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APPLICATION OF ANOMALOUS OPTICAL ROTATORY DISPERSION TO ORGANIC CHEMICAL PROBLEMS*

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ACCORDING to a system of nomenclature which has been introduced recently[1] and which has found general acceptance, an anomalous rotatory dispersion curve is one where a Cotton effect can be demonstrated experimentally. Curves, where this is not possible, are referred to as "plain", irrespective of whether they cross the zero rotation axis. Our nomenclature thus differs from that employed earlier by physical chemists[2] who used a mathematical criterion (Drude equation) and the reasons for this change have already been given elsewhere.[1]

Largely due to experimental difficulties, the overwhelming number of optical rotatory dispersion curves which have been recorded in the literature prior to 1955, have been of the plain type. While such curves—and the Drude equations derived from them—are more useful than the standard $[\alpha]_D$ values usually employed by organic chemists, such plain curves cannot possibly compare in scope with anomalous curves in terms of the information which can be extracted from them. This has been the main thesis of our work in the field of optical rotatory dispersion and the present lecture will be concerned with it.

With relatively few exceptions, most of the important work on optical rotatory dispersion of organic molecules prior to 1955 has been performed by physical chemists, whose motives and interests were usually different from those of organic and biological chemists. It is not surprising, therefore, that until recently, rotatory dispersion measurements, and the conclusions which might be derived from them, have not been employed to any extent for the solution of organic chemical problems. This is in marked contrast to the extensive use of monochromatic polarimetry (rotations measured at 589 mμ, the sodium D line), which has led to a number of generalizations.[3] It should be emphasized that the success of this approach is due to the fact that the sign and magnitude of the rotation at 589 mμ is usually a reflection of the same parameters of the corresponding rotatory dispersion curve. When this is not the case, then calculations of molecular rotation differences are invalid and this usually happens when the dispersion curve crosses the zero rotation axis. A typical example is given in Fig. 1, which contains the dispersion curves[4] of the three isomeric α-(iodophenoxy)-propionic acids (I, II, III). All three acids possess the same absolute configuration, and while all exhibit a plain positive dispersion curve, that of the

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* "Optical Rotatory Dispersion Studies XLVII." For paper XLVI see C. Djerassi, K. Undheim, R. C. Sheppard, W. G. Terry and B. Sjöberg, *Acta Chem. Scand.* **15**, In press (1961).

[1] C. Djerassi and W. Klyne, *Proc. Chem. Soc.* 55 (1957). For minor modifications and some additions see Chapter 2 in ref. 10.

[2] E.g., T. M. Lowry, *Trans. Faraday Soc.* **26**, 266 (1930).

[3] For review see W. Klyne in Chapter 3 of *Determination of Organic Structures by Physical Methods* (Edited by E. A. Braude and F. C. Nachod). Academic Press, New York (1955).

[4] B. Sjöberg, *Arkiv. Kemi* **15**, 451 (1960).

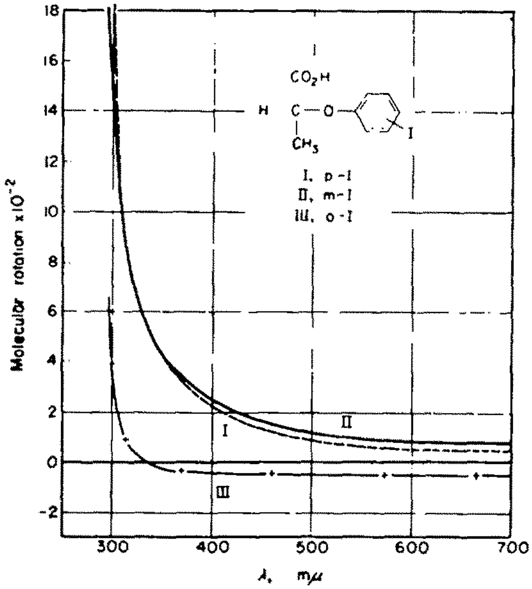
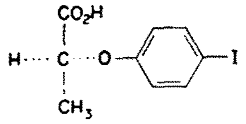
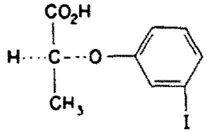
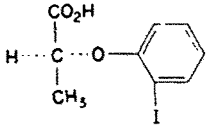


FIG. 1.

o-isomer (III) starts in the visible region on the negative rotation side. Therefore, rotation measurements conducted solely at the sodium D line lead to a negative value for the *o*-isomer (III), while the *p*- and *m*-isomers (I, II) exhibit positive rotations. This case represents only one of many which could be presented to indicate the advantage of rotatory dispersion measurements (irrespective of whether the curves are plain or anomalous) over monochromatic polarimetry.


I


II


III

We shall now turn to the actual subject matter of the lecture, namely anomalous rotatory dispersion curves and their use in organic chemistry. Prior to 1955, when our first paper[5] appeared, less than fifty rotatory dispersion curves had been recorded in the literature with an experimentally determined Cotton effect. In order to measure this dispersion feature, it is necessary to conduct rotation measurements through the region of absorption and from a practical standpoint, this requires a chromophore absorbing in an accessible region of the spectrum and with a low extinction. For our purpose—correlation of anomalous optical rotatory dispersion with structure and stereochemistry—the carbonyl chromophore appeared to be ideal since it exhibits selective ultraviolet absorption above 270 mμ with very low extinction. The earlier literature[6,7] contains about one dozen examples, largely from the terpene series, of

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[5] C. Djerassi, E. W. Foltz and A. E. Lippman, *J. Amer. Chem. Soc.* 77, 4354 (1955).

