In the case of 16,16-d_2-estrone methyl ether (V), the material crystallized directly upon cooling and was recrystallized once to afford the desired material, m.p. 167–169°, which contained 11% of monodeuterio ketone as contaminant as determined by mass spectrometric examination of the molecular ion peaks. In the equilenin methyl ether series, the 16,16-d_2 analog XXIV was isolated by methylene chloride extraction and filtration in benzene solution through a short column of neutral alumina (activity II). Recrystallization from acetone provided the dideuterio derivative XXIV, m.p. 184° dec., containing 13% of the monodeuterio contaminant.

16,16-d_2-Estradiol methyl ether (VI) was prepared by lithium aluminum hydride reduction of V in ether solution (1 hr. steam-bath), while the 16,16,17-d_3 derivative VII was synthesized in an analogous fashion employing lithium aluminum deuteride.

15-Deuterio-estrone Methyl Ether (XII).—A solution of 35 mg. of 15-dehydroestrone methyl ether (X)[17] in 4 cc. of purified ethyl acetate was stirred with 50 mg. of 10% palladized charcoal catalyst in an atmosphere of deuterium[40] for 45 min. Filtration followed by evaporation of the solvent provided 27 mg. of crystalline material (m.p. 160–167°) which consisted of the following mixture as determined from the mass spectral molecular ion peaks (corrected for the natural abundance isotope peaks): 3% *d*-, 9% d_2-, 27% d_3-, 40% d_4-, 19% d_5- and 2% d_6-estrone methyl ether. The excess deuterium beyond d_2 (XI) is located in the aromatic ring as is demonstrated below.

The above material was equilibrated at C-16 by standing overnight with 10 cc. of methanol, 50 mg. of sodium and 0.8 cc. of water followed by heating under reflux for 45 min. The product was isolated by dilution with water and filtration and consisted of 6% *d*-, 26% d_2-, 46% d_3-, 21% d_4- and 1% d_5-estrone methyl ether, all excess deuterium beyond one (XII) being located in the aromatic ring. This was removed by stirring the material for 1 hr. in ethyl acetate solution with hydrogen in the presence of 50 mg. of 10% palladized charcoal catalyst, whereupon mass spectral analysis indicated the presence of 10% estrone methyl ether (I), 58% of 15-*d*-estrone methyl ether (XII), 27% of d_2- and 5% of d_3-derivative. The reaction was repeated once more whereupon the product (m.p. 160–165°) consisted of 76% of the desired 15-*d*-estrone methyl ether (XII), contaminated by 13% of non-deuterated material (I) and 11% of d_2-estrone methyl ether.

Catalytic Deuteration of 6-Methyl-6-dehydroestrone.[10]—A sample (2.3 mg.) of 6-methyl-6-dehydroestrone was shaken in a deuterium atmosphere in a micro-hydrogenation apparatus in 5 cc. of ethyl acetate in the presence of 10 mg. of 10% palladized charcoal catalyst. The uptake of deuterium (0.24 cc.) ceased within 2 min. and the mixture was filtered immediately and the solvent evaporated to dryness. The residue was shown by mass spectrometry to consist of 42% 6,7-d_2- and 30% x, 6,7-d_3-6-methylestrone,[11] the remaining contaminants being 11% monodeuterio, 7% d_4-, 6% d_5- and 3% d_6-6-methylestrone.

Acknowledgment.—In addition to the sources indicated in refs. 9, 14b, 28 and 36, we are particularly indebted to Dr. Pierre Crabbé (Syntex, S.A., Mexico City) and Prof. W. S. Johnson (Stanford University) for fulfilling numerous requests for samples.

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(40) The course of the catalytic deuteration of steroidal olefins, dienes and enones will be discussed in detail in another paper.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF.]

Optical Rotatory Dispersion Studies. LXXVIII.[1] Comparative Studies of Circular Dichroism and Rotatory Dispersion Curves. Some Observations on Sulfur-containing Chromophores[2]

BY CARL DJERASSI, H. WOLF AND E. BUNNENBERG

RECEIVED JULY 23, 1962

Comparative ultraviolet absorption spectra, optical rotatory dispersion and circular dichroism curves are reported for a number of representative sulfur-containing chromophores such as xanthates, dithiocarbamates, thionocarbethoxy-α-amino acids, thiohydantoins, acylthioureas and cyclic disulfides (a cyclic diselenide also being included for comparison). These results are used to indicate that, for most stereochemical applications in organic chemistry, optical rotatory dispersion and circular dichroism measurements may be used interchangeably. The operation of background rotation effects in optical rotatory dispersion is discussed and it is pointed out, through examples among steroid ketones, that such background effects may often represent a desirable feature for structural work by optical rotatory dispersion, which is not as conveniently possible by means of circular dichroism. In other situations, especially where recognition of Cotton effects is masked by such background rotations or when overlapping, optically active absorption bands enter into operation, circular dichroism measurements are to be preferred, the recognition of very weak or hidden absorption bands being a particularly useful application.

Introduction

The phenomena of circular dichroism (C.D.) and of optical rotatory dispersion (O.R.D.) are intimately related.[3] The former refers to unequal absorption of right and left circularly polarized light by the optically active medium, while the latter corresponds to the change in optical rotation (unequal refractive indices of medium for right and left circularly polarized light) with wave length. Of particular interest are those wave length regions corresponding to absorption bands of the chromophore under discussion and, for most (colorless) organic substances, this means the ultraviolet range.

Both optical rotatory dispersion and circular dichroism have been determined in the ultraviolet in the past by physical chemists,[4] using laborious measurements on a few isolated organic substrates. The availability, in the early nineteen fifties, of a relatively simple spectropolarimeter led to the rapid determination of several thousand optical rotatory dispersion curves and to the now well-known[3] applications of this tool in organic chemistry, notably in stereochemistry and conformational analysis. If, instead of a spectropolarimeter, there had been available a convenient instrument

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(1) Paper LXXVII, C. Djerassi and W. Klyne, *J. Chem. Soc.*, in press (1962).

(2) Supported by the National Science Foundation (grant No. G-19905) and the National Cancer Institute (grant No. CRTY-5061) of the National Institutes of Health, U. S. Public Health Service.

(3) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960; see especially chapters 1 and 12.

(4) See especially T. M. Lowry, "Optical Rotatory Power," Longmans, Green and Co., London, 1935; and W. Kuhn, *Ann. Rev. Phys. Chem.*, **9**, 417 (1958).

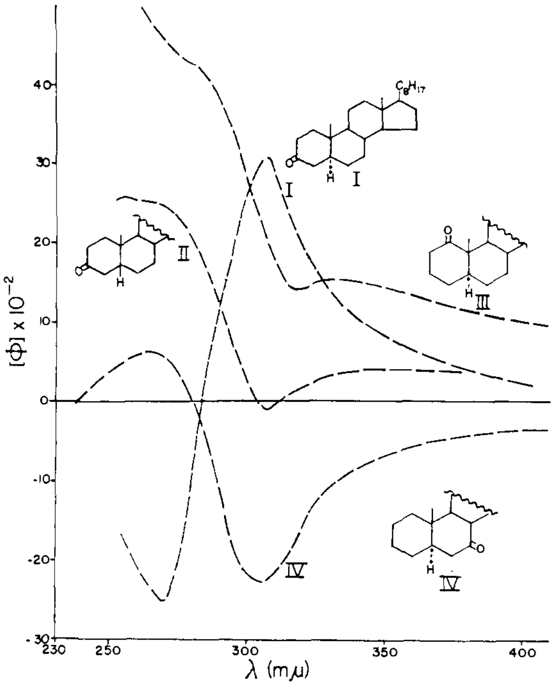

Fig. 1.—Optical rotatory dispersion curves (methanol solution) of cholestan-3-one (I). coprostan-3-one (II), cholestan-1-one (III) and cholestan-7-one (IV).

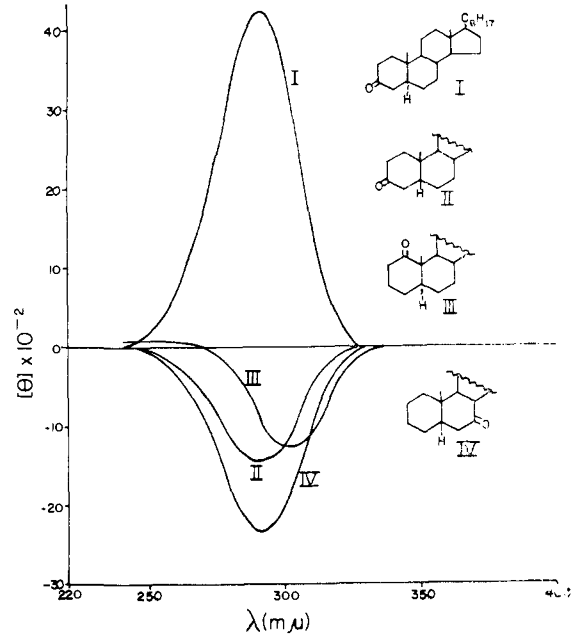

Fig. 2.—Circular dichroism curves (methanol solution) of cholestan-3-one (I), coprostan-3-one (II), cholestan-1-one (III) and cholestan-7-one (IV).

to measure circular dichroism, then, in our opinion' most of this work would have been performed in terms of circular dichroism rather than optical rotatory dispersion because either tool will offer the same information for the vast majority of applications in organic chemistry. However, it is only very recently[5] that rapid C.D. determinations have been made possible and the only large number of circular dichroism measurements that has been performed with such an instrument[5b] has been among steroid ketones.[6] This is precisely the area in which the original rotatory dispersion studies[7] were performed that led to the general organic chemical applications of optical rotatory dispersion and the question arises what the respective roles of the two methods will be in the future.

