial hydrogen atom and the isoprop-(en)yl group in XXV there seems also present some interference between the 4-methyl group and the bulky, axial alkyl substituent. This results in alteration of the molecular conformation and consequent reflection in the rotatory dispersion picture. One possible explanation is that ring B of XXV has now assumed a partial or complete boat conformation (in order to relieve the non-bonded interactions

(27) E. R. H. Jones, G. D. Meakins and collaborators, to be published.

(28) F. J. McQuillin, *J. Chem. Soc.*, 528 (1955), and R. Howe and F. J. McQuillin, *ibid.*, 2670 (1956).

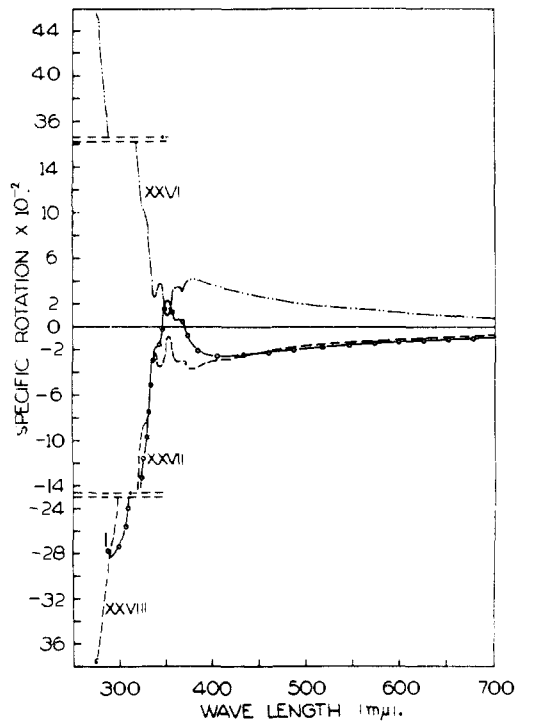


Fig. 6.—Rotatory dispersion curves (dioxane solution) of carissone (XXVI), (−)-1,14-dimethyl-2-keto-$\Delta^{1(11),6}$-decahydrophenanthrene (XXVII) and (−)-3-ketoeusanton-4-enic acid (XXVIII).

involving the isopropyl group) since the rotatory dispersion curves of XXVa and XXVb are virtually identical with that of 8α-testosterone[5] in which either ring B or C must exist as a boat. It should be noted that the dramatic change shown in the dispersion curves of XXIV and XXV could not have been anticipated purely by determining the specific rotation at the sodium D line.

In Fig. 6 are collected three additional examples of such bicyclic and tricyclic ketones. The dispersion curve of the sesquiterpene carissone (XXVI)[29] is essentially identical with that of natural α-cyperone (XXIV) from which it follows that both substances possess the same absolute configuration and also identical orientation of the isopropyl substituent.[30] The tricyclic ketone XXVII, of established absolute configuration in view of its conversion to cortisone,[11b] exhibits a rotatory dispersion curve which is the mirror image of that of carissone (XXVI) since the two substances are of enantiomeric types. A practically identical curve is observed with the synthetic (−)-3-keto-eusanton-4-enic acid (XXVIII)[31,32] which con-

(29) K. Mohr, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 462 (1954); D. H. R. Barton and E. J. Tarlton, *J. Chem. Soc.*, 3492 (1954).

(30) Carissone (XXVI) and α-cyperone (XXIV) have been interconverted experimentally (ref. 29) and since the former has also been obtained (W. A. Ayer and W. I. Taylor, *ibid.*, 3027 (1955); F. J. McQuillin and J. D. Parrack, *ibid.*, 2973 (1956)) from eudesmol, a direct correlation exists with the steroids (*cf.* ref. 14).

(31) M. Sumi, *Pharm. Bull. Japan*, **4**, 162 (1956). We are grateful to Dr. Y. Abe for a specimen of this acid which was ultimately transformed into (+)-santonin C (*cf.* Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, THIS JOURNAL, **78**, 1416 (1956)).

(32) For nomenclature see Y. Abe and M. Sumi, *Chemistry & Industry*, 253 (1955).

stitutes another confirmation for the absolute configuration of (−)-santonin (XXIX) discussed below.

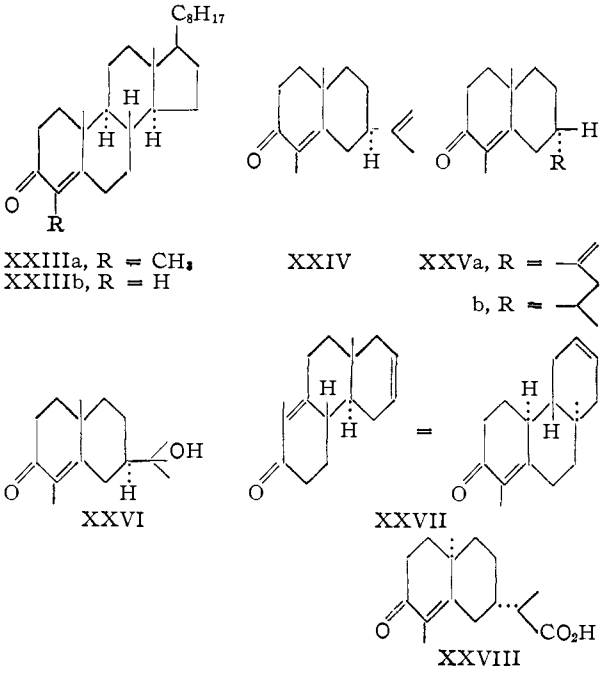


Figure 7 contains dispersion curves of compounds which have a bearing on the absolute configuration of natural (−)-santonin (XXIX) and this material also illustrates certain precautions which may have to be taken under given circumstances. The presently accepted stereoformula for (−)-santonin[33] is represented by XXIX and its rotatory dispersion curve is reproduced in Fig. 7. The closest comparison substance from the steroid series is 1,4-cholestadien-3-one (XXX) but its dispersion curve differs markedly,[34] especially below 350 mμ and no stereochemical conclusion could be drawn from such information. One alternate approach is to utilize synthetic intermediates which have been related to santonin (or its antipode) and an example is given above with the (antipodal) acid XXVIII. In the absence of synthetic intermediates, one could use suitable degradation products of natural (−)-santonin and this type of analysis is outlined below.

The utility of rotatory dispersion curves of bicyclic saturated ketones has been emphasized already (Figs. 1, 2, 3) and certain reduction products of santonin were consequently investigated. Catalytic hydrogenation of santonin leads to three isomeric tetrahydrosantonins[35] (XXXI, XXXII and XXXIII). Mild acid or base treatment of XXXII led[35] to XXXI, while XXXIII was unchanged.

(33) All of the pertinent references are given by Y. Abe, T. Miki, M. Sumi and T. Toga, *Chemistry & Industry*, 953 (1956).

(34) Purely on the basis of the close similarity of the rotatory dispersion curves of 4-methylcholestenone (XXIIIa) and cholestenone (XXIIIb), it seems unlikely that th eabsence of the 4-methyl group in 1,4-cholestadienone (XXX) is resp°nsible for the difference and it should probably be ascribed to the attachment of the lactone ring adjacent to the chromophore in santonin.

(35) For experimental details and earlier references see B. Riniker, Thesis, E. T. H. Zurich, 1955, ref. 35a, and O. Kovacs, V. Herout, M. Horak and F. Sorm, *Collection Czechoslov. Chem. Communs.*, **21**, 225 (1956).

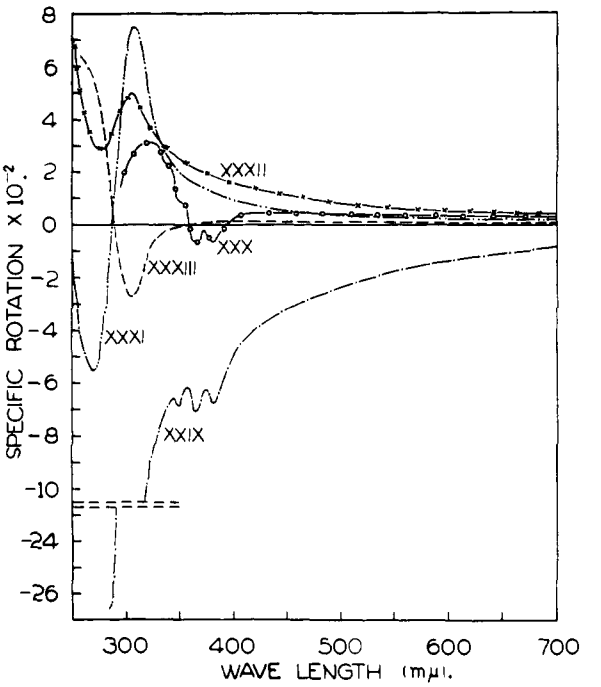
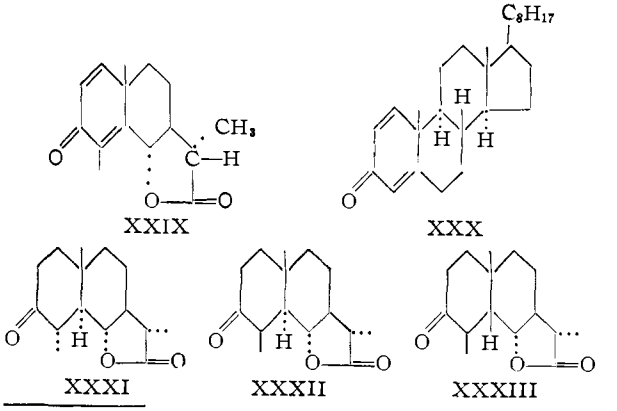


Fig. 7.—Rotatory dispersion curves (dioxane solution) of (−)-santonin (XXIX), 1,4-cholestadien-3-one (XXX), "α"-tetrahydrosantonin (XXXI), "γ"-tetrahydrosantonin (XXXII) and "β"-tetrahydrosantonin (XXXIII).

The rotatory dispersion curve of the stable isomer XXXI is typical of a 3-keto-5α-steroid (A/B *trans*) while that of XXXIII is nearly indistinguishable from a 3-keto-5β-steroid (A/B *cis*) (*cf.* Fig. 1). It follows that XXXI must be the *trans*[35a] and XXXIII the *cis*[35a] isomer and since XXXII is very readily isomerized to XXXI, the former must possess an axial methyl group at C-4. It should be noted (Fig. 7) that the dispersion curve of this unstable tetrahydrosantonin (XXXII) with an axial methyl group differs greatly from that of the equatorially substituted isomer XXXI and a considerable number of such shifts due to axial substituents have been collected.[24] The close resemblance of the rotatory dispersion curves of the two tetrahydroketones XXXI and XXXIII (Fig. 7) with the ap-



(35a) M. Yanagita and A. Tahara (*J. Org. Chem.*, **20**, 959 (1955)) reached the opposite conclusion (XXXI and XXXII *cis*, XXXIII *trans*) but their chemical evidence would be equally compatible with our present assignment. This applies even more to the reactions of the derived diketo acids reported by A. Tahara, *ibid.*, **21**, 442 (1956).

propriate reference ketones XIIa and XIIb (Fig. 1) of the steroid series confirms that the absolute configuration of (−)-santonin as expressed in XXIX (angular methyl group β) is correct.[35b]

An excellent example of the effect of an adjacent axial substituent is presented in Fig. 8. 2-Keto-