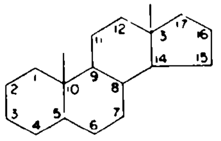
[6] The literature until 1934 is summarized by one of the pioneers in this field, T. M. Lowry, *Optical Rotatory Power*. Longmans, Green, London (1935).

[7] T. M. Lowry and R. E. Lishmund, *J. Chem. Soc.* 709 (1935); H. S. French and M. Naps, *J. Amer. Chem. Soc.* 58, 2303 (1936); S. Mitchell and K. Schwarzwald, *J. Chem. Soc.* 889 (1939).

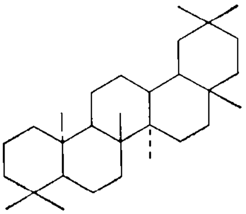
carbonyl compounds where a Cotton effect was measured experimentally. These investigations—notably the classic case of camphor[6] involving both rotatory dispersion and circular dichroism measurements by Kuhn and by Lowry—were prompted by theoretical considerations, and while they demonstrated clearly that the Cotton effect associated with a carbonyl group in an asymmetric environment can be measured experimentally, this information proved to be of no utility for the solution of organic chemical problems and no further studies appear to have been conducted after 1939.[7]

Indeed, what was necessary was to collect a large number of anomalous rotatory dispersion curves of closely related carbonyl-containing substances and to determine whether any correlation existed between the characteristic shape of a Cotton effect curve and some structural or stereochemical feature. We felt that if this could be demonstrated for carbonyl-containing organic substances, interest and research activity with other chromophores would follow automatically. Our work to date has been recorded in thirty-seven articles which have been published since 1955 and they are collected in the appendix to the proceedings of this conference. The most important results have already been reviewed[8,9] and early in 1960, a book has appeared[10] by the author which covers the entire subject as far as applications to organic chemistry are concerned. Therefore, only a few selected examples will be taken to show what information anomalous rotatory dispersion can offer in organic chemistry.

Our initial studies were conducted in the steroid series with carbonyl groups placed in every one of the possible positions of this nucleus (IV). It was possible to show[11] that with few exceptions, a keto group in a given location of the steroid nucleus exhibited a very characteristic dispersion picture which was not affected by the presence of "non-chromophoric" substituents. As a result, anomalous rotatory dispersion can be used as a unique tool to locate a carbonyl group (and hence an alcoholic function which can be oxidized to the ketone) in an unknown steroid. This is not possible by any other physical tool and it is not surprising, therefore, that the steroid field has been the first one in which rotatory dispersion has been accepted as practically a routine adjunct to research. The same statement should also apply to the triterpenoids (e.g. V), where similar structural conclusions could be reached.[12]



IV



V

In principle, a given Cotton effect curve can only be positive or negative, but there are also possible so many variations in shape and amplitude that the scope is enlarged

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[8] C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957).
[9] C. Djerassi, *Rec. Chem. Progr.* **20**, 101 (1959).
[10] C. Djerassi, *Optical Rotatory Dispersion. Applications to Organic Chemistry.* McGraw-Hill, New York (1960).
[11] Chapter 4 in ref. 10.
[12] Chapter 6 in ref. 10.

enormously and this has made possible the type of structural application indicated above. Clearly, these variations are due to the changes in asymmetric environment in which the carbonyl group finds itself as it is moved around the steroid nucleus. Such an environmental change can also be produced by stereochemical alterations in a given keto steroid. A typical example is shown in Fig. 2 with the rotatory dispersion curves of dihydrotestosterone (VI) and its 5β-isomer, VII. These two substances differ only in the nature of the A/B ring juncture, but this stereochemical alteration has profound consequences as far as the rotatory dispersion curves are concerned. These characteristic differences are not altered by the nature of the angular substituent and recent measurements in our Laboratory have shown that, for instance, the C-5 hydrogen atom can be substituted by a variety of other functional groups (VIII) without changing this typical rotatory dispersion pattern. Advantage has been taken of this observation in a number of instances in the recent literature (summarized in refs. 9 and 10) to determine the stereochemistry of the A/B ring juncture in the steroid series. Again, no other physical tool currently available will provide this answer.

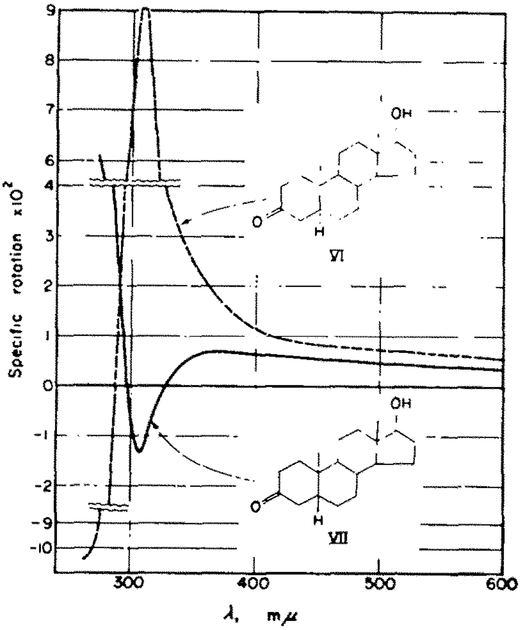
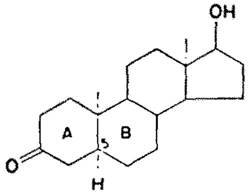
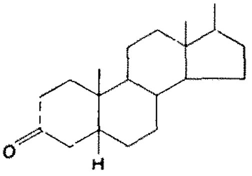


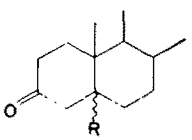
FIG. 2.



