come increasingly complex as concentrations are increased.

Experimental

Materials were the same as those described previously⁹ except that styrene was used without removal of a trace of phenolic inhibitor which did not interfere with any of the physical measurements.

Infrared spectra were taken with a Perkin-Elmer Model 421 grating spectrophotometer, using 0.1- or 1.0-mm. NaCl cells. Measurements at room temperature were at constant temperature within 1° determined by a thermometer attached to the cell. Measurements at 70° were made by enclosing the cell in a box with NaCl windows heated by circulating hot air, $\pm 0.5^{\circ}$. The spectrum from 3800-3500 (-OH) or 2900-2600 $cm.^{-1}$ (-OD) was scanned three times for each sample. During the time required for measurement there was no change attributed to evaporation or decomposition, and samples measured at 30°, heated to 70°, cooled, and remeasured gave identical spectra. At room temperature slit widths were 135 (3554 cm. $^{-1}$) and 308 μ (2630). Since the thermostating arrangement prevented considerable light from reaching the cell, 70° measurements were made with maximum source intensity and slit widths of 210 and 599 μ . Complex formation with aromatic bases was determined in CCl_4 solutions 0.3-1.5 M in aromatic and 0.02 M in TBHP (or 0.03 M TBDP), at which concentration dimer formation was negligible.

Distribution Experiments. Known concentrations of TBHP in solvent (previously saturated with water) were shaken with an equal volume of water (previously saturated with solvent) in a small separatory funnel. and the phases allowed to separate. An aliquot of the organic layer was removed and titrated for peroxide. and the concentration in the water layer calculated by the difference. Experiments with TBDP were carried out in the same way using 99.5% D₂O. Results from which distribution constants were calculated are listed in Table V.

Optical Rotatory Dispersion Studies. Anomalous Rotatory Dispersion and XCVII. Circular Dichroism Curves Associated with Thionamides. Application to Stereochemical Studies of Carboxylic Acids²

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In the past, a number of "chromophoric" derivatives containing the thione moiety (C=S) have been successfully employed for stereochemical correlations. However, these derivatives all had the structural feature that the thione was separated from the asymmetric center by one or two atoms. In the thionamide derivative (-C = S)-NRR'), prepared by reaction of phosphorus pentasulfide with an amide, the thione is adjacent to the asymmetric center. This favorable situation produces more reliable and pronounced Cotton effects when a thionamide is used as a "chromophoric" derivative for carboxylic acids than the formerly employed acylthiourea derivative (-C = 0)- $NHC(=S)NR'_{2}$). In general, a correlation can be made between the absolute configuration (R or S) of the asymmetric center closest to the chromophore and the sign of the Cotton effect associated with the derivative's low extinction ultraviolet absorption maximum near 330 m μ . The operation of free rotation in thionamides is demonstrated by circular dichroism measurements over the range -192 to $+168^{\circ}$.

The stereochemistry of many optically active compounds which are transparent in the 210–700-m μ region such as alcohols, amines, and carboxylic acids has been successfully investigated through optical rotatory dispersion measurements of Cotton effects associated with "chromophoric" derivatives. These derivatives contain the required low intensity and conveniently measurable absorption bands, and give rise to anomalous optical rotatory dispersion and circular dichroism curves. Dithiocarbamates (-NHC(==S)SR'), xanthates (-OC-(=S)SR', and acylthioureas $(-C(=O)NHC(=S)NR'_2)$ thus serve as useful "chromophoric" derivatives for amino acids, alcohols, and carboxylic acids, respectively.4

The three sulfur derivatives all possess a low intensity ultraviolet absorption maximum at 330–350 m μ which most likely arises from transitions in which the thione plays the principal role; the isolated thione is known to have a low intensity band at about 500 m μ .⁵ Since it is this grouping which is responsible for the long wave

⁽¹⁾ Paper XCVI: C. Djerassi, Proc. Chem. Soc., 314 (1964)

⁽²⁾ Supported by Grants No. GM-06840 and CA-07195 from the National Institutes of Health of the U. S. Public Health Service.
(3) Taken from part II of the Ph.D. Thesis of J. V. B., Stanford University, 1964

⁽⁴⁾ For leading references to these and many other "chromophoric"

<sup>derivatives, see Table I in ref. 1.
(5) See C. Djerassi and D. Herbst, J. Org. Chem., 26, 4675 (1961);
R. Mayer, G. Hiller, M. Nitzschke, and J. Jentzsch, Angew. Chem.</sup> Intern. Ed. Engl., 2, 370 (1963).

Table 1. Optical Rotatory Dispersion, Circular Dichroism, and Ultraviolet Absorption (Methanol Solution) of Some (S)-Thion- α -methylbutyramides



Derivative	R	O.R.D. first extremum	O.R.D. second extremum	O.R.D. Cotton effect sign	C.D. sign and mo- lecular ellipticity max.	Ultraviolet maximum of $n \rightarrow \pi^*$ band (ϵ), m _µ
I II	NH ₂ NHCH ₃	$[\phi]_{345} + 187^{\circ}$ $[\phi]_{352} + 524^{\circ}$	$[\phi]_{323} + 164^{\circ} \\ [\phi]_{315} + 65^{\circ}$	+	$[\theta]_{335} + 128 \\ [\theta]_{330} + 427$	328 (48) 324 (41)
III	$N(CH_3)_2$	$[\phi]_{376} - 116^{\circ}$			$[\theta]_{343} - 1200$	337 (47)
IV	N	$[\phi]_{370} - 85^{\circ}$		_	$[\theta]_{338} - 980$	330 (50)
V	NO	[\$\phi]_{390} -430°			$[\theta]_{355} - 1990$	348 (60)

