Tetrahedron, 1965, Vol. 21, pp. 3455 to 3479. Pergamon Press Ltd. Printed in Northern Ireland

OPTICAL ROTATORY DISPERSION STUDIES—CIV[1]

LOW-TEMPERATURE CIRCULAR DICHROISM BEHAVIOR OF VARIOUS CHROMOPHORIC DERIVATIVES OF ALCOHOLS AND AMINES[2]

W. SCOTT BRIGGS and CARL DJERASSI
Department of Chemistry, Stanford University, Stanford, California

(*Received* 14 *April* 1965; *in revised form* 14 *June* 1965)

Abstract—The low-temperature circular dichroism behavior of various cyclic and alicyclic systems containing the methyl xanthato-, N,N-diethyl-N'-acylthioureyl-, N-phthalimido-, nitrito- and dithiocarbalkoxy- chromophores is discussed. Rotational strength (R_0^T) values are reported where possible and changes in this parameter upon variation of the temperature are interpreted, where relevant, in terms of the degree of steric inhibition to free rotation about the various bonds connected to the asymmetric center bearing (or nearest to) the chromophore moiety.

INTRODUCTION

THE phenomena of circular dichroism (CD) and optical rotatory dispersion (ORD) are intimately related.[3] During the past ten years most of the emphasis in the studies of ORD and CD phenomena has been placed on the carbonyl chromophore, since this group possesses an optically active ultraviolet absorption of sufficiently low extinction in a region of the spectrum conveniently accessible with commercially available instrumentation.

More recently the technique of low-temperature circular dichroism has been introduced[4-10] to study conformational equilibria. These studies have concerned themselves mainly with changes of ring conformation and their effects on the observed CD behavior, although there have also been undertaken several attempts in which the effects of free rotation have been examined[5,11-14] by this method.

---

[1] For paper CIII see D. A. Lightner, C. Djerassi, K. Takeda, K. Kuriyama and T. Komeno, *Tetrahedron* **21**, 1581 (1965).

[2] Financial support by the National Science Foundation (grant No. GP-2886) and the National Institutes of Health (grant No. CA-07195) is gratefully acknowledged.

[3a] C. Djerassi, *Optical Rotatory Dispersion* McGraw-Hill, New York 1960; [b] P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* Holden-Day, San Francisco (1965).

[4] K. M. Wellman, E. Bunnenberg and C. Djerassi, *J. Amer. Chem. Soc.* **85**, 1870 (1963).

[5] G. Snatzke, D. Becher and J. R. Bull, *Tetrahedron* **20**, 2443 (1964); [b] R. Tschesche, F. Riemhofer, and G. Snatzke, *Chem. Ber.* **98**, 1188 (1965).

[6] G. Snatzke and D. Becher, *Tetrahedron* **20**, 1921 (1964).

[7] A. Moscowitz, K. M. Wellman and C. Djerassi, *J. Amer. Chem. Soc.* **85**, 3515 (1963).

[8] K. M. Wellman, R. Records, E. Bunnenberg and C. Djerassi, *J. Amer. Chem. Soc.* **86**, 492 (1964).

[9] C. Djerassi, J. Burakevich, J. W. Chamberlin, D. Elad, T. Toda and G. Stork, *J. Amer. Chem. Soc.* **86**, 465 (1964).

[10] K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz and C. Djerassi, *J. Amer. Chem. Soc.* **87**, 73 (1965).

[11] K. M. Wellman and C. Djerassi *J. Amer. Chem. Soc.* **87**, 60 (1965).

[12] K. M. Wellman, W. S. Briggs and C. Djerassi, *J. Amer. Chem. Soc.* **87**, 73 (1965).

[13] J. V. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.* **87**, 51 (1965).

[14] K. Takeda, K. Kuriyama, T. Komeno, D. A. Lightner, R. Records and C. Djerassi, *Tetrahedron* **21**, 1203 (1965).

The problem of isomerism associated with free rotation is particularly pertinent to the recently developed concept of chromophoric derivatives of otherwise "transparent"[15] functionalities.[16]

The hydroxyl and amino functions have not yet yielded to direct measurement, hence the employment of suitable chromophoric derivatives is still deemed necessary for rotatory dispersion studies of the free rotational behavior of compounds containing these functionalities. Relevant derivatives of such compounds include xanthates,[17–19] N,N-disubstituted-N′-acylthioureas derived from carboxylic acids,[18,20] dithiocarbalkoxy-derivatives of amines[19] and α-amino acids,[18] nitrite esters of steroidal alcohols,[17,21] and N-phthaloyl derivatives of amines and α-amino acids.[22]

The utility of such derivatives has been in the successful correlation of the sign of the resultant Cotton effect curves to the absolute configuration at the nearest asymmetric center.[19,20,23] A required corollary for such a relationship, however, is that the rotameric composition about single bonds within the chromophore moiety itself be more or less fixed. Experimental proof for this assumption is now at hand.

An observed CD curve is composed of the population-weighted contributions of the individual effects of all species present.[7] In terms of the measure of molecular dissymmetry, the rotational strength (R_0^T),[3,24] the observed CD curve may be expressed as in Eq. 1,

$$R_0^T = N_a R_a + N_b R_b + \cdots + N_i R_i \tag{1}$$

where $R_a \cdots R_i$ are the rotational strength contributions of the species $a \cdots i$, respectively, and $N_a \cdots N_i$ are the mole fractions of each species present in the sample.[12]

The experimental rotational strength of such a system is conveniently measured[12] by observing the wavelength-weighted area under the CD curve arising from the spectroscopic transition of interest. The resulting expression is:

$$R_0^T \approx 0{\cdot}696 \times 10^{-42} \int_{\lambda_1}^{\lambda_2} [\theta]/\lambda \, d\lambda \tag{2}$$

where $[\theta]$ is the molecular ellipticity and λ is the corresponding wavelength.

RESULTS AND DISCUSSION

At the outset of the work described in this communication, it was thought relevant to study the low-temperature CD behavior of chromophores in sterically hindered

---

[15] It is to be noted that functions previously considered to be spectroscopically "transparent," e.g., lactones, have now been shown to exhibit Cotton effect curves by employing instrumentation which is capable of penetrating farther into the ultraviolet. See for instance J. P. Jennings, W. Klyne and P. M. Scopes, *Proc. Chem. Soc.* 412 (1964) and T. Okuda, S. Harigaya and A. Kiyomoto, *Chem. Pharm. Bull. Tokyo* **12**, 504 (1964).

[16] For a tabular listing of various chromophoric groups and the "transparent" functionalities from which these were derived, as well as leading references to their preparation, see C. Djerassi, *Proc. Chem. Soc.* 320 (1964).

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

[18] C. Djerassi, H. Wolf and E. Bunnenberg, *J. Amer. Chem. Soc.* **84**, 4552 (1962).

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

[20] C. Djerassi, K. Undheim and A. -M. Weidler, *Acta Chem. Scand.* **16**, 1147 (1962).

[21] C. Djerassi, H. Wolf and E. Bunnenberg, *J. Amer. Chem. Soc.* **85**, 2853 (1963).

[22] H. Wolf, E. Bunnenberg and C. Djerassi, *Chem. Ber.* **97**, 533 (1964).

[23] See Refs 26, 31, 33, 34, 37 and 44 for recent applications to various stereochemical problems.

[24] For a detailed discussion of this parameter, see A. Moscowitz, Ref. 3a, chap. 12.

environments as compared to their unhindered counterparts. Such a comparative study should yield useful information on the extent of restriction to free rotation which might operate in sterically hindered cases.

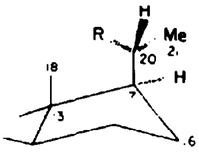
Xanthates

The earliest CD study of optically active compounds possessing the C=S chromophore was that carried out by Lowry and Hudson[25] on the xanthates and dithiourethanes of borneol and menthol. Xanthates possess UV absorption maxima near 355 and 280 mμ, and these early workers[25] found that the former, weaker band exhibited strong rotatory dispersion Cotton effects and associated CD maxima.

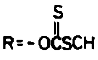
Subsequent studies in our laboratory have shown that the amplitude of both the ORD Cotton effect and the associated CD curve for the 350–355 mμ transition, is dependent upon the degree of substitution around the xanthate grouping[17] and that the sign of the Cotton effect may be used to good advantage in making stereochemical assignments based on the absolute configuration at the adjacent asymmetric center.[19,26]

The first model compounds employed in the present study were 5α-pregnan-20β-ol methyl xanthate[18] (I) and cholestan-3β-ol methyl xanthate[19] (II). The low-temperature CD curves for these two compounds are shown in Figs 1 and 2, respectively.