VI



VII



VIII

R = CH_3, CN, CO_2CH_3, OH, F, $CONH_2$

When such a change is produced in a keto steroid where the carbonyl group is adjacent to an invertible center, then the rotatory dispersion curve can be used not only for purposes of stereochemical differentiation, but also for kinetic studies. A number of such examples have been reported recently[13] and Fig. 3 offers one such illustration.

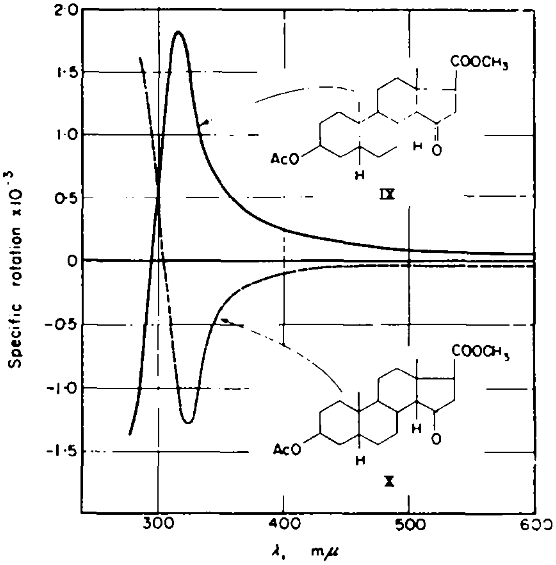
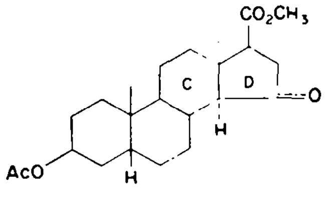
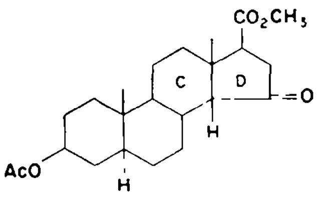


Fig. 3.

The rotatory dispersion curves of the isomeric 15-keto steroids IX and X are of mirror image type and are thus decisive, as far as assignment of configuration of the C/D ring juncture is concerned. Their specific rotations[14] differ by 80° at 589 mμ, while in the 320 mμ region this difference amounts to ca. 3000°. By taking advantage of this enormously increased rotation change in the ultraviolet (near the first extrema of the respective Cotton effects), the kinetics of the base-catalyzed equilibration of such isomers can be determined with 1·0 mg or less of material.



IX



X

The question then arose as to what portion of the molecule was really responsible for these very characteristic rotatory dispersion features. This could be attacked by "dissecting" the steroid molecule in terms of measuring the rotatory dispersion of tricyclic and bicyclic analogs and it was found[15] that qualitatively the dispersion picture is simulated by the bicyclic analog—provided the latter possessed the same

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[13] N. L. Allinger, R. B. Hermann and C. Djerassi, *J. Org. Chem.* **25**, 922 (1960).

[14] A. Lardon, H. P. Sigg and T. Reichstein, *Helv. Chim. Acta* **42**, 1457 (1959).

[15] Chapter 5 in ref. 10.

absolute configuration and conformation. This conclusion applies to saturated as well as α,β-unsaturated ketones and has far-reaching consequences as far as the determination of absolute configuration and conformation of organic molecules is concerned.

The subject of absolute configurational determination by this procedure has been covered in earlier reviews[9,16] and two recent examples will suffice. All that is involved is a rotatory dispersion examination of relevant chromophoric systems (one of them representing a reference compound of known absolute configuration) and the process can be illustrated by the recent assignment[17] of absolute configuration to the sesquiterpene petasin (XIV). The absolute configuration of the steroids has been settled by classical means[18] and testosterone (XI) can thus be employed as a reference standard. Alterations in the nature of the angular substituent attached to C-10 have no important effect[19] and 19-nortestosterone (XII), where the angular methyl group is replaced by hydrogen, exhibits substantially the same dispersion curve.[20] Indeed, this observation represents the most cogent evidence presently available for the stereochemistry at C-10 of 19-nor steroids.[21] The bicyclic octalol (XIII) also has the same absolute configuration as can be shown by the coincidence of its rotatory dispersion curve (Fig. 4) with that of testosterone (XI). Returning now to the actual problem at hand—

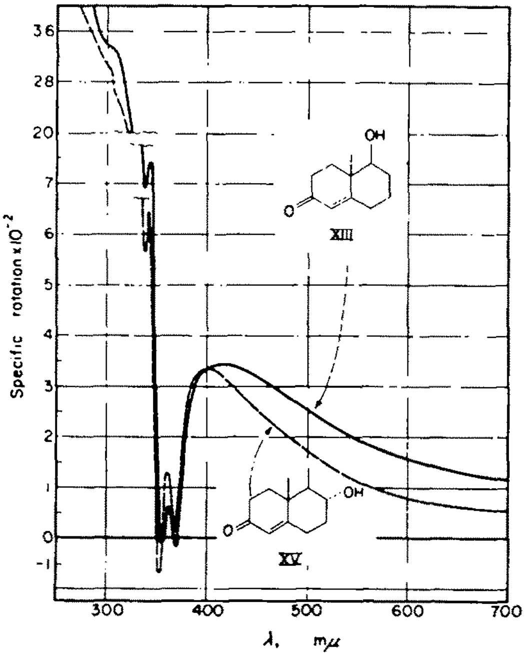

FIG. 4.

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[16] Chapter 10 in ref. 10.

[17] A. Aebi and C. Djerassi, *Helv. Chim. Acta* **42**, 1785 (1959).