For theoretical work, especially quantitative studies related to rotational strength,[8] circular dichroism is to be preferred (see Fig. 1 *vs.* Fig. 2), although the same information can be extracted[8,9]—albeit less conveniently—from the rotatory dispersion curve. For most organic chemical work. the quantitative information derivable from the amplitude of the rotatory dispersion curve (difference in molecular rotation between the two extrema of a Cotton effect) is completely adequate.[1,10] Similarly, the French authors[6] have shown in their recent circular dichroism measurements of steroid ketones that most of the applications of O.R.D. and C.D. to stereochemical problems are identical. Thus, the O.R.D. curves of the stereoisomers cholestan-3-one (I) and coprostan-3-one (II) are of mirror image type (Fig. 1) and the same applies to their C.D. curves (Fig. 2). There remains a small but important area of organic chemical problems where circular dichroism alone will provide the answer, and this involves relatively closely situated or even overlapping absorption bands, and where it is not evident from the rotatory dispersion curve whether one or both of the transitions are "optically active". Pertinent examples of this phenomenon are cited by the French group[6] in the steroid ketone series and in our own circular dichroism studies[11] with Mislow and Moscowitz dealing with optically active biaryls.

The reason for this important application of circular dichroism, as well as for the greater ease in securing quantitative rotational strength values from it, lies in the fact that most rotatory dispersion curves are subject to "background" rotations (due to more distant absorption bands of the same chromophore or of other atoms in the same molecule) which need to be subtracted for such quantitative work.[8,9] However, it is instructive to note that the operation of these background effects in O.R.D. (and absent in C.D.) is one of the important advantages of O.R.D. in many qualitative appli-

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(5) (a) J. Badoz, M. Billardon and J.-P. Mathieu, *Compt. rend.*, **251**, 1477 (1960); (b) M. Grosjean and M. Legrand, *ibid.*, **251**, 2150 (1960); (c) R. Deen, D. Sc. thesis, Leiden, 1961; (d) A. I. Scott and F. McCapra (University of Glasgow), private communication; see also S. Mitchell, "Unicam Spectrovision," No. **6**, 6 (1958); (e) S. Holzwarth, W. B. Gratzer and P. Doty, *J. Am. Chem. Soc.*, **84**, 3194 (1962).

(6) (a) L. Velluz and M. Legrand, *Angew. Chem.*, **73**, 603 (1961); (b) M. Legrand and J. Mathieu, *Bull. soc. chim. France*, 1679 (1961).

(7) For leading references see chapter 4 in ref. 3.

(8) A. Moscowitz, chapter 12 in ref. 3.

(9) See also A. Moscowitz, *Tetrahedron*, **13**, 48 (1961).

(10) For recent examples of the quantitative use of rotatory dispersion amplitudes see: (a) C. Djerassi, E. J. Warawa, J. M. Berdahl and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 3334 (1961); (b) J. Allinger, N. L. Allinger, L. E. Geller and C. Djerassi, *J. Org. Chem.*, **26**, 3521 (1961); (c) C. Beard, C. Djerassi, T. Elliott and R. C. C. Tao, *J. Am. Chem. Soc.*, **84**, 874 (1962); (d) C. Djerassi, E. Lund and A. A. Akhrem, *ibid.*, **84**, 1249 (1962); (e) C. Djerassi and W. Klyne, *J. Chem. Soc.*, in press (1963).

(11) E. Bunnenberg, C. Djerassi, K. Mislow and A. Moscowitz, *J. Am. Chem. Soc.*, **84**, 2833 (1962).

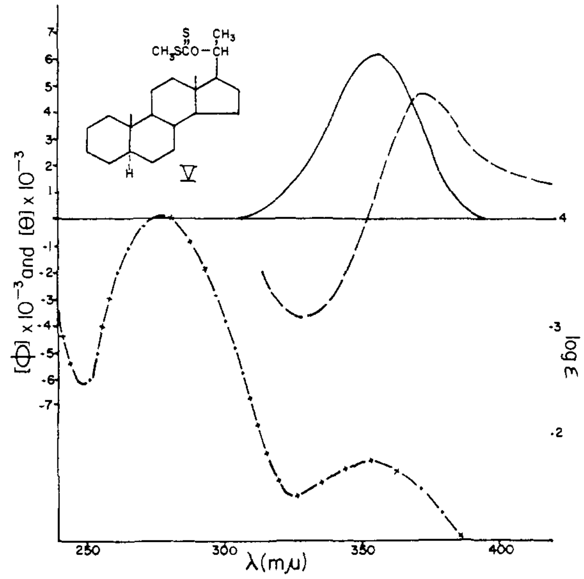

Fig. 3.—Circular dichroism (———), optical rotatory dispersion (– – – –) and ultraviolet absorption (—+—+) curves of 5α-pregnan-20β-ol methyl xanthate (V) in isoöctane solution.

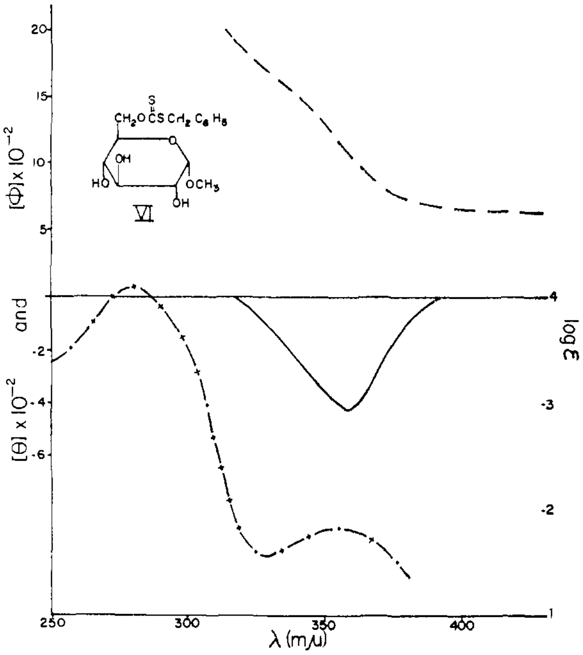

Fig. 4.—Circular dichroism (———), optical rotatory dispersion (– – – –) and ultraviolet absorption (—+—+) curves of methyl α-D-glycopyranoside 6-(S-benzyl) xanthate (VI) in dioxane solution.

cations in organic chemistry and some pertinent examples are shown in Figs. 1 and 2.

Thus, if one examines the O.R.D. curves of the three 5α-cholestane isomers with carbonyl groups in the 3-(I), 1-(III) and 7-(IV) positions, it will be noted immediately that the *shapes* of the rotatory dispersion curves are characteristically different. For instance, the 1-(III) and 7-(IV) keto isomers both show negative Cotton effects, but that of the 1-ketone III is very weak and is superimposed on a strongly positive background dispersion. Similarly, the negative Cotton effect of a 4-ketocholestane derivative is quite distinct[12] from that of the 7-ketone IV. These differences in shape as well as sign of the Cotton effect have proved to be very useful[7,12] for locating a carbonyl group in a steroid skeleton.

If the C.D. curves of these same three ketones (I, III, IV) measured in the identical solvent (methanol) are now examined (Fig. 2), it will be noted immediately that the virtue of C.D.—absence of background effects and hence simpler quantitative evaluation of rotational strength—becomes a drawback for structural work, since C.D. curves will differ qualitatively only in sign rather than shape. The shift (Fig. 2) in wave length for the C.D. minimum of cholestan-1-one (III) simply parallels the identical shift in the O.R.D. (Fig. 1) and ultraviolet (see Experimental) spectra. Similarly, 3-keto-5β-steroids, such as coprostan-3-one (II) (Fig. 1), always show a negative O.R.D. Cotton effect, which characteristically starts on a positive background (especially above 340 mμ), a feature which has proved to be extremely useful for recognition of the nature of the A/B stereochemistry in 3-keto steroids.[13] The C.D. curve (Fig. 2), on the other hand, does not reflect this feature at all and the C.D. curves of 5α-cholestan-7-one (IV) and coprostan-3-one (II) are virtually identical and differ only in intensity.