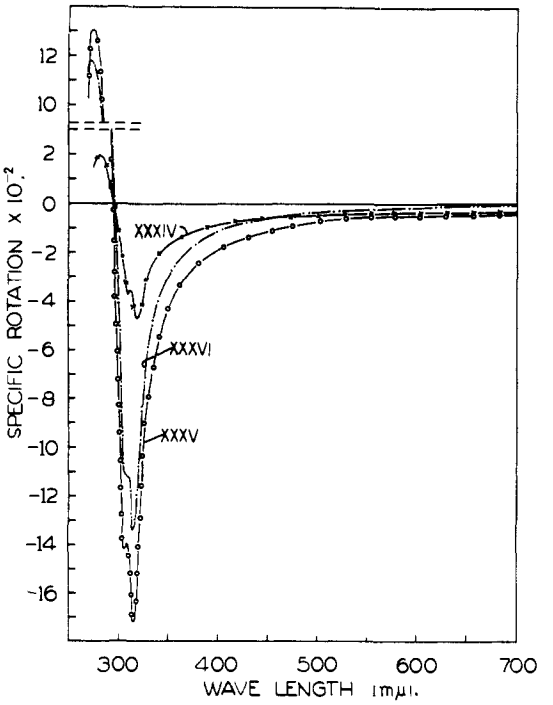
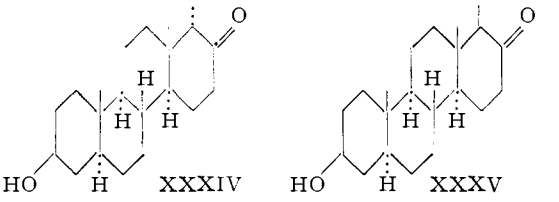


Fig. 8.—Rotatory dispersion curves (dioxane solution) of 17aα-methyl-D-homoandrostan-3β-ol-17-one (XXXIV), 17aβ-methyl-D-homoandrostan-3β-ol-17-one (XXXV) and friedelin (XXXVI).

steroids and 17-keto-D-homosteroids (XXXIV, XXXV) are typical examples of enantiomeric terminal rings by Klyne's definition[18] and their rotatory dispersion curves should be of approximately the same shape but of opposite sign. This prediction is borne out very nicely by the dispersion curve of 17aβ-methyl-D-homoandrostan-3β-ol-17-one (XXXV)[36] which is almost the exact mirror image of that of cholestan-2-one.[3] On the other hand, the axially substituted 17aα-isomer (XXXIV)[36] differs radically, insofar as the intensity is concerned, the respective "minima" at 320 mμ differing by over 1200° in terms of specific rotation.[37] This offered an independent means of confirming the correctness of the assigned stereochemistry implicit in structure XXXVI for friedelin.[38] The impressive coincidence in the rotatory dispersion curves of friedelin (XXXVI) and the equatorially substituted 17aα-methyl-D-homoandrostan-3β-ol-17-one (XXXV) can be accepted as independent support for the proposed friedelin stereochemistry.



The rotatory dispersion curves of three linearly conjugated dienones are collected in Fig. 9. (+)-β-Cyperone (XXXVII)[28] and the synthetic tri-

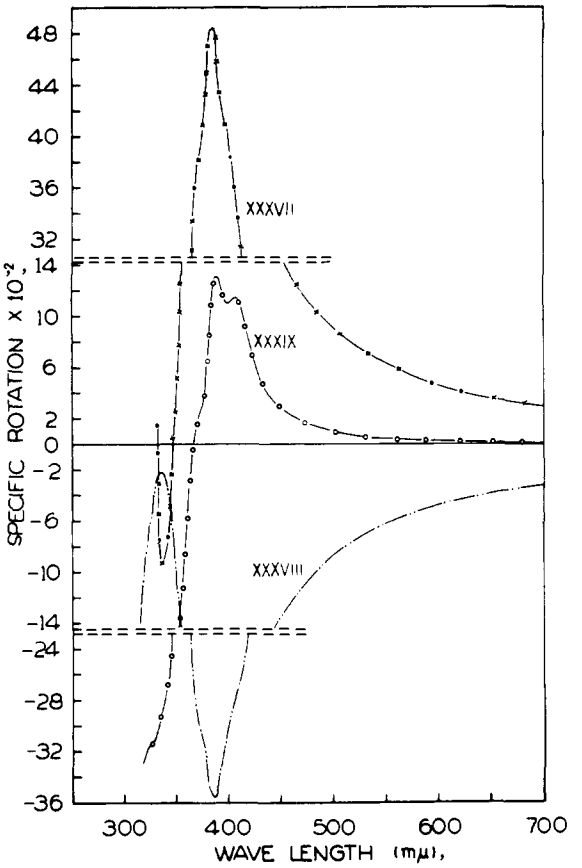


Fig. 9.—Rotatory dispersion curves (dioxane solution) of (+)-β-cyperone (XXXVII), (−)-1,14-dimethyl-2-keto-$\Delta^{1(11),6,9}$-octahydrophenanthrene (XXXVIII) and 4,6-cholestadien-3-one (XXXIX).

cyclic ketone XXXVIII[11b] exhibit similar rotatory dispersion curves[16] (identical position of "maxima" and "minima") as is to be expected in view of their assigned absolute configurations. The steroid 4,6-cholestadien-3-one (XXXIX) possesses a dispersion curve roughly similar in shape to that of β-cyperone (XXXVII) but it also exhibits fine structure in the 400 mμ region which is absent in the other two ketones XXXVII and XXXVIII. It remains to be seen whether this is due to the 4-methyl group or to some other factor.

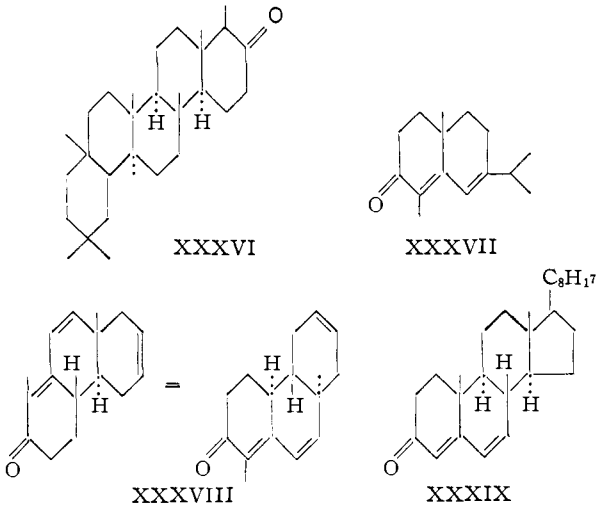
In nearly all of the above examples, the absolute configurations assigned on the basis of coincidence

(35b) *Note added in proof.*—The same conclusion has now been reached on chemical grounds by H. Bruderer, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 858 (1956).

(36) F. Ramirez and S. Stafiej, THIS JOURNAL, **78**, 644 (1956).

(37) This represents another instance (see ref. 1 for other examples) where the isomerization of XXXIV to XXXV could be studied kinetically in a very convenient manner by following the change in rotation at 320 mμ.

(38) E. J. Corey and J. J. Ursprung, THIS JOURNAL, **77**, 3668 (1955); H. Dutler, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **38**, 1268 (1955); G. Brownlie, F. S. Spring, R. Stevenson and W. S. Strachan, *Chemistry & Industry*, 1156 (1955); T. Takahashi and G. Ourisson, *Bull. soc. chim. France*, 353 (1956).



XXXVI XXXVII

XXXVIII XXXIX

of rotatory dispersion curves with those of reference samples have been deduced also by classical chemical interconversions (*e.g.*, ref. 30) or by application of Klyne's molecular rotation arguments.[18,25] In the remaining figures, we should like to present predominantly cases where the absolute configurations have either not been established or where the past results are at variance with those predicted by the rotatory dispersion method.

Structure XLa recently has been proposed[39] for cafestol and its close structural resemblance to phyllocladene (XLI)[40] has been emphasized. No information about the stereochemistry (relative or absolute) of either of these two diterpenes has been available until now. In Fig. 10 are reproduced the rotatory dispersion curves of two ketones XLII[40] and XLIII[41] derived, respectively, from phyllocladene and from cafestol and the virtual coincidence of the two rotatory dispersion curves leaves little doubt that the two diterpenes possess the same absolute configuration in so far as positions 7, 13 and 14 (and probably also 12) are concerned, since any changes at those centers would almost certainly manifest themselves in the rotatory dispersion curve. Consequently, proof for the absolute configuration of one of these substances would *ipso facto* apply to the other. In connection with our continuing interest in cafestol[39,42] there have been prepared the alcohol XLV and the corresponding ketone XLIV. The dispersion curve (Fig. 10) of the alcohol XLV simply shows the negative "background" rotation of the tetracyclic skeleton but the dispersion curve of the ketone XLIV *is clearly not that of a 3-keto-5α-steroid* (A/B *trans*) (see Fig. 1) unless one would

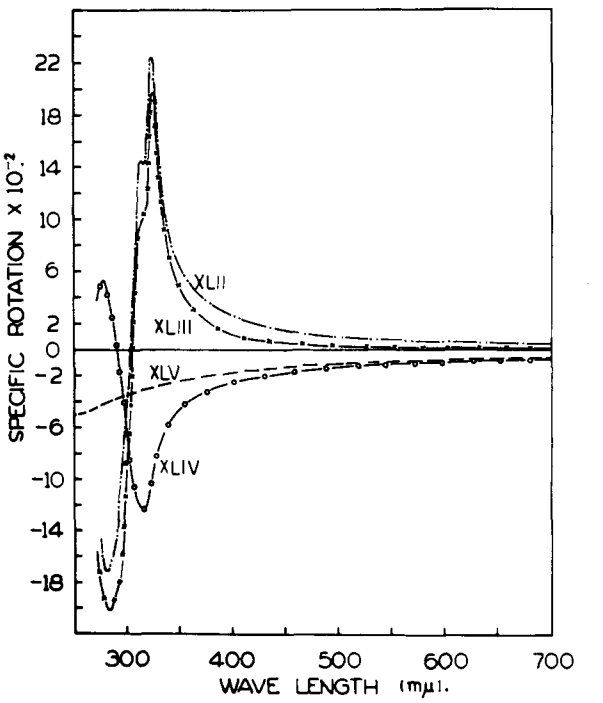


Fig. 10.—Rotatory dispersion curves (dioxane solution) of norketone XLII (derived from phyllocladene), epoxynorcafestanone (XLIII), ketone XLIV (derived from cafestol) and alcohol XLV (derived from cafestol, in methanol solution).

ascribe an unprecedented effect to the adjacent, equatorially oriented ethyl group.[43] The dispersion curve of this ketone XLIV is very suggestive of the *mirror image* of a 3-keto-5α-steroid (*cf.* Fig. 1) although an A/B *cis* structure is not definitely excluded. Degradation experiments are now under way to settle this point, but it appears from the dispersion evidence that the A/B ring juncture of cafestol (XL) and probably also of phyllocladene (XLI) is different (*cis* or antipodal *trans*) from that of the common diterpenes[25] (*cf.* XXII). An antipodal *trans* stereochemistry (XLIVb) would be particularly attractive based on structure XLb for cafestol[39] since this would suggest that cafestol might be a "friedelin" of the diterpene series. The same may also apply to phyllocladene (XLI, angular methyl group at 11) and the mechanistic and biogenetic implications will be considered in our future detailed paper[42] on cafestol.

Two other representatives of the phyllocladene type are considered in Fig. 11. The dispersion curve of steviol (XLVI)[44] should be considered the background for that of the ketone isosteviol (XLVII).[44] Consideration of the probable mechanism of the steviol–isosteviol rearrangement has led to

(39) H. Bendas and C. Djerassi, *Chemistry & Industry*, 1481 (1955). The position of the angular methyl group has been assumed tentatively by analogy to the other diterpenes and to phyllocladene (ref. 40). R. D. Haworth and R. A. W. Johnstone (*ibid.*, 168 (1956)) have presented evidence that the variant XLb (in which the angular methyl and hydrogen have been reversed) is more likely. The presently described stereochemical argument would apply to either XLa or XLb.

(40) C. W. Brandt, *New Zealand J. Sci. Tech.*, **34B**, 46 (1952); *cf.* W. Bottomley, A. R. H. Cole and D. E. White, *J. Chem. Soc.*, 2624 (1955). It should be noted that the position of the angular methyl group has only been assumed by analogy to other diterpenes and this also applies to structure XLa for cafestol.