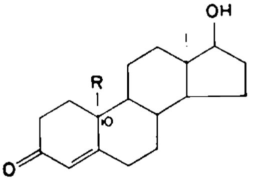
[18] L. F. Fieser and M. Fieser *Steroids* Chap. 10. Reinhold, New York (1959).

[19] The following substituents at C-10 in Δ^4-3-keto steroids have been examined in our laboratory: hydrogen, methyl, hydroxyl, hydroxymethyl, halogen, nitrile, carbalkoxy.

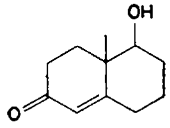
[20] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6377 (1956).

[21] See also C. Djerassi, M. Ehrenstein and G. W. Barber, *Liebigs Ann.* **612**, 93 (1958).

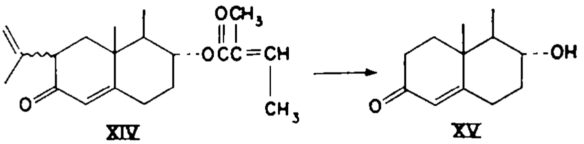
petasin (XIV) can be converted upon treatment with base into des-isopropylidenepetasol (XV). The latter represents a suitable substrate for rotatory dispersion examination and its dispersion curve (Fig. 4) is substantially identical with that of the octalol (XIII) or of testosterone (XI). This coincidental (rather than antipodal) relationship of the two dispersion curves shown in Fig. 4 settles the absolute configuration of petasin (XIV) insofar as its angular substituent is concerned and this rotatory dispersion conclusion[17] has now been confirmed by total synthesis.[22]



XI $R=CH_3$
XII $R=H$

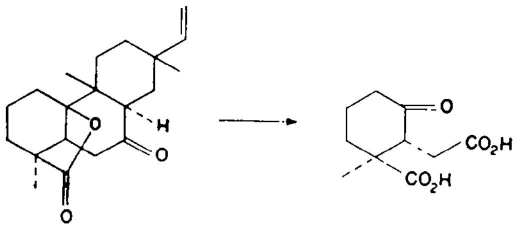


XIII

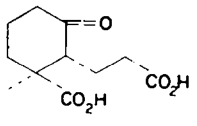


XIV XV

Such an approach has to be used with great caution when dealing with conformationally mobile molecules, such as monocyclic cyclohexanones, since one of the prerequisites of this method is conformational identity of the relevant cyclic systems. A successful application employing substituted cyclohexanones can be cited from the recent determination[23] of the absolute configuration of the mold metabolite rosenonolactone (XVI). This substance can be degraded to (—)-*trans*-2-methyl-2-carboxy-6-oxocyclohexylacetic acid (XVII), whose conformation is almost certainly that chair form in which both acid substituents assume an equatorial orientation. The same statement can also be made of (—)-*trans*-2-methyl-2-carboxy-6-oxocyclohexylpropionic acid (XVII), whose absolute configuration is known.[24] Since both dibasic acids XVII and XVIII exhibited negative Cotton effect curves of practically identical



XVI XVII



XVIII

amplitude, one can safely assign identical absolute configurations to them and this conclusion could be verified by further chemical interconversions.[23] Together with

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[22] D. Herbst and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 4337 (1960).

[23] W. B. Whalley, G. Green, D. Arigoni, J. J. Britt and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 5520 (1959).

[24] H. H. Inhoffen, S. Schütz, P. Rossberg, O. Berges, K. H. Nordsiek, H. Plenis and E. Höroldt. *Chem. Ber.* **91**, 2626 (1958).

earlier information on the relative stereochemistry of rosenonolactone, the determination of absolute configuration of the cyclohexanone derivative XVII also settles the absolute configuration of the mold metabolite.

The sensitivity of the anomalous rotatory dispersion curve to changes in the asymmetric environment of the optically active chromophore (in this instance the carbonyl group) makes it likely that rotatory dispersion should also be a useful tool for the detection of conformational alterations. This has been found to be the case in numerous instances[25] and a pertinent illustration can be presented from the *cis*-decalone series. Here again, rotatory dispersion has offered information which was not available from any other source.

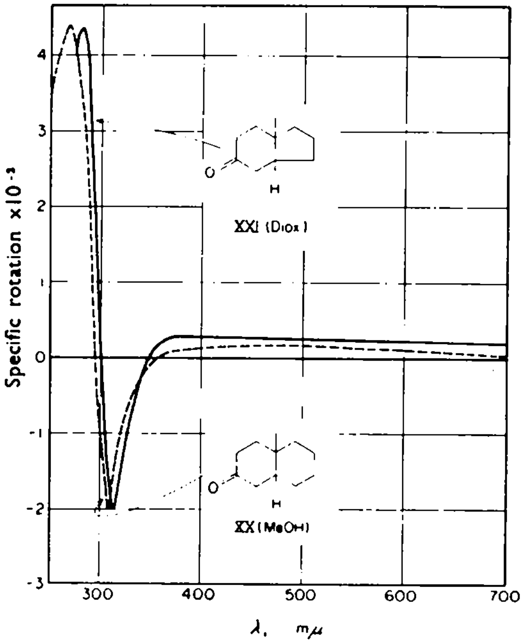

FIG. 5.

