

# APPLICATION OF OPTICAL ROTATORY DISPERSION STUDIES TO PROBLEMS IN NATURAL PRODUCTS CHEMISTRY. LV\*

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Modern natural products chemistry—in terms of isolation, structure elucidation, determination of relative and absolute configuration, and finally chemical or biological synthesis—covers more facets of organic chemistry than any other single area of this science. The remarkable progress which has been achieved in this field during the past twenty years can be ascribed, to a considerable extent, to the eagerness with which the natural products chemist has been willing to employ techniques which were either developed for his specific purpose or, more frequently, discovered in another connection but clearly helpful to his own needs. For instance, at the isolation stage, one can hardly conceive of a natural products laboratory that does not employ elution, partition, paper or gas-phase chromatography. At the next step, structure elucidation, the organic chemist dealing with natural products has always been very receptive to the use of physical methods which would offer him, rapidly, preliminary information to delineate the more profitable areas of chemical attack. These physical methods were invariably discovered by physicists or physical chemists, but their extensive application to organic chemistry was usually accomplished by a semi-empirical approach in which a great number of organic compounds were examined, and then the chemical structure and the particular physical property under discussion were correlated. Chronologically, ultra-violet spectroscopy was followed by infra-red absorption measurements, then nuclear magnetic resonance studies and, about the same time, by the more extensive use of mass spectrometry.

In each case, the organic chemist, and especially the natural products investigator, accepted the particular physical method as soon as instrumentation became sufficiently advanced, so that these measurements could be conducted easily in or near his own laboratory. Furthermore, it should be noted that all of the above-mentioned physical measurements have invariably added information which was not available from the others, so that they have always tended to complement one another. We have, therefore, reached the point where most new natural products, after isolation, purification and elementary analysis, are subjected to a gamut of physical measurements before serious degradative efforts are initiated. Even during the

\* For paper LIV, see C. Djerassi, *Endeavour*, **20**, 138 (1961).

degradative phase, which to many natural products chemists is intellectually the most stimulating and satisfying one, physical measurements of the type mentioned above play a crucial rôle.

All of these introductory statements apply to one of the newest physical methods introduced into organic chemistry, and especially into the chemistry of natural products, namely optical rotatory dispersion. In principle, it was known since the early part of the last century, yet its actual application by the organic chemist did not really commence until the nineteen-fifties, when the first readily operable (at least by the standards of the organic chemist!) spectropolarimeter became available. Once the utility of optical rotatory dispersion was demonstrated to the organic chemist, its use spread rapidly, and, barely five years after our first publications<sup>1</sup>, this tool has become a routine adjunct to many aspects of natural products chemistry. Again, one of the principal reasons for its rapid acceptance was that optical rotatory dispersion offers information which is usually not available from other physical methods. Rotatory dispersion suffers from one limitation, which does not apply to ultra-violet and infra-red spectroscopy or nuclear magnetic resonance measurements, namely, the requirement that the substance be optically active. This is indeed a limitation in the broad area of organic chemistry, but it is practically negligible among natural products, since the vast majority of them is optically active. It is not surprising, therefore, that the major impetus to the modern development of optical rotatory dispersion came from a natural products laboratory.

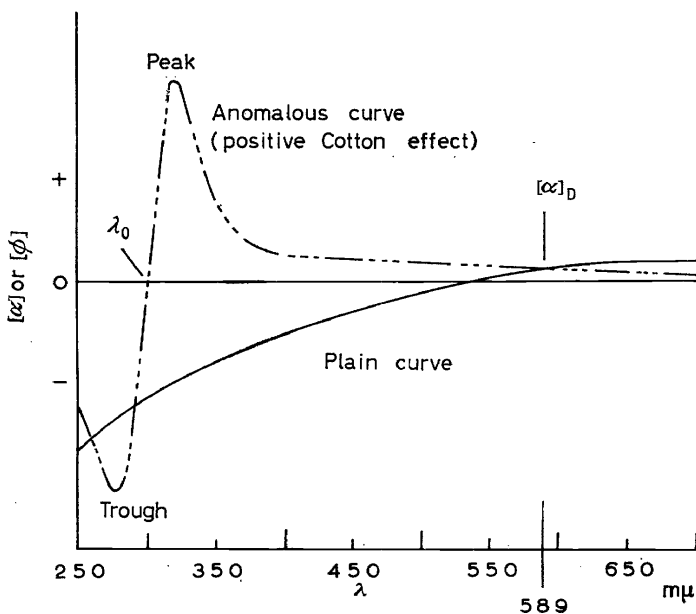
As mentioned earlier, the phenomenon of optical rotatory dispersion—the variation of optical rotation with wavelength—has been known for a long time and studied extensively by theoretical and physical chemists. These classical studies have already been covered by Lowry<sup>2</sup> and subsequently by Levene and Rothen<sup>3</sup> and by Kuhn<sup>4</sup>; but they have hardly made an impact upon organic chemists, as witnessed by the fact that essentially no significant\* rotatory dispersion measurements have been recorded in the literature between the nineteen-thirties and 1955. The recent and almost explosive developments in the field coincided with the appearance of the commercially available Rudolph spectropolarimeter<sup>5</sup>, and they have been discussed in detail by the present author in a book<sup>6</sup> and also in a number of review articles<sup>7, 8</sup>. Except for a very short introductory section, recapitulating some principles of nomenclature and presentation of data<sup>9</sup>, the remainder of this lecture will be concerned with direct applications to problems in the natural products field. During the past five years, optical rotatory dispersion has also played an important rôle in work on polypeptides and proteins<sup>10, 11</sup>, but this special area will not be included as my research group has not contributed to it.

In principle, we can distinguish between two types of optical rotatory dispersion curves, examples of which are illustrated in *Figure 1*. A *plain curve* is one which does not exhibit a "maximum" (peak) or "minimum"

\* By "significant" I am referring to dispersion measurements proceeding through the region of absorption of the particular chromophore under examination, rather than to a few rotation measurements carried out at several wavelengths outside the range of maximal absorption. Clearly, the latter will never result in the experimental determination of the Cotton effect, which forms the basis of most of the modern applications of rotatory dispersion in organic chemistry.

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(trough), and is typical of substances which do not possess an optically active chromophore in the measured spectral range. Typical compounds exhibiting such curves are alcohols, acids and hydrocarbons, and the term "plain" is employed irrespective of whether the curve crosses the zero rotation axis (see *Figure 1* for plain negative curve starting on the positive side in the visible), or whether it always possesses the same sign. In contrast to the nomenclature employed by the earlier physical chemists<sup>2</sup>, our term "plain" is not related to a single-term Drude equation. In fact, as discussed elsewhere<sup>6</sup> in detail, Drude equations are of no particular use for the purposes under discussion. While plain curves are distinctly more useful for configurational assignments<sup>12, 13</sup> than monochromatic rotation measurements (usually conducted at the sodium D line), the really important applications of rotatory dispersion measurements lie in the area of anomalous curves.



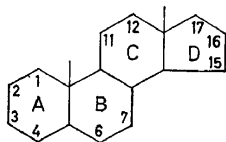
*Figure 1.* Plain and anomalous (showing positive Cotton effect) optical rotatory dispersion curves

*Anomalous* curves possess extrema such as peaks and troughs, and a typical example is shown in *Figure 1*. This represents a *single, positive Cotton effect curve*, such as would be exhibited by an optically active substance containing a chromophore absorbing around 300 mμ. It will be noted that the mean of the wavelengths at which the peak and trough occur corresponds approximately to the position ( $\lambda_0$ ) of the ultra-violet absorption maximum of this particular substance, and the chromophore, therefore, is considered to be "optically active". The theoretical basis for such Cotton effect curves is considered in detail elsewhere<sup>6</sup>, but it is obvious that, in order to measure such a curve experimentally and to cover the most interesting spectral range (below 350 mμ in *Figure 1*), it must be necessary to determine the rotation through the region of maximal absorption (*ca.* 300 mμ). This is possible

only with weakly absorbing chromophores, and the carbonyl group has proved to be ideal for such purposes. It absorbs in a region of the spectrum (280–330  $m\mu$ ) which is readily accessible with the presently available spectropolarimeters, and it possesses a sufficiently low extinction coefficient for rotation measurements to be conducted through its ultra-violet absorption maximum. The direct relationship between the ultra-violet absorption spectrum and the rotatory dispersion extrema explains why we prefer the terms “peak” and “trough” rather than “maximum” and “minimum”, which are employed in ultra-violet spectroscopy. A rotatory dispersion curve with several extrema (*e.g.* Figures 9 and 10) is called a *multiple Cotton effect curve*. The distance between the peak and trough is referred to as the *amplitude*. As will be shown, the sign (*positive* Cotton effect referring to a curve where the peak occurs at higher wavelength, *negative* Cotton effect to one where the trough appears first in going to lower wavelength), amplitude and shape of the anomalous rotatory dispersion curve can offer much scope for purposes of “fingerprinting”.

Most of the recent work<sup>6</sup> on rotatory dispersion in organic chemistry has been conducted with carbonyl-containing substances, because of the favourable properties of this chromophore and its extremely wide occurrence, notably among natural products. Other chromophores, however, are equally useful, and some of these will be discussed towards the end of the present article. The most important applications of optical rotatory dispersion measurements lie in the areas of relative and absolute configurational assignments (where other physical measurements are of little or no value) and for the solution of conformational problems. In addition, rotatory dispersion can also be employed for structural purposes—such as the location of a carbonyl chromophore in a polycyclic system—and examples of these applications to natural product chemistry will now be presented.