Table II. Solvent Dependence of the Circular Dichroism Curves of Some (S)-Thion- α -methylbutyramides

Compd.	Methanol	Acetonitrile	Methylene chloride	Dioxane	Isooctane
S_{C} NH ₂ H ₃ C-C-H CH ₂ -CH ₃ I	$[\theta]_{336} + 128$	[<i>θ</i>]349 +187	$[\theta]_{336}$ +184	$[\theta]_{345} + 171$	Insoluble
S NH-CH ₃ H ₃ C-C-H CH ₂ -CH ₃ II	$[heta]_{330}$ +427	[<i>θ</i>] ₃₄₀ +640	$[\theta]_{343} + 523$	$[\theta]_{345} + 457$	$[\theta]_{357} + 536$
$S_{C} = N_{O}$ $H_{3}C = C - H_{C}$ $CH_{4}CH_{3}$ V	[θ] ₃₅₅ - 1990	[θ] ₃₅₈ —1680	<i>[θ]</i> ₃₀₂ −1656	[θ]365 −751	$[\theta]_{875} - 2078$

length transition, it is a disadvantage to have it separated from the asymmetric center by one or two atoms as is the case in the above derivatives. It was therefore desirable to seek a "chromophoric" derivative in which the asymmetric center and the thione are next to each other. This would presumably aid rotamer fixation and hence lead to increased amplitudes in the optical rotatory dispersion curves.

The simple thionamide derivative (-C(=S)NRR') appeared as an attractive candidate by virtue of its low extinction ultraviolet absorption band at 325-360 m μ^6 and its relative ease of preparation by reaction of an amide with phosphorus pentasulfide.⁷ The validity of these suppositions can easily be determined by comparing the results from this study of thionamides as a

"chromophoric" derivative for carboxylic acids to those obtained from the former investigation⁸ of acyl-thioureas $(-C(=O)NHC(=S)NR'_2)$.

The location of the long wave-length $n \rightarrow \pi^*$ transition is highly dependent⁶ upon the nature of the solvent and upon the degree of N-alkyl substitution and may be shifted by these factors to the extent of 25-30 m μ . Such large shifts in ultraviolet absorption maxima make it necessary that a study of thionamide Cotton effects also include the effect of solvent and N-alkyl substitution. Variations in N-alkyl substitution may also result in variations in rotamer composition and thus merit examination.

It was with these purposes in mind that the various Nsubstituted thionamides of (+)-(S)- α -methylbutyric acid (I-V in Table I) were prepared by treatment of the corresponding amides with phosphorus pentasulfide and sulfurated potash $(K_m S_n)$ in xylene at 70°.^{7,9} All

⁽⁶⁾ J. Sandstrom, Acta Chem. Scand., 17, 678 (1963); M. J. Janssen, Rec. trav. chim., 79, 454 (1960).

⁽⁷⁾ For complete reviews of the many reactions employed in the formation of thionamides, see R. N. Hurd and C. DeLaMater, *Chem. Rev.*, **61**, 45 (1961); A. Schoberl and A. Wagner in "Methoden der Organischen Chemie," Vol. 9, Houben-Weyl, Ed., Georg Thieme Verlag, Stuttgart, 1955, pp. 762-769; E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 4, Chemical Publishing Co., New York, N. Y., 1962, pp. 45-130; P. Chabrier and S. H. Renard, *Bull. soc. chim. France*, D272 (1949).

⁽⁸⁾ C. Djerassi, K. Undheim, and A.-M. Weidler, Acta Chem. Scand., 16, 1147 (1962). Unless otherwise noted, the sources of starting acids used by these workers and the acids used in the present work are the same. The sign of the optical rotation of the O-acetyllactic acid given in this reference should be reversed.

Table III. Solvent Dependence of the Spectral Measurements of N-Methylthion- 3β -acetoxy- Δ^5 -norcholenamide (VII) and N-Methylthioncholanamide (VIII)

Compound⁴	Solvent	O.R.D. first extremum	O.R.D. second extremum	O.R.D. Cotton effect sign	C.D. sign and molecular ellipticity	Ultraviolet maximum of $n \rightarrow \pi^*$ band (ϵ), $m\mu$
AcO VII (R)	Methanol Dioxane	[¢]₃₃₃ −516° [¢]₃₅₅ −64°	[φ] ₃₃₄ —494°	- +	$[\theta]_{315} - 495$ $[\theta]_{347} + 252$	317 (53)
VIII (R)	Methanol Dioxane	[φ] ₄₀₀ +194° [φ] ₄₀₀ +195°		? ?	$[\theta]_{325} - 301 \\ [\theta]_{345} - 100$	309 (68)

^a Showing absolute configuration of asymmetric center closest to chromophore (R or S).

the thionamides exhibited Cotton effects at about 340 m μ , thus proving that the n $\rightarrow \pi^*$ band is "optically active" and might be useful for stereochemical correlations. The spectral data are summarized in Table I, and reveal that circular dichroism measurements are in



Figure 1. Optical rotatory dispersion, circular dichroism, and ultraviolet absorption curves (methanol solution) of N,N-dimethylthion- α -methylbutyramide (III) and N-(thion- α -methylbutyryl)morpholine (V).