In contrast to *trans*-10-methyl-2-decalone (XIX), whose conformation can be expressed unambiguously in terms of the representation XIXa, *cis*-10-methyl-2-decalone (XX) can exist in two all-chair conformations. The "steroid-like" conformation XXa is obligatory in the steroid series, because of the additional B/C ring juncture, but among decalones, the "non-steroid" conformation XXb is equally plausible and in fact has been favored.[26] In order to attack this problem, optically active *cis*-10-methyl-2-decalone (XX) of known absolute configuration has been synthesized[27] and its rotatory dispersion curve determined. As shown in Fig. 5, this is so similar to that (VII in Fig. 2) of a 3-keto-5β-steroid (VII) that it was concluded[27] that *cis*-10-methyl-2-decalone (XX) exists predominantly in the "steroid-like" conformation XXa. The same situation also applies to *cis*-8-methylhydrindan-5-one

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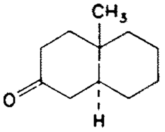
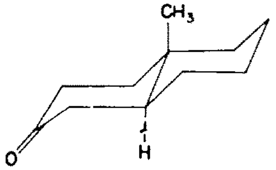
[25] E.g., C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *J. Amer. Chem. Soc.* **80**, 4001 (1958).
[26] W. Klyne, *Experientia* **12**, 119 (1956).
[27] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958).

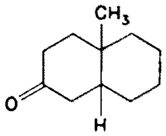
(XXI)[28] and as its rotatory dispersion curve (Fig. 5) is also of the steroid type, the identical conformational conclusion can also be applied to the hydrindanone XXI. Since the corresponding *trans*-8-methylhydrindan-5-one (XXII) had also been synthesized[29] and its rotatory dispersion curve (similar to VI and XIX) measured, there were available two reference curves which proved very useful for settling the outstanding question of the C-5 stereochemistry of B-nor-3-keto steroids (e.g. XXIII).[30]



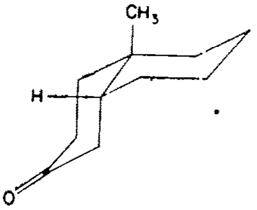
XIX



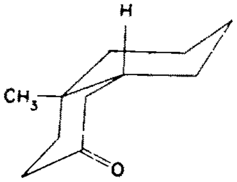
XIX a



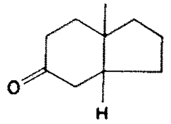
XX



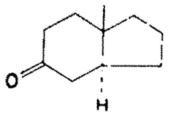
XX a



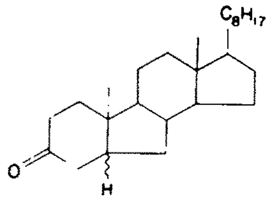
XX b



XXI



XXII



XXIII

A further and very important advance in conformational and absolute configurational assignments came from a systematic study of the rotatory dispersion behavior of steroidal α-halo ketones.[31] By analyzing the data from a large number of halogenated steroid ketones, where the orientation of the halogen atom had been established independently, an important generalization could be made[32] which is called the axial haloketone rule. This rule states[31,32] that while introduction of equatorial halogen does not change the sign of the Cotton effect of the parent ketone, axial chlorine, bromine or iodine can do so in a predictable manner. Briefly, if the observer looks down the O═C axis of a cyclohexanone as indicated in expression XXIV and the axial halogen atom is to the right (X = halogen), a positive Cotton effect will

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[28] H. Conroy and E. Cohen, *J. Org. Chem.* **23**, 616 (1958); W. Acklin and V. Prelog, *Helv. Chim. Acta* **42**, 1239 (1959).

[29] C. Djerassi, D. Marshall and T. Nakano, *J. Amer. Chem. Soc.* **80**, 4853 (1958).

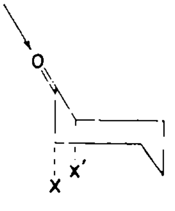
[30] T. Goto and L. F. Fieser, *J. Amer. Chem. Soc.* **81**, 2276 (1959); G. H. R. Summers, *J. Chem. Soc.* 2908 (1959); W. G. Dauben, G. A. Boswell and G. H. Berezin, *J. Amer. Chem. Soc.* **81**, 6082 (1959).

[31] Chapter 9 in ref. 10.

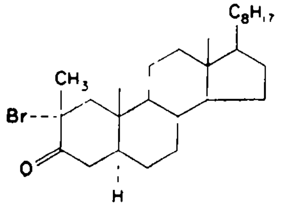
[32] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.* **79**, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *Ibid.* **80**, 1216 (1958).

be obtained, while a negative one will be exhibited if the halogen atom is to the left (X′=halogen). An obvious corollary of the axial haloketone rule is that if the absolute configuration of the α-haloketone is known, its conformation can be predicted from the observed Cotton effect, while conversely, an absolute configurational assignment can be made if the conformation is known. From the various applications[9,31] of the axial haloketone rule, two merit special mention.

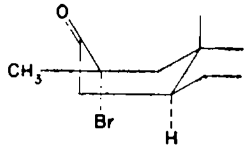
The first refers to an illustration from the steroid series; the negative Cotton effect of 2α-bromo-2β-methylcholestan-3-one (XXV) represented the first indication[33] that this type of steroid exists in the boat conformation (XXVa) and this conclusion could then be supported[33] by chemical and spectroscopic evidence.



XXIV



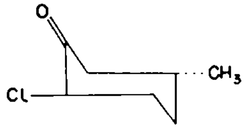
XXV



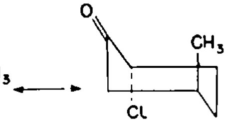
XXVa

A second example shows how the axial haloketone rule could be used to demonstrate[34] conformational mobility in *trans*-2-chloro-5-methylcyclohexanone. The rule predicts a positive Cotton effect for conformation XXVI (since the chlorine-free parent ketone shows a positive Cotton effect) and a negative one for conformation XXVII. As demonstrated in Fig. 6, the substance gives a negative Cotton effect in octane, while this is altered to a positive one in methanol. This is in accord with the generalization[35] that an increased proportion of the equatorial α-halo ketone (XXVI) can be expected in a polar medium (e.g. methanol) at the expense of the axial isomer (XXVII) which is favored in a non-polar solvent (e.g. octane). Full confirmation of these views could be presented when it was found[36] that the rotatory dispersion curve of *trans*-2-bromo-5-t-butylcyclohexanone (XXVIII) remained completely unaltered in octane or methanol—the positive Cotton effect demonstrating that the substance is "fixed" in the conformation XXVIII, by the anchoring effect of the bulky t-butyl group which requires an equatorial orientation.