Possibly the most important single reason why structural and stereochemical correlations among ketones by means of rotatory dispersion developed so rapidly was our original choice<sup>1</sup> of steroid ketones as substrates. By taking the steroid molecule (I) and examining the various possible monoketones at positions 1, 2, 3, 4, 6, 7, 11, 12, 15, 16 and 17, it was found<sup>6, 14</sup> that, in many instances, very characteristic rotatory dispersion curves were



(I)

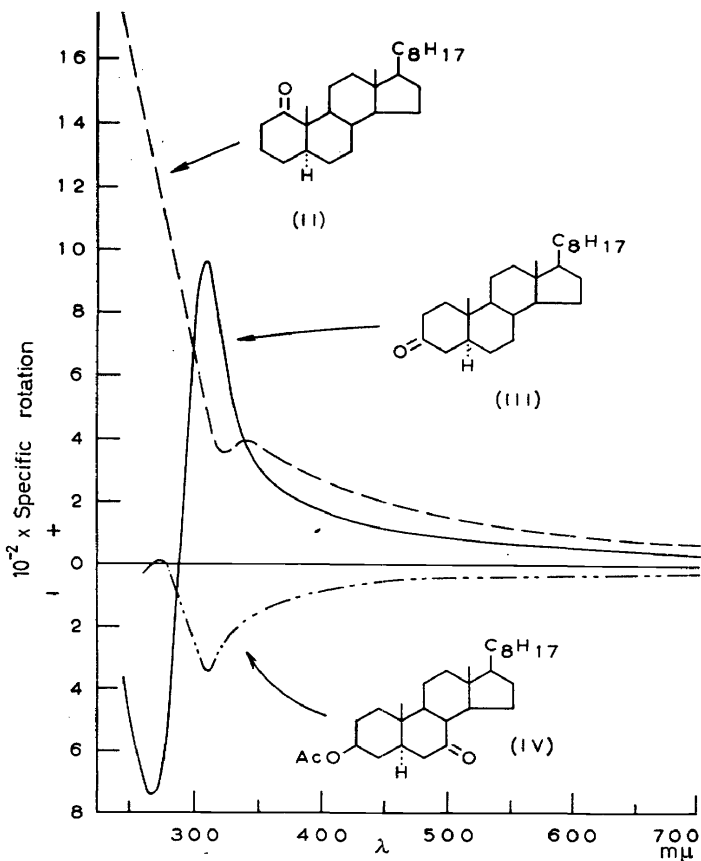
obtained, and that these were not affected by the addition of other, “non-chromophoric” substituents (*e.g.* esters, alcohols, lactones, *etc.*), provided these substituents did not affect the conformation of the parent molecule. We shall return later on to the importance of conformational changes. For instance, in Figure 2 there are reproduced the rotatory dispersion curves of the 1- (II), 3- (III) and 7- (IV) ketones of the cholestane series, and their respective shapes are so different that they can be used very readily for

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purposes of differentiation. No other physical method presently available can accomplish this.

As a second example, we can consider the three possible points of substitution in ring D of the steroids. Infra-red spectroscopy will enable us to decide immediately whether the carbonyl group forms part of a six-membered (rings A, B, C in (I)) or five-membered (ring D in (I)) ring, but it will not offer definite information about the precise location in that ring. As shown in *Figure 3*, the rotatory dispersion curves of steroidal 15- (V), 16- (VI) and 17- (VII) ketones are again distinct, the very strong negative Cotton effect of 16-keto-steroids being particularly noteworthy.

At this stage it is appropriate to emphasize a point which applies in general to rotatory dispersion as contrasted to monochromatic rotation measurement at the sodium D line (589  $m\mu$ ). As can be seen in *Figure 3*, the specific rotations of the three ketones (V), (VI) and (VII) at 589  $m\mu$  vary by a relatively small factor as compared with the region of their extrema (*ca.* 320  $m\mu$ ), where differences of several thousand degrees (in



*Figure 2.* Optical rotatory dispersion curves of 1-, 3- and 7-ketones of the cholestane series

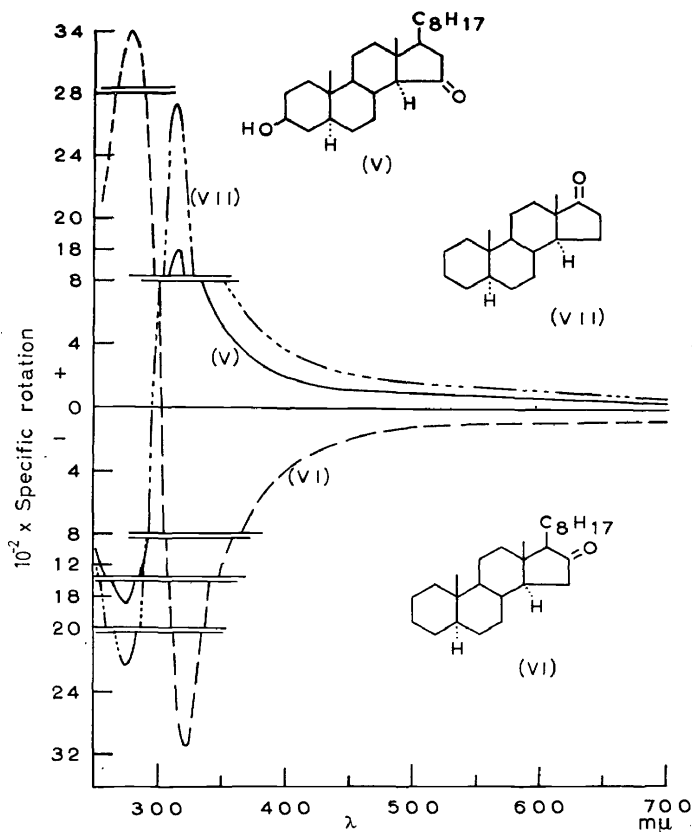


Figure 3. Optical rotatory dispersion curves of 15-, 16- and 17-keto-steroids

terms of specific rotation) may be observed. This has important analytical applications, particularly in kinetic problems<sup>15</sup>, where it is possible to carry out precise measurements with approximately one milligramme of material.

In some cases, the rotatory dispersion curves are not sufficiently distinct to be of secure diagnostic value. This is illustrated in *Figure 4* with the rotatory dispersion curve of a 3-keto-steroid, androstan-3-one (VIII) and the corresponding 2-keto-isomer (IX). However, by taking advantage of a simple experimental modification<sup>16</sup>, it is easy to differentiate between these two isomers. All that is necessary is to run the rotatory dispersion curve in methanol solution, to add a drop of concentrated hydrochloric acid, and then to repeat the dispersion measurement after a suitable interval. The addition of acid catalyses the formation of the corresponding methyl\* ketal (or hemiketal), and, since the latter does not absorb in the 300  $m\mu$  region, it will not show a Cotton effect and its rotation will be quite small compared with the peak rotation of the ketone. Any reduction in amplitude,

\* Only methanol is suitable for such studies. Ketal formation is greatly reduced in ethanol and completely inhibited in isopropanol<sup>16</sup>.

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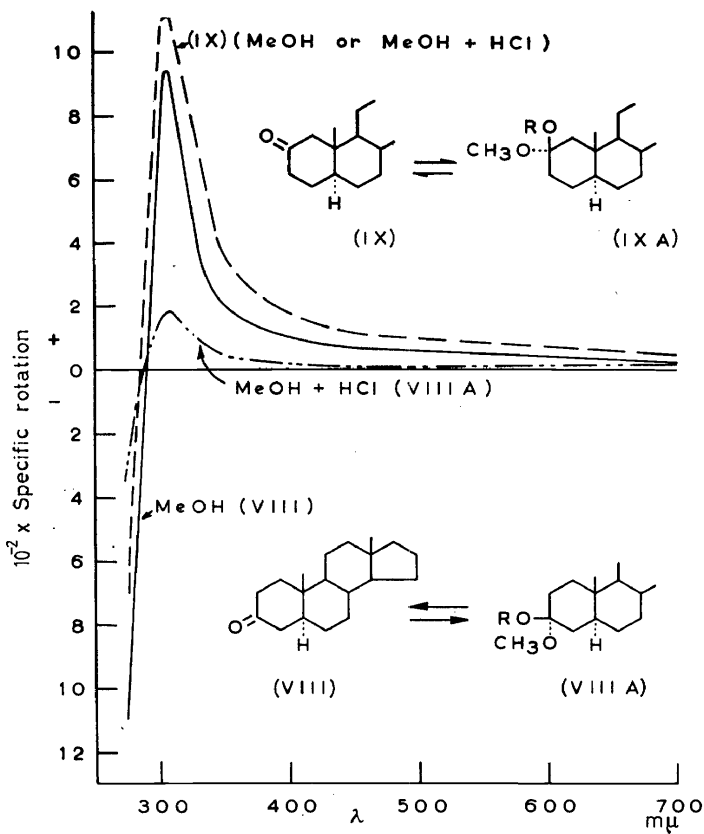


Figure 4. Optical rotatory dispersion curves of androstan-2-one and androstan-3-one, and of their methyl ketals

therefore, offers a semi-quantitative means of determining the extent of ketal production. Extensive studies<sup>16</sup> among 3-keto-steroids (*e.g.* (III) and (VIII)) and the corresponding decalones have shown that the acid-catalysed equilibrium lies on the side of the ketal (VIII A) to the extent of 64–75 per cent, and that it is extremely sensitive to steric factors. Thus, if the ketal involves a new 1,3-diaxial interaction, not present in the parent ketone, as would be the case in a 2-keto-steroid (IX) and its ketal (IX A), then the equilibrium remains almost completely on the side of the ketone. The Cotton effect amplitude of a 2-keto-steroid (IX), therefore, is essentially unaffected in the presence of hydrochloric acid, and thus offers a sensitive criterion for differentiating between a 2-keto- and a 3-keto-steroid.

Once standard curves have been secured for the various positions in the steroid series, then the location of an unknown carbonyl group in a steroid molecule becomes a relatively simple matter. Similar studies have also been conducted among the tetracyclic<sup>17</sup> and pentacyclic<sup>18</sup> triterpenes, and two illustrations of structural applications of rotatory dispersion measurements in this field will now be offered.