It is our impression that in balance, for the great majority of the *standard organic chemical applications*, either O.R.D. or C.D. will provide essentially the same information and that no striking advantage attaches to either one. As such a large number of O.R.D. curves have been measured during the past few years and so many spectropolarimeters are distributed, it would not appear fruitful to perform extensive C.D. measurements for such purposes. Rather, we feel at the present time that research on circular dichroism studies in organic chemistry—in contradistinction to quantitative theoretical studies—might be used more constructively in uncovering novel possible applications of C.D., not feasible by O.R.D., as well as confirming, in judiciously selected cases, the earlier assignments of optical activity of certain absorption bands reached by O.R.D. It is in these two areas that C.D. work is currently progressing in our laboratory and, as our earlier O.R.D. studies[7] with steroid ketones have been fully substantiated by C.D. measurements,[6] we have concentrated especially on chromophores other than the carbonyl group. No work has been performed among organic compounds during the last twenty years in this field and only very few isolated examples of ultraviolet C.D. curves of non-carbonyl containing chromophores have been described in the past.[4] The present paper is concerned with exploratory circular dichroism studies among a number of types of organic compounds containing the $C{=}S$ or disulfide chromophores, parallel

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[12] C. Djerassi, W. Closson and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956).

[13] C. Djerassi and W. Closson, *ibid.*, **78**, 3761 (1956), especially Fig. 2.

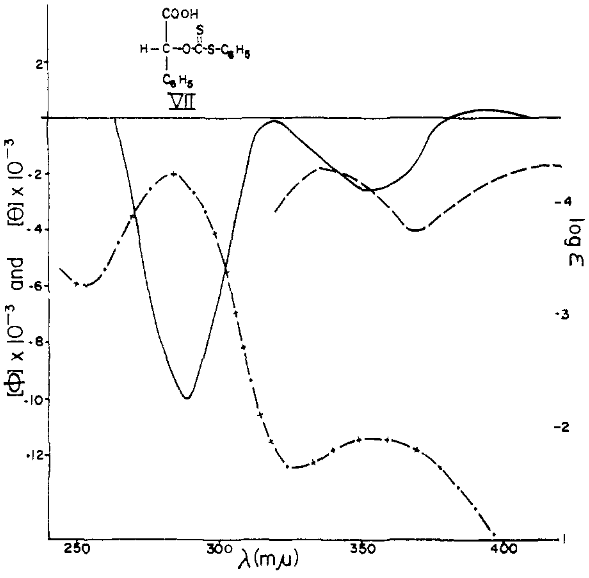

Fig. 5.—Circular dichroism (———), optical rotatory dispersion (– – – –) and ultraviolet absorption (—+—+) curves of D-(−)-mandelic acid ethyl dithiocarbonate (VII) in dioxane solution. The C.D. curve below 310 mμ is only of qualitative significance.

rotatory dispersion and ultraviolet absorption being presented at the same time because of the intimate relation of these three parameters.

Xanthates and Dithiocarbamates.—The only circular dichroism study performed in the past with optically active substances possessing the C═S chromophore is that by Lowry and Hudson[14] covering xanthates and dithiourethanes of menthol and borneol. Such xanthates possess ultraviolet absorption maxima near 355 and 280 mμ, the former being of rather low intensity, and the British workers[14] noted strong rotatory dispersion Cotton effects and corresponding circular dichroism maxima for this 355 mμ transition. In a detailed rotatory dispersion investigation covering over thirty different xanthates,[15,16] we have observed that the amplitude of the Cotton effect in the 350 mμ region can differ greatly, depending upon the degree of substitution around the xanthate grouping,[17] and that the sign of this Cotton effect can be utilized for stereochemical assignments.

For instance, the O.R.D. curves of the xanthates of the C-20 epimeric 20-hydroxypregnanes exhibit[17] Cotton effects of opposite sign which are very helpful in deciding on the stereochemistry at that center. In Fig. 3 is shown the O.R.D. curve of such a typical xanthate, 5α-pregnan-20β-ol methyl xanthate (V), its positive Cotton effect being associated with the 354 mμ low intensity absorption band. Circular dichroism measurements[18] (Fig. 3) corroborate this conclusion but do not offer any additional information of stereochemical consequence. However, with a few xanthates, this Cotton effect is very weak and masked by the background effect alluded to above. As an illustration, in Fig. 4 there is reproduced the rotatory dispersion curve[16] of methyl α-D-glucopyranoside-6-(S-benzyl)-xanthate (VI), which shows only a slight inflection in the region of the 354 mμ absorption maximum, indicative of a negative Cotton effect superimposed on a positive background rotation. The circular dichroism curve (Fig. 3) of this substance shows a clearly defined minimum, thus demonstrating that this absorption band is indeed optically active and that the earlier attributed[16] weak negative Cotton effect in the O.R.D. curve is real. The results summarized in Fig. 4 thus represent an illustration where the background effect in the O.R.D. curve is a disadvantage—in contrast to the situation obtaining in Fig. 1—and where the C.D. curve yields more precise and useful information.

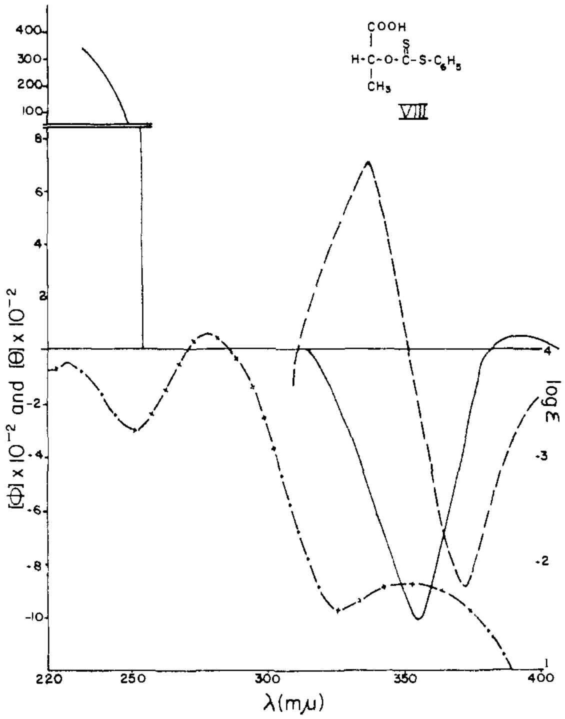

Fig. 6.—Circular dichroism (———), optical rotatory dispersion (———) and ultraviolet absorption (—+—+) curves of D-(−)-lactic acid ethyl dithiocarbonate (VIII) in methanol solution.

The two xanthates (V, VI) chosen illustrate two general situations which are encountered in this type of work. In the first instance (Fig. 3), background effects in O.R.D. play a negligible role and either O.R.D. or C.D. yields the equivalent information, while in the second example (Fig. 4), C.D. is certainly to be preferred. In most xanthates reported earlier,[14–17] the Cotton effect corresponding to the 355 mμ absorption band is very clearly defined and completely adequate for stereochemical studies: circular dichroism measurements, therefore, will not offer any additional information in those cases as far as this type of stereochemical work is concerned. Optical rota-

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[14] T. M. Lowry and H. Hudson, *Phil. Trans. Roy. Soc. London, Ser. A*, **232**, 117 (1933).

[15] For preliminary discussion, see chapter 15 in ref. 3.

[16] B. Sjöberg, D. J. Cram, L. Wolf and C. Djerassi, *Acta Chem. Scand.*, **16**, 1079 (1962).

[17] See also C. Djerassi, I. T. Harrison, O. Zagneetko and A. L. Nussbaum, *J. Org. Chem.*, **27**, 1173 (1962).

[18] All circular dichroism curves are plotted in terms of molecular ellipticity as defined in ref. 3, p. 155.