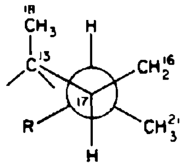
In the former compound, inspection of Dreiding or Framework Molecular Orbital (FMO)[27] models shows that free rotation about the C(17)-C(20) single bond (see I) is severely impaired due to steric interaction of the C(21)-methyl and methyl xanthato- groupings with the C(18) angular methyl substituent. One would therefore expect that the most stable rotamer about this bond would already predominate at −25° and, from further examination of models, the most likely candidate appears to be III, in which all skew interactions have been minimized. The Newman projection (IIIa) of this system viewed from C(17) towards C(20) is clearly that of lowest energy, having the two largest groups opposed.[28]



III



$R = -\overset{\overset{S}{\|}}{C}$: $R=-OC(=S)SCH_3$



IIIa

Free rotation about all other single bonds of the chromophore is possible, however, and at +25° the observed CD curve will be the net result of rotameric equilibria about all of these, although the system possessing the all-*trans* geometry might reasonably be expected to be very important. As the sample temperature is lowered to −192°, the all-*trans* conformation should be the one of choice.

---

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

[26] For recent examples of the employment of such derivatives in making stereochemical assignments, see [a] C. J. Collins, J. B. Christie and V. F. Raaen, *J. Amer. Chem. Soc.* **83**, 4267 (1961); [b] D. Horton and M. L. Wolfrom, *J. Org. Chem.* **27**, 1794 (1962); and [c] B. Sjöberg, B. Hansson and R. Dahlbom, *Acta Chem. Scand.* **16**, 1057 (1962).

[27] U.S. Pat. 3,080,662. Prentice-Hall, Inc., Englewood Cliffs, N.J.

[28] E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 138. McGraw-Hill, New York (1962).

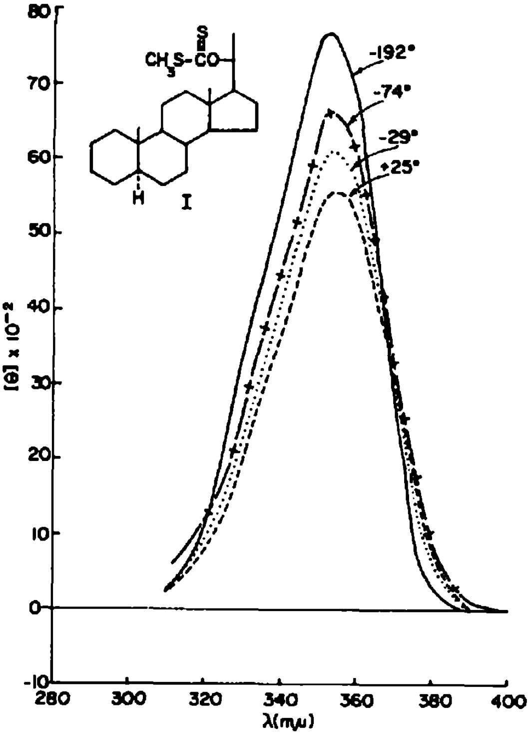


Fig. 1. Circular dichroism curves of 5α-pregnan-20β-ol methyl xanthate (I) in EPA solvent at +25, −29, −74 and −192°.

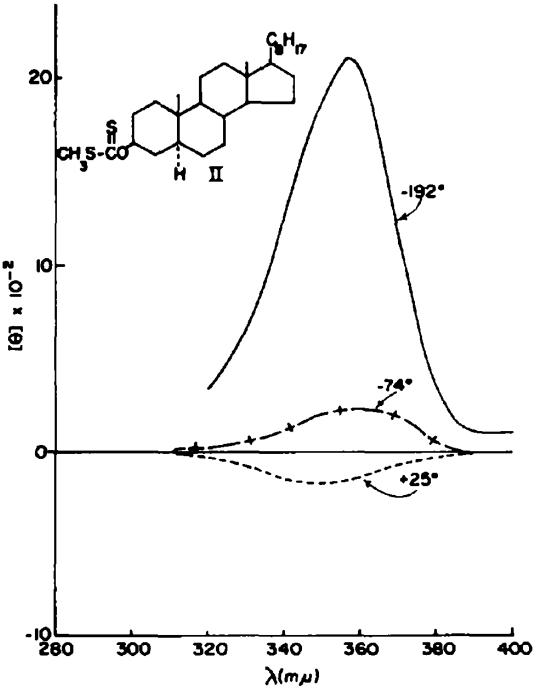


Fig. 2. Circular dichroism curves of cholestan-3β-ol methyl xanthate (II) in EPA solvent at +25, −74 and −192°.

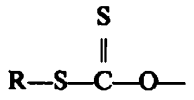
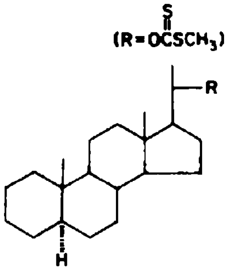
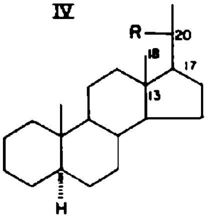
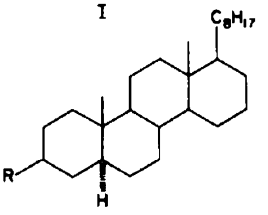
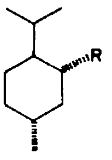
If we assume that the  $\mathrm{R{-}S{-}\overset{\displaystyle S}{\overset{\|}{C}}{-}O{-}}$ bonds already exist in the energetically preferred orientation and that the chief variable will be possible rotation about the O—C(20) bond, then from the foregoing discussion it is apparent that the net extra-chromophoric environment experienced by the electrons of the xanthate C=S group should be only slightly altered as the temperature is lowered from +25° to −192° and therefore little alteration in the magnitude of the experimentally observable rotational strength should be incurred in passing over this temperature range (Table 1).

TABLE 1. ROTATIONAL STRENGTH VALUES FOR SELECTED XANTHATES IN EPA[a] SOLVENT

Compound	Temp (°C)	$R_0^T \times 10^{40}$ (c.g.s.)	Cotton effect λ_{max}(mμ)
 IV	+ 25	−3·89	353
	− 74	−4·28	352·5
	−192	−4·29	352·5
 I	+ 25	+4·16	255
	− 29	+4·57	354
	− 74	+4·90	353·5
	−192	+5·29	352
 II	+ 25	−0·96	353
	− 74	+1·68	360
	−192	+15·20	357
 V	+ 25	+3·36	353
	− 29	+3·49	354
	− 74	+3·78	354
	−192	+3·96	353

---

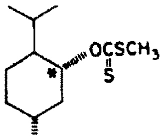
[a] Ethyl ether–isopentane–ethanol (5:5:2 by volume).

Additional support for this conclusion is offered in the following section dealing with dithiocarbamates.

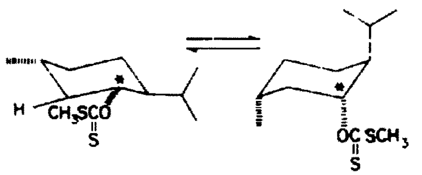
In cholestan-3β-ol methyl xanthate (II), on the other hand, only slight, if any, impediment to free rotation may be ascertained by inspection of models and one would expect that the extrachromophoric influences at 25°, while reflecting contributions from all possible rotamers, might be entirely different from those experienced by the chromophore when it is in its most stable rotameric form (both with respect to free rotation about single bonds within the xanthato- group and with respect to free rotation about the C(3β)—O bond which connects this moiety to the remainder of the steroid skeleton). In the light of earlier discussion, this situation should be reflected experimentally as an increase in the magnitude of the rotational strength. Indeed, a change in rotational strength of over 1400% is noted in Table 1.

The epimeric 5α-pregnan-20α-ol methyl xanthate (IV) was also examined and, in accord with previously reported ORD results,[18,19] it yielded low-temperature CD curves with maxima at 350–355 mμ, possessing the opposite sign (negative) to those obtained for the 20β-ol methyl xanthate (I). As for I, however, the observed rotational strength values, in accord with predictions, exhibited only limited change (Table 1) upon variation of the temperature.

(—)-Menthyl-S-methyl xanthate[19,25] (V) presents an additional problem, since, besides any capability of free rotation about the O—C bond joining the xanthate moiety to the ring, the possibility of conformational mobility (e.g., VI ⇌ VII) of the ring might be envisioned.[19] However, as may be seen from stereoformula VI, the more stable chair conformation would be expected to be that in which all three substituents lie in equatorial positions, analogous to menthyl acetate.[29]



V



VI VII

By inspection of FMO and Dreiding models of this compound in conformation VI, it is evident that in certain situations involving rotation about the C*—O— bond, a severe steric interaction exists between the thiocarbonyl group and the two substituents in the α-equatorial positions, namely, the isopropyl group and the equatorial hydrogen. Thus, free rotation about the C*—O—C single bonds is restricted. Again, as in the case of the 20ξ-ol steroidal methyl xanthates, no important change in the net extrachromaphoric environment of the chromophore would be anticipated upon lowering the temperature, and this feature should manifest itself again experimentally by only small changes in the magnitude of the rotational strength upon lowering the temperature. The observed results (Table 1 and Fig. 3) are in accord with the above arguments.

---

[29] N. B. Chapman, R. E. Parker and P. J. A. Smith, *J. Chem. Soc.* 3634 (1960).