(41) A. Wettstein, F. Hunziker and K. Miescher, *Helv. Chim. Acta*, **26**, 1197 (1943).

(42) Unpublished work by Dr. M. Cais of this Laboratory.

(43) An adjacent equatorial methyl group usually has no effect (*cf.* XXXI and XXXV). It should be noted that the only A/B *trans* compounds with a C-10 β-methyl group which show a dispersion curve similar to that of XLIV are those with an adjacent *gem*-methyl function (*e.g.*, lanostan-3-one; unpublished observation). It is unlikely that a migration had occurred in the formation of XLIV to produce such a structure.

(44) E. Mosettig and W. R. Nes, *J. Org. Chem.*, **20**, 884 (1955). The position of the angular methyl group is assumed by analogy to the diterpenes (see ref. 39 and 40).

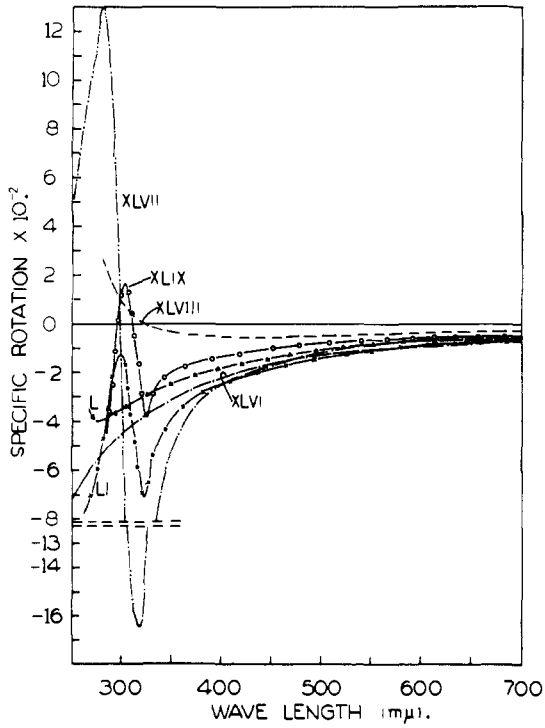
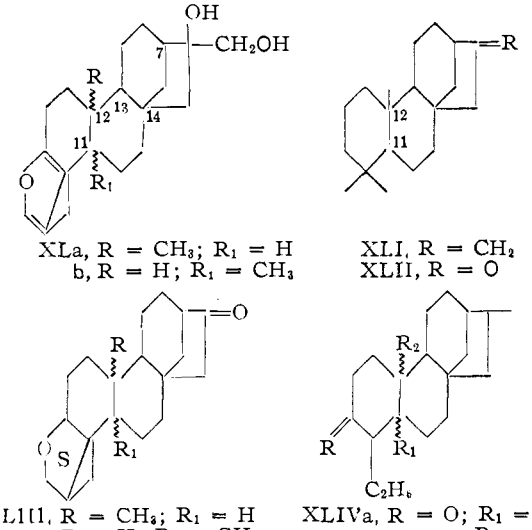
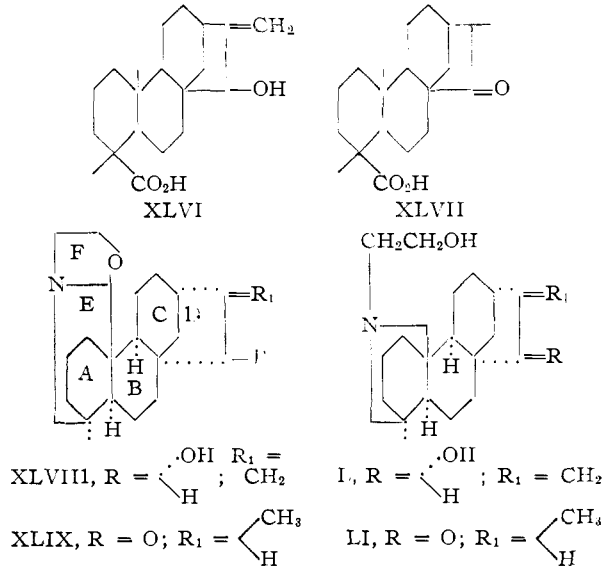


Fig. 11.—Rotatory dispersion curves (methanol solution) of steviol (XLVI), isosteviol (XLVII), garryfoline (XLVIII), cuauchichicine (XLIX), F-dihydrogarryfoline (L) and F-dihydrocuauchichicine (LI).

the suggestion[44,45] that this diterpene (XLVI) possesses the same relative configuration (at least as far as the fusion of the 5- and 6-membered rings is concerned) as the alkaloid garryfoline (XLVIII).[45] If one ignored the unknown influence of the additional two fused rings (E, F) of garryfoline, then the rotatory dispersion curves of isosteviol (XLVII) and cuauchichicine (XLIX)[45] should be very similar if the two substances possess the same absolute configuration since the carbonyl group and its environment should play the dominant role in governing the shape of the dispersion curves. For comparison purposes, the curves for F-dihydrogarryfoline (L) and F-dihydrocuauchichicine (LI) are also included in Fig. 11. The two alcohols XLVIII and L were measured to provide the "background" rotation and it can be seen that the oxazolidine ring plays a definite role. A comparison of the dispersion curves of the two *Garrya* alkaloid ketones XLIX and LI with that of isosteviol XLVII shows a general similarity in so far as the "minima" are concerned but there is an appreciable shift in the position of the "maxima" and the intensities also differ. This may very well be a reflection of the presence of the additional fused piperidine ring (E) in XLIX and LI but at the present time one can suggest only very tentatively that steviol (XLVI) and garryfoline (XLVIII) possess the same absolute configuration at positions 7, 13 and 14. If that should be the case and if an experimental connection could be accomplished between cafestol (XL) and steviol (XLVI), then the statements made earlier concerning the unusual feature of the former's A/B ring juncture would apply to all terpenoids of the phyllocladene group. However if cafestol possesses structure XLb[39] and is stereochemically of the friedelin type (*vide supra*), then on biogenetic grounds cafestol (XL) and the *Garrya* alkaloids (XLVIII, XLIX) should have opposite absolute configurations.





Further examples from the alkaloid series are given in Fig. 12. Klyne[46] has attempted to correlate the absolute configuration of yohimbine with that of the steroids by applying the generalized method of molecular rotation differences[18] to certain olefins and alcohols. Application of the rotatory dispersion method to the ketone yohimbone

(45) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, THIS JOURNAL, **77**, 4801, 6633 (1955); *cf.* K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955).

(46) W. Klyne, *Chemistry & Industry*, 1032 (1953).

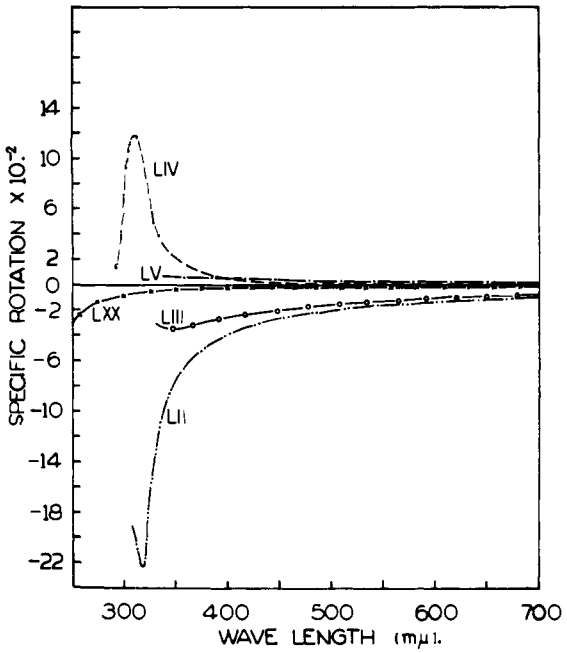
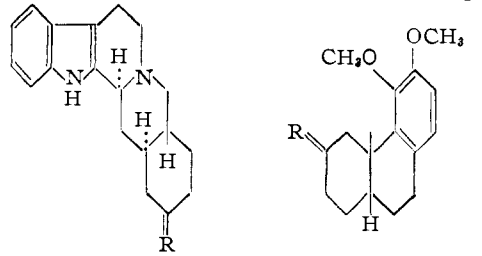


Fig. 12.—Rotatory dispersion curves of yohimbone (LII, dioxane), yohimbane (LIII, dioxane), (+)-*cis*-13-methyl-3,4-dimethoxy-6-keto-5,6,7,8,9,10,13,14-octahydrophenanthrene (LIV, methanol), (+)-*cis*-13-methyl-3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene (LV, methanol) and (−)-*trans*-1,1,3-trimethyl-3-carboxycyclohexane-2-acetic acid (LXX, methanol).

(LII) has now led to the same conclusion, this being an attractive example where both methods complement each other since rotatory dispersion curves would not have been of any particular utility in the case of the alcohols and olefins studied by Klyne.[46] If the absolute configuration of yohimbone is expressed correctly by LII, then the rotatory dispersion curve should be chiefly a reflection of rings D/E[47] and should be enantiomeric with that of 2-ketosteroids such as cholestan-2-one.[3] As shown in Fig. 12, this is actually the case and our results thus support the absolute configuration assigned by Klyne.[46] The remaining two curves in Fig. 12 show potential applications to the field of assignment of absolute configurations without leading to any definite conclusions. The ketone LIV is derived from morphine[10] and since the corresponding hydrocarbon (LV)[10] exhibits a negligible rotation throughout the spectral range examined, the strong "maximum" exhibited by the ketone should be typical of a 2-keto-5β-steroid (A/B *cis*) such as coprostan-2-one. Unfortunately, no such ketone has as yet been prepared and at least one such reference compound must become available before the rotatory dispersion method can be applied to such cases.[48]



LII, R = O
LIII, R = H_2

LIV, R = O
LV, R = H_2

Figure 13 contains dispersion data pertaining to eremophilone (LVIII or LIX),[49] one of the few sesquiterpenes which does not follow the isoprene rule. This is an important example because it demonstrates how at times opposite conclusions might be reached depending upon the use of rotatory dispersion curves as compared to molecular rotation differences. Klyne[25] assigned the absolute configuration LVIII to eremophilone on the very reasonable grounds that its rotation at the sodium D line is strongly negative, as is that of Δ⁵-cholesten-4-one (LVI) while Δ⁴-cholesten-6-one (LVII) (which would lead to expression LIX for eremophilone) exhibits a positive rotation at that wave length. However, as soon as the entire dispersion curves (Fig. 13) of the relevant compounds are inspected, it becomes clear that in this case comparisons of $[\alpha]_D$ will lead to the wrong conclusion because the dispersion curves "cross over" near 400 mμ. The characteristic feature of the dispersion curve—entrance into the optically active absorption band from either the negative or posi-

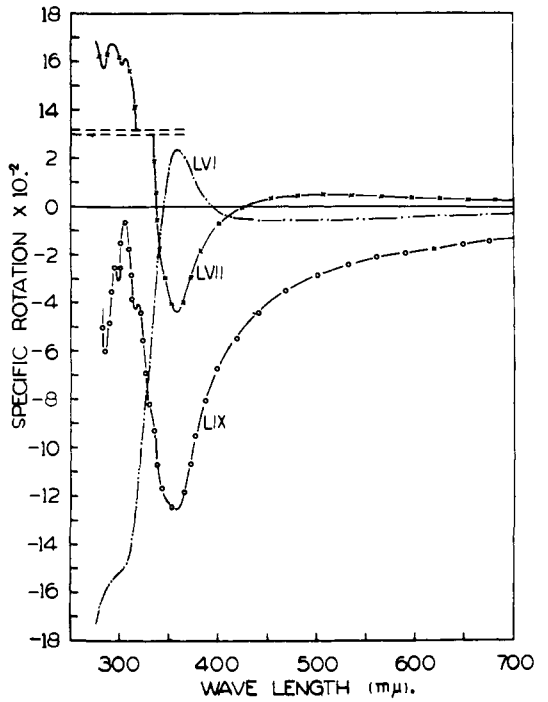


Fig. 13.—Rotatory dispersion curves (dioxane solution) of Δ⁵-cholesten-4-one (LVI), Δ⁴-cholesten-6-one (LVII) and eremophilone (LIX).