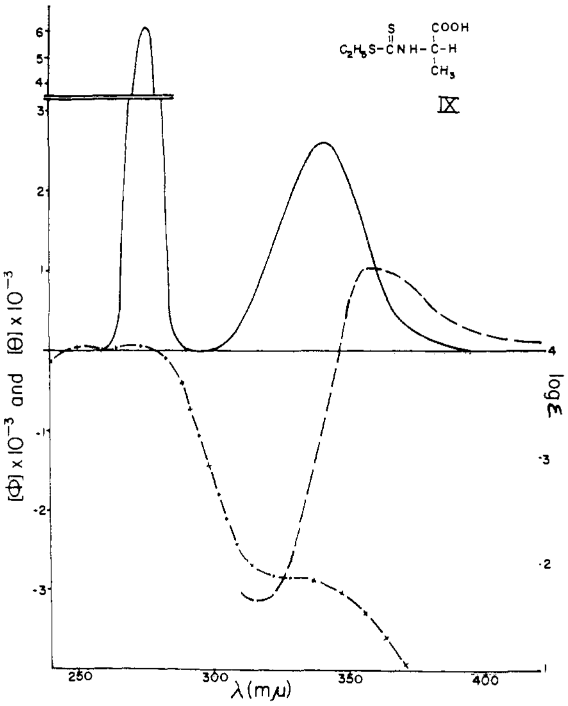

Fig. 7.—Circular dichroism (———), optical rotatory dispersion (– – –) and ultraviolet absorption (—+—+) curves of N-dithiocarbethoxy-L-alanine (IX) in methanol solution. The C.D. curve below 300 mμ is only of qualitative significance.

tory dispersion and circular dichroism measurements have not yet been performed with most xanthates below 300 mμ and, therefore, it is not known whether the high intensity 280 mμ absorption band is generally optically active. With improved spectropolarimetric instrumentation it should be possible to determine this point and to see whether the results show the same correspondence with C.D. measurements as has been observed for the 355 mμ absorption.

One of the most useful applications of our earlier O.R.D. measurements of xanthates has been the establishment of absolute configuration of α-hydroxy acids, the sign of their Cotton effect (in the 350 mμ region) corresponding to the sign of the O.R.D. Cotton effect of the dithiocarbamate of α-amino acids of like absolute configuration[19] (positive Cotton effect for L-configuration, negative effect for D-configuration). The relevant information for such xanthates is contained in Figs. 5 and 6, which show substantial negative Cotton effects for the xanthates of D-(−)-mandelic acid (VII) and D-(−)-lactic acid (VIII) centered around the 355 mμ absorption band, these negative Cotton effects now being substantiated by negative C.D. curves in this same region. Consequently, for absolute configurational assignment purposes, either the O.R.D. or the C.D. curve in the 350 mμ region will provide the identical answer.

While O.R.D. measurements have not as yet been performed for such α-hydroxy acid xanthates through the region of the strong 280 mμ absorption band, it has been possible to examine the circular dichroism in that spectral range by using very dilute solutions. This dilution factor makes the quantitative reliability of the C.D. curve (Fig. 5) below 310 mμ dubious, but there is no question that, qualitatively, the mandelic acid derivative VII exhibits a second C.D. minimum at 289 mμ. The latter is not observed in the C.D. curve (Fig. 6) of the lactic acid derivative VIII, which only shows the beginning of a C.D. maximum near 230 mμ. Whether the low wave-length C.D. feature in Fig. 5 is a reflection of the phenyl substituent[20] (mandelic acid itself shows several weak absorption bands between 250–263 mμ) or, more likely, is due to the 283 mμ xanthate absorption cannot be decided with the present instrument. Thus, if the lactic acid derivative VIII possesses a C.D. minimum of only one-half the intensity of that of VII, it would not have been detectable under present circumstances.

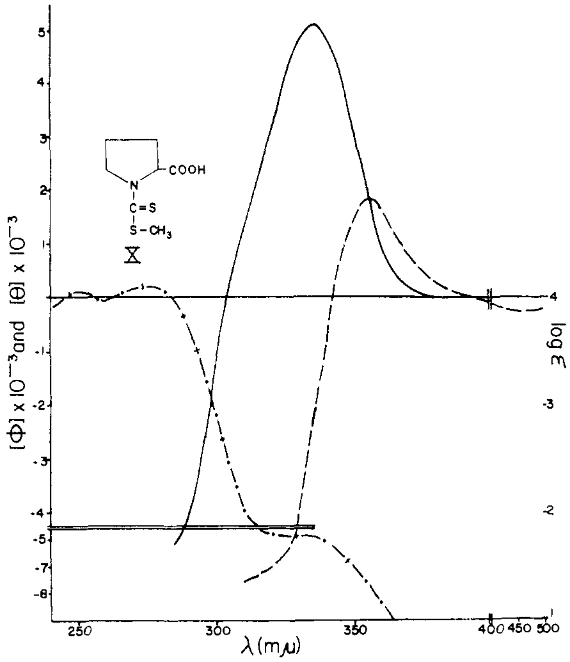

Fig. 8.—Circular dichroism (———), optical rotatory dispersion (– – –) and ultraviolet absorption (—+—+) curves of N-dithiocarbomethoxy-L-proline (X) in methanol solution.

As mentioned above, the sign of the O.R.D. Cotton effect of dithiocarbamates of α-amino acids can be related[19] to absolute configuration and also utilized for stereochemical assignments among optically active α-hydroxy acids. Thus, the dithiocarbamate derivatives IX and X, corresponding to L-alanine (IX) and L-proline (X), exhibit positive Cotton effects (Fig. 7 and 8) centered around the 330 mμ low extinction absorption band, while the corresponding derivative of D-aspartic acid (XI) shows a negative Cotton effect (Fig. 9). We have now measured the circular dichroism of these three derivatives and the sign of their C.D. curves corresponds to the sign of the O.R.D. Cotton effect (Figs. 7–9). Again, one can conclude that for absolute configurational studies—at present the

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(19) B. Sjöberg, A. Fredga and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 5002 (1959).

(20) See also W. Kuhn and H. Biller, *Z. physik. Chem. (Leipzig)*, (B)**29**, 1 (1935).

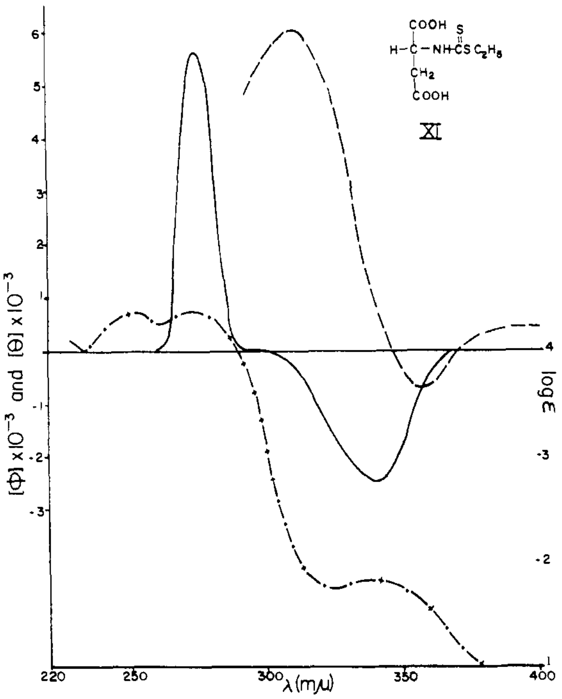

Fig. 9.—Circular dichroism (———), optical rotatory dispersion (– – –) and ultraviolet absorption (—+—+) curves of N-dithiocarbethoxy-D-aspartic acid (XI) in dioxane solution. The C.D. curve below 295 mμ is only of qualitative significance.

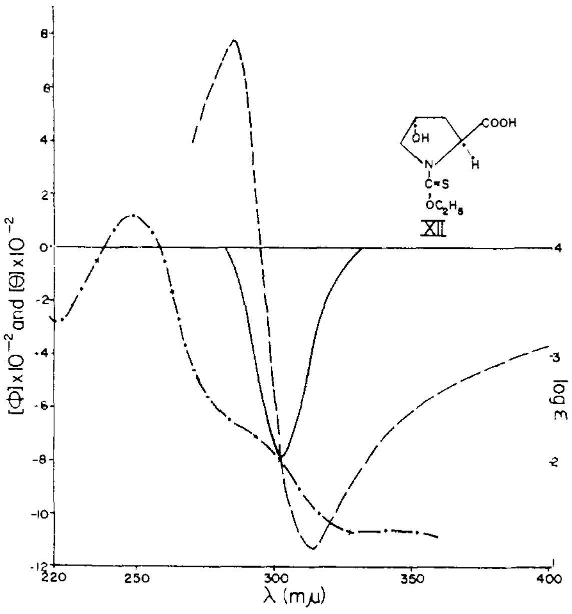

Fig. 10.—Circular dichroism (———), optical rotatory dispersion (– – –) and ultraviolet absorption (—+—+) curves of N-thionocarbethoxy-L-hydroxyproline (XII) in dioxane solution.