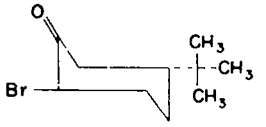
The axial α-haloketone rule appears also to be applicable[37] to certain α-bromocyclopentanones, which suggests that rotatory dispersion may offer some useful



XXVI



XXVII



XXVIII

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[33] C. Djerassi, N. Finch and R. Mauli, *J. Amer. Chem. Soc.* **81**, 4997 (1959).

[34] C. Djerassi and L. E. Geller, *Tetrahedron* **3**, 319 (1958); C. Djerassi, L. E. Geller and E. J. Eisenbraun, *J. Org. Chem.* **25**, 1 (1960).

[35] J. Allinger and N. L. Allinger, *Tetrahedron* **2**, 64 (1958).

[36] C. Djerassi, E. J. Warawa, R. E. Wolff and E. J. Eisenbraun, *J. Org. Chem.* **25**, 917 (1960).

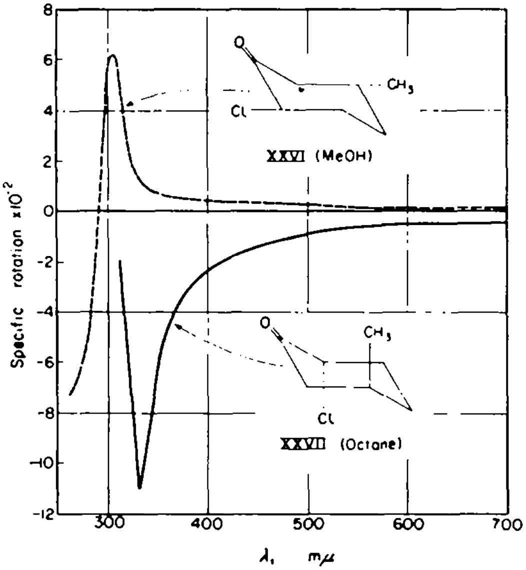

FIG. 6.

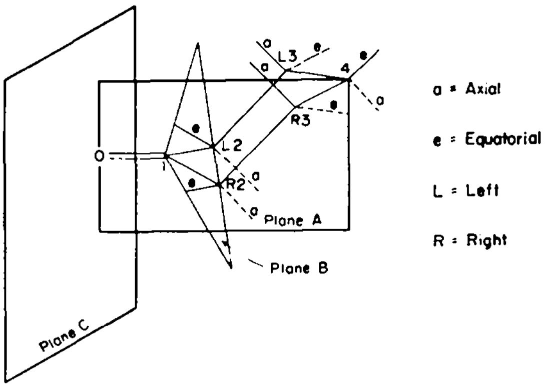

FIG. 7.

contribution to the as yet open problem of the conformation of cyclopentanone.

Recent theoretical studies by Moffitt and Moscowitz[38] on the ultraviolet light absorption of the carbonyl chromophore in an asymmetric environment has led to a generalization, called the octant rule[39] and its applicability to organic chemical problems has already been discussed.[40] The theoretical arguments will be discussed by Dr. Moscowitz[38] and for our purposes, it should suffice that we are dividing the cyclohexanone model as shown in Fig. 7 by three planes corresponding to the nodal and symmetry planes of the 290 mμ transition of the carbonyl chromophore. These three planes create eight octants and the presence of substituents in each octant is given a qualitative rotational contribution. Substituents in the planes (substituents at C-4

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[37] J. Fishman and C. Djerassi, *Experientia* 16, 138 (1960).

[38] To be discussed by Dr. Albert Moscowitz in the succeeding lecture. See also chapter 12 (by A. Moscowitz) in ref. 10.

[39] W. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne and C. Djerassi, in preparation.

[40] Chapter 13 in ref. 10

as well as equatorial groups attached to carbon atoms L2 and R2 in Fig. 7) are assumed to make no important contribution, while the axial substituents adjacent to the carbonyl group (attached to L2 and R2) behave exactly as expressed above in the axial haloketone rule. Therefore, so far the axial haloketone and octant rules are identical except that the former was limited to halogen atoms while the latter attributes such rotational effects to other substituents as well (e.g. alkyl groups). A further consequence of the octant rule is that it also takes into consideration substituents at the two β-carbon atoms (L3 and R3): the axial and equatorial substituents at carbon atom R3 are assumed to make a negative rotatory contribution while a positive one is attributed to the axial and equatorial groups attached to L3.

In certain cyclohexanones, substituents may also be present to the left of plane C (Fig. 7) in one of the four near octants, and groups in these near octants are assumed to make a rotational contribution opposite in sign to that of a substituent in the corresponding far octant. In terms of application, the octant rule covers the same area as the axial haloketone rule except that its scope is much broader since it is not limited to halogen substituents. When an axial chlorine, bromine or iodine atom is present in the α-position, then for qualitative purposes alkyl substituents at other carbon atoms in the cyclohexanone can usually be ignored because of the halogen's much more powerful rotatory contribution associated with its much higher atomic refractivity,[41] and the simpler axial haloketone rule may be employed.