(47) The fundamental hydrocarbon yohimbane (LIII) of this series has no important effect other than producing a slow drift toward progressively more negative rotation in going to lower wave length (Fig. 12).

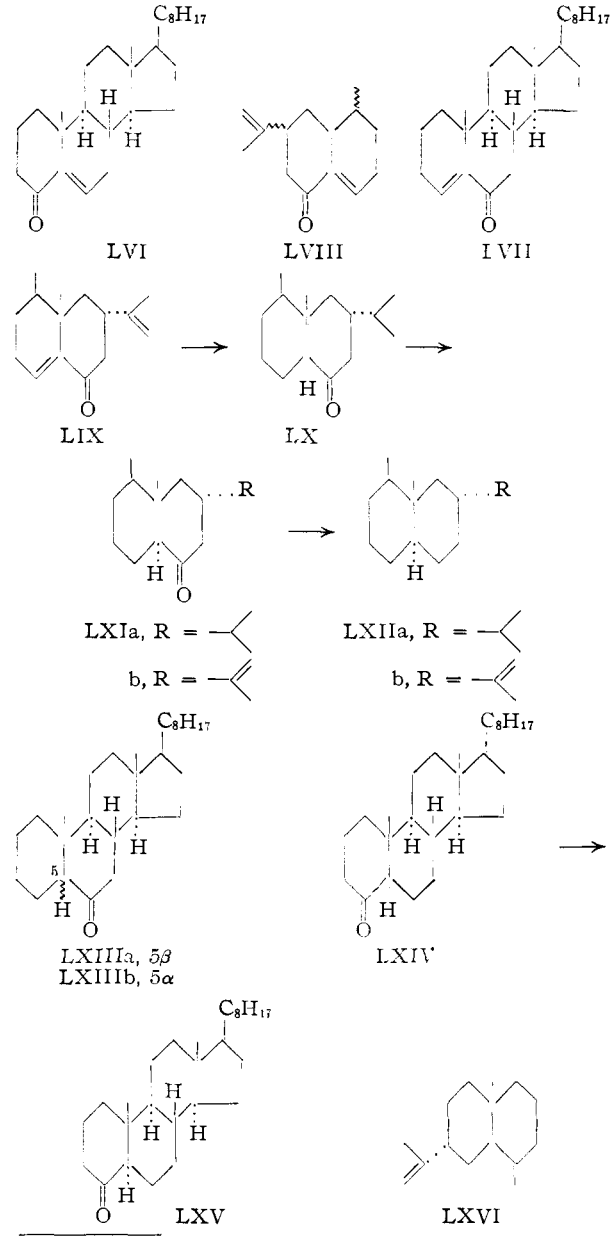
(48) Conversely, since the ketone LIV has been configurationally related[10] to the steroids by a chemical method, the dispersion curve of LIV can now be used as a standard for *cis*-9-methyl-2-decalones, provided the aromatic ring plays no important part.

(49) A complete summary of the work of Simonsen, Penfold and their associates is given by J. Simonsen and D. H. R. Barton in "The Terpenes," Cambridge University Press, New York, N. Y., 1952, Vol. III, pp. 212–224.

tive side—manifests itself usually only in or near the ultraviolet region, but the typical trend extends often also to the 600 mμ region. It is only when a situation such as shown in Fig. 13 exists that erroneous conclusions will be reached by using the method of molecular rotation differences. The general shapes of the rotatory dispersion curves of eremophilone (now represented as LIX) and Δ^4-cholesten-6-one (LVII) are quite similar except for some differences in the fine structure in the 300 mμ region and the fact that the entire eremophilone curve shows more negative values.

In order to confirm this new stereochemical assignment to eremophilone, the dispersion curves of several transformation products[50] were investigated. Hydrogenation of eremophilone (LIX) led to an unstable tetrahydroketone LX, which is now represented as the *cis* isomer and which was characterized as the crystalline 2,4-dinitrophenylhydrazone.[51] Mild acid treatment caused isomerization with formation of the known[49] *trans* isomer LXIa, and the rotatory dispersion curves (Fig. 14) of the two ketones bear exactly the same relationship to each other as do the curves[1] of the pair coprostan-6-one (LXIIIa) and cholestan-6-one (LXIIIb). *A priori*, this could be considered further convincing evidence for the absolute configuration LIX of eremophilone were it not for the fact that cholestan-4-one (LXV)[3] and cholestan-6-one (LXIIIb)[1] possess similar rotatory dispersion curves.[52] One of the reported syntheses[53] of cholestan-4-one (LXV) involves catalytic hydrogenation of Δ^5-cholesten-4-one (LVII) and we have re-investigated this reaction in the hope of securing the unknown coprostan-4-one (LXIV).[54] Indeed, when the products from the palladium hydrogenation of LVI were worked up carefully, there was isolated coprostan-4-one (LXIV) and as was to be anticipated, it could be isomerized readily with acid to the stable cholestan-4-one (LXV). The rotatory dispersion curve of the *cis*-4-ketone is reproduced in Fig. 14 and it will be noted that the curve of coprostan-4-one (LXIV) is positive and consequently completely different from that of coprostan-6-one (LXIIIa)[1] or of *cis*-tetrahydroeremophilone (LX).[55]

The above stereochemical assignment to the hydrogenation products LX and LXIa also has a bearing on the stereochemistry of the isopropyl group (and consequently the isopropenyl group in eremophilone (LIX)). If the isopropyl substituent were axially oriented (β), then it is quite likely that the stable isomer would be *cis* (LX) rather than *trans* (LXIa) in order to minimize the steric interference between the angular methyl group and the isopropyl function. In that event, no definite conclusion could be reached from the dispersion curve of the unstable *trans* isomer (unknown axial effect), but the stable *cis* isomer should have a dispersion curve similar to that of coprostan-6-one (LXIIIa) while in fact the curve of the stable compound resembles that of cholestan-6-one (LXIIIb). We consider the above analysis as further



(50) A generous sample of eremophilone was provided through the courtesy of Messrs. H. H. G. McKern and F. R. Morrison (Museum of Applied Arts and Sciences, Sydney, Australia) and this served as the starting material for the preparation of the other compounds (LX-LXII).

(51) This derivative had to be prepared at room temperature in acetic acid; at elevated temperature, the dinitrophenylhydrazone of the *trans* isomer LXIa was obtained. This explains why the *cis*-tetrahydroketone LX was not isolated by the earlier workers (ref. 49) since they converted the hydrogenation product directly into the semicarbazone and regenerated the ketone by acid cleavage.

(52) The similarity of the rotatory dispersion curves of cholestan-4-one (LXV) and cholestan-6-one (LXIIIb) demonstrates that they are not of enantiomeric type and that caution should be exercised in comparing terminal with non-terminal rings. On the other hand, the corresponding unsaturated ketones (LVI and LVII) are clearly enantiomeric as shown in Fig. 13.

(53) A. Butenandt and H. Ruhenstroth-Bauer, *Ber.*, **77**, 397 (1944).

(54) Since completion of our work, R. Stevenson and L. F. Fieser (THIS JOURNAL, **78**, 1409 (1956)) have prepared coprostan-4-one by a different procedure.

(55) For comparison purposes and in order to determine whether any marked rotational effect might be exerted by the isopropenyl substituent (as compared to isopropyl), the dispersion curves of *trans*-dihydroeremophilone (LXIb) and of the two hydrocarbons LXIIa and LXIIb were also measured (see Experimental) but no marked change was noted.

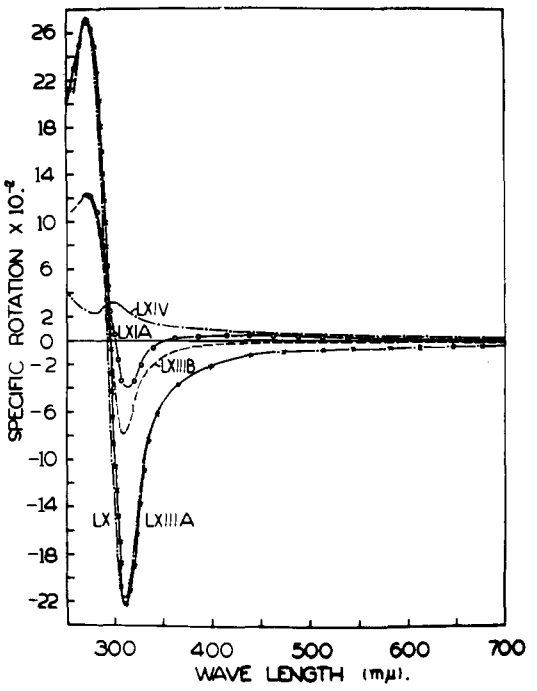


Fig. 14.—Rotatory dispersion curves (methanol solution) of *cis*-tetrahydroeremophilone (LX), *trans*-tetrahydroeremophilone (LXIa), coprostan-6-one (LXIIIa), cholestan-6-one (LXIIIb) and coprostan-4-one (LXIV).

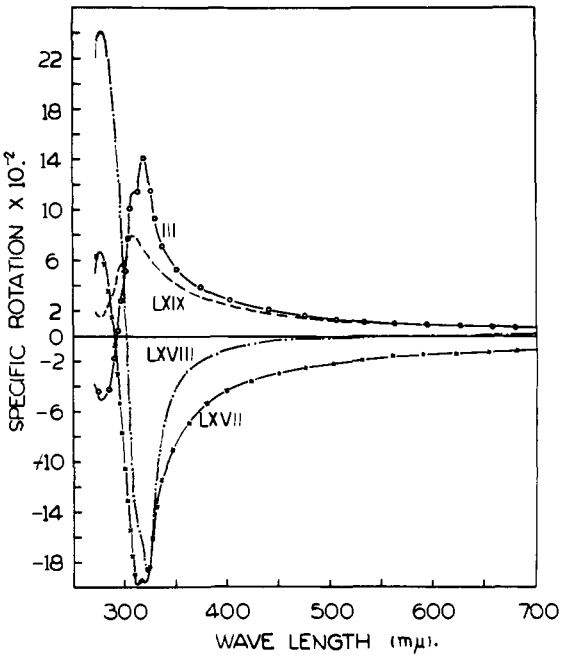


Fig. 15.—Rotatory dispersion curves (dioxane solution) of (+)-*trans*-9-methyldecalone-1 (III), ψ-santonin (LXVII), 1-keto-7-hydroxy-$\Delta^{5(10)}$-santenic acid (LXVIII) and 1-keto-7-hydroxysantanic acid (LXIX).

support for the correctness of our assignment of absolute configuration LIX to eremophilone[56] and this in turn implies that its biogenetic precursor (if methyl migration is involved in such a process) should be based on the skeleton LXVI, which bears an antipodal relationship to naturally occurring eudesmol.[14]

In the last figure (Fig. 15) are included certain ketones which may be considered to be bicyclic analogs of 1-ketosteroids. Attention already has been called[3] to the very unusual shapes of the dispersion curves of 1-ketocholestane and the enantiomeric D-homoandrostan-17a-one-3β-ol since they did not show any pronounced "maxima" or "minima." This was one of the purposes for synthesizing the bicyclic 1-ketone III of the decalin series and its dispersion curve (Fig. 15) is quite different from that of 1-ketocholestane and rather of the expected type (rough mirror image of 4-ketone such as cholestan-4-one (LXV). The only conclusion that can be drawn from this observation is that the dispersion curve of 1-ketosteroids is not just typical of the bicyclic structure III but rather that the additional ring system also exerts a pronounced effect.