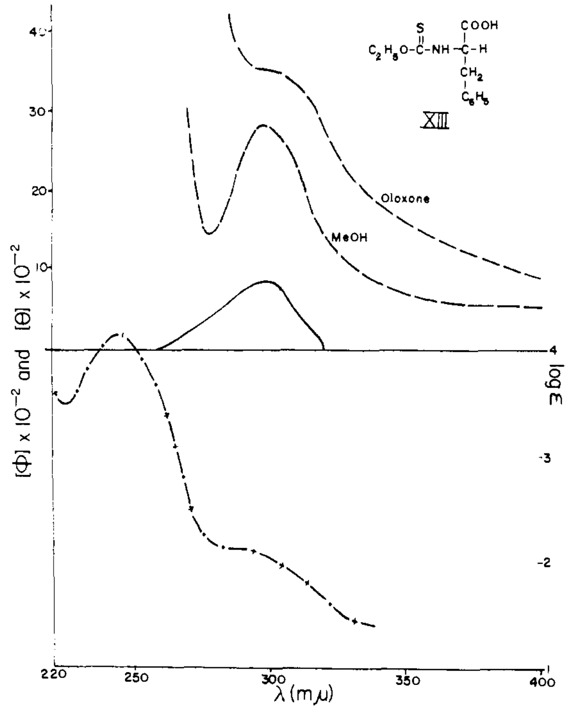

Fig. 11.—Circular dichroism (———), optical rotatory dispersion (– – –) and ultraviolet absorption (—+—+) curves of N-thionocarbethoxy-L-phenylalanine (XIII) in dioxane solution (O.R.D. curve in methanol and dioxane).

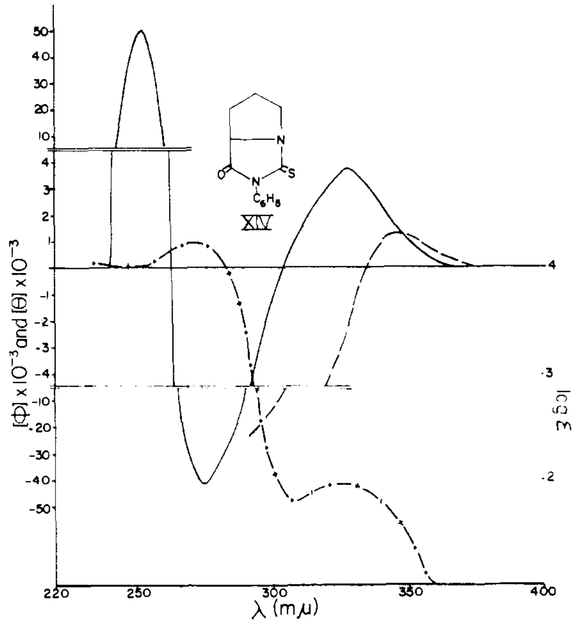

Fig. 12.—Circular dichroism (———), optical rotatory dispersion (– – –) and ultraviolet absorption (—+—+) curves of 1,5-cyclotrimethylene-3-phenyl-2-thiohydantoin (XIV) in dioxane solution. The C.D. curve below 295 mμ is only of qualitative significance.

only organic chemical application of optical measurements with these derivatives—either O.R.D. or C.D. will offer the identical information.

Brief mention is warranted of preliminary C.D. results below 300 mμ, a spectral region which, because of the high extinction of the 275 mμ absorption band, has not yet been investigated by O.R.D. High dilution C.D. measurements, though of doubtful quantitative significance, indicate that, while the alanine (IX) and aspartic acid (XI) dithiocarbamates belong to the opposite configura-

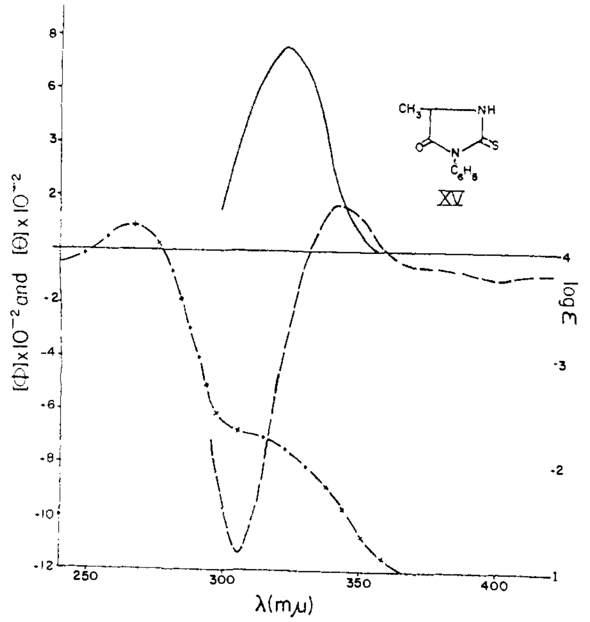

Fig. 13.—Circular dichroism (———), optical rotatory dispersion (——) and ultraviolet absorption (—+—+) curves of 5-methyl-3-phenyl-2-thiohydantoin (XV) in methanol solution.

tional series, both appear to show positive C.D. curves (Figs. 7 and 9) in that region, in contrast to an incipient C.D. minimum (Fig. 8) in the L-proline derivative X.

N-Thionocarbethoxyamino Acids and 3-Phenyl-2-thiohydantoins.—The rotatory dispersion curves of a series of N-thionocarbethoxy α-amino acids have recently been discussed[21] in terms of their absolute configuration and it was noted that the slight shoulder in their ultraviolet absorption spectra around 290 mμ corresponded to an optically active absorption band giving rise to Cotton effects. To substantiate this conclusion, we have selected two different N-thionocarbethoxy-α-amino acids for circular dichroism measurements. The first—a derivative of L-hydroxyproline (XII)—exhibits a very noticeable negative Cotton effect (Fig. 10) in the region of this ultraviolet absorption shoulder and the presently observed negative C.D. curve (Fig. 10) fully substantiates our earlier conclusions[21] about the optical activity of this weak absorption band.

The second example is N-thionocarbethoxy-L-phenylalanine (XIII), which exhibits in methanol solution (see Fig. 11) a well-defined positive Cotton effect[21] superimposed on a positive background. In dioxane solution, however, this Cotton effect becomes less well defined as illustrated in Fig. 11 and the corresponding C.D. curve (Fig. 11) permits much clearer recognition of this feature. With the exception of this O.R.D. curve, all other thionocarbethoxy derivatives exhibited[21] standard Cotton effects and one can conclude that, for stereochemical studies, either measurement will provide the identical information and that it would seem superfluous, therefore, to repeat C.D. curves for any of the substances in this series where O.R.D. curves have already been recorded.[21]

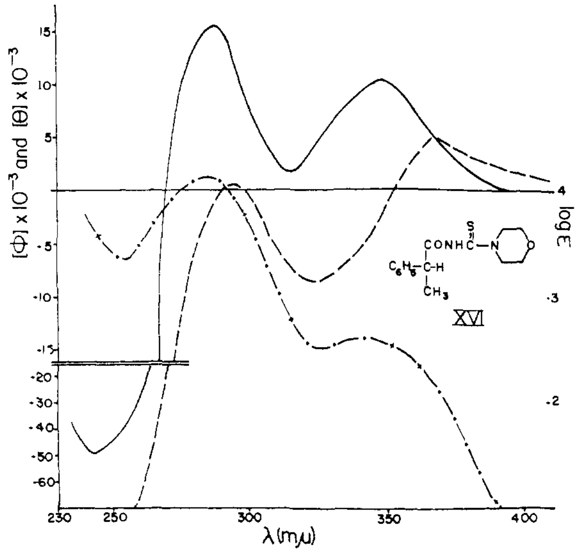

Fig. 14.—Circular dichroism (———), optical rotatory dispersion (——) and ultraviolet absorption (—+—+) curves of (−)-(*R*)-hydratropyl-morpholinothiocarbamide (XVI) in dioxane solution. The C.D. curve below 330 mμ is only of qualitative significance.

3-Phenyl-2-thiohydantoins, derivable from α-amino acids, yield O.R.D. Cotton effects which can be employed for stereochemical conclusions,[21] although these derivatives are not as suitable as the dithiocarbamates IX–XI or thionocarbethoxy derivatives XII,XIII because of their ease of racemization. The hydantoins possess a weak absorption maximum near 320 mμ (XIV: $\lambda_{\max}^{\mathrm{MeOH}}$ 318 mμ, $\lambda_{\max}^{\mathrm{diox}}$ 327 mμ, log ε 1.96: XV: $\lambda_{\mathrm{shoulder}}^{\mathrm{MeOH}}$ 310 mμ) which gives rise to positive O.R.D. Cotton effects as illustrated in Fig. 12 for L-prolin (XIV) and in Fig. 13 for the L-alanine analog XV. These conclusions[21] from the O.R.D. curves could be verified now by C.D. measurements as shown in Figs. 12 and 13, both hydantoin derivatives showing positive C.D. curves. High dilution C.D. measurements below 310 mμ with the proline derivative reveal (in dioxane solution; Fig. 12) a C.D. minimum at 277 mμ and a C.D. maximum at 252 mμ. These appear to be real and were also observed in methanol solution, thus indicating that the high intensity absorption maximum in the 270 mμ regions apparently consists of two overlapping absorption bands. Similar measurements in the alanine derivative XV did not lead to any observable C.D. extrema (see Fig. 13) below 300 mμ, which might well be due to partial racemization and consequent inability to detect weaker circular dichroism extrema in such dilute solution. It might be profitable to examine in detail the circular dichroism behavior of a group of thiohydantoins in this high intensity region of their absorption spectra once instrumentation has been improved to provide quantitatively significant values.