Dithiocarbamates of α-amino acids

The ORD and CD behavior at room temperature of several members of this class has previously been reported.[18,30] All of them possess a weak ultraviolet absorption maximum at ca. 335–350 mμ which is optically active and whose Cotton effect sign could be related to the absolute configuration at the asymmetric center.[18,26,30,31,33] It was thought pertinent for the purposes of this study to examine the low-temperature CD behavior of three representative compounds: N-dithiocarbethoxy-L-aspartic acid (VIII. Fig. 4), N-dithiocarbomethoxy-L-proline (IX, Fig. 5) and N-dithiocarbethoxy-L-glutamic acid (X, Fig. 6).[32]

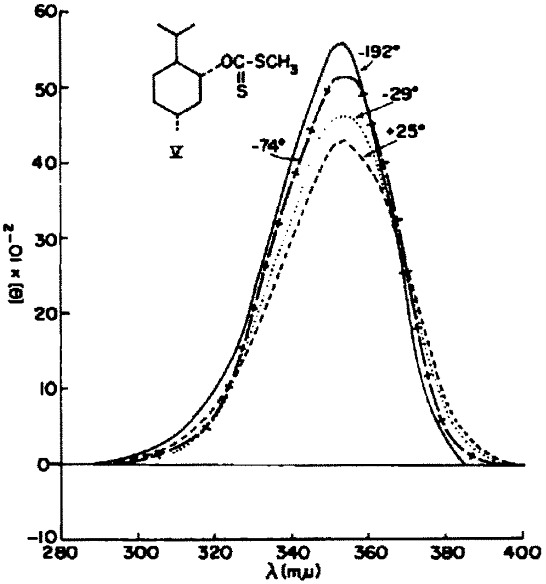


FIG. 3. Circular dichroism curves of (−)-menthyl-S-methyl xanthate (V) in EPA solvent at +25, −29, −74 and −192°.

N-Dithiocarbethoxy-L-aspartic acid (VIII) and N-dithiocarbethoxy-L-glutamic acid (X) both show (Table 2) fairly large increases in the rotational strength upon

---

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

[31] For recent applications of such derivatives in making stereochemical correlations see [a] J. S. Dalby, G. W. Kenner and R. C. Sheppard, *J. Chem. Soc.* 4387 (1962); [b] I. P. Dirkx and Th. J. de Boer, *Rec. Trav. Chim.* **83**, 535 (1964); [c] I. P. Dirkx, D.Sc. Thesis, University of Amsterdam (1962); [d] H. Kipperger and K. Schreiber, *Tetrahedron* **21**, 407 (1965); [e] S. Gronowitz, I. Sjögren, L. Wernstedt and B. Sjöberg, *Arkiv Kemi* **23**, 129 (1964).

[32] A private communication from Prof. S. Yamada (Faculty of Pharmaceutical Sciences, Tokyo University) has called to our attention the existence of a rather unique solvational effect in the case of N-dithiocarbethoxy-L-aspartic acid. Prof. Yamada and his co-workers have found that this derivative exhibits a positive Cotton effect in methanol solution, while in non-polar solvents, such as chloroform or dioxane, a complete inversion in sign is observed. These observations have been reproduced in our laboratory, and in addition it has been found that in EPA solvent a negative Cotton effect results. This solvent-induced inversion of sign points to the need for caution in basing configurational assignments on ORD results of dithiocarbamates in solvents other than methanol (the solvent actually employed in ref. 30). It should be noted that, due to a typing error, the aspartic acid derivative used in Fig. 9 of Ref. 18 for the CD measurements in dioxane was listed as the D- rather than the L-isomer (see also Ref. 30).

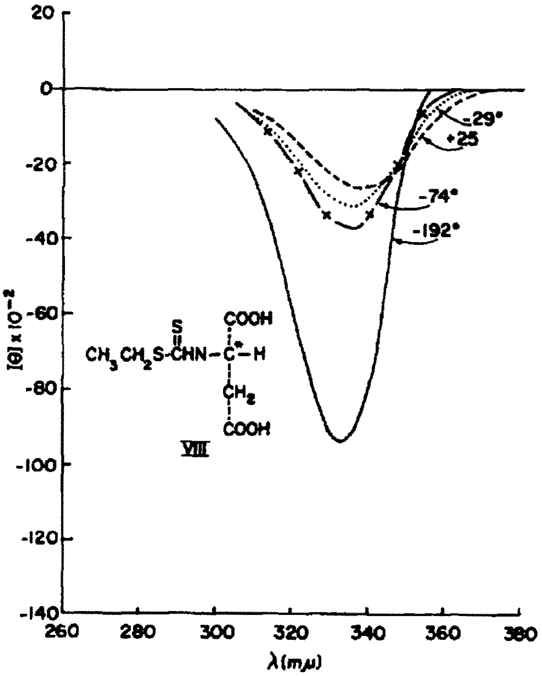


Fig. 4. Circular dichroism curves of N-dithiocarbethoxy-L-aspartic acid (VIII) in EPA solvent at +25, −29, −74 and −192°.

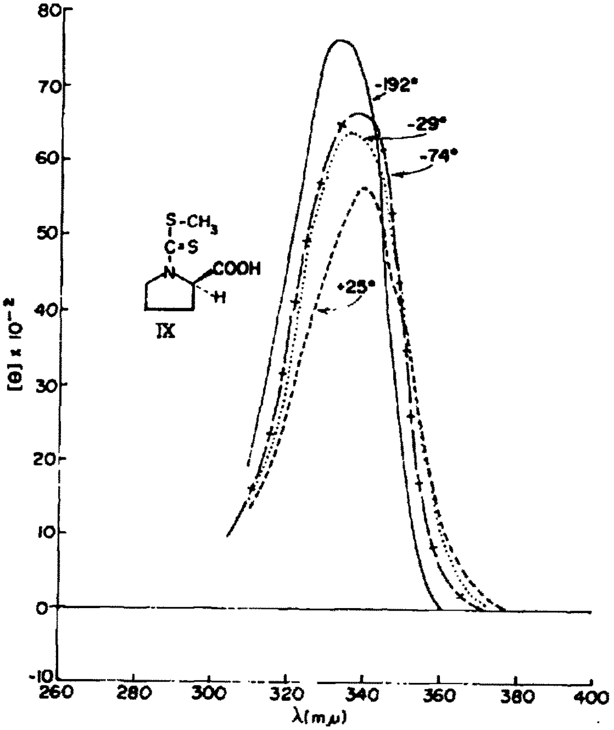


Fig. 5. Circular dichroism curves of N-dithiocarbomethoxy-L-proline (IX) in EPA solvent at +25, −29, −74 and −192°.

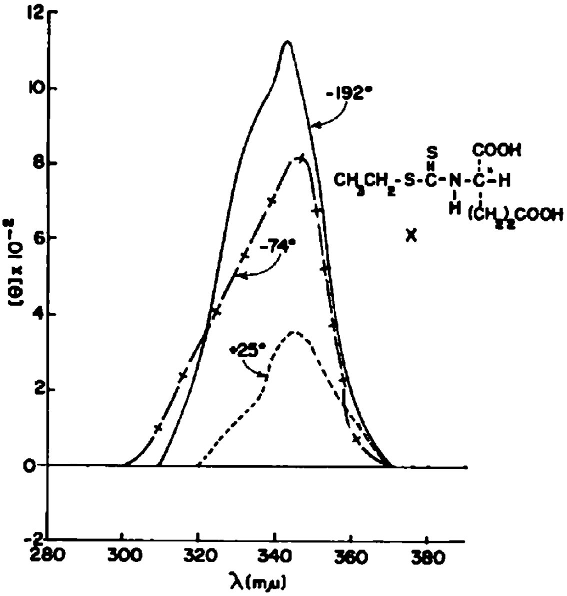
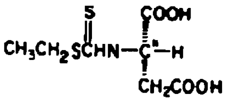
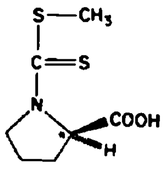
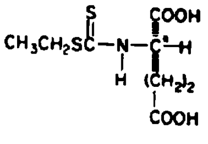


FIG. 6. Circular dichroism curves of N-dithiocarbethoxy-L-glutamic acid (X) in EPA solvent at +25, −74 and −192°.

TABLE 2. SELECTED ROTATIONAL STRENGTH VALUES FOR DITHIOCARBAMATES OF α-AMINO ACIDS IN EPA SOLVENT

Compound	Temp (°C)	$R_0^T \times 10^{40}$(c.g.s.)	Cotton effect λ_{max}
 $CH_3CH_2SC(=S)HN{-}C^{*}H(COOH)CH_2COOH$ VIII	+25	−2·15	338
	−29	−2·39	336
	−74	−2·62	335
	−192	−6·60	333
 IX	+25	+4·03	339
	−29	+4·62	337
	−74	+4·52	337
	−192	+5·01	334
 $CH_3CH_2SC(=S){-}NH{-}C^{*}H(COOH)(CH_2)_2COOH$ X	+25	+0·25	345
	−74	+0·52	345
	−192	+0·60	348

passing from +25° to −192°, while N-dithiocarbomethoxy-L-proline (IX) exhibits only a limited increase over the same temperature range.