ψ-Santonin (LXVII)[57] and its transformation products constitute naturally occurring members of the 1-ketodecalin series and no information has as yet been provided concerning their absolute configuration. It should be clear from the above discussion that if recourse is to be taken to the rotatory dispersion method, the shape of the dispersion curve of *trans*-9-methyldecalone-1 (III) should be used for reference purposes rather than that of 1-ketocholestane[2] where other factors seem to play a decisive role. The shapes of the dispersion curves (Fig. 15) of the reference ketone III and of 1-keto-7-hydroxysantanic acid (LXIX)[57] are sufficiently similar so that we feel justified in assigning the absolute configuration LXVII (angular methyl group β) to ψ-santonin. The dispersion curves of ψ-santonin (LXVII) and of its hydrogenolysis product 1-keto-7-hydroxy-$\Delta^{5(10)}$-santenic acid (LXVIII)[57] are also included in Fig. 15, but no definite conclusions can be drawn from them since suitable reference ketones (with double bonds at the ring juncture) are as yet unavailable.

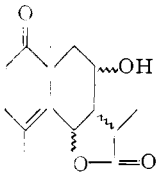
Jeger and collaborators have recently presented in summary form[58] the physical constants of a number of dibasic acids which can serve as reference compounds for the experimental assignment of absolute configuration to various terpenoids.

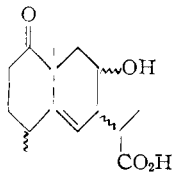
(56) The relative stereochemistry of "hydroxydihydroeremophilone" (ref. 49) has been determined by X-ray analysis (D. F. Grant and D. Rogers, *Chemistry & Industry*, 278 (1956)) and establishes a *cis* fusion of the two rings (*cf.* W. Klyne, *Experientia*, **12**, 119 (1956)). Whether these results have any bearing on the stereochemistry of the tetrahydroeremophilones (LX, LXI) depends on the stereochemical validity of the reported chemical interconversions (ref. 49) of eremophilone and "hydroxydihydroeremophilone." The first of these proceeds *via* "hydroxyeremophilone" (T. A. Geissman, THIS JOURNAL, **75**, 4008 (1953)) and involves destruction of all the relevant asymmetric centers. The second one (A. E. Bradfield, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 2745 (1932)) includes as the crucial step the sodium amalgam reduction (in aqueous alcohol) of "hydroxytetrahydroeremophilone" in unspecified yield to tetrahydroeremophilone (LXIa); epimerization of the ring juncture and of the isopropyl group (*via* the ene-diol) in the alkaline medium is quite conceivable. If no inversion occurred, then the X-ray results of "hydroxydihydroeremophilone" imply that the isopropyl group in LIX–LXII is β-oriented and that LX is more stable that LXIa.

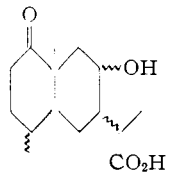
(57) For leading references see W. G. Dauben, P. D. Hance and W. K. Hayes, THIS JOURNAL, **77**, 4609 (1955), and N. M. Chopra, W. Cocker, J. T. Edward, T. B. H. McMurray and E. R. Stuart, *J. Chem. Soc.*, 1828 (1956).

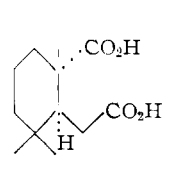
(58) K. Schaffner, R. Viterbo, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 174 (1956).

It is noticeable that many of these reference acids have only very low specific rotations at 589 mμ (*e.g.*, LXX, $[\alpha]_D$ −7°) and attention should be called to another aspect where the rotatory dispersion curve can be of some advantage. Even a substance with only weakly optically active chromophores such as the dibasic acid LXX will show a larger rotation in the ultraviolet spectral


LXVII


LXVIII


LXIX


LXX

region and, as can be seen from Fig. 12, the acid LXX already exhibits $[\alpha]$ −92° at 300 mμ and correspondingly larger values at lower wave length. Another pertinent example is provided by the acid X and the relevant data are given in the Experimental section. Consequently, rotatory comparison of two such antipodes will be much more significant if carried out in the ultraviolet rather than at the sodium D line and, furthermore, much less material is required because of the larger values observed in that region.

Experimental[59]

(+)-*trans*-9-**Methyldecalone-1** (III).—A solution of 4.75 g. of *trans*-9-methyl-1-keto-$\Delta^{2,6}$-hexahydronaphthalene (II)[12] in 50 g. of methanol was hydrogenated with 200 mg. of 10% palladized charcoal for 40 minutes at which time the hydrogen uptake corresponded to two equivalents. The catalyst was filtered, the solvent was evaporated and the residue was chromatographed on 30 g. of neutral alumina. The hexane–benzene (1:1) eluates were combined and distilled at 10 mm. and a bath temperature of 120°, $\lambda_{max}^{microcap}$ 5.84 μ.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.49; H, 11.11; R.D. (Fig. 15), *c* 0.11 in dioxane: $[\alpha]_{700}$ +64°, $[\alpha]_{589}$ +100°, $[\alpha]_{272.5}$ −407°, "max." $[\alpha]_{317.5}$ +1415°, "shoulder" $[\alpha]_{310-312.5}$ +1145°, "min." $[\alpha]_{277.5}$ −506°.

The 2,4-dinitrophenylhydrazone crystallized from methanol–methylene chloride as orange needles, m.p. 159–160°.

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40; N, 16.18. Found: C, 58.70; H, 6.31; N, 15.98.

(−)-*trans*-9-**Methyl-2-hydroxymethylenedecalone-1** (IV).—The above ketone III (1.0 g.) was added to a mixture of 2.6 g. of sodium methoxide (freshly prepared and dried at 220° *in vacuo*), 60 cc. of dry benzene and 4.5 cc. of ethyl formate and stirring was continued at 30° overnight. The base-soluble product (1.15 g.) was distilled at 150° and 12 mm. to give 850 mg. of a pale yellowish oil, $[\alpha]_D$ −16.5° (methanol); dark purple color with methanolic ferric chloride solution.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.43; H, 9.43.

A sample of IV in methanol solution was treated in the presence of hydrochloric acid with excess 2,4-dinitrophenylhydrazine. The initial product was dark red but changed to yellow leaflets on warming. The pyrazole was recrystallized from methanol–methylene chloride whereupon it melted at 228–229°.

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72; O, 17.96. Found: C, 60.09; H, 5.66; N, 15.78; O, 18.37.

(+)-*trans*-9-**Methyldecalin-1,2-dione** (V).—A 305-mg. sample of the hydroxymethylene ketone IV in 25 cc. of ethylene chloride was ozonized at −70° until a permanent blue color was formed (*ca.* 4 minutes), the solvent was removed and the residue was boiled with 10 cc. of water for 30 minutes. Extraction with ether, washing with ferrous sulfate solution, dilute alkali and water followed by distillation at 90° and 0.02 mm. gave 210 mg. of the diketone as a yellowish oil; $\lambda_{max}^{microcap}$ 2.94, 5.80, 5.92 and inflections at 5.98 and 6.10 μ; dirty violet color with ferric chloride.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.50; H, 9.14; R.D., *c* 0.098 in dioxane: $[\alpha]_{700}$ +32°, $[\alpha]_{589}$ +46°, $[\alpha]_{317.5}$ −112°, "max." $[\alpha]_{350}$ +781°.

(−)-*trans*-1-**Methyl-1-carboxycyclohexane-2-acetic Acid** (VI).[14]—The diketone V (270 mg.) was dissolved in 60 cc. of 5% methanolic potassium hydroxide and 15 cc. of 30% hydrogen peroxide was added over a period of 45 minutes while maintaining a reflux temperature. The acid was isolated in the usual manner and recrystallized from acetone–hexane; yield 180 mg., m.p. 133–136°. The analytical sample was obtained from the same solvent pair, m.p. 137–138°.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.72; H, 8.47; R.D., *c* 0.10 in methanol: $[\alpha]_{700}$ −15°, $[\alpha]_{589}$ −24°, $[\alpha]_{400}$ −71°, $[\alpha]_{300}$ −156°, $[\alpha]_{280}$ −189°, $[\alpha]_{270}$ −216°, $[\alpha]_{260}$ −239°, $[\alpha]_{250}$ −261°.

(−)-*trans*-8-**Methylhydrindan-1-one** (VII).—An intimate mixture of 300 mg. of the dicarboxylic acid VI and 16 mg. of barium hydroxide was heated in a microdistillation apparatus at 300° whereupon a vigorous evolution of gas ensued. The bath temperature was raised to 330° and the colorless distillate (160 mg.) was chromatographed on 10 g. of neutral alumina. The pentane–benzene (4:1) eluates were distilled at 90–95° and 10 mm., $\lambda_{max}^{microcap}$ 5.70 μ.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.77; H, 10.89; R.D. (Fig. 2), *c* 0.068 in dioxane: $[\alpha]_{700}$ −67°, $[\alpha]_{589}$ −88°, $[\alpha]_{272.5}$ +2300°, "min." $[\alpha]_{322.5}$ −3110°, "max." $[\alpha]_{280}$ +2700°.

The 2,4-dinitrophenylhydrazone crystallized from methylene chloride–methanol as orange leaflets, m.p. 162–162.5°.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.91; H, 6.05; N, 16.92.

(−)-*trans*-9-**Methyldecalone-3** (IX) was prepared by catalytic hydrogenation of VIII[11a] according to Riniker, *et al.*,[14] where both antipodes have been reported.

R.D. (Fig. 1), *c* 0.08 in dioxane: $[\alpha]_{700}$ −21°, $[\alpha]_{589}$ −34°, $[\alpha]_{272.5}$ +1418°, "min." $[\alpha]_{317.5}$ −1356°, "max." $[\alpha]_{275}$ +1485°.

(−)-*trans*-8-**Methylhydrindan-2-one** (XI).[60]—A mixture of 40 mg. of (+)-*trans*-1-methyl-cyclohexane-1,2-diacetic acid (X), prepared from (−)-IX as reported for the antipode,[14] was pyrolyzed with 3 mg. of barium hydroxide exactly as described above for VI. The product (25 mg.) was distilled at 95° and 10 mm., $\lambda_{max}^{microcap}$ 5.70 μ; no analysis was secured, characterization being accomplished *via* its 2,4-dinitrophenylhydrazone.

R.D. (Fig. 3), *c* 0.10 in methanol: $[\alpha]_{700}$ −177°, $[\alpha]_{589}$ −276°, $[\alpha]_{350}$ +4780°, "min." $[\alpha]_{325}$ −6570°, "max." $[\alpha]_{322.5}$ −6525°, "min." $[\alpha]_{315}$ −7445°, "max." $[\alpha]_{275}$ +6975°, "inflect." $[\alpha]_{265}$ +6400°.

The orange **2,4-dinitrophenylhydrazone** was recrystallized from methylene chloride–methanol, whereupon it exhibited m.p. 157–161°.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.80; H, 6.10; N, 16.70.

(59) Melting points (Kofler block) and boiling points are uncorrected. We are grateful to Mrs. Dolores Phillips for the ultraviolet and infrared spectral measurements and to Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses. The rotatory dispersion measurements were carried out by the procedures outlined in refs. 3 and 4a at room temperature (20–27°, the temperature range for any given day being less than 2°) using either methanol or dioxane (for solvent effect, see footnote 11 in ref. 1). Where no source is given, the substance came from the collection of C. D.

(60) The optical antipode already has been prepared by F. Gautschi, O. Jeger, V. Prelog and R. B. Woodward, *Helv. Chim. Acta*, **38**, 296 (1955).

(+)-*cis*-**8-Methylhydrindan-5-one (XIII)**[15]: R.D. (Fig. 1), *c* 0.81 in dioxane: $[\alpha]_{700}$ +12°, $[\alpha]_{589}$ +19°, $[\alpha]_{280}$ +441°, "max." $[\alpha]_{375-400}$ +36°, "min." $[\alpha]_{316}$ −190°.