this instance more useful than optical rotatory dispersion measurements because the second extremum in the O.R.D. Cotton effect is not always discernible (see Figure 1). This is evidently due to the background effects arising from the high intensity $\pi \rightarrow \pi^*$ band at 265 mµ.⁶ In a few cases (see Tables III-IV) not even the sign of the Cotton effect could be determined un-

(9) The only other method of preparation which was attempted was base-catalyzed addition of hydrogen sulfide to a nitrile.⁷ Reaction of optically active hydratroponitrile (2-phenylpropionitrile) with ammonium bisulfide in a sealed tube at 60° gave a completely racemic thionamide.

ambiguously from the O.R.D. curve. The increase in amplitude upon monomethylation (see Table I and Figure 2) is in keeping with the assumption that free rotation is reduced as a result of interactions between the asymmetric center and the bulkier substituted chro-



Figure 2. Optical rotatory dispersion, circular dichroism, and ultraviolet absorption curves (methanol solution) of N-methyl-thion- α -methylbutyramide (II).

mophore. While all compounds exhibited the reported⁶ shifts in ultraviolet absorption maximum accompanying N-alkyl substitution, the inversion in sign of the Cotton effects of the N-methyl- (II) and the N,N-dialkyl- (III-V) thionamides is completely unexpected.

This inversion from a strong positive Cotton effect (Figure 2) to a strong negative one (Figure 1) between the N-alkyl- and the N,N-dialkylthionamides suggests that alterations in rotamer composition are operating. Perhaps restricted rotation about the C-N bond is en-



Figure 3. Optical rotatory dispersion and circular dichroism curves (methanol and dioxane solutions) of N-methylthion-3 β -acetoxy- Δ^5 -norcholenamide (VII).

tering into play as was reported^{10a} for N-methyl-Nbenzylthionformamide (VI) which was partially separated into its two isomeric forms VIa and VIb.^{10a} Restricted rotation may also be responsible for the difference in signs of optical rotation of some N-benzoyl- α -phenyl-



ethylamines in methanol and in benzene as has been suggested.^{10b} Such an effect may be responsible for the large shifts in ultraviolet maximum of thionamides from 327 m μ in a polar solvent to 367 m μ in a hydrocarbon solvent.⁶

The effect of solvent was examined using as model compounds the N-unsubstituted (I), the N-methyl (II), and the morpholine (V) derivatives of (+)-(S)- α -methylbutyric acid. As can be seen from Table II, solvents of widely varying polarity from methanol to isooctane did not change the sign of any of the Cotton effects and, in general, did not cause great amplitude changes in the circular dichroism curves. Especially noteworthy are the shifts in circular dichroism maxima accompanying changes in solvent. The effects and direction of shift are the same as were encountered earlier⁶ in the ultraviolet absorption studies of thionamides (325-m μ region in methanol to 365-m μ region in hydrocarbon solvents). These results showed methanol to be suitable and it became the solvent of choice because of its high

(10) (a) W. Walter and G. Maerten, Ann., 669, 66 (1963); (b) L. Skulski, G. C. Palmer, and M. Calvin, Tetrahedron Letters, 1773 (1963).

solvating power for a large variety of compounds of both high and low molecular weight.

Since at this stage no clear choice could be made as to whether the N-methyl derivative with a large rotation in one direction or the morpholine derivative with a large opposite rotation would be superior for stereochemical correlations, it was decided that both derivatives of each acid would be made until one proved superior over the other. Before long, the N-methyl derivative became the more attractive one with respect to ease of synthesis. Often the N-methylthionamide could be obtained with little difficulty, whereas the corresponding morpholine derivative could not be isolated. The N-methyl derivative then received priority especially in those acids where quantities were limited. Therefore only a few selected morpholine derivatives were prepared in an attempt to discover the factors causing sign reversal with an increase in N-alkylation.

In the α -methylbutyric acid derivatives, the asymmetric center is next to the chromophore. It was important, therefore, to determine whether Cotton effects are obtained in thionamides in which the chromophore is separated from the asymmetric center by one or two methylene groups. Accordingly, the N-methyl-thionamides of 3β -acetoxy- Δ^{5} -norcholenic acid (VII) and cholanic acid (VIII) were prepared.

As shown in Table III, the Cotton effects produced by both derivatives were very weak. While a change in solvent from methanol to dioxane does not significantly alter the Cotton effect of the N-methylthioncholanamide (VIII), this is not the case with the N-methylthion-3 β acetoxy- Δ^5 -norcholenamide (VII) which exhibits Cotton effects of differing sign in methanol and in dioxane (Table III and Figure 3).¹¹ This result demands that in any attempted correlation between absolute configuration and Cotton effect the measurements must be performed in the same solvent.

With these results on the effects of solvent, N-substitution, and distance as a basis, the gathering of a wide variety of thionamides can be begun with a view to correlating the absolute stereochemistry of the asymmetric center closest to the thionamide chromophore with the sign of the Cotton effect as determined by optical rotatory dispersion and circular dichroism.