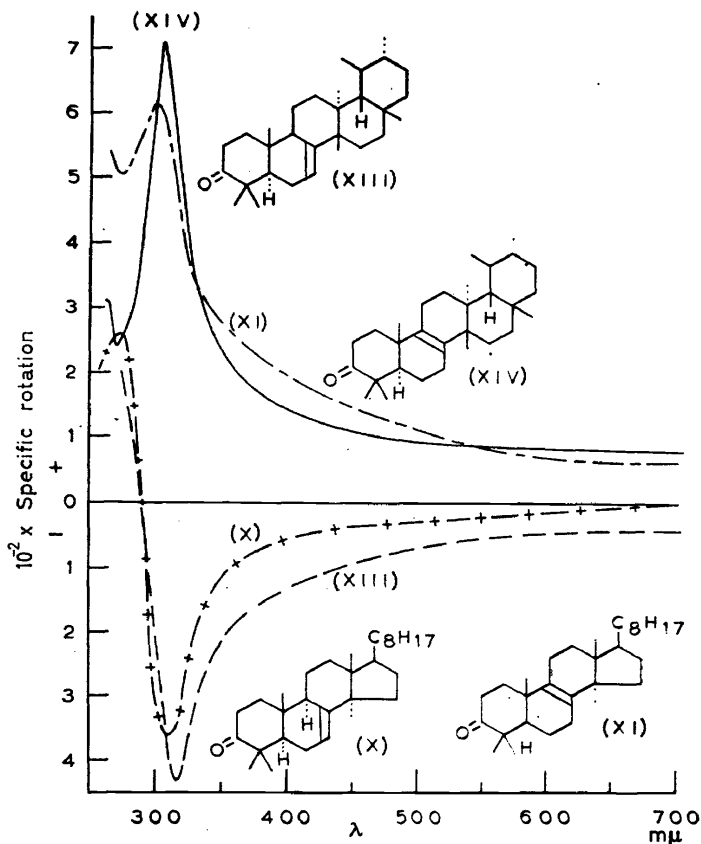
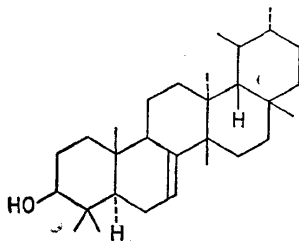


Figure 5. Optical rotatory dispersion curves of  $\Delta^7$ - and  $\Delta^8$ -lanosten-3-one, and of baurenone and isobaurenone

In connection with an examination of the sensitivity of rotatory dispersion to subtle conformational factors, the rotatory dispersion curves of  $\Delta^7$ - (X) and  $\Delta^8$ - (XI) lanosten-3-one were measured<sup>17</sup>. In spite of the fact that these two ketones differ only in the location of the double bond, their respective rotatory dispersion curves (Figure 5) differ greatly. This has been ascribed<sup>17</sup> to conformational distortion, as has the earlier observed<sup>19</sup> difference in their respective rates of condensation with benzaldehyde. Recent studies by Lahey and Leeding<sup>20</sup> at the University of Queensland have led



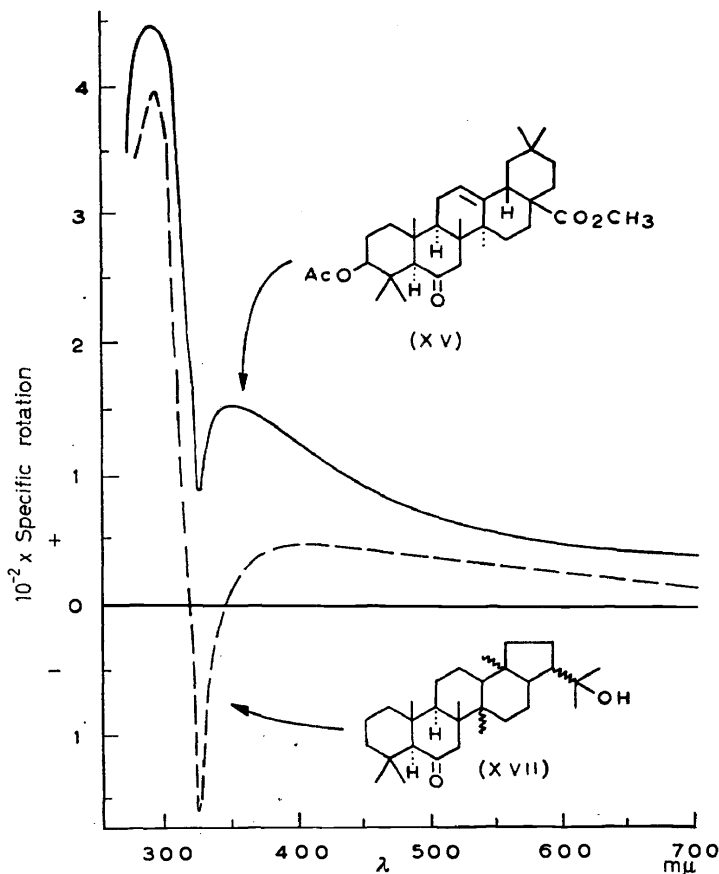
(XII)



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to the proposal of the biogenetically intriguing structure (XII) for the triterpene bauerenol. Through the courtesy of Professor Lahey, the rotatory dispersion curves of the derived ketone bauerenone (XIII) and its double-bond isomer isobauerenone (XIV) were measured in our laboratory. Their respective curves (*Figure 5*) bear the same relationship to each other as has been noted<sup>17</sup> in the reference pair  $\Delta^7$ -lanosten-3-one (X) and  $\Delta^8$ -lanosten-3-one (XI), thus supporting the earlier structural conclusions<sup>20</sup>.

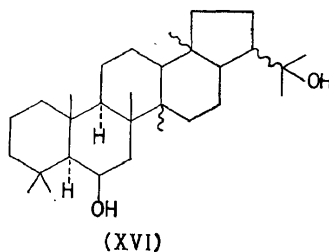
Among ketones of the pentacyclic triterpene series<sup>18</sup>, the rotatory dispersion curve of methyl sumaresinonate 3-acetate (XV) exhibited a unique shape, and its curve (*Figure 6*) can thus be considered as a reference standard



*Figure 6.* Optical rotatory dispersion curves of methylsumaresinonate 3-acetate and zeorinone

for 6-ketones among such triterpenoids. Oxygenation in this position of the triterpene skeleton is very rare, but recently Barton and collaborators<sup>21</sup> have presented degradative evidence that zeorin (XVI) bears a hydroxyl group in this position. Since zeorin has so far not been related directly to any other triterpenoid, it was desirable to secure independent support for this structural detail. As shown in *Figure 6*, the rotatory dispersion curve of zeorinone (XVII), kindly supplied by Professor Barton, is so similar in

shape and amplitude to that of the known ketone (XV) of the sumaresinolic acid series that there is little doubt that the carbonyl group is indeed located at C-6. Furthermore, it can be stated with a very great degree of certainty that the hitherto undefined stereochemical arrangement of rings A and B in zeorin (XVI) must coincide with that of sumaresinolic acid and the other members of the  $\beta$ -amyrin class of triterpenes.



The remarkable changes in the rotatory dispersion curves of isomeric ketones differing only in the location of the carbonyl group can be ascribed to the different asymmetric environment in which the carbonyl chromophore finds itself as it is moved around the polycyclic nucleus. Obviously, a change in the asymmetric environment is also produced if the carbonyl group remains in the same location, but its immediate stereochemical

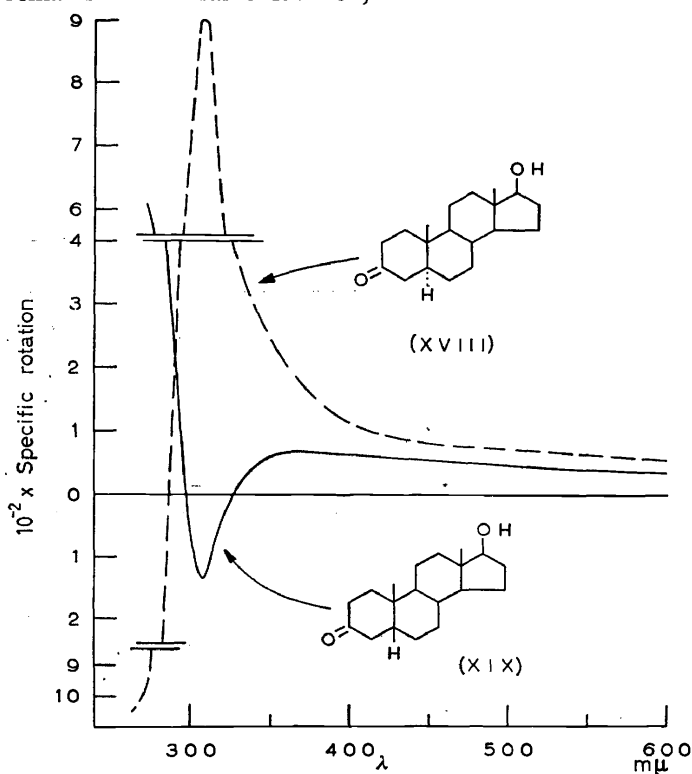
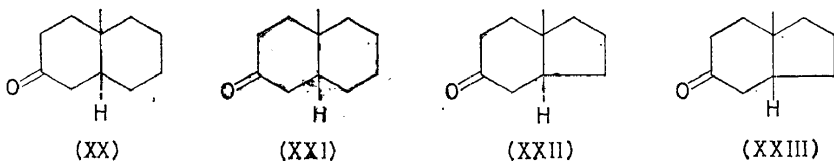


Figure 7. Optical rotatory dispersion curves of 5 $\alpha$ - and 5 $\beta$ -androstan-17 $\beta$ -ol-3-one

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environment is altered. This is illustrated in a striking fashion in *Figure 7*, where it is shown that the rotatory dispersion curves of 5 $\alpha$ -androstan-17 $\beta$ -ol-3-one (XVIII) and its 5 $\beta$ - isomer (XIX) actually show opposite sign Cotton effects even though the two ketones differ only in the nature of the A/B ring juncture. These two curves were found<sup>22</sup> to be typical, irrespective of additional non-chromophoric substitution. In fact, the characteristic shapes of these dispersion curves were retained in their bicyclic analogues (XX)<sup>23</sup> and (XXI)<sup>24</sup>, and even remained unchanged when the adjacent ring became five-membered as in the hydrindanones (XXII) and (XXIII).



These results, coupled with many others mentioned in the original papers<sup>23-25</sup>, permitted the conclusion that the characteristic shape of a given rotatory dispersion curve of a cyclic ketone is very largely governed by its bicyclic stereochemical environment. The validity of this assumption has been tested by us with numerous substances, and any divergence from this "rule" could invariably be shown to be due to conformational alteration, since this, of course, could affect the asymmetric environment around the carbonyl chromophore.