Methyl 2-keto-A-norcholanate (XIVa) (W. Klyne): R.D. (Fig. 3), *c* 0.107 in methanol: $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −40°, $[\alpha]_{260}$ +1845°, "inflect." $[\alpha]_{322.5}$ −1510°, "min." $[\alpha]_{312.5}$ −1900°, "max." $[\alpha]_{272.5}$ +2180°.

3-Keto-A-norcholanic acid (XIVb) (W. Klyne): R.D. (Fig. 2), *c* 0.11 in methanol: $[\alpha]_{700}$ +76°, $[\alpha]_{589}$ + 133°, $[\alpha]_{255}$ −454°, "max." $[\alpha]_{314}$ +2260°, "min." $[\alpha]_{275}$ − 1420°.

Androstan-17-one (XV).—This substance was measured again in the ultraviolet using a xenon lamp in order to define the "minimum" which could not be obtained earlier[4a] with the zirconium lamp. R.D. (Fig. 2), *c* 0.106 in dioxane: "max." $[\alpha]_{318}$ +2740°, "min." $[\alpha]_{279}$ −2390°.

14β-Androstan-3β-ol-17-one acetate (XVI): R.D. (Fig. 2), *c* 0.074 in methanol: $[\alpha]_{700}$ +31°, $[\alpha]_{589}$ +76°, $[\alpha]_{252.5}$ +271°, "max." $[\alpha]_{301}$ +992°, "min." $[\alpha]_{267.5}$ −22°.

14β,22a,25a,5α-Spirostane-2α,3β-diol-15-one (XVIII)[17]: R.D. (Fig. 2), *c* 0.08 in dioxane: $[\alpha]_{700}$ −80°, $[\alpha]_{589}$ −118°, $[\alpha]_{275}$ +374°, "min." $[\alpha]_{347}$ −1480°, "max." $[\alpha]_{298}$ +942°.

Androstan-3β-ol-16-one (XVIII) (F. Sorm[61]): R.D. (Fig. 3), *c* 0.10 in methanol: $[\alpha]_{700}$ −129°, $[\alpha]_{589}$ −191°, $[\alpha]_{260}$ +2640°, "shoulder" $[\alpha]_{320-323}$ −4260°, "min." $[\alpha]_{314}$ −4782°, "max." $[\alpha]_{275}$ +4327°.

Δ⁵-Pregnene-3,16,20-trione 3,20-bis-ethylene ketal (XIX)[21] (S. Bernstein): R.D. (Fig. 3), *c* 0.055 in dioxane: $[\alpha]_{700}$ −95°, $[\alpha]_{589}$ −133°, $[\alpha]_{270}$ +1685°, "min." $[\alpha]_{325}$ −2910°, "shoulder" $[\alpha]_{315-318}$ −2300°, "max." $[\alpha]_{280}$ +2190°.

2-Keto-A-norcholestane (XX)[22] (H. R. Nace): R.D. (Fig. 3), *c* 0.052 in methanol: $[\alpha]_{700}$ +65°, $[\alpha]_{589}$ +125°, $[\alpha]_{255}$ −1890°, "shoulder" $[\alpha]_{322.5-325}$ +2936°, "max." $[\alpha]_{315}$ +3310°, "min." $[\alpha]_{275}$ −2950°.

3-Hydroxy-16-keto-1,3,5-estratriene ("estrone-16") (M. N. Huffman): R.D., *c* 0.10 in methanol $[\alpha]_{700}$ −44°, $[\alpha]_{589}$ −86°, $[\alpha]_{295}$ +505°, "min." $[\alpha]_{322.5}$ −3739°, "max." $[\alpha]_{320}$ −3672°, "min." $[\alpha]_{313}$ −4075°.

19-Nortestosterone (XXI) (J. A. Hartman): R.D. (Fig. 4); *c* 0.108 in dioxane: $[\alpha]_{700}$ +33°, $[\alpha]_{589}$ +44°, $[\alpha]_{272.5}$ +2338°, "max." $[\alpha]_{425-475}$ + 57°, "min." $[\alpha]_{365}$ −544°, "max." $[\alpha]_{359}$ −405°, "min." $[\alpha]_{351}$ −567°, "shoulder" $[\alpha]_{337-340}$ +175°, "inflect." $[\alpha]_{322.5}$ +1210°, "inflect." $[\alpha]_{310}$ +1782°.

8,13-Dimethyl-8-methoxycarbonyl-2-keto-Δ¹⁽¹¹⁾-dodecahydrophenanthrene (XXII)[26] (W. M. Hoehn): R.D. (Fig. 4), *c* 0.10 in dioxane: $[\alpha]_{700}$ +22°, $[\alpha]_{589}$ +32°, $[\alpha]_{275}$ +3455°, "min." $[\alpha]_{367.5}$ −737°, "max." $[\alpha]_{360}$ −581°, "min." $[\alpha]_{352.5}$ −789°, "inflect. $[\alpha]_{340}$ +207°, "inflect" $[\alpha]_{325}$ +1575°, "inflect." $[\alpha]_{312.5}$ +2395°.

4-Methyl-Δ⁴-cholesten-3-one (XXIIIa)[27] (G. D. Meakins): R.D. (Fig. 5), *c* 0.074 in dioxane: $[\alpha]_{700}$ +69°, $[\alpha]_{589}$ +108°, $[\alpha]_{280}$ +2562°, "max." $[\alpha]_{400-410}$ +216°, "inflect." $[\alpha]_{365}$ +31°, "min." $[\alpha]_{352.5}$ −146°, "max." $[\alpha]_{343}$ +208°, "min." $[\alpha]_{339}$ +146°, "inflect." $[\alpha]_{325}$ +999°, "inflect." $[\alpha]_{312.5}$ +1676°; *c* 0.076 in octane: $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ +81°, $[\alpha]_{302.5}$ +1672°, "max." $[\alpha]_{410-415}$ +176°, "min." $[\alpha]_{375}$ −14°, "max." $[\alpha]_{367.5}$ +38°, "min." $[\alpha]_{358}$ −190°, "max." $[\alpha]_{349}$ +210°, "min." $[\alpha]_{342.5}$ +101°, "max." $[\alpha]_{332.5}$ +800°, "min." $[\alpha]_{330}$ +768°, "inflect." $[\alpha]_{315}$ +1370°; *c* 0.076 in methanol: $[\alpha]_{700}$ +63°, $[\alpha]_{589}$ +97°, $[\alpha]_{282.5}$ +2960°, "max." $[\alpha]_{395-405}$ +198°, "min." $[\alpha]_{342}$ −140°.

Δ⁴-Cholesten-3-one (XXIIIb).—The earlier measurements[4c] were repeated using a xenon lamp in the ultraviolet region. R.D., *c* 0.10 in dioxane: $[\alpha]_{700}$ +53°, $[\alpha]_{589}$ +73°, $[\alpha]_{275}$ +2100, "max." $[\alpha]_{410-420}$ + 142°, "min." $[\alpha]_{366}$ −93°, "max." $[\alpha]_{359}$ −51°, "min." $[\alpha]_{352}$ −164°, "shoulder" $[\alpha]_{337.5-340}$ +265°, "inflect." $[\alpha]_{325}$ +1000°, "inflect" $[\alpha]_{312.5}$ +1475°, "inflect" $[\alpha]_{300}$ +1695°.

(+)-α-Cyperone (XXIV)[28] (F. J. McQuillin): R.D. (Fig. 5), *c* 0.094 in dioxane: $[\alpha]_{700}$ +52°, $[\alpha]_{589}$ +81°, $[\alpha]_{275}$ +4200°, "max." $[\alpha]_{390-405}$ +198°, "min." $[\alpha]_{367.5}$ +1°, "max." $[\alpha]_{362.5}$ +20°, "min." $[\alpha]_{354}$ −293°, "max." $[\alpha]_{343}$ +53°, "min." $[\alpha]_{339}$ +30°, "inflect." $[\alpha]_{325}$ +905°, "inflect." $[\alpha]_{312.5}$ +1782°, "inflect." $[\alpha]_{302.5}$ +2320°.

(+)-Epi-α-cyperone (XXVa)[28] (F. J. McQuillin): R.D. (Fig. 5), *c* 0.078 in dioxane: $[\alpha]_{700}$ +108°, $[\alpha]_{589}$ +193°, $[\alpha]_{287.5}$ +533°, "max." $[\alpha]_{374}$ +1172°, "min." $[\alpha]_{366}$ +1128°, "max." $[\alpha]_{360}$ +1211°, "inflect." $[\alpha]_{346}$ +685°, "min." $[\alpha]_{322.5}$ −147°, "max." $[\alpha]_{317.5}$ −25°, "min." $[\alpha]_{315}$ −45°.

(61) J. Fajkos and F. Sorm, *Collection Czechoslov. Chem. Communs.*, 19, 349 (1954); *C.A.*, 49, 357 (1955).

(+)-Dihydro-epi-α-cyperone (XXVb)[28] (F. J. McQuillin): R.D. (Fig. 5), *c* 0.134 in dioxane: $[\alpha]_{700}$ +72°, $[\alpha]_{589}$ +122°, $[\alpha]_{285}$ +1620°, "max." $[\alpha]_{372.5}$ +835°, "min." $[\alpha]_{365}$ +782°, "max." $[\alpha]_{360}$ +800°, "inflect." $[\alpha]_{345}$ +458°, "min." $[\alpha]_{335}$ +30°, "max." $[\alpha]_{330}$ +291°, "min." $[\alpha]_{325}$ +149°, "max." $[\alpha]_{315}$ +597°, "min." $[\alpha]_{312.5}$ +568°, "inflect." $[\alpha]_{301}$ +1030°.

Carissone (XXVI)[29] (T. Reichstein): R.D. (Fig. 6), *c* 0.06 in dioxane: $[\alpha]_{700}$ +77°, $[\alpha]_{589}$ +137°, $[\alpha]_{275}$ +4560°, "max." $[\alpha]_{375-380}$ +415°, "min." $[\alpha]_{367.5}$ +315°, "max." $[\alpha]_{361}$ +346°, "min." $[\alpha]_{351}$ +102°, "max." $[\alpha]_{342.5}$ +375°, "min." $[\alpha]_{337.5}$ + 260°, "inflect." $[\alpha]_{326}$ +1040°.

(−)-1,14-Dimethyl-2-keto-Δ¹⁽¹¹⁾,⁶-decahydrophenanthrene (XXVII)[11b,12]: R.D. (Fig. 6, *c* 0.12 in dioxane: $[\alpha]_{700}$ −91°, $[\alpha]_{589}$ −135°, $[\alpha]_{285}$ −2620°, "min." $[\alpha]_{400-415}$ −250°, "shoulder" $[\alpha]_{360-366}$ +55°, "max." $[\alpha]_{351}$ +231°, "inflect." $[\alpha]_{340}$ −177°, "inflect." $[\alpha]_{325}$ −1220°, "min." $[\alpha]_{290}$ −2830°.

(−)-3-Ketoeusanton-4-enic Acid (XXVIII)[31,32] (Y. Abe): R.D. (Fig. 6), *c* 0.077 in dioxane: $[\alpha]_{700}$ −61°, $[\alpha]_{589}$ −105°, $[\alpha]_{275}$ −3750°, "min." $[\alpha]_{375-380}$ −371°, "shoulder" $[\alpha]_{360-370}$ −305°, "max." $[\alpha]_{352.5}$ −96°, "min." $[\alpha]_{345}$ −347°, "max." $[\alpha]_{338}$ −244°, "inflect." $[\alpha]_{327.5}$ −857°, "inflect." $[\alpha]_{315}$ −1620°.

(−)-Santonin (XXIX) (purified commercial material from Merck and Co.): R.D. (Fig. 7), *c* 0.10 in dioxane: $[\alpha]_{700}$ −85°, $[\alpha]_{589}$ −147°, $[\alpha]_{285}$ −2655°, "min." $[\alpha]_{382.5}$ −676°, "max." $[\alpha]_{375}$ −627°, "min." $[\alpha]_{365}$ −710°, "max." $[\alpha]_{357.5}$ −614°, "min." $[\alpha]_{349}$ −689°, "max." $[\alpha]_{345}$ −659°.