These results may again be reconciled with earlier conclusions regarding xanthates where rotation about the O—C* bond is the principal factor which is being measured in the low-temperature CD studies. An analogous situation should apply to the N—C* bond in the dithiocarbamates, and this observation is again borne out by the experimental facts, the cyclic proline derivative IX being least capable of free rotation.

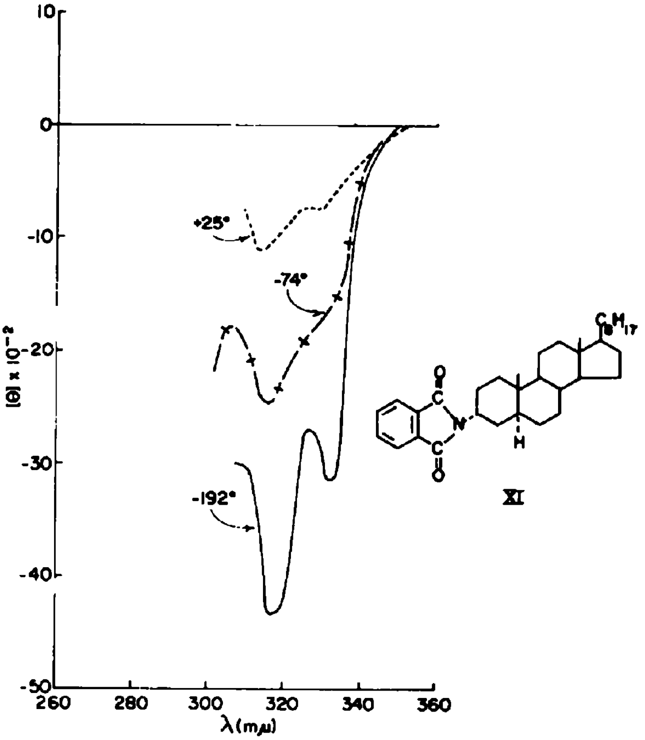


Fig. 7. Circular dichroism curves of N-phthaloyl-3α-aminocholestane (XI) in EPA solvent at +25, −74 and −192°.

N-*Phthaloyl- derivatives of amines and α-amino acids*

Circular dichroism and rotatory dispersion measurements have been reported previously for N-phthaloyl- derivatives of steroidal amines,[22] aliphatic amines,[22] and various α-amino acids,[22,33,34] and these studies have proved to be of stereochemical utility. It was thought relevant in the present study to investigate the possible influences on rotameric composition imposed by steric interactions with neighboring functionalities in certain typical members of this class.

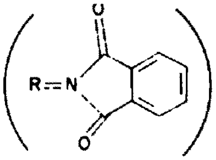
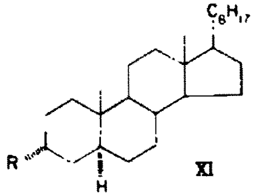
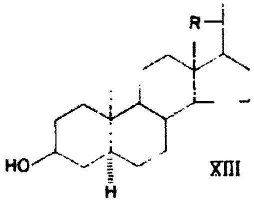
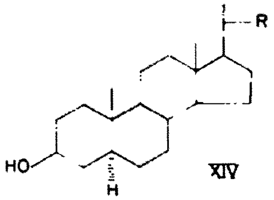
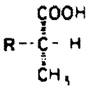
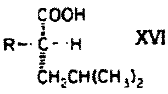
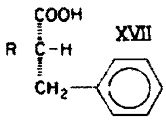
The steroidal phthalimido- derivatives chosen for this investigation were N-phthaloyl-3α-aminocholestane[22] (XI), N-phthaloyl-3β-aminocholestane (XII), N-phthaloyl-20β-amino-5α-pregnan-3β-ol (XIII) and N-phthaloyl-20α-amino-5α-pregnan-3β-ol (XIV).

As may be noted from Fig. 7 (and the associated rotational strength data reported in Table 3), the low-temperature CD curves of N-phthaloyl-3α-aminocholestane

[33] H. Pracejus and S. Winter, *Chem. Ber.* **97**, 3173 (1964)

[34] S. Yamada and K. Achiwa, *Chem. Pharm. Bull, Japan* **9**, 412 (1961).

Table 3. Selected rotational strength values for the N-phthaloyl derivatives of amines and α-amino acids in EPA solvent

Compound	Temp (°C)	$R_0^T \times 10^{40}$ (c.g.s.)	Cotton effect λ_{max} (mμ)
			
 XI	+ 25 −74 −192	−0·60 −1·71 −2·57	316 318 318
 XIII	+ 25 −74 −192	−0·59 −0·61 −0·57	318 318 318
 XIV	+ 25 − 29 − 74 −192	+0·52 +0·59 +0·57 *a*	328 328 326 (333, 315)
 XV	+ 25 − 74 192	see text	(330, 316) (330, 315) (330, 322)
 XVI	− 25 −74 −192	see text	(331, 321) (331, 321) (329, 318)
 XVII	+ 25 − 74 −192	see text	(328, 313) (328, 309) (328, 311)

---

[a] Double maxima developed in curve at this temp (one positive and other negative). $R_+ = +0{\cdot}10 \times 10^{-40}$ c.g.s. and $R_- = -0{\cdot}13 \times 10^{-40}$ c.g.s., where R_+ equals the rotational strength under the positive portion of the curve, and R_- equals that under the negative portion. For further discussion of such double-maxima CD curves see Ref. 10.

exhibit a negative maximum[35] at ca. 316–320 mμ with a shoulder at 330–335 mμ. The latter develops into a full-fledged extremum as the temperature is lowered to −192°.

Upon inspection of both FMO and Dreiding models of this compound and of N-phthaloyl-3β-aminocholestane (XII), it is seen that in the former even slight steric interactions of the chromophoric group with the 1α- and 5α- axial hydrogens would impair free rotation about the C(3)—N single bond, while in the latter the only impediment to such free rotation arises from interactions with the 2β- and 4β-equatorial hydrogens. In fact, no measurable CD could be detected for the 3β-isomer (XII)- either at room temperature[22] or at −192°.

From the above observations and by analogy to the results obtained for the 3β-ol methyl xanthate (II), substantial alteration of the net extrachromophoric environment experienced by the electrons involved in the spectroscopic transitions of the phthalimido- chromophore might be anticipated upon lowering of the temperature and the rotational strength results presented in Table 3 bear out this conclusion.

In the N-phthaloyl-20β-amino- compound (XIII) it would be predicted (by analogy to the methyl xanthate of 5α-pregnan-20β-ol (I)) that rotation about the C(17)—C(20) single bond would be precluded even at +25° due to steric interactions of the phthalimido- and C(21)-methyl groups with the C(18) angular methyl group and other adjacent atoms of the steroid skeleton. An argument identical with that invoked in the xanthate case may be applied to the present compound, and only a small net change in the extrachromophoric environment of the chromophore upon such rotation would be expected. The observed lack of temperature dependence (Table 3 and Fig. 8) corroborates this prediction, although the low absolute value of the rotational strength (e.g., XIII and XIV *vs.* XI as compared to I and IV *vs.* II) is unexpected.

The corresponding 20α-phthalimido- derivative (XIV; Fig. 9) behaves in a somewhat different manner. While the rotational strength over the temperature range +25° to −74° (analogous to the previous discussion) shows little change, the −192° curve (Fig. 9) shows a different shape through appearance of a negative CD maximum at 313 mμ. While models indicate a lesser degree of steric interference to rotation about the C(20)—N bond, as compared to the 20β- isomer XIII, the results could also be interpreted in part by assuming an equilibrium between solvated and non-solvated species, since a blue shift in the CD maximum can be associated with solvated species,[36] and the population of such forms should increase as the temperature is lowered to −192°.

On the other hand, recent calculation[10] has shown that such complex CD curves possessing oppositely signed maxima separated by up to 30 mμ may arise by superposition of two oppositely signed, simple, Gaussian-type absorption curves having their own maxima separated by as little as 1–2 mμ. These computations have further shown[10] that, for two such curves of equal amplitude, the observed rotational strength for the resulting curve will be substantially less than that for either of the two parent curves (e.g., approximately 1/25 th of its former magnitude for a separation of 1 mμ).

---

[35] For CD nomenclature see C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.* 299 (1963).

[36] A. Moscowitz, K. M. Wellman and C. Djerassi, *Proc. Natl. Acad. Sci. U.S.* **50**, 799 (1963) and C. Colombeau and A. Rassat, *Bull. Soc. Chim. Fr.* 2673 (1963).