It is the spatial relationship between the thionamide chromophore and the various substituents which controls the Cotton effect associated with the $n \rightarrow \pi^*$ (340 mµ) transition. In the case of cyclic ketones, the number of possible spatial arrangements between the substituents and the chromophore is small and is usually known, thus leading to the valuable octant rule.¹² Unfortunately, the opposite situation is present in the thionamide derivatives and in most other "chromophoric" derivatives reported in the literature.⁴ The free rotation that exists about all single bonds allows for a great variety of possible conformational isomers. The Cotton effects of such compounds are a composite of the individual contributions of all the rotamers present. In the future, modern computers may be able to offer a

⁽¹¹⁾ The operation of the strong negative background associated with the Δ^{5} -double bond [C. Djerassi, W. Closson, and A. E. Lippman, J. Am. Chem. Soc., 78, 3163 (1956)] is especially noteworthy in the positive O.R.D. Cotton effect in dioxane solution.

⁽¹²⁾ W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961); C. Djerassi and W. Klyne, J. Chem. Soc., 4929 (1962); C. Djerassi and W. Klyne, *ibid.*, 2390 (1963).

Compound₄	O.R.D. first extremum	O.R.D. second extremum	O.R.D. Cotton effect sign	C.D. sign and molecular ellipticity maximum	Ultraviolet maximum of $n \rightarrow \pi^*$ band (ϵ) , $m\mu$
$ \begin{array}{c} S \\ C \\ H \\ C \\ C \\ C \\ C \\ C \\ C$	[φ]365 +1720°	[φ] ₃₁₈ —1003°	+	[θ] ₃₄₂ +2457	335 (66)
$ \underbrace{ \begin{array}{c} S \\ C \\ -C \\ -H \\ CH_2CH_3 \\ X^{b}(R) \end{array} } $	[φ]369 -870°	[φ] ₃₂₀ +579°	_	$[\theta]_{340} - 1293$	334 (72)
C-NHCH,	[¢]₃₅₅ −863°		?	[<i>θ</i>] ₃₅₃ -352	335 (48)
S $XI(R)$ OAc $C-NHCH_{s}$ S $XII(S)$	$[\phi]_{x_{60}}+3650^\circ$		ņ	[θ] ₂₄₃ +539	340 (45)
Aco XIII (S)	[φ] ₃₇₀ +975°		+	$[\theta]_{340} + 3460$	333 (51)
$S \qquad NHCH_{a}$ $AcO - C - H$ CH_{a} $XIV (S)$	$[\phi]_{3*3}-608^\circ$	[φ] _{\$10} +960°	-	[θ] ₈₄₂ -1113	323 (42)

Table IV. Optical Rotatory Dispersion, Circular Dichroism, and Ultraviolet Absorption (Methanol Solution) of Various N-Methylthionamides Parious N-Methylthionamides

^a Showing absolute configuration of asymmetric center closest to chromophore (R or S). ^b Optical purity 68 %.

complete picture of the rotamer composition,¹³ but at present an empirical approach can lead to valuable generalizations as was done in the acylthiourea study,⁸ where the same problems exist to an even greater extent since the acylthiourea chromophore contains three more single bonds than the thionamide.

In the earlier acylthiourea investigation,⁸ it was concluded that any attempted correlation between the sign of the Cotton effect and the absolute configuration of the nearest asymmetric center should be based on the Cahn-Ingold-Prelog (R) and (S) convention¹⁴ since, in general, it reflects the relative bulk of the substituents surrounding the asymmetric center. However, this system is not perfect since it is founded on the atomic number of the atom linked to the asymmetric center. It is possible for a heteroatom of relatively small spatial volume to take priority over a bulkier hydrocarbon moiety—for example, the hydroxyl group over the notoriously bulky *t*-butyl group. Another complication which may cause this correlation to fail is hydrogen bonding which could produce a different spatial arrangement between the chromophore and the substituents than would bulk alone. These considerations must be kept in mind during the following discussion.

It was found⁸ that, in general, an (*R*)-acylthiourea gives a positive Cotton effect and an (*S*)-acylthiourea a negative one. Except for two anomalies, the generalizations applied to all examined acids outside of small ring carboxylic acids, where some rather subtle interactions came into play.⁸ The two open-chain anomalies were the acylthioureas of O-acetyllactic acid and α methylbutyric acid. The anomaly of the lactic acid derivative can be attributed to the failure of the (*R*) and (*S*) system to correlate with bulk when a hetero-

⁽¹³⁾ See, for instance, J. B. Hendrickson, J. Am. Chem. Soc., 83, 4537 (1961).

⁽¹⁴⁾ For a full discussion of the (R) and (S) notation for defining absolute configuration, see R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956).

Table V.	Optical Rotatory Dispersion,	Circular Dichroism,	and Ultraviolet	Absorption ^a of
Some N-(7	Thionoyl)morpholines			

Compound ^b	O.R.D. first extremum	O.R.D. second extremum	O.R.D. Cotton effect sign	C.D. sign and molecular ellipticity maximum	Ultraviolet maximum of $n \rightarrow \pi^*$ band (ϵ)
	[¢]₃₃₀ +4418°	[φ]₃₃₅ — 3901 °	+	[θ] ₃₆₀ +6700	355 (72)
$ \begin{array}{c} S \\ C \\ C \\ C \\ C \\ C \\ C \\ C \\ $	[φ]386 −1375°	[φ] ₃₃₄ +1560°	_	$[\theta]_{363} - 1623$	359 (66)
C C C C C C C C C C C C C C C C C C C	[φ] ₃₈₅ +490°	[φ] ₃₃₅ -267°	+	$[\theta]_{360} + 604$	353 (53)
$XVII^{d}(\mathbf{R})$					

^{*a*} In methanol solution except where noted. ^{*b*} Showing absolute configuration of asymmetric center closest to chromophore (R or S). ^{*c*} Optical purity 68%. ^{*d*} Determined in dioxane because of insufficient solubility in methanol.

atom is involved. However, there is no simple explanation for the failure of the α -methylbutyric acid derivative to conform to the generalization and it is particularly this type of anomaly that we wished to resolve in this thionamide study.