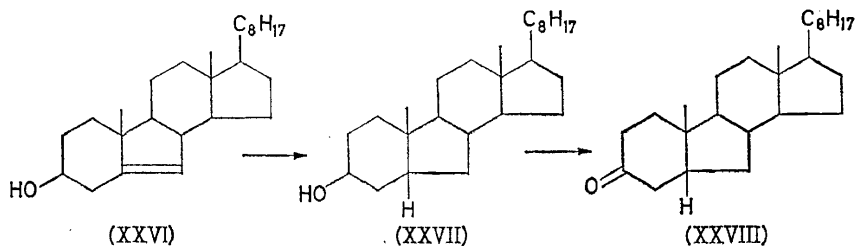
The above reduction to a bicyclic common denominator has increased greatly the scope of rotatory dispersion measurements, and has made them unsurpassed as far as applications to relative and absolute configurational problems are concerned. A number of examples will be given to illustrate this point, but, before doing so, it is pertinent to mention some other applications of the rotatory dispersion information covered by *Figure 7*. The *cis*-decalone (XXI) can exist in two chair conformations, the "steroid-like" form (XXIV) (steroids such as (XIX) are locked in this conformation by the *trans*- B/C ring juncture) and the "non-steroid" one (XXV). Originally,



it was believed<sup>26</sup> that, in the decalone series (XXI), the "non-steroid" conformation (XXV) was the preferred one, but the coincidence of the rotatory dispersion curve of the *cis*-decalone (XXI) with that of the steroid (XIX) of known conformation has led to the decision<sup>24</sup> that the reverse is the case. A similar conclusion can also be reached in the hydrindanone series, since the rotatory dispersion curve of (XXIII) was again of the steroid type ((XIX) in *Figure 7*). It was thus possible to solve a rather

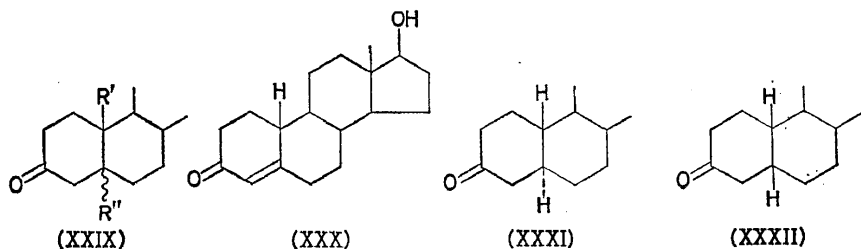
subtle conformational problem in the decalone and hydrindanone series from rotatory dispersion information among steroids.

Conversely, the rotatory dispersion data<sup>25</sup> for the bicyclic hydrindanones (XXII) and (XXIII) offered the first correct information about the stereochemistry of the hydrogenation products of B-norcholesterol (XXVI). The principal product (XXVII)<sup>27</sup>, had been oxidized to the ketone



(XXVIII) and its rotatory dispersion curve<sup>25</sup> proved to be of the A/B *cis*-type (XIX). Since studies in the bicyclic series had demonstrated<sup>25</sup> that the size of the adjacent ring does not play an important rôle, provided the stereochemical situation is not otherwise altered, it was suggested by us that the principal product was the 5β-alcohol (XXVII) rather than the anticipated 5α- isomer. This conclusion has since been verified by other studies<sup>28</sup>.

During the past few years, we have measured the rotatory dispersion curves of steroids with a variety of angular substituents ((XXIX), R' = H, CH<sub>3</sub>, halogen; R'' = H, CH<sub>3</sub>, OH, CN, CO<sub>2</sub>CH<sub>3</sub>, CONH<sub>2</sub>), and in every instance the characteristic rotatory dispersion difference between the A/B *trans*- and A/B *cis*- isomers (see Figure 7) was retained, thus offering a tool of unsurpassed value for solving configurational problems of this type. As an illustration, we may cite the reduction of the double bond of 19-nortestosterone (XXX), which with chemical agents<sup>29</sup> leads to one isomer (XXXI) and under catalytic hydrogenation conditions<sup>30</sup> to another (XXXII). The rotatory dispersion curves of these products were typical

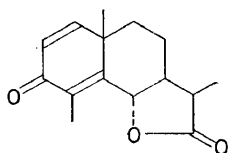


of an A/B *trans*- ((XVIII) in Figure 7) and A/B *cis*- ((XIX) in Figure 7) ring fusion respectively, and thus immediately settled a stereochemical point which, at this time, would not be amenable to attack by any other physical method. A similar problem arose in determining the stereochemistry of certain steroids<sup>31</sup> into which a methyl group was introduced at

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C-5 (XXIX),  $R' = R'' = CH_3$ ), and this was again solved in terms of an A/B *cis*-ring fusion by rotatory dispersion measurements.

In the light of the above discussion that the typical rotatory dispersion features of steroid ketones are also retained in their bicyclic analogues, it is



(XXXIII)

not surprising that this tool has been also of great utility in fixing stereochemical details in other molecules. Of the many examples which have been cited<sup>6-8</sup>, it may be useful to consider one of the first applications<sup>23</sup> of this approach in the sesquiterpene series.

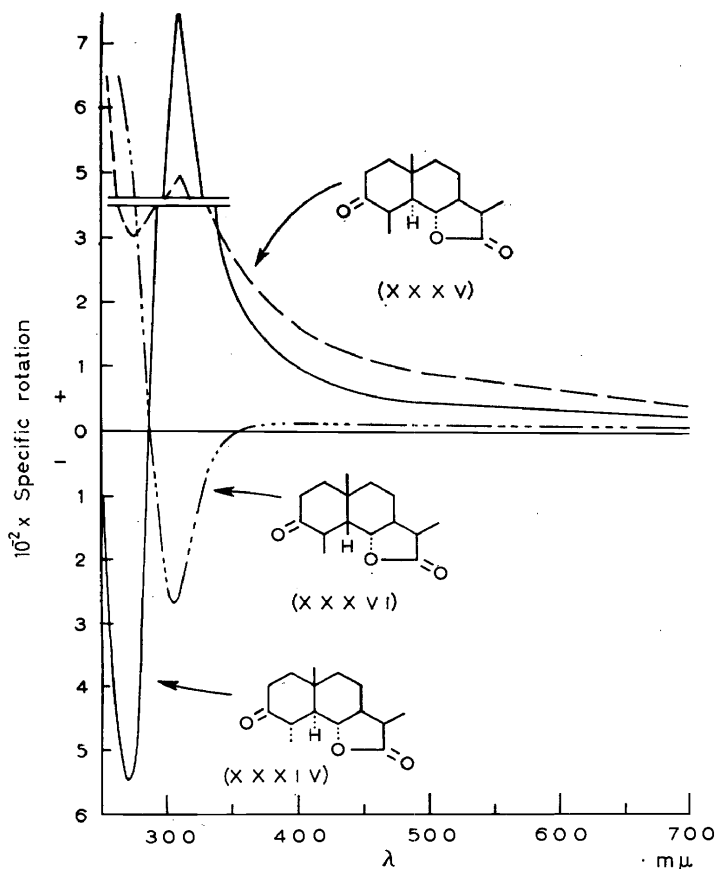
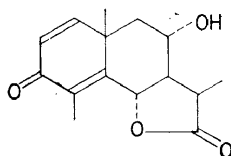


Figure 8. Optical rotatory dispersion curves of three stereoisomeric products formed by catalytic hydrogenation of (-)- $\alpha$ -santonin

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Catalytic hydrogenation of (–)- $\alpha$ -santonin (XXXIII) can produce four stereoisomers, of which three (XXXIV), (XXXV) and (XXXVI) are readily accessible. Their rotatory dispersion curves are reproduced in *Figure 8*, and it will be noted immediately that the curves of (XXXIV) and (XXXVI) are typical (see *Figure 7*) of an A/B *trans*- and A/B *cis*- junction respectively. Both substances were stable to acid or alkali, thus implying an equatorial orientation for the C-4 methyl group, and this information was sufficient, therefore, to lead to the complete stereochemical assignments<sup>23</sup> expressed in formulae (XXXIV) and (XXXVI). The rotatory dispersion curve of the third isomer (XXXV) was distinct (*Figure 8*), but, since acid or alkali transformed it into (XXXIV), it obviously could differ from the latter only in the orientation of the C-4 methyl group and this can be accommodated only in terms of structure (XXXV). At the time<sup>23</sup> that we made these stereochemical assignments, they were contrary to conclusions then existing in the literature<sup>32</sup>, but the correctness of the rotatory dispersion



(XXXVII)

deductions was verified subsequently<sup>33</sup>. The identical rotatory dispersion approach was then employed<sup>34</sup> to determine conclusively the stereochemistry of the hydrogenation products of artemisin (XXXVII).

Until now, the discussion has been limited to saturated ketones. While  $\alpha,\beta$ -unsaturated ketones absorb in the 220–260  $m\mu$  region with an intensity which precludes (with the spectropolarimeters available at present) rotation measurements in this region of strong absorption, they also possess a weak absorption band above 300  $m\mu$ , which was found<sup>35</sup> to be optically active. The rotatory dispersion curves of such  $\alpha,\beta$ -unsaturated ketones are usually characterized by fine structure which is particularly well resolved in non-polar solvents such as dioxan or octane. An illustration of the typical multiple Cotton effect observed with steroidal  $\Delta^4$ -3-ketones is given with the rotatory dispersion curve of testosterone (XXXVIII) (see *Figure 9*). Addition of “non-chromophoric” substituents at positions 1, 2, 4, 6 and 7 and in more distant portions of the molecule did not affect this picture, provided these substituents did not result in conformational or electronic disturbances (see below). Even more importantly, extensive measurements in our laboratory of a variety of steroidal, tricyclic and bicyclic ketones with the octalone system (XXXIX) have demonstrated that the nature of the angular substituent can be varied over a wide range (XXXIX, R = H, CH<sub>3</sub>, OH, halogen, CH<sub>2</sub>OH, CN, CO<sub>2</sub>CH<sub>3</sub>) without changing the typical features of the dispersion curve, the controlling factor being simply the configuration of this angular substituent which governs the sign of the multiple Cotton effect. Thus, 19-nortestosterone (XXX), a substance which differs from testosterone (XXXVIII) only in the replacement of the angular methyl group by hydrogen, possesses essentially the same rotatory dispersion

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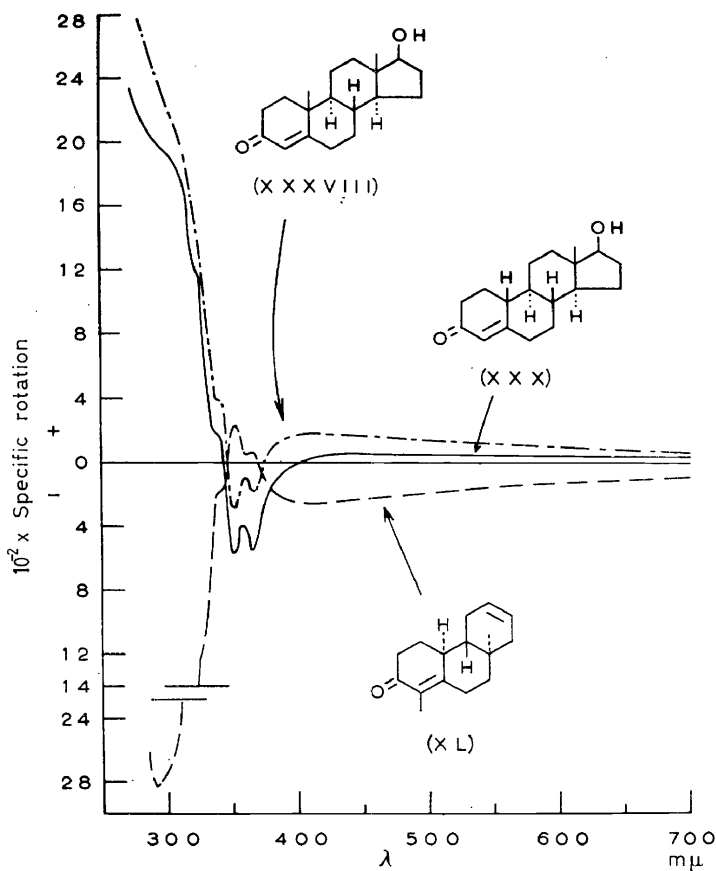
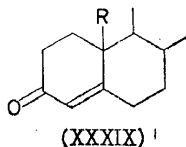


Figure 9. Optical rotatory dispersion curves of testosterone, 19-nortestosterone and a related tricyclic ketone

curve\*, while that<sup>35</sup> of the tricyclic ketone (XL)<sup>36</sup> is of mirror-image type since, in terms of its angular substituent it belongs to the antipodal series.