1,4-Cholestadien-3-one (XXX): R.D. (Fig. 7), *c* 0.104 in dioxane: $[\alpha]_{700}$ +25°, $[\alpha]_{589}$ +34°, $[\alpha]_{295}$ +140°, "max." $[\alpha]_{425-450}$ + 46°, "min." $[\alpha]_{380}$ −67°, "max." $[\alpha]_{374}$ −28°, "min." $[\alpha]_{365}$ −67°, "shoulder" $[\alpha]_{350-355}$ + 80°, "shoulder" $[\alpha]_{337.5-340}$ +229°, "max." $[\alpha]_{322.5}$ +310°.

"α"-Tetrahydrosantonin (XXXI)[35]: m.p. 157–159°; R.D. (Fig. 7), *c* 0.10 in methanol: $[\alpha]_{700}$ +22°, $[\alpha]_{589}$ +27°, $[\alpha]_{250}$ −105°, "max." $[\alpha]_{307.5}$ +747°, "min." $[\alpha]_{270}$ −555°.

"γ"-Tetrahydrosantonin (XXXII)[35]: m.p. 147–149°; R.D. (Fig. 7), *c* 0.10 in methanol: $[\alpha]_{700}$ +40°, $[\alpha]_{589}$ +52°, $[\alpha]_{250}$ +710°, "max." $[\alpha]_{305}$ +506°, "min." $[\alpha]_{276}$ +288°.

"β"-Tetrahydrosantonin (XXXIII)[35]: m.p. 101–102°; R.D. (Fig. 7), *c* 0.10 in methanol: $[\alpha]_{700}$ + 3°, $[\alpha]_{589}$ +7°, $[\alpha]_{257.5}$ +644°, "max." $[\alpha]_{400-425}$ +17°, "min." $[\alpha]_{305}$ −270°.

17aα-Methyl-D-homoandrostan-3β-ol-17-one (XXXIV)[36] (F. Ramirez): R.D. (Fig. 8), *c* 0.046 in dioxane: $[\alpha]_{700}$ −39°, $[\alpha]_{589}$ −39°, $[\alpha]_{275}$ +145°, "min." $[\alpha]_{320}$ −463°, "max." $[\alpha]_{312.5}$ −359°, "min." $[\alpha]_{310}$ −367°, "max." $[\alpha]_{281}$ +195°.

17aβ-Methyl-D-homoandrostan-3β-ol-17-one (XXXV)[36] (F. Ramirez): R. D. (Fig. 8), *c* 0.086 in dioxane: $[\alpha]_{700}$ −43°, $[\alpha]_{589}$ −52°, $[\alpha]_{270}$ +1021°, "min." $[\alpha]_{315}$ −1723°, "max." $[\alpha]_{309}$ −1392°, "min." $[\alpha]_{306}$ −1413°, "max." $[\alpha]_{275}$ +1308°.

Friedelin (XXXVI): R.D. (Fig. 8), *c* 0.22 in dioxane: $[\alpha]_{700}$ −7°, $[\alpha]_{589}$ −16°, $[\alpha]_{272.5}$ +1078°, "min." $[\alpha]_{315}$ −1331°, "inflect." $[\alpha]_{307.5}$ −1111°, "max." $[\alpha]_{275}$ +1178°.

(+)-β-Cyperone (XXXVII)[28] (F. J. McQuillin): R.D. (Fig. 9), *c* 0.115 in dioxane: $[\alpha]_{700}$ +293°, $[\alpha]_{589}$ +484°, $[\alpha]_{332.5}$ +152°, "inflect." $[\alpha]_{395}$ +4140°, "max." $[\alpha]_{384}$ +4820, "inflect." $[\alpha]_{372.5}$ +3920°, "min." $[\alpha]_{337.5}$ −933°.

(−)-1,14-Dimethyl-2-keto-Δ¹⁽¹¹⁾,⁶,⁹-octahydrophenanthrene (XXXVIII)[11b,12]: R.D. (Fig. 9), *c* 0.080 in dioxane: $[\alpha]_{700}$ −310°, $[\alpha]_{589}$ −502; $[\alpha]_{315}$ −1390°, "inflect." $[\alpha]_{400}$ −3000°, "min." $[\alpha]_{386}$ −3559, "inflect." $[\alpha]_{372.5}$ −3020°, "max." $[\alpha]_{336}$ −209°.

4,6-Cholestadien-3-one (XXXIX): R.D. (Fig. 9), *c* 0.10 in dioxane: $[\alpha]_{700}$ +2°, $[\alpha]_{589}$ +38°, $[\alpha]_{315}$ −3270°, "max." $[\alpha]_{407.5}$ +1151°, "min." $[\alpha]_{400}$ + 1100°, "max." $[\alpha]_{389}$ +1307°, "inflect." $[\alpha]_{372.5}$ +244°.

Norketone XLII derived from Phyllocladene (XLI)[62]: R.D. (Fig. 10), *c* 0.09 in dioxane: $[\alpha]_{700}$ +41°, $[\alpha]_{589}$ +65°, $[\alpha]_{275}$ −1468°, "max." $[\alpha]_{322.5}$ +2240°, "min." $[\alpha]_{315}$ +1426°, "max." $[\alpha]_{312.5}$ + 1443°, "min." $[\alpha]_{281}$ −1718°.

Epoxynorcafestanone (XLIII)[41]: R.D. (Fig. 10), *c* 0.102 in dioxane: $[\alpha]_{700}$ +2°, $[\alpha]_{589}$ +12°, $[\alpha]_{272.5}$ −1560°, "max." $[\alpha]_{324}$ +2000; "inflect." $[\alpha]_{315}$ +1015°, "min." $[\alpha]_{282.5}$ −2012°.

(62) Obtained by Dr. M. Cais by ozonization (*cf.* ref. 40) of phyllocladene, which was kindly supplied by Dr. W. I. Taylor of Ciba Pharmaceutical Products, Inc., Summit, N. J.

Ketone XLIV derived from cafestol[42]: R.D. (Fig. 10), *c* 0.077 in dioxane: $[\alpha]_{700}$ −65°, $[\alpha]_{589}$ −88°, $[\alpha]_{272.5}$ +412°, "min." $[\alpha]_{315}$ −1233°, "max." $[\alpha]_{277.5}$ +535°.

Alcohol XLV derived from cafestol[42]: R.D. (Fig. 10), *c* 0.094 in methanol: $[\alpha]_{700}$ −63°, $[\alpha]_{589}$ −72°, $[\alpha]_{250}$ −499°.

Steviol (XLVI)[44] (E. Mosettig): R.D. (Fig. 11), *c* 0.104 in methanol: $[\alpha]_{700}$ −69°, $[\alpha]_{589}$ −92°, $[\alpha]_{250}$ −724°.

Isosteviol (ketoisostevic acid) (XLVII)[44] (E. Mosettig): R.D. (Fig. 11), *c* 0.124 in methanol: $[\alpha]_{700}$ −52°, $[\alpha]_{589}$ −72°, $[\alpha]_{250}$ +512°, "min." $[\alpha]_{317.5}$ −1643°, "max." $[\alpha]_{280}$ +1295°.

Garryfoline (XLVIII)[45]: R.D. (Fig. 11), *c* 0.10 in methanol: $[\alpha]_{700}$ −28°, $[\alpha]_{589}$ −37°, "min." $[\alpha]_{400-450}$ −55°, $[\alpha]_{280}$ +265°.

Cuauchichicine (XLIX)[45]: R.D. (Fig. 11), *c* 0.10 in methanol: $[\alpha]_{700}$ −55°, $[\alpha]_{589}$ −57°, $[\alpha]_{285}$ −445°, "min." $[\alpha]_{324}$ −379°, "max." $[\alpha]_{302.5}$ +165°.

F-Dihydrogarryfoline (L)[45]: R.D. (Fig. 11), *c* 0.10 in methanol: $[\alpha]_{700}$ −58°, $[\alpha]_{589}$ −81°, "min." $[\alpha]_{275}$ −407°, $[\alpha]_{265}$ −362°.

F-Dihydrocuauchichicine (LI)[45]: R.D. (Fig. 11), *c* 0.10 in methanol: $[\alpha]_{700}$ −65°, $[\alpha]_{589}$ −96°, $[\alpha]_{262.5}$ −777°, "min." $[\alpha]_{322.5}$ −712°, "max." $[\alpha]_{299}$ −131°.

Yohimbone (LII) (B. Witkop): R.D. (Fig. 12), *c* 0.10 in dioxane: $[\alpha]_{700}$ −99°, $[\alpha]_{589}$ −130°, $[\alpha]_{307.5}$ −1910°, "min." $[\alpha]_{317.5}$ −2235°.

Yohimbane (LIII) (B. Witkop): R.D. (Fig. 12), *c* 0.10 in dioxane: $[\alpha]_{700}$ −74°, $[\alpha]_{589}$ −112°, $[\alpha]_{330}$ −310°, "min." $[\alpha]_{345-350}$ −344°.

(+)-*cis*-13-Methyl-3,4-dimethoxy-6-keto-5,6,7,8,9,10,13,-14-octahydrophenanthrene (LIV).[10] (O. Jeger): R.D. (Fig. 12), *c* 0.10 in methanol: $[\alpha]_{700}$ +1°, $[\alpha]_{589}$ −4°, $[\alpha]_{292.5}$ +160°, "max." $[\alpha]_{310}$ +1172°.

(+)-*cis*-13-Methyl-3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene (LV)[10] (O. Jeger): R.D. (Fig. 12), *c* 0.083 in methanol: $[\alpha]_{700}$ +11°, $[\alpha]_{589}$ +25°, $[\alpha]_{337.5}$ +65°.

Δ^5-Cholesten-4-one (LVI)[53]: R.D. (Fig. 13), *c* 0.072 in dioxane: $[\alpha]_{700}$ −31°, $[\alpha]_{589}$ −42°, $[\alpha]_{277.5}$ −1723°, "min." $[\alpha]_{425-475}$ −55°, "max." $[\alpha]_{360}$ +232°, "inflect." $[\alpha]_{300}$ −1509°.

Δ^4-Cholesten-6-one (LVII) (C. W. Shoppee)[63]: R.D. (Fig. 13), *c* 0.103 in dioxane: $[\alpha]_{700}$ +29°, $[\alpha]_{589}$ +40°, $[\alpha]_{275}$ +1685°, "max" $[\alpha]_{475-525}$ +45°, "min." $[\alpha]_{359}$ −435°, "max." $[\alpha]_{305}$ +1611°, "min." $[\alpha]_{302.5}$ +1591°, "max." $[\alpha]_{292.5}$ +1675°, "min." $[\alpha]_{285}$ +1570°.

Eremophilone (LIX).—The sample used for the rotatory dispersion work was freshly prepared from eremophilone semicarbazone[50] which is stable; R.D. (Fig. 13), *c* 0.093 in dioxane: $[\alpha]_{700}$ −124°, $[\alpha]_{589}$ −194°, $[\alpha]_{282.5}$ −425°, "min." $[\alpha]_{357}$ − 1258°, "max." $[\alpha]_{317.5}$ − 409°, "min." $[\alpha]_{315}$ −419°, "max." $[\alpha]_{305}$ −59°, "min." $[\alpha]_{297.5}$ −301°, "max." $[\alpha]_{295}$ −237°, "min." $[\alpha]_{285}$ −608°.

***cis*-Tetrahydroeremophilone (LX)**.—A solution of 600 mg. of freshly prepared eremophilone[60] in 40 cc. of methanol was hydrogenated with 200 mg. of 10% palladized charcoal at room temperature and atmospheric pressure. Hydrogen uptake, corresponding to two equivalents, stopped after one hour whereupon the catalyst was filtered, the solvent was removed and the product (560 mg.) was distilled at 10 mm. and a bath temperature of 160°, $\lambda_{max}^{microcap}$ 5.81 μ.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.61; H, 11.55; R.D. (Fig. 14), *c* 0.088 in methanol: $[\alpha]_{700}$ −32°, $[\alpha]_{589}$ −46°, $[\alpha]_{257.5}$ +2086°, "min." $[\alpha]_{310}$ −2170°, "max." $[\alpha]_{270}$ +2750°.