The full effectiveness of the octant rule will only become apparent when quantitative parameters may be assigned to different types of substituents at the various

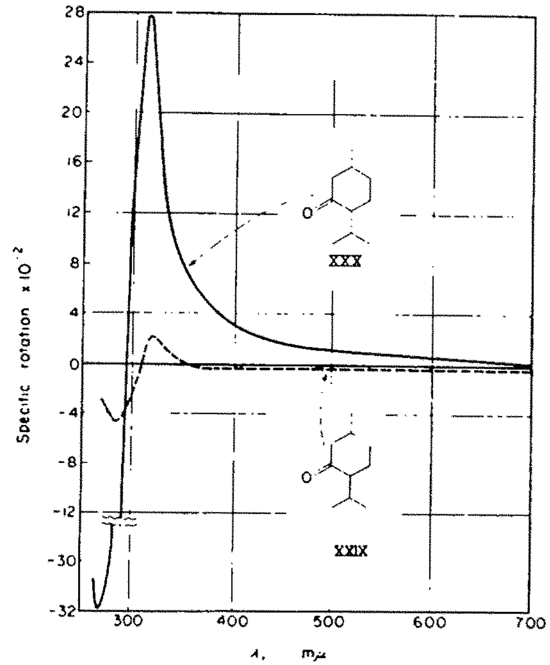

FIG. 8.

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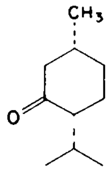
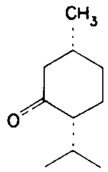
[41] See for instance J. H. Brewster, *J. Amer. Chem. Soc.* **81**, 5475 (1959), Table I.

carbon atoms of such cyclohexanones. Many of the Cotton effect curves measured in our laboratory are now being analyzed in terms of reduced rotational strength[38] by a procedure proposed by Dr. Moscowitz and this will be covered briefly in his lecture. (At the present qualitative stage, the octant rule has served to confirm conformational conclusions reached earlier[27] by direct visual comparisons of rotatory dispersion curves e.g. conformation XXa rather than XXb for *cis*-10-methyl-2-decalone (XX)), to establish certain absolute configurations[40] and most importantly, to pose certain problems in conformational analysis.

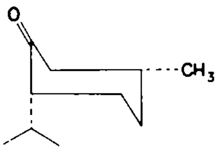
For instance, inversion of the isopropyl group of (−)-menthone (XXIX) leads to (+)-isomenthone (XXX). Of the two possible chair conformations for XXX, the octant rule would predict a strong positive Cotton effect for XXXa and a negative one for XXXb and *a priori*, the latter might be expected to predominate. However, the strong positive Cotton effect (Fig. 8) of (+)-isomenthone (XXX) suggests that conformation XXXa is the preferred one and this conclusion raises some interesting questions with respect to the "2-alkyl ketone effect".[26] Extensive work on the synthesis and rotatory dispersion of such alkylated cyclohexanones is now in progress in our laboratory[42] and the predominance of a given conformational isomer can in many instances be predicted by the octant rule.



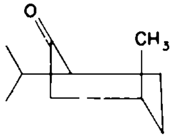
XXIX



XXX



XXX a



XXX b

A final rotatory dispersion approach, which is of some significance[43] in conformational analytical work, concerns the detection and extent of ketal formation. Since ketals would not be expected to show any Cotton effect in the 300 mμ region because of lack of absorption, the extent to which the amplitude of the Cotton effect associated with a given carbonyl group is diminished under ketal-forming conditions, would represent a quantitative indication of such a derivative. In fact, this can be accomplished[44] very readily by measuring the rotatory dispersion curve of a ketone in methanol followed by the addition of hydrochloric acid and repetition of the dispersion measurement. Since mineral acid promotes ketal formation, the reduction in the amplitude of the Cotton effect affords a direct measure of the extent of ketal production and since this is very sensitive to steric factors, there is available still

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[42] Unpublished work with J. Osiecki and E. J. Eisenbraun.

[43] Chapter 11 in ref. 10.

[44] C. Djerassi, L. A. Mitscher and B. J. Mitscher, *J. Amer. Chem. Soc.* **81**, 947 (1959).

another tool for determining such steric interactions on a microscale. The applications of this approach to structural and stereochemical problems in organic chemistry have already been reviewed recently,[9,43] and it will only be necessary to state at this time that ketal formation is inhibited by the introduction of alkyl substituents adjacent to the carbonyl group as well as by the generation of new 1,3-diaxial interactions. The operation of these effects can be demonstrated with *trans*-1,9-dimethyldecaline-2,6-dione (XXXI), which has recently been synthesized.[22] The isolated 6-keto group exhibits a positive Cotton effect (similar to XIX), while the 2-keto function shows a very strong negative Cotton effect. The latter is more powerful and as a consequence the 2,6-diketone XXXI possesses a negative Cotton effect curve (Fig. 9). In methanol solution in the presence of hydrochloric acid, the ketone at C-6 is largely converted into its ketal, because of the unhindered nature of the carbonyl group and the absence of any serious steric hindrance in the ketal. On the other hand, the 2-keto group does not react since it is flanked by a methyl group, which greatly reduces ketal formation and even more importantly, it has an axial methyl group two carbon atoms removed. Consequently, in the ketal, there would be set up a new 1,3-diaxial interaction and both these factors eliminate any possibility