These results would imply that the characteristic rotatory dispersion curve of such octalones (XXXIX) is immune to any type of manipulation. Actually, this is only true if the modifications do not affect the geometrical (conformational) or electronic environment of the  $\alpha,\beta$ -unsaturated carbonyl chromophore. If this is disturbed, then major aberrations in the



\* This coincidence in the rotatory dispersion curves of 19-nortestosterone (XXX) and testosterone (XXXVIII) represents the most cogent argument for the  $\beta$ -orientation of the C-10 hydrogen atom. Similar rotatory dispersion studies have been carried out to establish this point in other steroidal (C. Djerassi, M. Ehrenstein and G. W. Barber. *Ann.*, **612**, 93 (1958) ) and tricyclic (O. Schindler. *Helv. Chim. Acta*, **43**, 754 (1960) ) 19-nor- analogues.

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rotatory dispersion curve will be noted, even though they may involve only minor structural variations. For instance, the rotatory dispersion curve (Figure 10) of 6 $\alpha$ -methyltestosterone (XLI) is practically identical with that

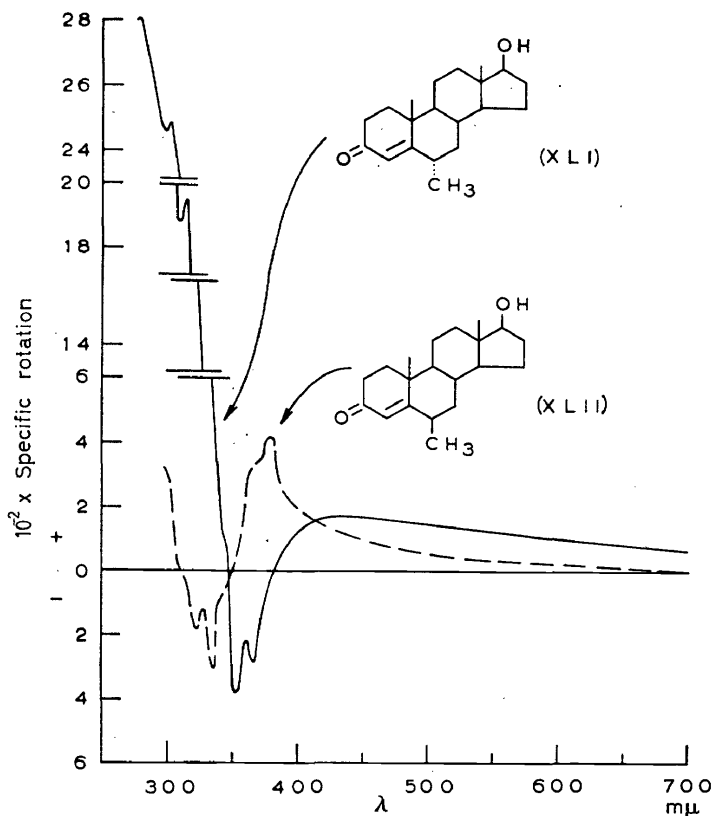


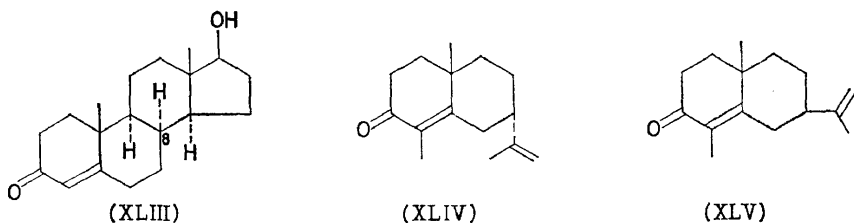
Figure 10. Optical rotatory dispersion curves of 6 $\alpha$ - and 6 $\beta$ -methyltestosterone

of testosterone (XXXVIII) (Figure 9), while the introduction of an axial substituent as in 6 $\beta$ -methyltestosterone (XLII) produces a drastic change<sup>17</sup> (see Figure 10). That this is due to conformational distortion caused by the steric interaction between the axial methyl groups at C-6 and C-10 could be demonstrated<sup>37</sup> conclusively by the synthesis of the corresponding 19-nor-analogue ((XLII), with angular hydrogen atom attached to C-10), in which the original undisturbed rotatory dispersion picture ((XLI) in Figure 10) was again restored.

Ample use has been made of the sensitivity of the rotatory dispersion curve of  $\Delta^4$ -3-keto-steroids to conformational and electronic disturbances accompanying the introduction of axial substituents at C-6 to assign configurations to various 6-alkylated<sup>38</sup>, halogenated<sup>39, 40</sup>, and nitrated<sup>41</sup> steroids. Variations, similar to those exhibited in Figure 10, have also been encountered in 8-isotestosterone (XLIII)<sup>35</sup> (contrasted with testosterone (XXXVIII)) and in epi- $\alpha$ -cyperone (XLIV)<sup>23</sup> (contrasted with  $\alpha$ -cyperone



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(XLV) ), and in each instance have been associated with conformational alterations (chair to boat) in ring B. The detection of conformational distortion in the axially oriented epi- $\alpha$ -cyperone (XLIV) was particularly striking, and would not have been readily noticeable by other means.

The above discussion may be considered to be the background to perhaps the most significant contribution of optical rotatory dispersion to the armamentarium of the organic chemist, namely the determination of absolute configuration. The subject was first developed in an early paper<sup>23</sup> in our series on *Optical Rotatory Dispersion Studies*, and has since been covered

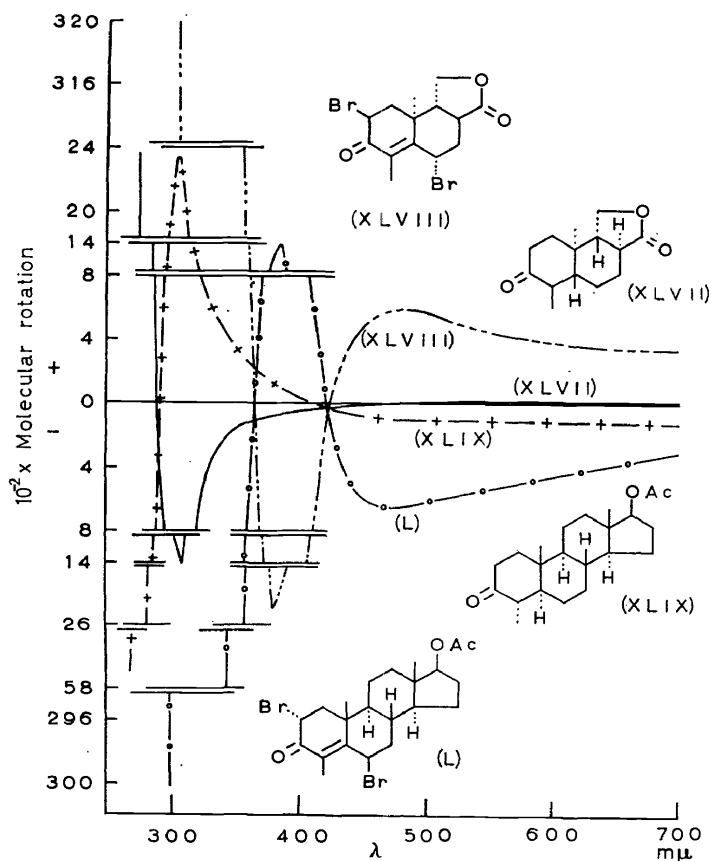
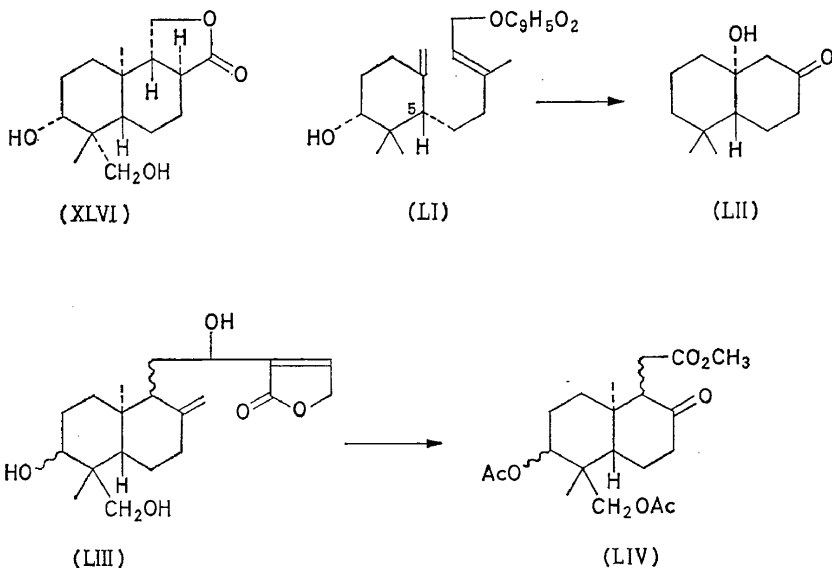


Figure 11. Optical rotatory dispersion curves of saturated nor-ketone and unsaturated dibromo-ketone derivatives of irisin, compared with those of related steroid models

in detail<sup>6,7</sup>. At present, we shall consider only some of the more recent applications of this approach in the natural products field, where it has found immediate and widespread use. We have shown that non-chromophoric substituents play no significant qualitative rôle, the all-important factor being the stereochemical and conformational identity of the appropriate bicyclic environments around the carbonyl chromophore; hence, the rotatory dispersion approach<sup>23</sup> to the determination of absolute configuration consists simply in comparing the dispersion curves of the unknown ketone\* with that of a reference compound of known absolute configuration and possessing the appropriate bicyclic system. For many of our initial studies, we have selected steroids as reference substances, as their absolute configurations are known, and virtually all significant bicyclic systems can be found in appropriate steroid substrates.