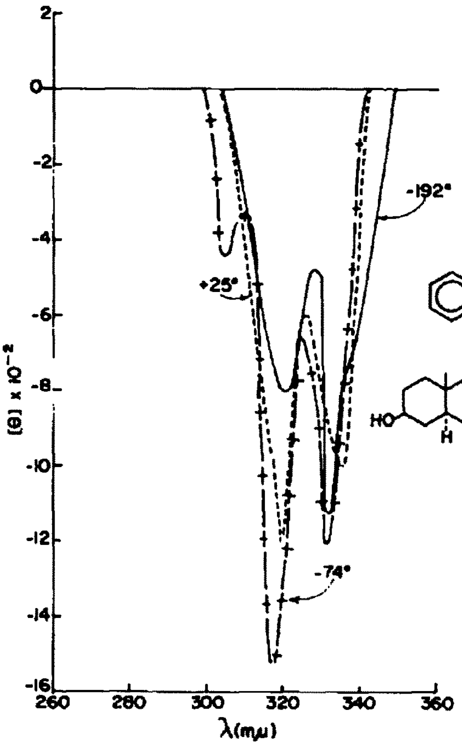


FIG. 8. Circular dichroism curves of N-phthaloyl-20β-amino-5α-pregnan-3β-ol (XIII) in EPA solvent at +25, −74 and −192°.

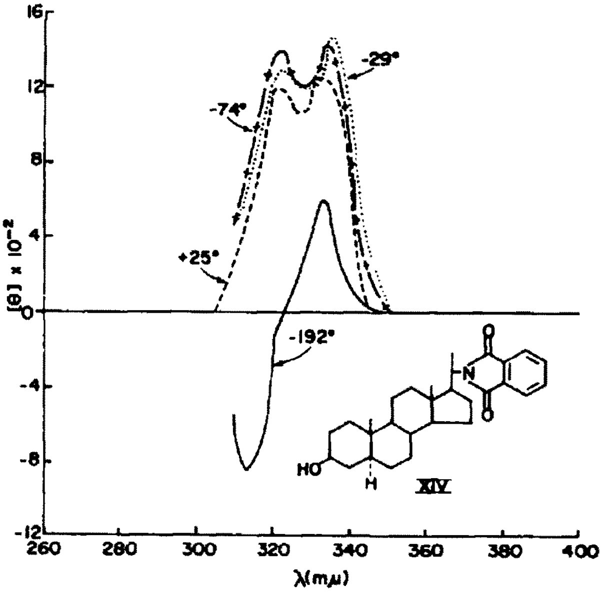


FIG. 9. Circular dichroism curves of N-phthaloyl-20α-amino-5α-pregnan-3β-ol (XIV) in EPA solvent at +25, −29, −74 and −192°.

The operation of such factors makes the interpretation of certain temperature-dependent CD curves (e.g., Fig. 9) tenuous as far as free rotational equilibria are concerned, since one cannot state, *a priori*, which form (solvated or rotamer) possesses a slightly shifted, oppositely signed CD maximum. Fortunately, this possible ambiguity applies only to the phthalimido- derivatives (Figs 7–12) and not to the other chromophoric derivatives (Figs 1–6 and 13–18) discussed in this paper.

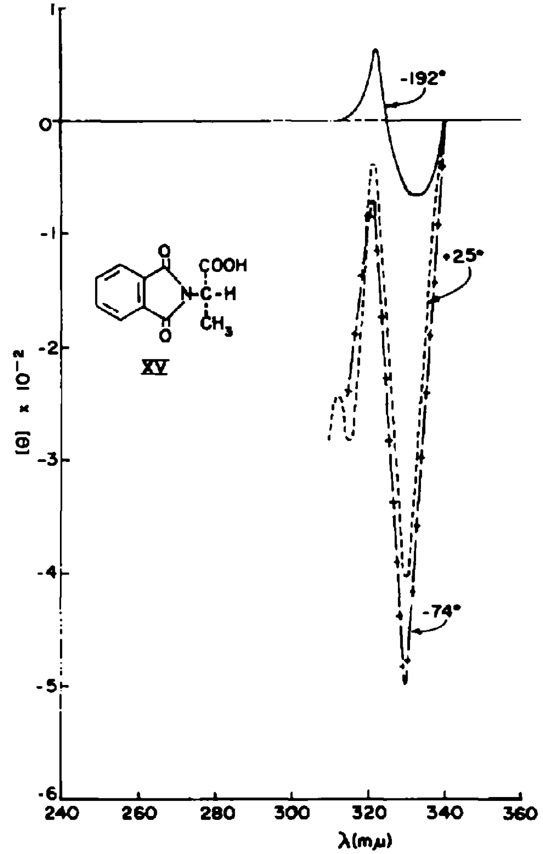


Fig. 10. Circular dichroism curves of N-phthaloyl-L-alanine (XV) in EPA solvent at +25, −74 and −192°.

The CD and ORD curves of several N-phthaloyl-α-amino acids have been previously reported in the literature.[22,33,34] It was thought pertinent for the purposes of this study to examine the low-temperature CD behavior and to attempt to extend the concepts of free rotational isomerism to members of this class. The three homologs chosen were N-phthaloyl-L-alanine,[22,34] (XV), N-phthaloyl-L-leucine[22] (XVI) and N-phthaloyl-L-phenylalanine[22,34] (XVII).

The low-temperature CD curves for all three compounds (Figs 10, 11 and 12, respectively) suffer changes indicative of some degree of free rotational mobility as the temperature is lowered; however, concomitant blue-shift and fine structural changes,[36] as well as the nature of the double-humped curves[10] themselves, greatly complicate the interpretation of these results.

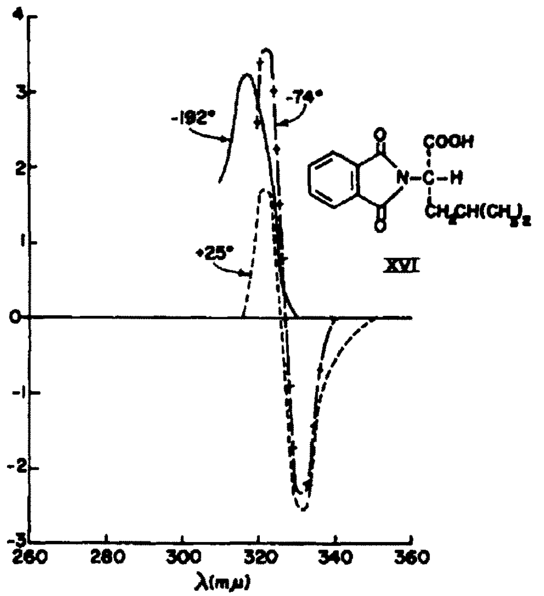


Fig. 11. Circular dichroism curves of N-phthaloyl-L-leucine (XVI) in EPA solvent at +25, −74 and −192°.

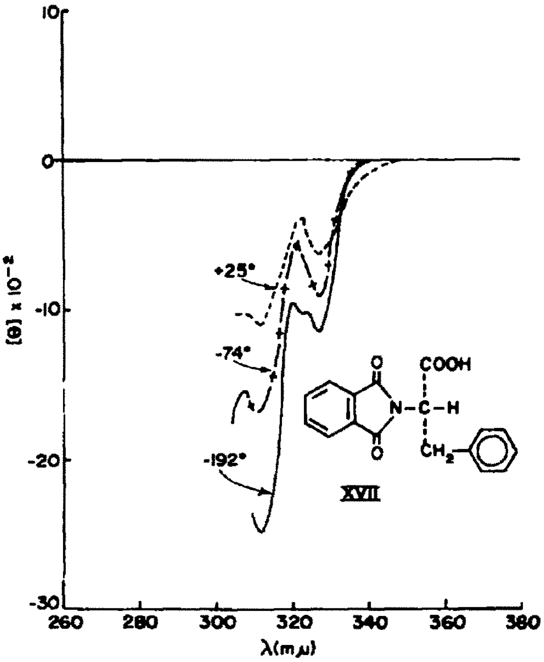


Fig. 12. Circular dichroism curves of N-phthaloyl-L-phenylalanine (XVII) in EPA solvent at +25, −74 and −192°.

Acylthioureas

The rotatory dispersion curves[20,37] of a number of N,N-disubstituted-N′-acylthioureas have been previously reported, and the resulting conclusions based on the Cotton effects associated with the low-intensity absorption band at 340–345 mμ have again proved to be of stereochemical utility.

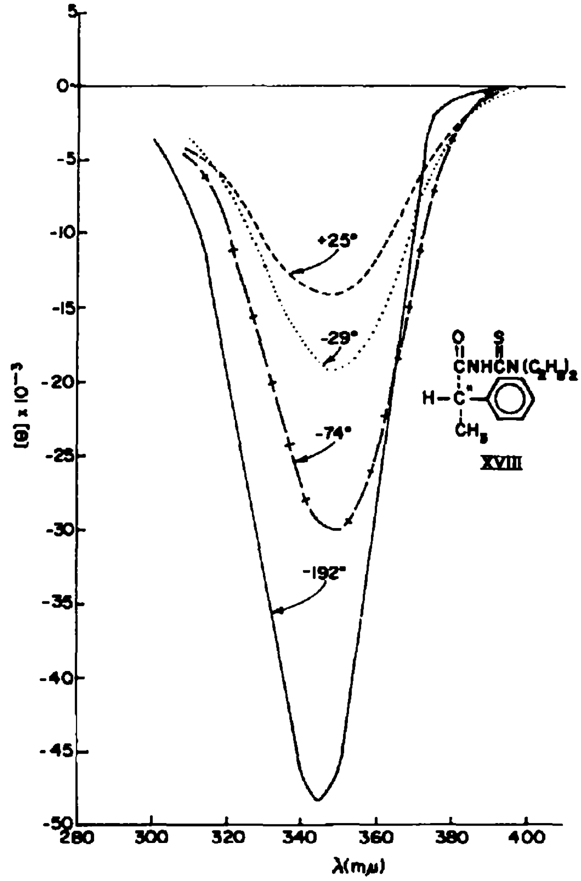


Fig. 13. Circular dichroism curves of (+)-S-hydratropyl-N,N-diethylaminothiocarbamide (XVIII) in EPA solvent at +25, −29, −74 and −192°.