Acyl Thioureas.—Conversion of the optically transparent[22] carboxyl function into an acyl

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[21] C. Djerassi, K. Undheim, R. C. Sheppard, W. G. Terry and B. Sjöberg, *Acta Chem. Scand.*, **15**, 903 (1961).

[22] This statement refers to the spectral region above 220 mμ.

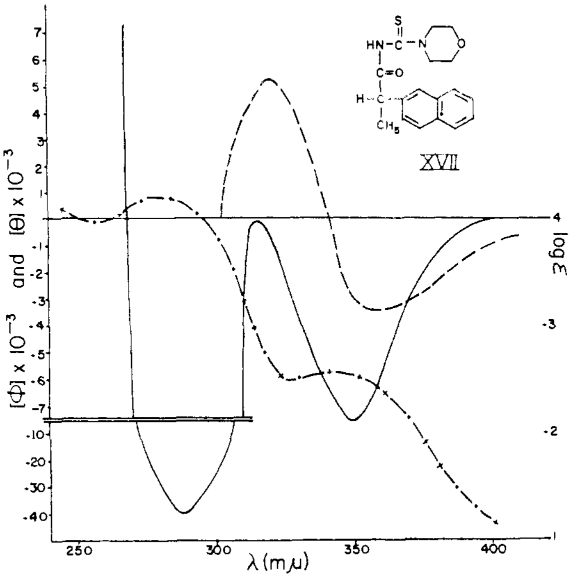

Fig. 15.—Circular dichroism (———), optical rotatory dispersion (——) and ultraviolet absorption (—+—+) curves of (+)-(S)-α-(2-naphthyl)-propionyl-morpholinothiocarbamide (XVII) in dioxane solution. The C.D. curve below 310 mμ is only of qualitative significance.

thiourea results in "chromophoric" derivatives which exhibit O.R.D. Cotton effects in a very convenient spectral range as a result of a weak absorption band near 345 mμ. This has made possible[23] for the first time a correlation between ultraviolet Cotton effects and absolute configuration of α-substituted carboxylic acids. These correlations were based on the sign of the Cotton effect centered around 345 mμ, as shown in Fig. 14 for (−)-(R)-hydratropyl-morpholinothiocarbamide (XVI) (positive Cotton effect) and in Fig. 15 for (+)-(S)-α-(2-naphthyl)-propionyl-morpholinothiocarbamide (XVII) (negative Cotton effect). Circular dichroism measurements have now been performed with these acylthioureas which demonstrate in the hydratropyl derivative (Fig. 14) the existence of two positive C.D. curves followed by a negative one (only partially defined). New rotatory measurements with further penetration into the ultraviolet (Fig. 14) are in complete accord with these results and show the two positive Cotton effects as well as a negative background rotation. That these observations in the region below 300 mμ are not artifacts resulting from stray light phenomena[24] was established by parallel measurements utilizing the racemate of XVI which exhibited only a straight line (O.R.D. as well as C.D.) throughout this spectral region. Similar observations were made in the 2-naphthyl derivative XVII (Fig. 15) except that the O.R.D. (not measured below 310 mμ) and C.D. curves are of opposite sign as compared to XVI (Fig. 14) because of the antipodal relationship of the two substances. These preliminary results demonstrate that, for stereochemical studies,[23] O.R.D. or C.D. measurements of acylthioureas will offer the identical information.

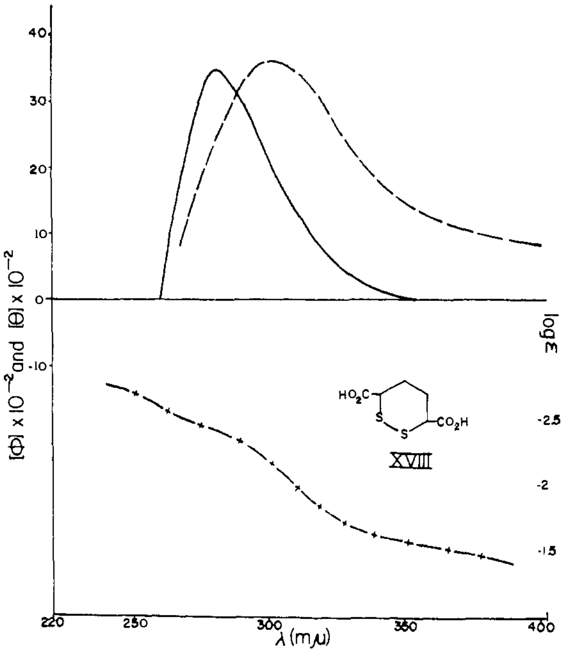

Fig. 16.—Circular dichroism (———), optical rotatory dispersion (——) and ultraviolet absorption (—+—+) curves of (+)-1,2-dithiane-3,6-dicarboxylic acid (XVIII) in dioxane solution.

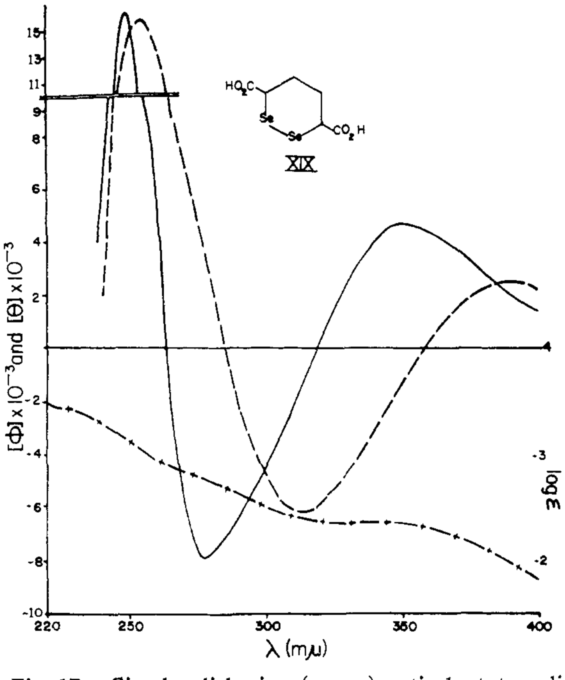

Fig. 17.—Circular dichroism (———), optical rotatory dispersion (——) and ultraviolet absorption (—+—+) curves of (+)-1,2-diselenane-3,6-dicarboxylic acid (XIX) in dioxane solution. The C.D. curve below 318 mμ is only of qualitative significance.

Disulfides and Diselenides.—The above-discussed substances all contained the C═S chromophore, which gave rise to optically active absorp-

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[23] C. Djerassi and K. Undheim, *J. Am. Chem. Soc.*, **82**, 5755 (1960); C. Djerassi, K. Undheim and A.-M. Weidler, *Acta Chem. Scand.*, **16**, 1147 (1962).

[24] For discussion see C. Djerassi, E. Lund, E. Bunnenberg and J. C. Sheehan, *J. Org. Chem.*, **26**, 4509 (1961).

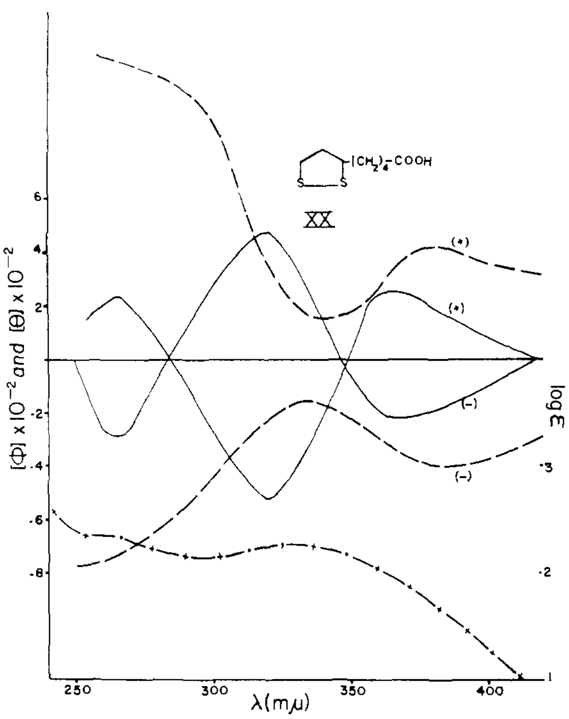

Fig. 18.—Circular dichroism (———), optical rotatory dispersion (– – –) and ultraviolet absorption (—+— +) curves of (+)- and (–)-6,8-thioctic acid (XX) in dioxane solution. The C.D. curve below 285 mμ is only of qualitative significance.

tion bands in a convenient spectral range. Another group of organic sulfur compounds possessing this desirable property are the disulfides, especially cyclic ones, and rotatory dispersion measurements have been performed recently[25] with a number of them. Thus, the inflection in the ultraviolet absorption spectrum (Fig. 16) of (+)-1,2-dithiane-3,6-dicarboxylic acid (XVIII) is responsible for a positive Cotton effect, the first extremum of which had been observed earlier[25] in methanol solution. Repeat measurements (Fig. 16) in dioxane solution still did not lead to complete definition of the Cotton effect since its trough could not be reached, but determination of its circular dichroism (Fig. 16) confirmed our earlier conclusion that we are dealing here with a positive Cotton effect associated with the 280 mμ absorption band.