Table IV summarizes the spectral data obtained in methanol solution with the N-methylthionamides of a variety of acid substrates. It can be seen that in all cases (Tables I, III, and IV) where the asymmetric center closest to the N-methylthionamide chromophore is composed of only carbon and hydrogen atoms, an (R) configuration produces a negative Cotton effect and an (S) configuration a positive one. The signs and amplitudes of the Cotton effects can easily be determined in all cases from the circular dichroism curves. However, this is not true of all the optical rotatory dispersion curves which are subject to background effects caused by the $\pi \rightarrow \pi^*$ band at 270 m μ resulting in inability to determine experimentally the second extremum of a Cotton effect.

The single anomaly to this generalization is again the N-methylthionamide of O-acetyllactic acid (XIV) where an (S) configuration produced a negative curve. It is reasonable to expect that this arises from the lack of correlation of bulk and the (R) and (S) system¹⁴ when a heteroatom is involved.

The original motive for this work was the attachment of the thione to the asymmetric center in order to produce more reliable and pronounced Cotton effects. The study is to be judged successful on the grounds that even the α -methylbutyric acid derivative II conforms to the generalization, and the N-methylthion-3 β acetoxy- Δ^5 -norcholenamide (VII) exhibited a usable rotatory dispersion curve (Figure 3) which was not the case with the acylthiourea derivatives.⁸

The spectral data (Tables I and V) obtained on a limited number of morpholine derivatives stand in sharp contrast to those of the N-methylthionamides

(Tables I and IV) because no correlation between absolute configuration and Cotton effect is evident. The validity of the attempted correlation in N-(thioncholanyl)morpholine (XVII) can be questioned since it was performed in dioxane rather than methanol for solubility reasons.

The solvent-induced inversion in sign (see Figure 3) of the N-methylthion- 3β -acetoxy- Δ^5 -norcholenamide (VII) Cotton effect remains to be explained. Two factors responsible for this phenomenon may be differences in rotamer population and/or solvation.¹⁵ A possible answer to this question may be derived from measurements over a wide temperature range, since compounds which are conformationally mobile often show significant differences in circular dichroism curves on changing the temperature—notably at low temperatures.¹⁶

It might be expected that the N-unsubstituted thionamide (e.g., I) would exist in a number of conformational isomers (rotamers), since there are only relatively small barriers to rotation. The N-methylthionamide (e.g., II) should be more restricted in rotation and the morpholine derivative (e.g., V) even more so. This last statement is suggested by the reluctance of some morpholine amides to form thionamides, notably the amides of 3β -acetoxy- Δ^{5} -etienic acid and dehydroabietic acid. The amplitude changes of the differently N-substituted thionamides show that in actual fact there is significant conformational mobility in all compounds. In the α -methylbutyric acid series (Table VI), the amplitude of the N-unsubstituted compound I underwent a sixfold increase on lowering the temperature to -192° as compared to a three- to fourfold one in the N-methyl (II) and morpholine (V) analogs. High-temperature

⁽¹⁵⁾ A. Moscowitz, K. Wellman, and C. Djerassi, *Proc. Natl. Acad. Sci. U. S.*, **50**, 799 (1963); C. Coulombeau and A. Rassat, *Bull. soc. chim. France*, 2673 (1963).

⁽¹⁶⁾ K. M. Wellman, E. Bunnenberg, and C. Djerassi, J. Am. Chem. Soc., 85, 1870 (1963); A. Moscowitz, K. M. Wellman, and C. Djerassi, *ibid.*, 85, 3515 (1963).

Table VI. Temperature Dependence of the Circular Dichroism Maxima of Some (S)-Thion- α -methylbutyramides in Ether-Isopentane-Ethanol (5:5:2) (EPA) and in Decalin

Com- pound	a	-192°	-74°	25°	66°	128°	168°	25° (after heating)
I	EPA	$[\theta]_{348} + 546$	$[\theta]_{340} + 230$	$[\theta]_{352} + 91$				
	Decalin	Preci	pitates	$[\theta]_{360} + 184$	$[\theta]_{365} + 115$	$[\theta]_{370} + 69$	$[\theta]_{370} + 46$	$[\theta]_{365} + 115$
H	EPA	$[\theta]_{340} + 1150$	$[\theta]_{341} + 648$	$[\theta]_{340} + 418$				
	Decalin	Precip	pitates	$[\theta]_{355} + 504$	$[\theta]_{355} + 420$	$[\theta]_{358} + 284$	$[\theta]_{358} + 179$	$[\theta]_{355} + 451$
V	EPA	$[\theta]_{357} - 7590$	$[\theta]_{363} - 3825$	$[\theta]_{369} - 2064$				
	Decalin	-	$[\theta]_{373} - 3266$	$[\theta]_{375} - 1764$	$[\theta]_{376} - 1476$	$[\theta]_{377} - 1224$	$[\theta]_{377} - 864$	$[\theta]_{375} - 1332$

^a Structures for these compounds are shown in Table II.

measurements (Table VI) result in the anticipated diminution in amplitudes which would be associated with increased free-rotational mobility. There is some decomposition at the higher temperatures as evidenced by the fact (see last column in Table VI) that the room temperature curves after heating are not identical with the room temperature curves before heating. The increase in amplitude on going from the highest temperature ($+168^\circ$) back to room temperature proves that the effect being observed cannot be attributed to partial racemization. The increase in amplitude on cooling and the decrease on heating accompanied by only insignificant wave-length changes support the assumption that rotamers play the principal role.