Low-temperature studies have now been carried out on three representative members of this class (see Table IV): (+)-S-hydratropyl-N,N-diethylaminothiocarbamide[20] (XVIII), (+)-R-α-(*p*-methylphenoxy)-propionyl-N,N-diethylaminothiocarbamide[20,38] (XIX) and (+)-S-α-(1-naphthyl)-propionyl-N,N-diethylaminothiocarbamide[20,39] (XX).

In all cases, the low-temperature CD curves (Figs 13, 14 and 15) increase in

---

[37] For recent examples of the application of such derivatives to stereochemical problems, see B. Åkermark, *Acta Chem. Scand.* **16**, 599 (1962); V. Tortorella, *Gazz. Chim. Ital.* **92**, 271 (1962); H. M. Walborsky and C. G. Pitt, *J. Amer. Chem. Soc.* **84**, 4831 (1962); A. K. Bose, S. Harrison and L. Farber, *J. Org. Chem.* **28**, 1223 (1963); V. Tortorella and L. Toscano, *Gazz. Chim. Ital.* **94**, 1438 (1965).

[38] For preparation of acid see B. Sjöberg, *Arkiv. Kemi* **15**, 451 (1960).

[39] For preparation of acid see A. Fredga, *Arkiv. Kemi* **8**, 463 (1955).

magnitude in an absolute sense as the temperature is lowered. In the light of earlier discussion concerning the xanthato- and dithiocarbalkoxy- chromophores, this rather large increase would appear indicative of the presence of some degree of free rotational mobility within each species.

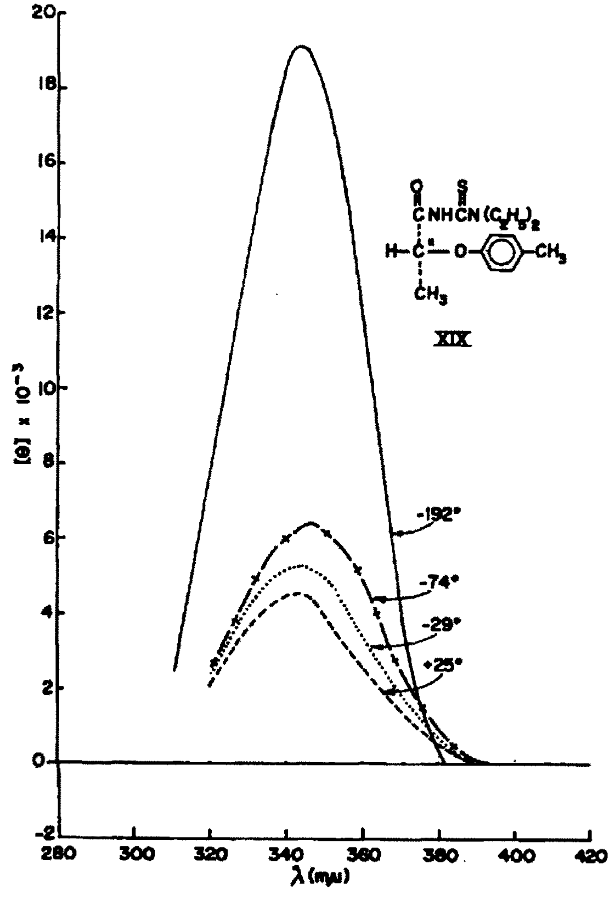


FIG. 14. Circular dichroism curves of (+)-R-α-(*p*-methylphenoxy)-propionyl-N,N-diethylaminothiocarbamide (XIX) in EPA solvent at +25, −29, −74 and −192°.

It is relevant to note that the largest changes in rotational strength (Table 4) occur between −74° and −192° in each case. This observation would indicate that the energy differences between the various rotamers in any one species are slight. The employment of Cotton effects of such derivatives in the assignment of absolute configuration is seen to be justified in spite of free rotation since, on passing to −192°, no inversion of the Cotton effect sign has occurred.

From studies employing numerous N,N-disubstituted aminothiocarbamides, where the N-linked substituent(s) varies in steric bulk, Djerassi and co-workers[30] have concluded that the size of these moieties does not affect appreciably the rotameric composition of the system. Also, these authors[30] conclude that free rotation about the two central bonds connected to nitrogen (see XXI) should be of little consequence, since the same electrostatic factors (due to all *trans*- geometry resulting in parallel

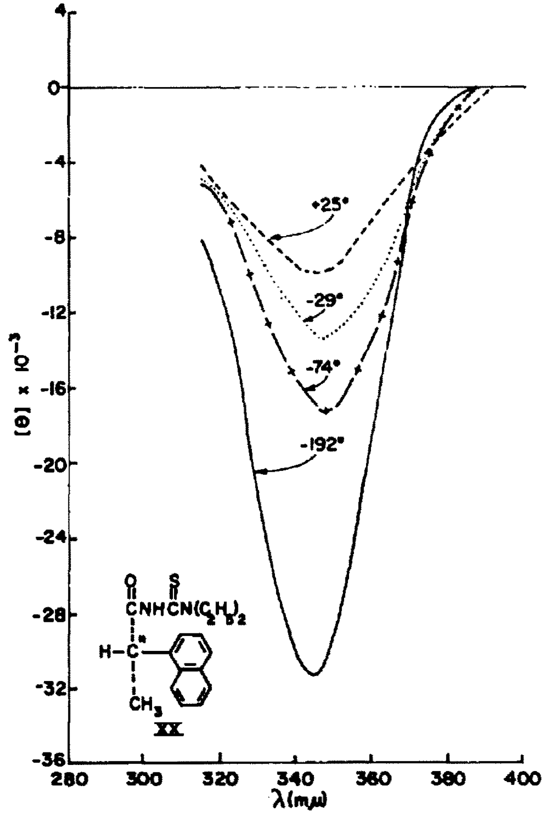
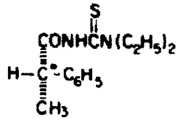
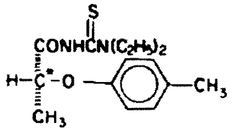
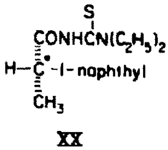
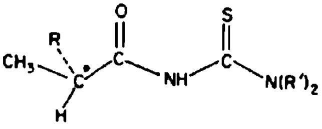


Fig. 15. Circular dichroism curves of (+)-S-α-(1-naphthyl)-propionyl-N,N-diethylaminothiocarbamide (XX) in EPA solvent at +25, −29, −74 and −192°.

Table 4. Selected rotational strength values for thiocarbamides of α-substituted carboxylic acids in EPA solvent

Compound	Temp (°C)	$R_0^T \times 10^{40}$ (c.g.s.)	Cotton effect λ_{max} (mμ)
	+ 25	−13·4	347
	− 29	−17·2	348
	− 74	−25·1	350
XVIII	−192	−36·7	346
	+ 25	+4·30	343
	− 29	+4·60	343
	− 74	+5·72	346
	−192	+15·50	343
XIX			
	+ 25	− 9·31	345
	− 29	−11·5	346
	− 74	−12·9	347
	−192	−24·5	344
XX			

alignment of the C=S and C=O dipoles—unless some alternative arrangement is energetically more favorable) should apply to all thiocarbamides and, therefore, roughly the same rotameric preference around these bonds should obtain. Thus, changes in the magnitude and sign of the Cotton effect (and the associated CD curve) are ascribed[20] to alteration of the rotameric equilibria about the four bonds attached to the asymmetric carbon atom (C* in XXI). Here, steric factors would be expected to play the greatest role.



XXI

It was ascertained in the studies cited[20] that, in most cases, the sign of the Cotton effect and the absolute configuration of the thiourea (and consequently that of the parent acid) may be correlated, using the Cahn-Ingold-Prelog (R) and (S) system[40] in which the relative bulk of the substituents about the asymmetric center is taken into account.

Upon examination of Dreiding and FMO models of the compounds in question (XVIII–XX), it is apparent that free rotation about the four bonds attached to C* is easily feasible in XVIII and XIX. In XX, steric interaction of the *peri*-hydrogen on the naphthyl group with both the methyl group and the carbonyl oxygen might inhibit to a certain extent free rotation about the C*—C(1) (naphthyl) single bond. However, experimentally, it is noted that there is a close resemblance in the low-temperature CD behavior of all three compounds, thus implying only minimal differences in free rotational behavior.