For purposes of illustration of the power and scope of this method, examples will be given where rotatory dispersion has so far offered the only means of arriving at an absolute configurational assignment.

The structure of the sesquiterpene iresin (XLVI) has been established by classical chemical means<sup>42</sup> and confirmed by X-ray studies<sup>43</sup>. Because of the important position of iresin in the biogenetic scheme<sup>44</sup> of the terpenoids, its absolute configuration was clearly of interest, and the problem was solved<sup>45</sup> exclusively by means of optical rotatory dispersion. Iresin (XLVI) was degraded<sup>45</sup> to the saturated nor-ketone (XLVII) and the unsaturated dibromo-ketone (XLVIII), and their respective rotatory dispersion curves were compared with the steroid models (XLIX) and (L), where rings A and B coincide stereochemically and conformationally with the iresin degradation products. As shown in *Figure 11*, the respective pairs (XLVII)-(XLIX) and (XLVIII)-(L) exhibit mirror-image type curves



\* Obviously, this statement also applies to other chromophores such as the thione grouping.

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whereupon it can be concluded that iresin (XLVI) and its degradation products possess an absolute configuration which is antipodal to that of the steroids. The absolute configuration of the biogenetically related farnesiferol B (LI) was established<sup>46</sup> in a similar fashion by degradation to the bicyclic ketone (LII), and that of andrographolide (LIII)<sup>47</sup> by transformation to the decalone (LIV). Both degradation products (LII) and (LIV) exhibited positive Cotton effects, which could be evaluated by reference to similar Cotton effects (see Figure 4) of 2- and 3-keto-steroids of the 5 $\alpha$ -series.

The importance of conformational as well as stereochemical identity between the reference substance and the unknown product cannot be over-emphasized. Thus, it was noted in an earlier study<sup>17</sup> that introduction of a *gem*-dimethyl substituent into a 3-keto-steroid of the 5 $\alpha$ -series resulted in inversion of the Cotton effect, 4,4-dimethylcholestan-3-one (LV) exhibiting a negative one (see Figure 12) in contrast to the positive one (see Figure 2)

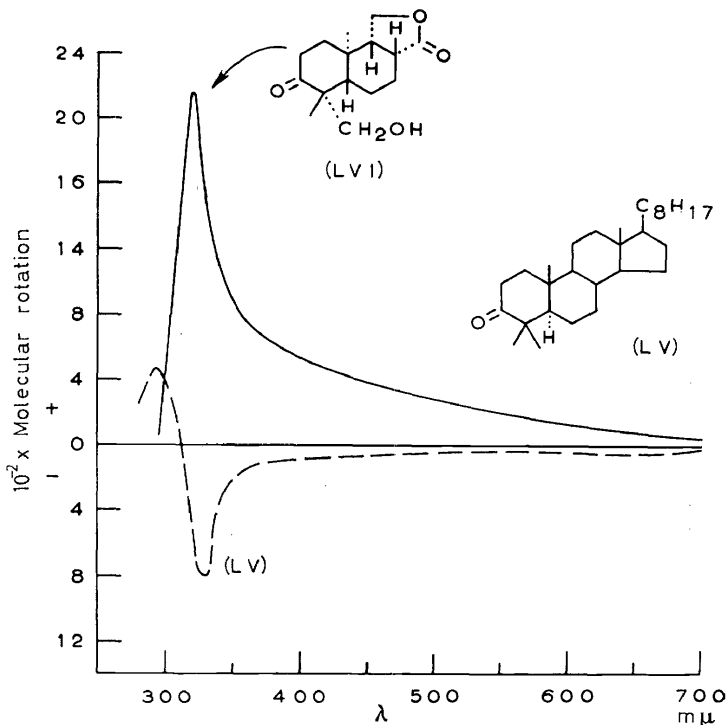


Figure 12. Optical rotatory dispersion curves of 4,4-dimethylcholestan-3-one and dihydroiresone

of cholestan-3-one (III). This behaviour is also observed in 4,4-dimethyl-3-ketones of the 19-nor-steroid series<sup>17</sup>, and in fact even among decalones<sup>24</sup>, and a possible explanation has already been discussed<sup>17</sup>. If the problem of the absolute configuration of iresin (XLVI) is attacked through the related naturally occurring ketone dihydroiresone (LVI)<sup>48</sup>, then an incorrect answer would have been obtained if an ordinary 3-keto-steroid (*e.g.* (III) in

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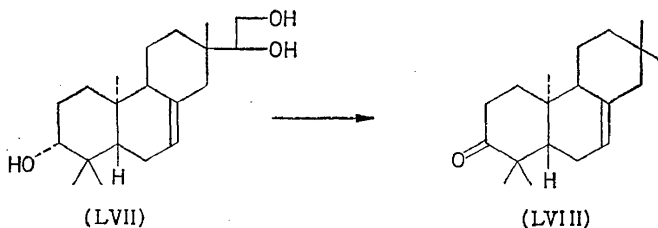


Figure 2) or a 4-monomethyl derivative ((XLIX) in Figure 11) had been employed as the reference ketone. However, by using the negative Cotton effect of 4,4-dimethylcholestan-3-one (LV) (see Figure 12) for comparison purposes, the correct conclusion with respect to the antipodal nature of the ring juncture of iresin is obtained, since dihydroiresone (LVI) possesses a positive Cotton effect (see Figure 12). A similar situation exists in the diterpene darutigenol (LVII)<sup>49\*</sup>, where its absolute configuration was

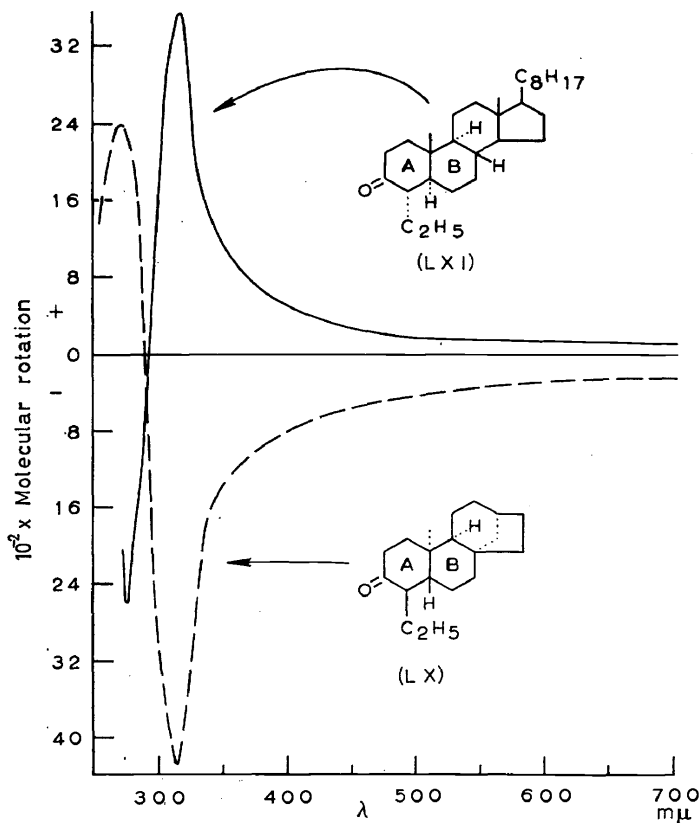


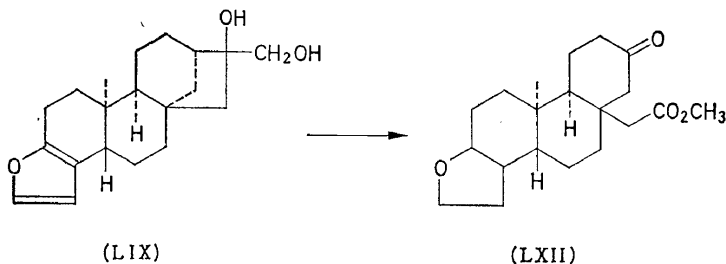
Figure 13. Optical rotatory dispersion curve of a cafestol degradation ketone, compared with that of the steroid reference ketone 4 $\alpha$ -ethylcholestan-3-one

\* Recent work by A. Diara, C. Asselineau and E. Lederer, *Bull. soc. chim. France*, **1960**, 2171, has shown that the double bond in (LVII) is actually located in the 8—14 position (steroid numbering system). The absolute configurational conclusions, however, are still valid.

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determined by comparing the rotatory dispersion curve (positive Cotton effect) of the derived ketone (LVIII) with the negative Cotton effect of an appropriate 4,4-dimethyl- $\Delta^7$ -ketone,  $\Delta^7$ -lanosten-3-one (X) in *Figure 5*).

Another pertinent example is the diterpene cafestol (LIX), whose structure had recently been established in our laboratory<sup>50</sup>. Its absolute configuration rests on two different rotatory dispersion arguments. The first<sup>50</sup> pertains to the stereochemistry of the A/B ring fusion, which is assigned a stereochemistry antipodal to that of the steroids since the rotatory dispersion curves (see *Figure 13*) of the cafestol degradation ketone (LX) and the steroid reference ketone, 4 $\alpha$ -ethylcholestan-3-one (LXI) bear a mirror-image relation to each other. It should be noted that, for chemical reasons, cafestol (LIX) is believed<sup>50</sup> to possess a *syn*-backbone, in contrast to the *anti*-relationship existing at C-9 and C-10 in the steroids. In order for the rotatory dispersion comparison outlined in *Figure 13* to be valid, it must first be demonstrated that a 9,10-*syn*-arrangement does not affect the characteristic positive Cotton effect (see *Figure 2*) of 3-keto-steroids. This was accomplished by comparing the rotatory dispersion curves of ergostan-3-one and its 9 $\beta$ -analogue, both of them being characterized by positive Cotton effect curves of similar amplitude. There is no doubt, therefore, of the existence of an antipodal A/B ring juncture in cafestol.