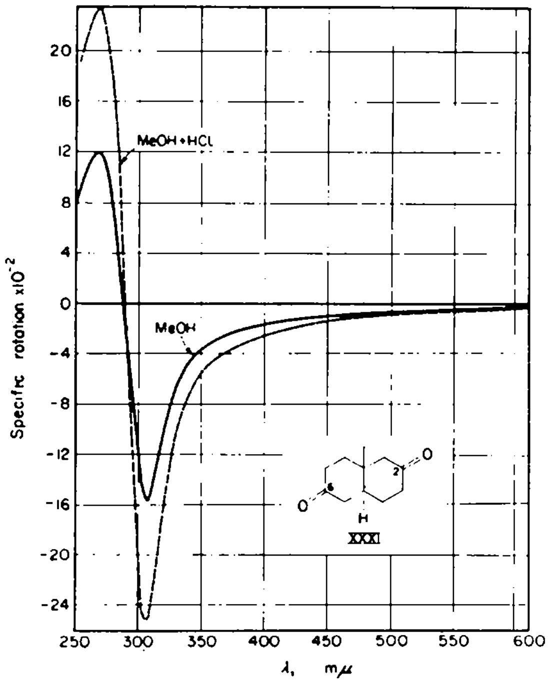
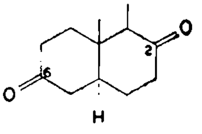


FIG. 9.

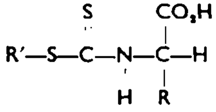


XXXI

of ketal production. As a result, the positive contribution of the 6-keto function is removed in the presence of hydrochloric acid in the form of its "transparent" ketal and the Cotton effect (Fig. 9) is now much more negative since it reflects only the strong negative contribution of the carbonyl group at C-2.

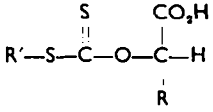
The above discussion of the various ramifications and uses to which the anomalous rotatory behavior of only one chromophore—the carbonyl chromophore—can be put serves to show the enormous scope associated with anomalous rotatory dispersion measurements as compared to plain dispersion curves, let alone monochromatic polarimetry. These results have already led to a wide acceptance of rotatory dispersion as a tool in organic chemistry and they have stimulated the examination of other chromophores in a similar manner. Indeed, it is this area which now forms the bulk of current investigations under way in our laboratory and preliminary results with several chromophores (e.g. thiones, nitroalkanes, disulfides, etc.) have already been reported.[45]

At this time, mention will be made of only one such series, namely the dithiocarbamates, which appear to be of particular utility in the α-amino acid and peptide fields.[46] Briefly, we found that dithiocarbamates of type XXXII show very strong Cotton effects in the 350–400 mμ region and that the sign of the Cotton effect is directly related to the configuration of the asymmetric center. Thus all such derivatives of L-α-amino acids will exhibit positive Cotton effect curves while negative ones will be shown by members of the D-series. This offers an extremely simple device for determining the absolute configuration of such a center and this appears to be also applicable to terminal amino acids in peptides, irrespective of the configuration of the asymmetric center to which the amide nitrogen is linked. Thus, N-dithiocarbomethoxy L-alanyl-L-alanine and N-dithiocarbomethoxy L-alanyl-D-alanine give positive Cotton effect curves of nearly identical amplitude. A similar behavior was noted[46] with xanthates of α-hydroxy acids (XXXIII), membership in the L-series carrying with it a positive Cotton effect. This affords a very simple alternative to the frequently quite vexing problem[47] of assigning absolute configurations to α-hydroxy acids—the sign of rotation at the sodium D line offering only little information (e.g. (+)-lactic acid and (−)-malic acid, both belonging to the L-series).



$$R'{-}S{-}\overset{\displaystyle S}{\overset{\|}{C}}{-}\underset{\displaystyle H}{\underset{|}{N}}{-}\overset{\displaystyle CO_2H}{\overset{|}{\underset{\underset{\displaystyle R}{|}}{C}}}{-}H$$

XXXII



$$R'{-}S{-}\overset{\displaystyle S}{\overset{\|}{C}}{-}O{-}\overset{\displaystyle CO_2H}{\overset{|}{\underset{\underset{\displaystyle R}{|}}{C}}}{-}H$$

XXXIII

These last examples demonstrate that the choice of a proper chromophore can convert an optically active substance possessing a plain dispersion curve into a derivative with an anomalous one with all of its inherent advantages. Work currently under way in our laboratory[48] has shown that even the unpromising mono-olefins (which absorb in a region which is currently quite inaccessible as far as rotatory dispersion measurements are concerned) can be converted into complexes with Cotton effect curves above 300 mμ.

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[45] Chapter 14 in ref. 10.

[46] B. Sjöberg, A. Fredga and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 5002 (1959).

[47] See for instance the summary by K. Mislow, *J. Amer. Chem. Soc.* 73, 3954 (1951) concerning the absolute configuration of (+)-mandelic acid.

[48] E. Bunnenberg and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 5953 (1960)

It is my feeling that a great deal of very fruitful work still remains to be done in the area of anomalous dispersion curves and that as additional chromophores are investigated, the applications of rotatory dispersion to organic chemistry will multiply manifold. In this connection, it should be emphasized that improvements in instrumentation should not be neglected. As spectropolarimeters are developed with greater penetration into the ultraviolet, more and more plain dispersion curves will become anomalous and to that extent will increase the scope of this tool. Finally, it would be highly desirable if rotatory dispersion studies would be supplemented or even substituted by direct determinations of circular dichroism. A commercially available instrument permitting rapid measurement of circular dichroism would represent a great advance in this field.

Acknowledgment—My deep gratitude is due to those students of mine who have collaborated with me in developing rotatory dispersion measurements as a tool for the solution of organic problems. Their names are listed in the bibliography in the appendix, which contains references to the thirty-seven papers which have so far appeared from our laboratory in the rotatory dispersion field.

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