Nitrosteroids and steroidal nitrite esters

A study of the low-temperature CD behavior of various nitrosteroids has recently been published by Snatzke and co-workers,[5a] and we refrain, therefore, from a description of our studies other than to note agreement with the results of the German investigators.

The nitrite group has previously been recognized as a useful "chromophoric" derivative for alcohols.[41,42] Kuhn[43] demonstrated that various alkyl nitrites exhibit multiple ORD Cotton effects, however, these compounds are labile and not of much use for this purpose. The ORD and CD curves for a number of quite stable steroidal nitrites have been previously reported in communications from this laboratory.[17,21] These compounds display multiple Cotton effects in the region 320–440 mμ and have again proven highly useful in arriving at stereochemical conclusions.[44]

Those representative members selected for the present study (Table 5) were a pair of 20-epimeric steroidal nitrites, Δ^5-pregnene-3β,20β-diol 3-acetate 20-nitrite[17,45]

---

[40] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).

[41] See Ref. 3*a*, pp. 195–196.

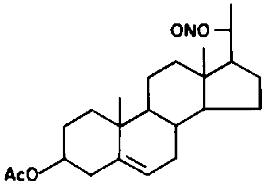
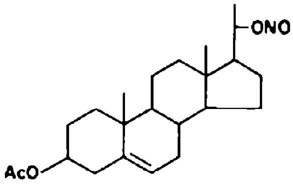
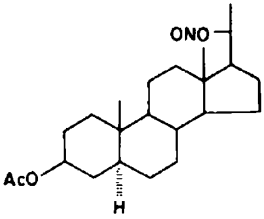
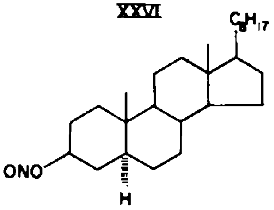
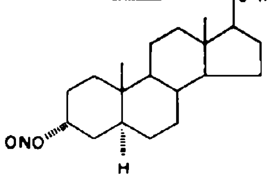
[42] C. Djerassi, E. Lund, E. Bunnenberg and B. Sjöberg, *J. Amer. Chem. Soc.* **83**, 2307 (1961).

[43] W. Kuhn and H. L. Lehmann, *Z. physik. Chem.* **B18**, 32 (1932) and W. Kuhn and H. Biller, *Ibid.* **B29**, 1 (1935).

[44] See also: W. R. Benn, R. Tiberi and A. L. Nussbaum, *J. Org. Chem.* **29**, 3712 (1964) and M. Legrand and R. Viennet, *C.R. Acad. Sci., Paris* **255**, 2985 (1962).

[45] D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Amer. Chem. Soc.* **82**, 2640 (1960).

Table 5. Selected rotational strength values for steroidal nitrite esters in EPA solvent

Compound	Temp (°C)	$R_0^T \times 10^{40}$ (c.g.s.)	Cotton effect λ_{max} (mμ)
 XXII	+ 25	−2·91	(392, 378, 367, 363, 348, 337)
	− 74	−3·59	(382, 377, 362, 349, 339)
	−192	−3·74	(390, 375, 361, 348, 338)
 XXIII	+ 25	+0·70	(393, 377, 368, 362, 353, 342)
	− 29	+1·38	(388, 370, 356, 342)
	− 74	+1·27	(388, 373, 357, 351, 345, 334)
	−192	+1·79	(386, 370, 356, 343)
 XXVI	+ 25	−2·99	(391, 375, 360, 348, 337)
	− 29	−3·72	(392, 375, 361, 348, 339)
	− 74	−3·93	(392, 375, 362, 349, 340)
	−192	−3·92	(388, 372, 358, 347, 337)
 XXIV	+ 25	+0·28	(386, 370, 357)
	− 29	+0·33	(385, 370, 356·5, 344)
	− 74	+0·57	(386, 371, 357·5)
	−192	+1·92	(390, 374, 359, 347, 336, 325)
 XXV	+ 25	a	(————)
	− 29	a	(————)
	− 74	−0·04	(369, 355, 343)
	−192	+0·21	(391, 374, 362)

[a] Effect too small to be calculated quantitatively.

(XXII, Fig. 16) and Δ^5-pregnene-3β,20α-diol 3-acetate 20-nitrite[17] (XXIII, Fig. 16): a pair of 3-epimeric steroidal nitrites, cholestan-3β-ol nitrite[17] (XXIV, Fig. 17) and cholestan-3α-ol nitrite[17] (XXV, Fig. 18), and 5α-pregnane-3β,20β-diol 3-acetate 20-nitrite (XXVI).

By analogy to the steroidal xanthates and phthalimides previously mentioned, the experimental results (Table 5) may be easily rationalized by considering the capability of the species to undergo free rotation. In the 20β- and 20α-nitrites (XXII and XXIII) free rotation about the C(17)—C(20) single bond is again impaired and, as before, only limited change in the observed rotational strength upon lowering of the temperature would be expected. This expectation is again borne out by the experimental data.

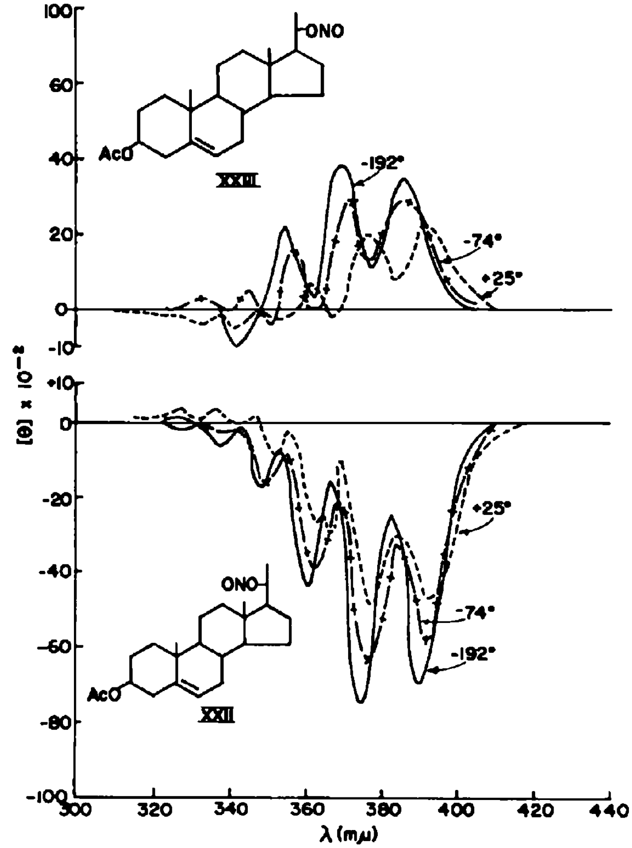


FIG. 16. Circular dichroism curves of Δ^5-pregnene-3β,20β-diol 3-acetate 20-nitrite (XXII) and Δ^5-pregnene-3β, 20α-diol 3-acetate 20-nitrite (XXIII) in EPA solvent at +25, −74 and −192°.

In the 3-epimeric nitrites (XXIV and XXV) little inhibition to free rotation should exist by analogy to the phthalimido- and xanthato- derivatives previously examined. The observed large increase in the magnitude of the rotational strength (Table 5) upon lowering the temperature is exactly what would be predicted. It is interesting to note that, in the 3α-nitrite (Fig. 18 and Table 5), the CD curves undergo a complete inversion of sign as the temperature is lowered from −74° to −192°. This result

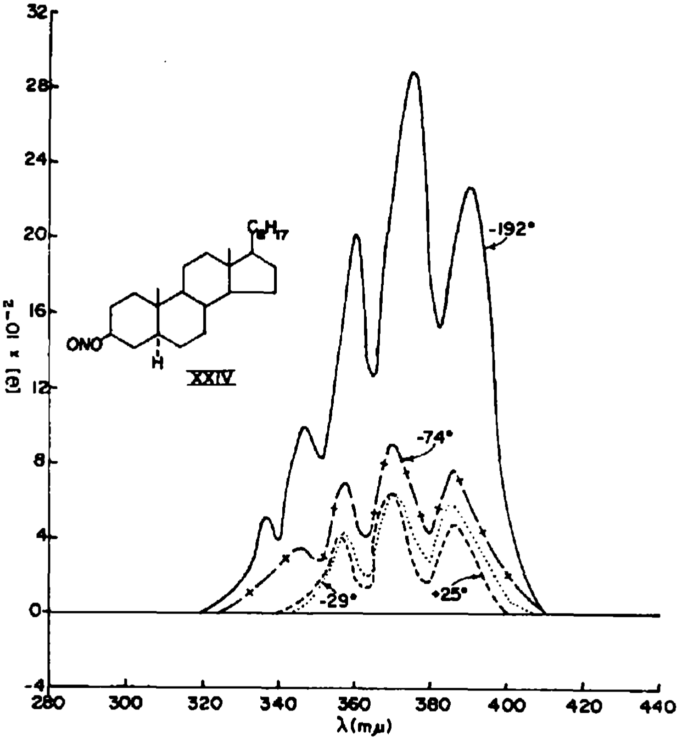


Fig. 17. Circular dichroism curves of cholestan-3β-ol nitrite (XXIV) in EPA solvent at +25, −29, −74 and −192°.