The low temperature circular dichroism study (Figure 4) on N-methylthion-3 β -acetoxy- Δ^5 -norcholenamide (VII) yielded some insight into the cause of the inversion of the Cotton effect sign with change in solvent. Two maxima of opposite sign appear in the circular dichroism curve at room temperature in the mixed solvent ether-isopentane-ethanol (5:5:2) and both increase in amplitude on lowering the temperature. The results contained in Figures 3 and 4 are consistent with the assumption of the existence of two rotamers of approximately equal energy but solvated differently.

In summary, N-methylthionamides can be used for absolute stereochemical determination of hydrocarbon centers by measuring their optical rotatory dispersion and circular dichroism curves in methanol. If one employs an (R) and (S) system founded on decreasing bulk alone, then such an (R)-N-methylthionamide (including asymmetric centers with heteroatoms) will produce a negative Cotton effect and an (S)-N-methylthionamide a positive one. For hydrocarbon centers, the ordinary (R) and (S) notation¹⁴ can be used as a good approximation in place of such a system. Care must obviously be exercised when one is dealing with the extreme subtleties of the (R) and (S) convention, such as cis vs. trans stereoisomers, since no appropriate example is as yet available. The problems caused by hydrogen bonding must also be kept in mind.

Experimental¹⁷

Preparation of Amides. All amides in this work were obtained by one of the following methods, the appro-

priate one for each compound being listed below under the specific substances. All acid chlorides were prepared by reaction with thionyl chloride either according to the method of Hauser and Brasen¹⁸ or by stirring the reagents at room temperature overnight, with subsequent removal of excess thionyl chloride by means of a rotary evaporator.



Figure 4. Temperature dependence of the circular dichroism curve of N-methylthion- 3β -acetoxy- Δ^{5} -norcholenamide (VII) in ether-isopentane-ethanol (5:5:2).

In all cases where the reagent is an aqueous amine solution or morpholine or pyrrolidine in benzene, the procedure of Hauser and Brasen¹⁸ was used with appropriate extraction and washing of the product. The reaction time was normally 15–30 min. except when dealing with solid or semisolid acid chlorides; the reaction was then allowed to proceed for several hours in order to ensure complete dispersion of the acid chloride.

⁽¹⁷⁾ Melting points are uncorrected. All rotatory dispersion and circular dichroism measurements were performed by Mrs. Ruth Records using a Japan Spectroscopic Co., Ltd., automatically recording spectropolarimeter and a Baird-Atomic/Jouan dichrograph, modified in our laboratory to permit measurements over a wide temperature range. Specific rotations were determined in chloroform unless otherwise noted. The rotatory dispersion and circular dichroism curves were obtained on concentrations of the order of 1 mg./ml. in the solvents noted in the

<sup>tables. Microanalyses were performed by Messrs. E. Meier and J. Consul of the Stanford Microanalytical Laboratory.
(18) C. R. Hauser and W. R. Brasen, J. Am. Chem. Soc., 78, 494</sup>

^{(1956).}

Reactions of gaseous amine in benzene were performed at room temperature and were followed by the appropriate combinations of extractions and washings.

In all cases in which the compound possessed an acetoxyl function and where gaseous amines in methylene chloride were reagents, the reactions were performed with ice cooling, and a reaction time of only 10 min. was allowed. Moisture was always carefully excluded. At the end, the amine hydrochloride was removed from the cold mixture by filtration, and the solvent was evaporated *in vacuo*. All operations were performed quickly so as to minimize moisture absorption from the air. The residue was then extracted with methylene chloride and the appropriate washings were performed.

Preparation of Thionamides. All the thionamides were prepared by essentially the same procedure¹⁹; two representative examples are given below. If a gummy adduct formed, it was extracted by adding xylene and collecting the supernatant liquid; if a suspension formed, it was filtered and the residue was washed well with hot xylene. Purification usually was accomplished by preparative thin layer chromatography on silica gel G. The exact position of the thionamide was determined on an analytical plate by the dark spot produced in ultraviolet light (black light) and by the orange color obtained on exposure to iodine vapor which turned to a characteristic red brown upon subsequent spraying with acidic ceric sulfate solution.