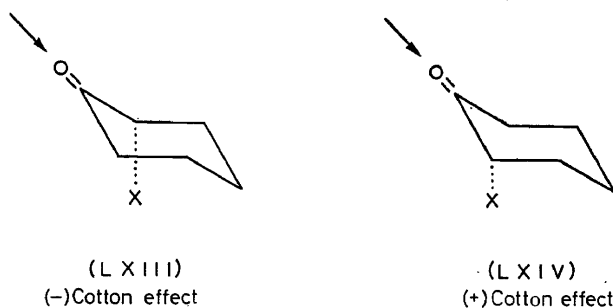
As far as the stereochemistry of the B/C/D environment is concerned, this rests on several rotatory dispersion arguments, including the positive Cotton effect of the tricyclic ketone (LXII) which was recently obtained<sup>51</sup> from cafestol.

All of the above terpenoids exhibit the outstanding feature of possessing an absolute configuration which is antipodal to that of the steroids. This very unusual point rests completely on rotatory dispersion studies, and it will be admitted that any classical chemical procedure for arriving at an absolute configurational assignment for these substances would have been extremely complicated. It is not surprising, therefore, that this particular rotatory dispersion application has been accepted so quickly in the domain of natural products chemistry; the absolute configuration of as diverse a group as columbin<sup>52</sup>, gibberellic acid<sup>53</sup>, the ergot alkaloids<sup>54</sup> and limonin<sup>55</sup>, just to mention a few recent examples, is based completely on optical rotatory dispersion studies of the type illustrated above.

In connection with our extensive investigations of the rotatory dispersion behaviour of the carbonyl chromophore, it was particularly pertinent to examine  $\alpha$ -halogenated ketones, since a number of correlations had already been noted between the orientation of a halogen atom and the position of

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the ultra-violet absorption maximum<sup>56</sup> of such  $\alpha$ -halogenocyclohexanones. As a result of the initial rotatory dispersion studies<sup>39</sup> of a variety of steroidal  $\alpha$ -halogenoketones, an empirical rule was evolved<sup>57</sup> which was called the "axial haloketone rule". This rule states that introduction of equatorial halogen in either of the positions adjacent to a cyclohexanone does not affect qualitatively the Cotton effect of the parent ketone. On the other hand, axial halogen has a profound effect. First of all, in agreement with earlier ultra-violet spectroscopic measurements<sup>56</sup>, the rotatory dispersion curve suffers a bathochromic shift with a concomitant increase in the amplitude of the Cotton effect. Secondly, the sign of the Cotton effect of such an  $\alpha$ -halogenocyclohexanone (this applies to chlorine, bromine and iodine, but not to axial fluorine where the opposite effect is noted) can be predicted in the following empirical manner. A model of the cyclohexanone ring is placed in such a manner (see *Figure 14*) that the carbonyl group occupies the "head" of the chair (or boat<sup>58</sup>). By looking down the O=C axis as indicated by the arrow in *Figure 14*, a cyclohexanone with an



*Figure 14.* Model of  $\alpha$ -halogenocyclohexanone, illustrating the "axial haloketone rule"

axial halogen atom on the left side of the observer (LXIII) will show a negative Cotton effect, while a positive one will be observed if the halogen atom is situated on the right side (LXIV). No exceptions to this rule have as yet been encountered, and it is apparent that, if the absolute configuration of a given axial  $\alpha$ -halocyclohexanone is known, its conformation can be established, while conversely the absolute configuration can be deduced if the conformation of the molecule is settled. Several important applications of this rule to structural, conformational and stereochemical problems have already been recorded and these have been reviewed recently<sup>59</sup>. Three examples will suffice to illustrate the power and scope of this rule.

Chlorination of (+)-3-methylcyclohexanone (positive Cotton effect) leads to a crystalline chloro-ketone for which structure (LXV) (or its "flipped-over" chair form (LXVI)) has been established<sup>60</sup>. Allinger and Allinger<sup>61</sup> had already indicated earlier that the conformational equilibrium in the case of 2-bromocyclohexanone is dependent upon the polarity of the solvent, and that the axial form predominates in a non-polar medium (*e.g.* octane), but that in a polar solvent (*e.g.* methanol) an increased proportion of the equatorial form would be expected. Turning now to the specific example of 2-chloro-5-methylcyclohexanone, the form with the equatorial chlorine atom (LXV) would be expected to possess a positive

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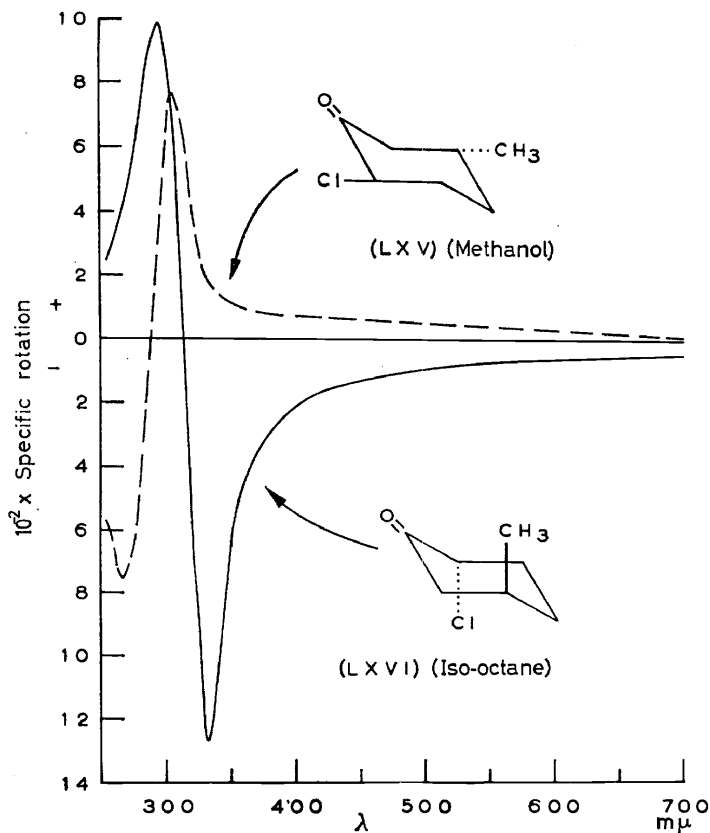
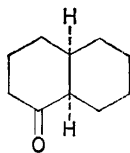


Figure 15. Optical rotatory dispersion curves of 2-chloro-5-methylcyclohexanone in methanol and in iso-octane. The curves represent new measurements in which the spectral range has been extended somewhat over that previously reported<sup>60</sup>

Cotton effect (similar to that of the chlorine-free parent ketone), while the axial haloketone rule would predict a strongly negative Cotton effect for the axial isomer (LXVI). Indeed, when the rotatory dispersion curve of (LXV) was measured in the polar medium methanol, a positive Cotton effect was noted (Figure 15) consistent with a predominance of (LXV), while in iso-octane a strongly negative Cotton effect was generated, indicating the increased presence of the axial form (LXVI). Figure 15 thus represents an excellent graphical illustration of conformational mobility in a cyclohexanone.

Quite recently, we have been able to demonstrate<sup>62</sup> a similar conformational equilibrium in a brominated *cis*-decalone. (–)-*cis*-1-Decalone



(LXVII)

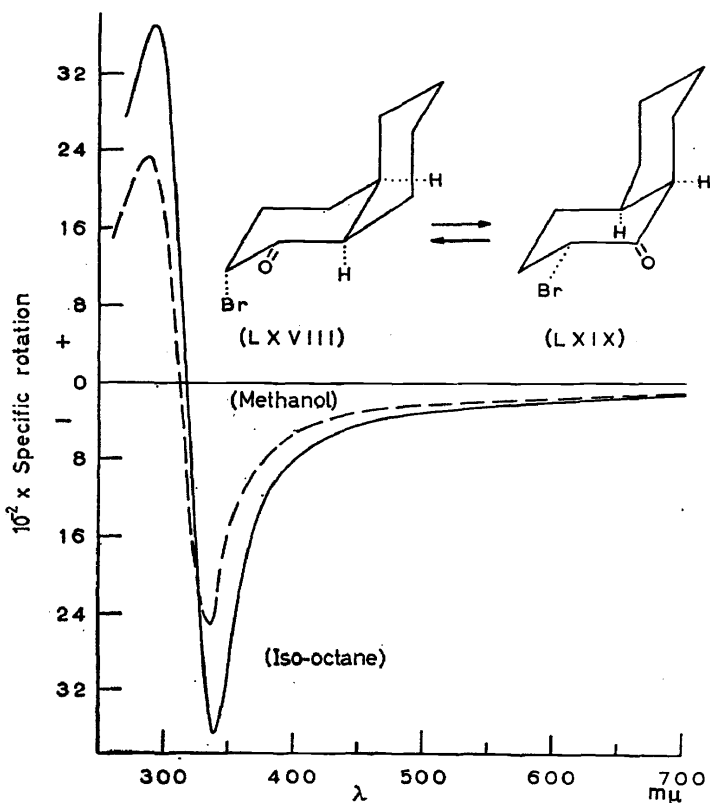
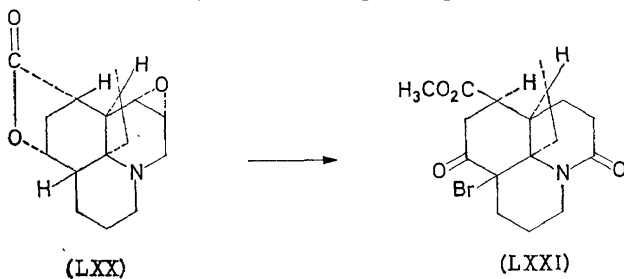


Figure 16. Optical rotatory dispersion curves of (—)-2-bromo-*cis*-1-decalone in methanol and in iso-octane

(LXVII) was converted into the axially oriented (—)-2-bromo-*cis*-1-decalone (LXVIII), whose strongly negative Cotton effect (see Figure 16) in iso-octane solution requires that the compound exist in the "steroid" conformation (LXVIII). When the dispersion measurement was repeated in the polar solvent methanol, there occurred a reduction in amplitude, which is only possible if a certain proportion of the "non-steroid" compound (LXIX) with the equatorial bromine atom is generated. That this diminution in amplitude in methanol actually reflects a shift in the conformational equilibrium towards (LXIX) is verified by the observation that other brominated decalones, *e.g.* the corresponding *cis*-9-bromo-1-decalone,





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exhibit rotatory dispersion curves of identical amplitude in either methanol or iso-octane.

The above two examples illustrate the use to which the axial haloketone rule can be put for attacking conformational problems if the absolute configuration is known. The converse—proof of absolute configuration by the axial haloketone rule—is strikingly illustrated by the alkaloid annotinine (LXX), which has recently been transformed<sup>63</sup> into the axial bromoketone (LXXI) possessing a strong negative Cotton effect<sup>64</sup>. Application of the axial haloketone rule shows that this is compatible only with the stereoformula (LXXI), whereupon the absolute configuration (LXX) follows automatically for the parent alkaloid annotinine.