The corresponding diselenide XIX was also available from the earlier O.R.D. work,[25] where a positive Cotton effect could be associated with the 340 mμ absorption. New O.R.D. measurements (Fig. 17) resulted in further ultraviolet penetration and detection of another peak in the 270 mμ region. Particularly instructive are the C.D. results (Fig. 17) with this diselenide, which exhibits three successive circular dichroism extrema at 351, 277 and 249 mμ. The first (positive) and second (negative) C.D. extrema correspond to the observed (Fig. 17) positive and negative Cotton effects in the 340 and 270 mμ regions, respectively. Both O.R.D. and C.D. in this instance represent much clearer indicators of the relevant absorption bands than the ultraviolet absorption spectrum.

Both antipodes of the biologically important 6,8-thioctic acid (XX) became available[26] for optical measurements and, as shown in Fig. 18, it has now been possible to measure the entire first Cotton effect, which quite obviously does not correspond to the well-known long wave length maximum[27] at 330 mμ but rather to a hidden transition around 365 mμ. Just as with the diselenide XIX (Fig. 17), the circular dichroism curve exhibits successive positive (367 mμ), negative (320 mμ) and positive (265 mμ) extrema (for the (+)-antipode), of which the first two have their easily recognizable counterparts in the O.R.D. Cotton effects and where even partial entry into the third (positive) Cotton effect may be noted. The 367 and 265 mμ C.D. extrema and the corresponding Cotton effects (Fig. 18) indicate the existence of nearly or completely hidden optically active absorption bands, the detection of which by C.D. or O.R.D. represents another illustration of the utility of such optical measurements in situations of this type.

Conclusion

The results outlined in this paper as well as the data reported for steroid ketones by Velluz and Legrand[6] indicate that, for the largest proportion of present O.R.D. applications in organic chemistry, C.D. measurements will yield the same information. This direct applicability of O.R.D. results to C.D. work is a fortunate circumstance because it will permit in most instances future interchangeable use of O.R.D. or C.D., thus rendering superfluous the repetition in terms of circular dichroism of the many measurements which had been necessary in the original correlations[3] between optical rotatory dispersion and structural, stereochemical or conformational parameters.

The well-known superimposition of background rotations (at times negligible, but often appreciable) in O.R.D. curves can be either an advantage or a disadvantage, depending upon the circumstances and these will become more clearly defined as additional parallel O.R.D. and C.D. studies are performed. When the operation of such background effects is of advantage—as, for instance, in structural work as outlined in Fig. 1—then O.R.D. is to be preferred. On the other hand, when the background rotation masks the recognition of a Cotton effect (*e.g.*, Fig. 4), or when overlapping absorption bands play an important role, then C.D. measurements are more useful. Furthermore, the latter method, in particular, may prove invaluable in the recognition of hidden electronic transitions as illustrated in Figs. 5 and 6 (broad 355 mμ ultraviolet maximum corresponding to C.D. extrema at 386 and 355 mμ), Fig. 12 (no observable ultraviolet maximum corresponding to 252 mμ C.D. extremum), Fig. 17 (only slight inflection in ultraviolet regions corresponding to C.D. extrema or midpoints of O.R.D. Cotton effects) and Fig. 18

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(25) C. Djerassi, A. Fredga and B. Sjöberg, *Acta Chem. Scand.*, **15**, 417 (1961).

(26) We are indebted to Dr. Karl Folkers (Merck and Co.) and Dr. L. J. Reed (University of Texas) for these valuable specimens.

(27) J. A. Barltrop, P. M. Hayes and M. Calvin, *J. Am. Chem. Soc.*, **76**, 4348 (1954).

(no observable ultraviolet absorption maximum corresponding to 367 mμ C.D. extremum and corresponding O.R.D. Cotton effect).

Experimental[28]

Cholestan-3-one (1), C.D. (Fig. 2) in methanol: *c* 1.25 (327–240 mμ), $[\theta]_{292}$ +4230; ultraviolet in methanol: $\lambda_{279}^{\max}$ log ϵ 1.76.

Coprostan-3-one (II), C. D. (Fig. 2) in methanol: *c* 2.27 (330–245 mμ), $[\theta]_{291}$ −1455.

Cholestan-1-one (III), C. D. (Fig. 2) in methanol: *c* 1.81 (340–240 mμ); $[\theta]_{301}$ −1270, $[\theta]_{250}$ +80; ultraviolet in methanol: $\lambda_{285}^{\max}$ log ϵ 1.83.

Cholestan-7-one (IV), C.D. (Fig. 2) in methanol: *c* 1.71 (330–245 mμ), $[\theta]_{291}$ −2320; O.R.D. (Fig. 1) in methanol, *c* 0.106 (410–235 mμ): $[\phi]_{306}$ −2290°, $[\phi]_{262}$ +640°.

5α-Pregnan-20β-ol methyl xanthate (V), (Fig. 3) C.D. in isoöctane: *c* 1.015 (400–305 mμ), $[\theta]_{375}$ + 6190; ultraviolet in isoöctane: $\lambda_{354}^{\max}$ log ϵ 1.72, $\lambda_{276}^{\max}$ log ϵ 4.03.

Methyl-α-D-glucopyranoside-6-(S-benzyl)-xanthate (VI) (Fig. 4) C.D. in dioxane: *c* 3.50 (395–315 mμ), $[\theta]_{359}$ −420; ultraviolet in dioxane: $\lambda_{354}^{\max}$ log ϵ 1.81, $\lambda_{281}^{\max}$ log ϵ 4.08.

D-(−)-**Mandelic acid ethyl dithiocarbonate (VII)**, (Fig. 5) C.D. in dioxane: *c* 0.954 (410–320 mμ), *c* 0.191 (320–310 mμ), *c* 0.00954 (310–260 mμ); $[\theta]_{386}$ + 150, $[\theta]_{354}$ −2520, $[\theta]_{289}$ −10000; O.R.D. in dioxane, *c* 0.1065 (420−320 mμ); $[\phi]_{368}$ −4030°, $[\phi]_{336}$ −1825°; ultraviolet in dioxane: $\lambda_{354}^{\max}$ log ϵ 1.88, $\lambda_{283}^{\max}$ log ϵ 4.23.

D-(−)-**Lactic acid ethyl dithiocarbonate (VIII)**, (Fig. 6) C.D. in methanol: *c* 0.426 (430–315 mμ), *c* 0.00426 (260–232 mμ); $[\theta]_{393}$ +50, $[\theta]_{355}$ −1010; ultraviolet in methanol: $\lambda_{355}^{\max}$ log ϵ 180, $\lambda_{270}^{\max}$ log ϵ 4.14, $\lambda_{227}^{\max}$ log ϵ 3.88.

N-Dithiocarbethoxy-L-alanine (IX), (Fig. 7) C.D. in methanol: *c* 0.738 (395–320 mμ), *c* 0.147 (320–300 mμ); *c* 0.00738 (300–260 mμ); $[\theta]_{340}$ +2580. $[\theta]_{275}$ +6100; ultraviolet in methanol: $\lambda_{325\text{-}35}^{\text{shoulder}}$ log ϵ 1.87, $\lambda_{273}^{\max}$ log ϵ 4.04, $\lambda_{252}^{\max}$ log ϵ 4.04.

N-Dithiocarbomethoxy-L-proline (X), (Fig. 8) C.D. in methanol: *c* 0.936 (390–315 mμ), *c* 0.187 (315–300 mμ); *c* 0.00936 (315–285 mμ); $[\theta]_{336}$ +5120; ultraviolet in methanol: $\lambda_{320\text{-}30}^{\text{shoulder}}$ log ϵ 1.80, $\lambda_{275}^{\max}$ log ϵ 4.16, $\lambda_{250}^{\max}$ log ϵ 4.05.

N-Dithiocarbethoxy-D-aspartic acid (XI), (Fig. 9) C.D. in dioxane: *c* 1.15 (370–320 mμ); *c* 0.115 (320–295 mμ); *c* 0.0115 (295–260 mμ); $[\theta]_{340}$ −2500, $[\theta]_{275}$ + 5600: O.R.D. in dioxane: *c* 0.119 (400–320 mμ), *c* 0.0119 (320–290 mμ); $[\phi]_{356}$ −760°, $[\phi]_{310}$ +5980°; ultraviolet in dioxane: $\lambda_{339}^{\max}$ log ϵ 1.81, $\lambda_{274}^{\max}$ log ϵ 4.37, $\lambda_{251}^{\max}$ log ϵ 4.36.