The 2,4-dinitrophenylhydrazone was prepared in *cold*[61] acetic acid solution and was recrystallized from methylene chloride–methanol as yellowish orange needles, m.p. 148–150°.

Anal. Calcd. for $C_{21}H_{30}N_4O_4$: C, 62.66; H, 7.51; N, 13.92. Found: C, 62.51; H, 7.56; N, 14.00.

***trans*-Tetrahydroeremophilone (LXIa)**.—The above *cis*-ketone LX (400 mg.) was isomerized to the known[49] *trans*-isomer by heating under reflux with 5 cc. of 2 *N* hydrochloric acid and 5 cc. of methanol for 30 minutes. The distilled sample (bath temperature of 160° and 10 mm.) exhibited $\lambda_{max.}^{microcap}$ 5.81 μ, the 8–9 μ region differing from that of LX. **The 2,4-dinitrophenylhydrazone** exhibited m.p. 179–180° in good agreement with the literature value[49] (m.p. 178–179°); R.D. (Fig. 14), *c* 0.12 in methanol: $[\alpha]_{700}$ +17°, $[\alpha]_{589}$ +27°, $[\alpha]_{267.5}$ +1222°, "max." $[\alpha]_{375-450}$ +44°, "min." $[\alpha]_{312.5}$ −403°, "max." $[\alpha]_{271}$ +1235°.

***trans*-Dihydroeremophilone (LXIb)**.[49]—A sample was prepared by reduction of eremophilone with sodium in alcohol to dihydroeremophilol followed by oxidation with chromium trioxide in acetic acid; R.D., *c* 0.0645 in methanol: $[\alpha]_{700}$ +25°, $[\alpha]_{589}$ +40°, $[\alpha]_{260}$ +1990°, "max." $[\alpha]_{390-425}$ +65°, "min." $[\alpha]_{313}$ −635°, "max." $[\alpha]_{267}$ +2050°.

***trans*-Desoxytetrahydroeremophilone (LXIIa)**.—Reduction was accomplished by heating 150 mg. of *trans*-tetrahydroeremophilone (LXIa) with 150 mg. of sodium and 0.15 cc. of anhydrous hydrazine in 5 cc. of absolute ethanol in a sealed tube at 210° overnight. The neutral product (130 mg.) was chromatographed on 5 g. of alumina whereupon 120 mg. of nearly odorless and colorless oil was eluted with petroleum ether. The analytical sample was distilled at 10 mm. and a bath temperature of 130° and did not exhibit any infrared carbonyl band. The substance did not give any color with tetranitromethane.

Anal. Calcd. for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 86.40; H, 13.58; R.D., *c* 0.149 in dioxane: $[\alpha]_{700}$ +34°, $[\alpha]_{589}$ +42°, $[\alpha]_{275}$ +202°.

***trans*-Desoxydihydroeremophilone (LXIIb)**.—*trans*-Dihydroeremophilone (LXIb) (130 mg.) was subjected to the Wolff–Kishner reduction as described above and yielded 98 mg. of hydrocarbon with a pleasant odor; yellowish-brown color with tetranitromethane and $\lambda_{max}^{microcap}$ 6.02 and 11.26 μ.

Anal. Calcd. for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.32; H, 12.68; R.D., *c* 0.10 in dioxane: $[\alpha]_{700}$ +15°, $[\alpha]_{589}$ +18°, "max." $[\alpha]_{325-375}$ +35°, $[\alpha]_{287.5}$ +24°.

Coprostan-4-one (LXIV).[54]—The catalytic hydrogenation of 350 mg. of Δ^5-cholesten-4-one (LVI)[53] (m.p. 110–112°) in 50 cc. of ether and 40 cc. of methanol using 200 mg. of 10% palladized charcoal catalyst was complete in 5 minutes whereupon the catalyst was filtered. Concentration of the filtrate to one-half its volume and cooling produced 150 mg. of coprostan-4-one with m.p. 103–110°, raised to 111–112° upon further recrystallization from methanol–ether. The infrared spectrum in carbon disulfide proved to be appreciably different from that of cholestan-4-one.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.78; H, 11.89; R.D. (Fig. 14), *c* 0.067 in methanol: $[\alpha]_{700}$ +20°, $[\alpha]_{589}$ +46°, $[\alpha]_{250}$ +430°, "max." $[\alpha]_{300}$ +318°, "min." $[\alpha]_{277.5}$ +240°.

From the mother liquors of the hydrogenation there was isolated 120 mg. of impure cholestan-4-one, m.p. 77–95°. The melting point was raised to 95–100° when this material was heated on the steam-bath for 10 minutes with 5 cc. of methanol and 0.2 cc. of concd. hydrochloric acid. The isomerization also could be carried out under basic conditions as demonstrated when 20 mg. of pure coprostan-4-one was warmed for 15 minutes with 5 cc. of 5% methanolic potassium hydroxide solution. Dilution with water, filtration and recrystallization from methylene chloride–methanol afforded pure cholestan-4-one, m.p. 99–100°; for R.D. see ref. 3.

ψ-Santonin (LXVII) (W. G. Dauben) R.D. (Fig. 15), *c* 0.096 in dioxane: $[\alpha]_{700}$ −106°, $[\alpha]_{589}$ −140°, $[\alpha]_{272.5}$ +503°, "min." $[\alpha]_{320}$ −1960°, "max." $[\alpha]_{317}$ −1940°, "min." $[\alpha]_{313}$ −1970°, "max." $[\alpha]_{276}$ +676°.

1-Keto-7-hydroxy-$\Delta^{5(10)}$-santenic acid (LXVIII) (W. G. Dauben): R.D. (Fig. 15), *c* 0.102 in dioxane: $[\alpha]_{700}$ +13°, $[\alpha]_{589}$ +14°, $[\alpha]_{272.5}$ +2210°, "min." $[\alpha]_{322.5}$ −1870°, "inflect." $[\alpha]_{315}$ −1570°, "max." $[\alpha]_{278}$ +2410.°

1-Keto-7-hydroxysantanic acid (LXIX) (W. G. Dauben): R.D. (Fig. 15), *c* 0.078 in dioxane: $[\alpha]_{700}$ +67°, $[\alpha]_{589}$ +98°, $[\alpha]_{272.5}$ +190°, "max." $[\alpha]_{309}$ +788°, "inflect." $[\alpha]_{297.5}$ +570°, "min." $[\alpha]_{277.5}$ +159°.

(−)-*trans*-1,1,3-Trimethyl-3-carboxycyclohexane-2-acetic acid (LXX)[58] (O. Jeger): R.D. (Fig. 12), *c*, 0.095 in methanol: $[\alpha]_{700}$ −10°, $[\alpha]_{589}$ −7°, $[\alpha]_{400}$ −16°, $[\alpha]_{300}$ −92°, $[\alpha]_{275}$ −136°, $[\alpha]_{250}$ −320°.

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(63) D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

London) for stimulating correspondence. Grateful thanks are due to the many investigators mentioned in this paper who have supplied us promptly and generously with various specimens required in this study.

DETROIT, MICHIGAN

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

Optical Rotatory Dispersion Studies. VIII.[1] α,β-Unsaturated Ketones and Solvent Effects[2]

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The rotatory dispersion curves of a variety of steroidal as well as of simpler alicyclic unsaturated ketones are reported and correlations of certain structural groupings with characteristic dispersion features are discussed. The rotatory dispersion method has been used to settle certain stereochemical ambiguities of 19-nor steroids, and attention is called to the remarkable rotatory dispersion changes—ascribable to conformational alterations—observed with certain Δ^4-3-ketosteroids. The fine structure of many of the dispersion curves is particularly well resolved in non-polar solvents and is almost completely obscured in methanol. It is proposed that dioxane be used as the solvent of choice for all rotatory dispersion work concerned with α,β-unsaturated ketones.

The striking correlations between shapes of rotatory dispersion curves and chemical structure—initially encountered with steroidal ketones[3]—have recently been shown[1] to be applicable also to simpler alicyclic ketones. This enormous extension of the "rotatory dispersion method" with its important bearing on assignment of absolute configuration[1,4] and detection of subtle conformational factors[1,5] has made it necessary to collect rotatory dispersion curves of as many reference compounds as possible. The dispersion curves of some unsaturated ketones—chiefly Δ^4-3-ketosteroids[3b]—have already been recorded in the preceding seven papers[1,3] of this series, but it is the purpose of the present article to discuss this particular subject more fully and to offer a large number of additional examples.

Solvent Effect.—The relationship between ultraviolet absorption and anomalous rotatory dispersion has already been discussed.[6] It was pointed out that the rotatory dispersion method will generally be of value only where the dispersion curve shows "maxima" and "minima,"[3a] and these in turn will be produced only by optically active chromophores which absorb in a suitable spectral range. This range should not be too far in the ultraviolet in order to preclude measurements because of experimental limitations nor should the absorption be so intense as to prevent measurements because of lack of light transmission. This explains why ketones and aldehydes are nearly ideally suited for our purposes since saturated carbonyl compounds show a definite but weak absorption in the 270–300 mμ region[7] which produces strong abnormal rotatory dispersion[1,3] amenable to precise experimental detection by means of a spectropolarimeter.[8] From a practical standpoint, we have found dioxane and methanol to be the most satisfactory solvents—methanol because of its great optical transparency and dioxane because of its great solvent power for the compounds under investigation. It has already been noted earlier[9] that the shapes of the dispersion curves of *saturated* carbonyl compounds are identical in those two solvents but that in dioxane, the entire curve is shifted to longer wave length by about 8 mμ, a correction factor which easily can be taken into consideration.

α,β-Unsaturated ketones exhibit maximal ultraviolet absorption in the 220–260 mμ region which is so intense as to prevent rotatory dispersion measurements beyond *ca.* 280 mμ with the equipment available at the present time. However, in addition these ketones also show a weak band[10] above 300 mμ, and it is this absorption which is probably responsible for the rotatory dispersion features associated[1,3] with this chromophore. Attention has been called to the fact[10] that this low-intensity long wave absorption maximum—usually ill defined and frequently only appearing as an inflection with ethanol as the solvent—is shifted to longer wave length with concomitant increased resolution when a hydrocarbon solvent is employed for the spectral measurements. Such an effect should also be noticeable in the rotatory dispersion curves of unsaturated ketones, and we have selected octane, dioxane and methanol as typical solvents with increasing polarity. Two examples—the bicyclic (−)-*trans*-3 - keto - 9 - methyl - $\Delta^{1,6}$ - hexahydronaphthalene

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

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

(3) (a) C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4350 (1955); (b) E. W. Foltz, A. E. Lippman and C. Djerassi, *ibid.*, **77**, 4359 (1955); (c) A. E. Lippman, E. W. Foltz and C. Djerassi, *ibid.*, **77**, 4364; (d) C. Djerassi and R. Ehrlich, *ibid.*, **78**, 440 (1956); (e) C. Djerassi, W. Closson and A. E. Lippman, *ibid.*, **78**, 3163 (1956); (f) C. Djerassi and W. Closson, *ibid.*, **78**, 3761 (1956).

(4) C. Djerassi and W. Klyne, *Chemistry & Industry*, 988 (1956).

(5) To be published.

(6) Reference 3a and leading review articles given therein.

(7) *Cf.* A. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold, Ltd., London, 1954, p. 48.

(8) H. Rudolph, *J. Optical Soc. Am.*, **45**, 50 (1955); E. Brand, E. Washburn, B. F. Erlanger, E. Ellenbogen, J. Daniel, F. Lippmann and M. Scheu, THIS JOURNAL, **76**, 5037 (1954).

(9) Reference 3f, especially footnote 11.

(10) *Cf.* R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 1651 (1955), and references cited therein.