(+)-(S)-Thion- α -methylbutyramide (I). To a mixture of 308 mg. of (+)-(S)- α -methylbutyramide²⁰ (m.p. 112– 114°, needles from benzene-petroleum ether, $[\alpha]^{25}D$ $+22^{\circ}$ (c 3.535), obtained from the (+)-acid²¹ by treatment of the acid chloride with concentrated aqueous ammonia) in 3 ml. of xylene was added a homogeneous mixture of 297 mg. of sulfurated potash ($K_m S_n$, Baker and Adamson, General Chemical Co., New York, N. Y.) and 317 mg. of phosphorus pentasulfide. The mixture was stirred in a flask fitted with a drying tube for 1 hr. at room temperature whereupon the temperature was raised to 70° and kept there. One hour after the application of heat, the stirring was stopped, the supernatant liquid was collected and filtered while hot, and 3 ml. of xylene was added to the residue; heating and stirring were continued. This extraction procedure was repeated every half-hour until a total of eight extractions was accomplished. The solvent was removed from the combined xylene extracts. The residue was recrystallized from benzene-petroleum ether to give 126 mg. of white crystals, m.p. 77-79°, $[\alpha]^{26}D + 24.6^{\circ}$ (c 1.22); $\lambda_{\max}^{CHC1_3}$ 2.86, 2.94, and 6.25 μ ; $\lambda_{\max}^{CH_{3}OH}$ 328 m μ (ϵ 48) and 267 m μ (ϵ 11,700).

Anal. Calcd. for $C_5H_{11}NS$: C, 51.26; H, 9.46. Found: C, 51.06; H, 9.31.

(+)-(S)-(Thionhydratropyl)morpholine (XV). To a mixture of 409 mg. of (+)-(S)-N-(hydratropyl)morpholine [b.p. 120–130° (bath, 0.4 mm.), $[\alpha]^{27}D$ +85° (c 0.878), made from (+)-hydratropic acid²² by treatment

(20) H. J. Taverne, Rec. trav. chim., 19, 107 (1900).

(21) W. von E. Doering and T. C. Aschner, J. Am. Chem. Soc., **75**, 393 (1953); K. J. Sax and W. Bergman, **77**, 1910 (1955). For stereochemistry see "Progress in Stereochemistry," Vol. 1, W. Klyne, Ed., Butterworths Scientific Publications, London, 1954, p. 188.

(22) (a) A. Fredga, Arkiv Kemi, 7, 241 (1954); H. S. Raper, J. Chem. Soc., 2557 (1923); (b) K. Pettersson, Arkiv Kemi, 10, 283 (1956).

of the acid chloride with 50% morpholine in benzene] in 2 ml. of xylene was added a homogeneous mixture of 205 mg. of sulfurated potash and 233 mg. of phosphorus pentasulfide. The mixture was stirred in a flask fitted with a drying tube for 1 hr. at room temperature whereupon the temperature was raised to 70° and kept there. One hour after the application of heat, the stirring was stopped, the supernatant liquid was collected and filtered while hot, and 2 ml. of xylene was added to the residue; heating and stirring were continued. This extraction procedure was repeated every half-hour until a total of eight extractions was accomplished. The solvent was removed and an analytical thin layer chromatogram using silica gel G and benzene-ethyl acetate (8:2) showed four spots. The thionamide position was determined as explained above, and the appropriate band, on a preparative thin layer chromatogram with the same solvent system, was collected, using ultraviolet light for detection. The crude thionamide was recrystallized from benzenepetroleum ether to give 121 mg. of colorless needles, m.p. 72-74°, no infrared absorption between 4 and 6.6 μ except for a small aromatic peak, $[\alpha]^{25}D + 161^{\circ}$ (c 0.67), $\lambda_{\max}^{CH_{3}OH}$ 355 m μ (ϵ 72) and 283 m μ (ϵ 19,800).

Anal. Calcd. for $C_{13}H_{17}NOS$: C, 66.36; H, 7.28. Found: C, 66.32; H, 7.41.

(+)-(S)-N-Methylthion-α-methylbutyramide (II). The reaction was performed as above with 362 mg. of (+)-(S)-N-methyl-α-methylbutyramide [m.p. 35-37° (solid distillate), b.p. 110-120° (bath, 0.75 mm.), [α]²⁵D +29° (c 2.43), obtained from the (+)-acid²¹ by treatment of the acid chloride with methylamine in benzene], 3 ml. of xylene, 306 mg. of sulfurated potash, and 333 mg. of phosphorus pentasulfide, to give, after preparative thin layer chromatography with 20% ethyl acetate in benzene and vacuum distillation, 180 mg. of a clear oil, b.p. 100° (bath, 0.65 mm.), [α]²⁶D +49° (c 1.14), $\lambda_{max}^{CHCl_1}$ 2.91 and 6.54 μ, λ_{max}^{CHOH} 324 mμ (ε 41) and 261 mμ (ε 11,700).

Anal. Calcd. for C₆H₁₃NS: C, 54.94; H, 9.99. Found: C, 54.85; H, 9.88.

(+)-(S)-N,N-Dimethylthion- α -methylbutyramide (III). In a similar fashion, 352 mg. of (+)-(S)-N,Ndimethyl- α -methylbutyramide [b.p. 60–70° (bath, 0.25 mm.), [α]²⁴D +43.8° (c 7.93), obtained from the (+)acid²¹ by treatment of the acid chloride with 30% aqueous dimethylamine], was transformed into 200 mg. of a slightly yellow green oil, b.p. 90° (bath, 0.75 mm.), [α]²⁷D +68° (c 1.17), no infrared absorption between 5 and 6.5 μ , $\lambda_{max}^{CH_{3}OH}$ 337 m μ (ϵ 47) and 272 m μ (ϵ 13,000).

Anal. Calcd. for $C_7H_{15}NS$: C, 57.90; H, 10.41. Found: C, 57.98; H, 10.27.