N-Thionocarbethoxy-L-hydroxyproline (XII), (Fig. 10) C.D. in dioxane: *c* 0.78 (330–284 mμ), $[\theta]_{302}$ −780; O.R.D. in dioxane: *c* 0.112 (400–300 mμ), *c* 0.0224 (300–270 mμ); $[\phi]_{315}$ −1130°, $[\phi]_{285}$ +770°; ultraviolet in dioxane: $\lambda_{295}^{\text{shoulder}}$ log ϵ 2.20, $\lambda_{248}^{\max}$ log ϵ 4.29.

N-Thionocarbethoxy-L-phenylalanine (XIII), (Fig. 11) C.D. in dioxane: *c* 0.585 (320–275 mμ), *c* 0.0585 (275–260 mμ); $[\theta]_{297}$ +860; ultraviolet in dioxane: $\lambda_{285\text{-}95}^{\text{shoulder}}$ log ϵ ∼ 210, $\lambda_{245}^{\max}$ log ϵ 4.14.

1,5-Cyclotrimethylene-3-phenyl-2-thiohydantoin (XIV), (Fig. 12) C.D. in dioxane: *c* 0.618 (365–305 mμ), *c* 0.309 (305–295 mμ), *c* 0.00309 (295–240 mμ); $[\theta]_{328}$ +3740, $[\theta]_{277}$ − 42000, $[\theta]_{252}$ +50000; O.R.D. in dioxane: *c* 0.108 (400 − 290 mμ), $[\phi]_{345}$ + 1330°; ultraviolet in dioxane: $\lambda_{327}^{\max}$ log ϵ 1.96, $\lambda_{272}^{\max}$ log ϵ 4.24.

5-Methyl-3-phenyl-2-thiohydantoin (XV), (Fig. 13) C.D. in methanol: *c* 0.67 (355–305 mμ), *c* 0.335 (305–298 mμ); $[\theta]_{321}$ +760; ultraviolet in methanol: $\lambda_{305\text{-}315}^{\text{shoulder}}$ log ϵ ∼2.25, $\lambda_{265}^{\max}$ log ϵ 4.24.

(−)-(R)-**Hydratropyl-morpholinothiocarbamide (XVI)**, (Fig. 14) C.D. in dioxane: *c* 0.290 (400–330 mμ), *c* 0.0425 (330–315 mμ), *c* 0.0084 (315–270 mμ), *c* 0.00116 (270–235 mμ); $[\theta]_{349}$ + 10400, $[\theta]_{315}$ +1700, $[\theta]_{288}$ +15500, $[\theta]_{243}$ − 50000; O.R.D.[29] in dioxane: *c* 0.110 (410–315 mμ), *c* 0.0022 (315–260 mμ); $[\phi]_{368}$ +4800°, $[\phi]_{322}$ 8600°, $[\phi]_{295}$ + 100°; ultraviolet in dioxane: $\lambda_{343}^{\max}$ log ϵ 2.59, $\lambda_{285}^{\max}$ log ϵ 4.12.

(+)-(S)-α-(**2-Naphthyl)-propionyl-morpholinothiocarbamide (XVII)**, (Fig. 15) C.D. in dioxane: *c* 0.655 (400–330 mμ), *c* 0.131 (330–310 mμ), *c* 0.00524 (310–265 mμ); $[\theta]_{249}$ − 7450, $[\theta]_{315}$ O, $[\theta]_{289}$ −40000; O.R.D. in dioxane: *c* 0.82 (420–305 mμ); $[\phi]_{360}$ −3500°, $[\theta]_{320}$ + 5250°; ultraviolet in dioxane: $\lambda_{343}^{\max}$ log ϵ 2.55, $\lambda_{279}^{\max}$ log ϵ 4.21.

(+)−**1,2-Dithiane-3,6-dicarboxylic acid (XVIII)**, (Fig. 16) C.D. in dioxane: *c* 0.300 (360–270 mμ), *c* 0.150 (270–250 mμ); $[\theta]_{280}$ +3450; O.R.D. in dioxane: *c* 0.021 (400–270 mμ), $[\phi]_{300}$ +3580°; ultraviolet in dioxane: $\lambda_{270\text{-}90}^{\text{shoulder}}$ log ϵ ∼ 2.4.

(+)-**1,2-Diselenane-3,6-dicarboxylic acid (XIX)**, (Fig. 17) C.D. in dioxane: *c* 0.900 (420–318 mμ), *c* 0.090 (318–265 mμ), *c* 0.018 (265–240 mμ); $[\theta]_{351}$ +4740, $[\theta]_{277}$ −7900), $[\theta]_{249}$ + 16200; O.R.D. in dioxane: *c* 0.0198 (400–270 mμ, *c* 0.0232 (270–240 mμ); $[\phi]_{390}$ + 2500°, $[\phi]_{313}$ −6200°, $[\phi]_{255}$ +15600°; ultraviolet in dioxane: $\lambda_{340}^{\max}$ log ϵ 2.38, $\lambda_{265\text{-}75}^{\text{shoulder}}$ log ϵ ∼ 2.85, $\lambda_{230\text{-}40}^{\text{shoulder}}$ log ϵ ∼ 3.35.

6,8-Thioctic Acid (XX) (Fig. 18). (−)-**Antipode**, C.D. in dioxane: *c* 1.55 (425–355 mμ), *c* 0.18 (355–285 mμ), *c* 0.045 (285–250 mμ); $[\theta]_{367}$ −230, $[\theta]_{320}$ +460, $[\theta]_{265}$ −295; O.R.D. in dioxane: *c* 0.155 (420–370 mμ), *c* 0.076 (370–300 mμ), *c* 0.019 (300–250 mμ); $[\phi]_{386}$ −400°, $[\phi]_{336}$ −156°; ultraviolet in dioxane: $\lambda_{328}^{\max}$ log ϵ 2.16, $\lambda_{255\text{-}70}^{\text{shoulder}}$ log ϵ ∼ 2.24.

(+)-**Antipode**, C.D. in dioxane: *c* 1.61 (425–360 mμ). *c* 0.644 (360–285 mμ), *c* 0.322 (285–255 mμ); $[\theta]_{365}$ +255, $[\theta]_{321}$ −520, $[\theta]_{266}$ +240; O.R.D. in dioxane: *c* 1.61 (420–390 mμ), *c* 0.0644 (390–300 mμ), *c* 0.0322 (300–260 mμ); $[\phi]_{380}$ +420°, $[\phi]_{340}$ +160°.

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[28] All circular dichroism measurements were performed with a Baird–Atomic/Jouan Dichrograph, utilizing dilutions so as to maintain the slit width below 1.3 mm. Molecular ellipticities $[\theta]$ were calculated as outlined in ref. 11, the concentration *c* being defined in g./l. Optical rotatory dispersion results (peaks and troughs in terms of molecular rotation $[\phi]$) are listed in the Experimental section (*c* being defined as g./100 cc.) only for those substances where new measurements were performed, in which case an automatically recording Nippon-Bunko (Japan Spectroscopic Manufacturing Co., Ltd.) spectropolarimeter was utilized.

[29] The lower amplitude observed in methanol solution (ref. 23) has been confirmed, thus demonstrating a significant solvent effect.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY, DETROIT 2, MICH.]

Conformational Analysis. XXXII. The Conformation of Ring A in 2,2- and 4,4-Dimethyl-3-ketosteroids[1,2]

BY NORMAN L. ALLINGER AND MARGARET A. DAROOGE[2b]

RECEIVED MAY 17, 1962

Dipole moment and rotatory dispersion data for a series of 3-ketosteroids containing the 2,2- or 4,4-*gem* dimethyl group have shown that with these compounds ring A does not exist as a regular chair or as a boat, but rather has a flattened chair structure. Similarly, it was shown that in the analogous 4,4-dimethyl-19-nor-3-ketone, ring A is an ordinary chair.

A determination of the conformation of ring A in 2,2-dimethyl and 4,4-dimethyl substituted 3-keto-5α-steroids was of particular interest because of the widespread occurrence of this type of structure in nature. Recently boat forms for ring A in similar compounds have been proposed in a number

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[1] (a) Paper XXXI, N. L. Allinger, L. A. Freiberg and S. Hu, *J. Am. Chem. Soc.*, **84**, 2836 (1962). (b) A brief description of a portion of the present work has been published in *Tetrahedron Letters*, 676 (1961).

[2] (a) This work was supported in part by Grant No. A-5836 from the Public Health Service, National Institutes of Health. (b) Predoctoral National Institutes of Health Fellow, Division of Medical Sciences, 1960–1962.