Until now, our discussion has been limited to carbonyl-containing substances, largely because these were the first to be studied by us on the grounds that the carbonyl chromophore has particularly favourable properties for rotatory dispersion studies, and because ketones and aldehydes are among the most widely distributed functional groups. Just as with ultra-violet<sup>66, 65</sup> and infra-red spectroscopy<sup>66</sup>, the carbonyl chromophore will continue to occupy a very important place, but it is obvious that other chromophores are available which are optically active and absorb in a convenient spectral region with a sufficiently low extinction to be useful for spectropolarimetric investigations. Many of these potentially useful chromophores have already been reviewed<sup>67</sup>, and, at this time, we shall limit ourselves to some recent developments in the natural products field which have been studied in our laboratory.

Apart from the carbonyl moiety, the most widely distributed functional

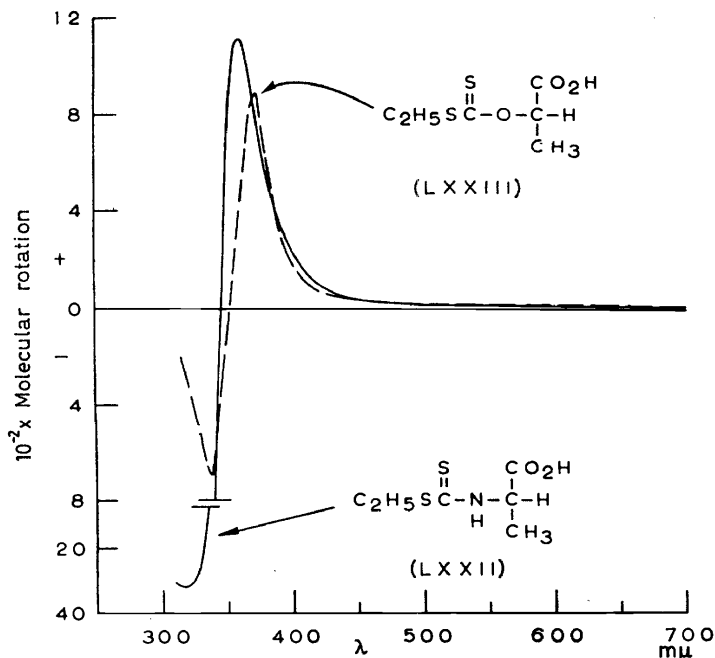
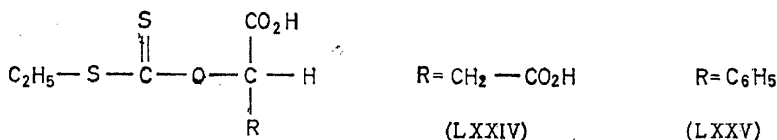


Figure 17. Optical rotatory dispersion curves of dithiocarbamate derivatives of L-(+)-alanine and L-(+)-lactic acid

groups in organic chemistry are carboxylic acid, amine and alcohol groupings. None of these absorbs in a suitable spectral range, and, in order to subject them to the type of rotatory dispersion scrutiny illustrated above for ketones, it is necessary to transform them into derivatives with more favourable spectroscopic properties. The feasibility of this approach can be demonstrated by several examples. Thus we have shown<sup>68</sup> that dithiocarbamate derivatives (*e.g.* (LXXII)) of  $\alpha$ -amino-acids (readily prepared by treating an alkaline solution of the  $\alpha$ -amino-acid with carbon disulphide and an alkyl halide) absorb near  $330\text{ m}\mu$  with a very low extinction, and that these derivatives exhibit Cotton effect curves. The same applies to the xanthates of  $\alpha$ -hydroxy-acids (*e.g.* (LXXIII)), whose low-intensity ultra-violet absorption maximum falls near  $356\text{ m}\mu$ . An extensive rotatory dispersion study of a series of such derivatives of  $\alpha$ -amino- and  $\alpha$ -hydroxy-acids has shown<sup>68</sup> that their rotatory dispersion curves afford by far the most convenient means of establishing the absolute configuration of the  $\alpha$ -asymmetric centre, since all members of the L-series exhibit a positive Cotton effect, while a negative one is given by those of the D-series. This is illustrated in *Figure 17* with the rotatory dispersion curves of the appropriate derivatives of L-(+)-alanine (LXXII) and L-(+)-lactic acid (LXXIII), the curve of the latter being displaced somewhat to the visible, since its ultra-violet absorption maximum occurs approximately  $30\text{ m}\mu$  closer to the red than that of the dithiocarbamate (LXXII). The nature of the  $\alpha$ -alkyl substituent is not important, since  $\alpha$ -hydroxy-acids such as L-(−)-malic acid and L-(+)-mandelic acid behave in an identical fashion, their respective xanthates ((LXXIV) and (LXXV)) exhibiting positive Cotton effect curves even though the parent acids show D line rotations of opposite sign.



The simplicity of this rotatory dispersion approach can be contrasted with the substantial difficulties which were encountered in the classical proof of absolute configuration of mandelic acid<sup>69</sup>.

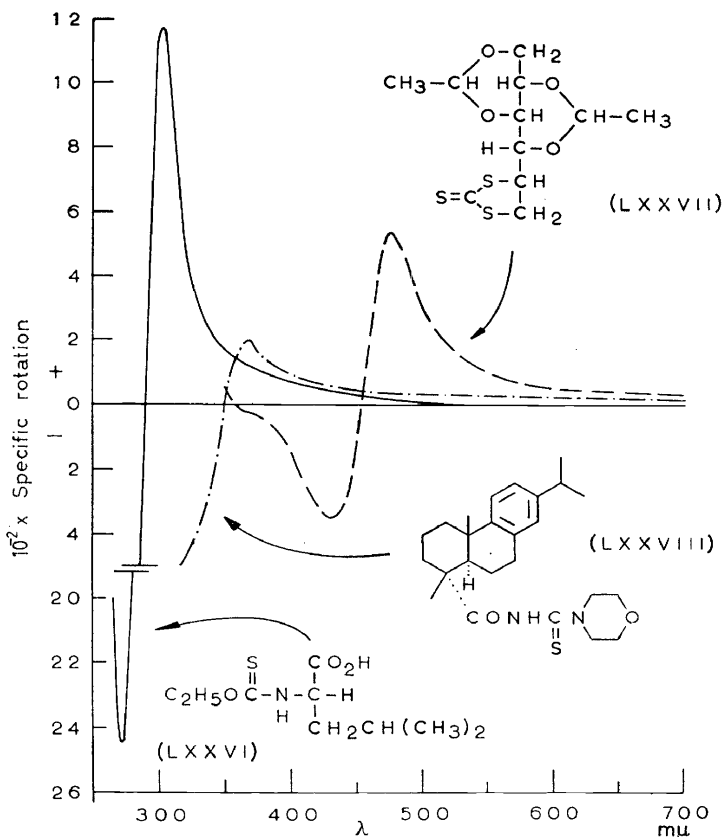
As far as applications in the  $\alpha$ -amino-acid field are concerned, the method should not only be useful for establishing the absolute configuration of new  $\alpha$ -amino-acids that may be discovered in the future, but also for determining the configuration of a terminal amino-acid in a peptide, a problem which is particularly pertinent in the antibiotic field. In support of this statement may be cited the observation<sup>68</sup> that the dithiocarbamate derivatives of L-alanyl-L-alanine and L-alanyl-D-alanine exhibit positive Cotton effect curves of identical amplitude, the governing factor being the stereochemistry of the  $\alpha$ -asymmetric centre to which the free amino-acid group is attached.

Some time ago, Kenner and Khorana<sup>70</sup> suggested *N*-thioncarbethoxy- $\alpha$ -amino-acids (*e.g.* (LXXVI)) as suitable intermediates for peptide degradation. Their work was limited to the preparation of such derivatives in the DL-series, but preparation of the optically active derivatives and optical rotatory dispersion measurements<sup>71</sup> have shown that *N*-thioncarbethoxy- $\alpha$ -amino-acids of the L-series (*e.g.* L-leucine derivative (LXXVI))

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in *Figure 18*) exhibit positive Cotton effect curves, similar to the analogous dithiocarbamates (LXXII).

The spectroscopic properties of the C=S chromophore have proved to be useful in a number of environments. Thus, Owen and collaborators<sup>72</sup> have prepared several trithiocarbonates in the carbohydrate field. These derivatives are characterized by a low-intensity absorption band at 450 m $\mu$ , which was shown to be optically active. Several members of this class have already been studied in our laboratory, and, as an example, there is reproduced in *Figure 18* the positive Cotton effect exhibited by 5,6-dideoxy-1,3:2,4-di-*O*-ethylidene-5,6-(thiocarbonyldithio)-*L*-iditol (LXXVII).



*Figure 18.* Optical rotatory dispersion curves of *N*-thioncarbethoxy-*L*-leucine, 5,6-dideoxy-1,3:2,4-di-*O*-ethylidene-5,6-(thiocarbonyldithio)-*L*-iditol, and a thiourea derivative of dehydroabietic acid

In a search for derivatives of carboxylic acids<sup>73</sup> which will exhibit Cotton effect curves suitable for configurational correlations, we have selected<sup>74</sup> certain acylthioureas. Of particular utility proved to be the thioureas obtained upon successive treatment of an acid chloride with potassium thiocyanate and morpholine. In *Figure 18*, there is shown the positive Cotton effect of such a derivative (LXXVIII) ( $\lambda_{\text{max}} = 340 \text{ m}\mu$ ) obtained from dehydroabietic acid. The synthesis and optical rotatory dispersion

curves of a variety of such acid derivatives are now under way in our laboratory, and the results to date suggest that this approach will be useful for assigning configurations to the  $\alpha$ -asymmetric centre of optically active carboxylic acids.

My somewhat cursory review of the present position of optical rotatory dispersion measurements in the natural products field has shown that, in a period of less than five years, this physical tool has become an important adjunct to investigations in this area. A great deal of research is now going on in a large number of laboratories on various practical and theoretical applications of rotatory dispersion to the entire field of organic chemistry. It is very unlikely that research on optical rotatory dispersion on the part of organic chemists would have proceeded so rapidly, and been accepted so generally, were it not for the fact that a variety of suitable test substances was available from the field of natural products. Indeed, in the development of no other physical method have natural products played so essential a rôle as in optical rotatory dispersion.

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