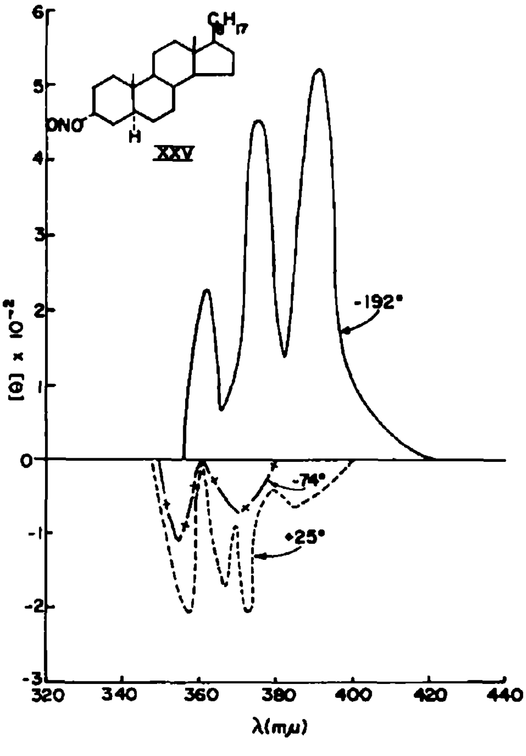


Fig. 18. Circular dichroism curves of cholestan-3α-ol nitrite (XXV) in EPA solvent at +25, −74 and −192°.

points to the need for caution in the employment of sterically unhindered nitrites in stereochemical applications of rotatory dispersion studies since, while the data from such determinations are valid in the present case from +25° to −74°, the most stable rotamer about the O—C(3) bond evidently makes a strongly *positive* contribution which would lead to an erroneous configurational assignment if the results over the temperature range −74° to −192° were employed.

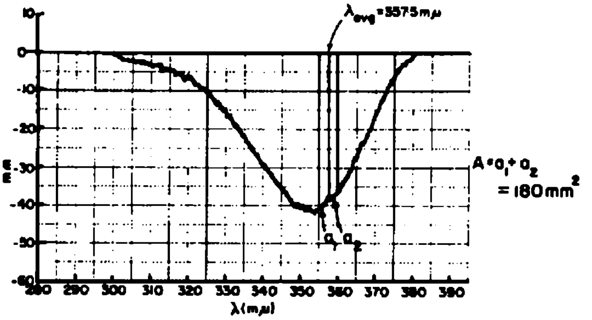


FIG. 19. Circular dichroism machine trace for 5α-pregnan-20α-ol methyl xanthate (IV) at −192°.

It may again be noted that, as for the 3-xanthato- and 3-phthalimido- derivatives, the largest change in the amplitude of the CD curves of the 3-epimeric nitrites XXIV and XXV occurs over the temperature range −74° to −192°, thus indicating the small magnitude of the energy barrier to free rotation about the O—C(3) single bond.

As would be expected, the introduction of a double bond at a position in the steroid skeleton far removed from the site of the chromophoric group produces no alteration in the sign and essentially no change in the amplitude of the observed CD effects (see Table 5 for XXII vs. XXVI).

CONCLUSION

Low-temperature circular dichroism has again been shown to be a highly useful tool in the instrumental armamentarium of the organic chemist. In addition to studies of conformational equilibria, this technique has now been extended in scope to facilitate the examination of rotameric isomerism.

The employment of suitable chromophoric derivatives in the determination of absolute configuration by rotatory dispersion methods is now placed on a firmer basis, since in these present studies it has been demonstrated that even though free rotation is possible about all single bonds within the chromophore moiety, the most stable configuration is usually already predominant at +25°. This is demonstrated most strikingly by the low-temperature CD behavior of compounds such as N-dithiocarbomethoxy-L-proline (IX) and the 20-substituted steroid derivative, 5α-pregnan-20β-ol methyl xanthate (I), when contrasted with sterically less hindered counterparts.

EXPERIMENTAL

All measurements were performed in EPA solvent composed of Spectrograde or purified ether–isopentane–EtOH in the ratio 5:5:2 by volume.

Circular dichroism measurements were carried out with a Baird-Atomic/Jouan dichrograph, operating at a photomultiplier voltage of 1·25 kv and following the procedures and molecular ellipticity calculations outlined previously.[18,35,46]

The rotational strength (R_0^T) values were calculated in the following manner[47]:

The CD machine trace (Fig. 19), which was recorded on chart paper ruled in square millimeters, was broken into suitable wavelength increments (usually 5 mμ). The area of each increment was counted manually in square millimeters and the wavelength value (λ_{avg}) which makes $a_1 = a_2$ (Fig. 19) for each 5 mμ increment determined by inspection. The rotational strength was then calculated by the equation

$$R_0^T \simeq 0{\cdot}695 \times 10^{-42} \times [\theta]' \times V_{25}^T \times \sum_1^n (mm^2)_n/\lambda_n) \tag{3}$$

Here, $[\theta]'$ is the proportionality constant relating the pen deflection and the molecular ellipticity and is given by the relationship

$$[\theta]' = [(0{\cdot}33 \times sens \times M.W. \times k)/(c \times l)] \times (s)$$

TABLE 6. DENSITY CORRECTION FACTORS FOR EPA[a]

V_{25}^T = (Vol. at T°)/(Vol. at 25°) = (Density at 25°)/(Density at T°)

T (°C)	+25	−5	−29	−74	−192
V_{25}^T	1·000	0·956	0·924	0·874	0·798

[a] Taken from data of R. Passerini, I. G. Ross, W. Ramsey and R. Foster, *J. Sci. Instrum.* **30**, 274 (1953) and adjusted to a 25° base.

For example, for 5α-pregnan-20α-ol methyl xanthate (Table 1 and Fig. 19) at −192°:

M.W. = 394·24 a.w.u. l = 0·975 cm
c = 1·16 g/l. speed = 2
sens. = 1·5

Therefore: $[\theta]' = (0{\cdot}33 \times 1{\cdot}09 \times 1{\cdot}5 \times 394{\cdot}24)/(1{\cdot}16 \times 0{\cdot}975) = 188{\cdot}07$

$\lambda_{avg.}$ (mμ)	λ (mμ)	Area $(mm^2)^{50}$	$(mm^2/\lambda_{avg.})$
377	380–375	−11	−0·0292
372	375–370	−47	−0·1263
367	370–365	−100	−0·2725
362	365–360	−148	−0·4088
357·5	360–355	−180	−0·5035
352·5	355–350	−196	−0·5560
347·5	350–345	−190	−0·5468
343	345–340	−166	−0·4840
338	340–335	−131	−0·3876
333	335–330	−94	−0·2823
328	330–325	−67	−0·2043
323	325–320	−38	−0·1176
317·5	320–315	−24	−0·0756
312·5	315–310	−15	−0·0480
307·5	310–305	−10	−0·0325
302·5	305–300	−8	−0·0264
299	300–295	−3	−0·0100

$$\sum_1^n ((mm^2)_n/\lambda_n) = -4{\cdot}111$$

Since $V_{25}^{-192} = 0{\cdot}798$,

$$R_0^{-192} = 0{\cdot}695 \times 10^{-42} \times 0{\cdot}798 \times -4{\cdot}111 \times 188{\cdot}07 = -4{\cdot}29 \times 10^{-40} \text{ c.g.s.}$$

---

[46] K. Mislow, E. Bunnenberg, R. Records, K. M. Wellman and C. Djerassi, *J. Amer. Chem. Soc.* **85**, 1342 (1963).

[47] We are grateful to Drs. K. M. Wellman and P. H. A. Laur for developing and refining the technique of this calculation.

where *sens* refers to the sensitivity setting of the machine (1·5, 2 or 3), *M.W.* is the mol. wt. of the solute,[48] *k* is a machine correction factor checked periodically by comparison of CD curves for isoandrosterone with known CD curves of this compound[49] (presently equal to 1·09), *c* is the sample solution concentration in grams/liter, *l* is the length of the cell in cm (equal to 0·975 cm for our low-temperature cell), and *s* is a chart speed correction factor equal to 1 under normal operating conditions, i.e., chart speed instrument setting equal to 2. V_{25}^{T} corrects for the density change of the solution with temperature. Table 6 gives values of V_{25}^{T} for EPA at various temperatures.

Acknowledgment—We should like to thank Mrs. Ruth Records for her able technical assistance and utmost patience in carrying out the many necessary circular dichroism measurements required for this investigation.

---

[48] All mol. wts. employed in this study were computed on the basis C = 12·000 atomic weight units. (a.w.u.)

[49] L. Velluz and M. Legrand, *Angew. Chem.* 73, 603 (1961).

[50] The negative sign is introduced only in order to call attention to the fact that one is dealing with a negative rather than a positive CD curve.