(+)-(S)-N-(Thion- α -methylbutyryl)pyrrolidine (IV). A yield of 45% was realized in the conversion of (+)-(S)-N-(α -methylbutyryl)pyrrolidine [b.p. 60–70° (bath, 0.25 mm.), [α]²⁵D +31° (c 0.653), obtained from the (+)-acid²¹ by treatment of the acid chloride with 40% pyrrolidine in benzene] into the thionamide: yellow green oil; b.p. 100° (bath, 0.3 mm.); [α]²²D +34° (c 0.53); no infrared absorption between 5 and 6.5 μ ; $\lambda_{max}^{CH_{3}OH}$ 330 m μ (ϵ 50) and 273 m μ (ϵ 13,400).

Anal. Calcd. for $C_9H_{17}NS$: C, 63.13; H, 10.00. Found: C, 62.87; H, 9.74.

⁽¹⁹⁾ K. Kindler, Ann., 431, 187 (1923).

(+)-(S)-N- $(Thion-\alpha$ -methylbutyryl)morpholine (V). A sample of 296 mg. of (+)-(S)-N- $(\alpha$ -methylbutyryl)morpholine [b.p. 90–100° (bath, 0.35 mm.), $[\alpha]^{25}D$ $+23^{\circ}$ (c 4.11), obtained from the (+)-acid²¹ by treatment of the acid chloride with 50% morpholine in benzene], gave 163 mg. of a bright yellow oil, b.p. 100-110° (bath, 0.4 mm.), $[\alpha]^{27}D + 38°$ (c 0.549), no infrared absorption between 4 and 6.5 μ , $\lambda_{max}^{CH_{3}OH}$ 348 $m\mu$ (ϵ 60) and 280 $m\mu$ (ϵ 14,200).

Anal. Calcd. for C₉H₁₇NOS: C, 57.73; H, 9.15. Found: C, 57.77; H, 9.17.

N-Methylthion-3 β -acetoxy- Δ^{5} -norcholenamide (VII). The usual reaction conditions applied to 150 mg. of Nmethyl-3 β -acetoxy- Δ^5 -norcholenamide [m.p. 253° dec., white crystals from methanol, obtained from 3β acetoxy- Δ^5 -norcholenic acid (m.p. 194°, white crystals from dilute acetic acid)23 by treatment of the acid chloride with methylamine in methylene chloride] provided 27 mg. of white needles, m.p. 234° dec.; $\lambda_{max}^{CHC1_2}$ 2.98, 5.80, and 6.58 μ ; $\lambda_{max}^{CH_3OH}$ 317 m μ (ϵ 53) and 262 m μ (ϵ 12,100).

Anal. Calcd. for $C_{26}H_{41}NO_2S$: C, 72.35; H, 9.58. Found: C, 72.02; H, 9.53.

N-Methylthioncholanamide (VIII). The reaction of 214 mg. of N-methylcholanamide (m.p. 186-189°, white crystals from acetone, obtained from cholanic acid²⁴ by treatment of the acid chloride²⁵ with 40% aqueous methylamine), was performed as usual, and after recrystallization from ethanol-water there was isolated 132 mg. of white powder, m.p. 121.5-123.5°, $\lambda_{max}^{CHCl_3}$ 2.93 and 6.58 μ , $\lambda_{max}^{CH_2OH}$ 309 m μ (sh) (ϵ 68) and 262 m μ (ϵ 12,000).

Anal. Calcd. for C₂₅H₄₃NS: C, 77.07; H, 11.13. Found: C. 76.75; H. 10.92.

(S)-N-Methylthionhydratropamide (IX). (S)-N-Methylhydratropamide (m.p. 86.5-89°, needles from benzene-petroleum ether, $[\alpha]^{25}D + 40^{\circ}$ (c 0.734) obtained from the (+)-acid²² by treatment of the acid chloride with 40% aqueous methylamine), was transformed in 50% yield into a slightly yellow tinted oil, b.p. 95-110° (bath, 0.65 mm.), $\lambda_{max}^{CHO_{13}}$ 2.92 and 6.53 μ , H_{30H} 335 m μ (ϵ 66) and 265 m μ (ϵ 10,800).

Anal. Calcd. for C₁₀H₁₃NS: C, 67.02; H, 7.31. Found: C, 66.88; H, 7.40.

(R)-N-Methylthion- α -phenylbutyramide (X). The reaction was performed as above with 300 mg. of (R)-N-methyl- α -phenylbutyramide [m.p. 98–99.5°, white crystals from benzene-petroleum ether, $[\alpha]^{26}D - 20^{\circ}$ (c 3.50), obtained from the (-)-acid of 68% optical purity, $[\alpha]^{25}D - 65^{\circ}$ (near), 22b,26 by treatment of the acid chloride with 40% aqueous methylamine] to give 177 mg. of a yellow oil, b.p. 128-140° (bath, 0.5 mm.), $\lambda_{max}^{CHCl_3}$ 2.90 and 6.52 μ , $\lambda_{max}^{CH_3OH}$ 334 m μ (ϵ 72) and 267 $m\mu$ (ϵ 11,800).

Anal. Calcd. for C₁₁H₁₅NS: C, 68.37; H, 7.82; S. 16.56. Found: C. 67.89; H. 7.71; S. 16.64.

N-Methylthiondehydroabietamide (XI). N-Methyldehydroabietamide (m.p. 171-172°, needles from ethanol-water, obtained from dehydroabietic acid²⁷ by treatment of the acid chloride²⁷ with 40% aqueous methylamine), gave, after the usual reaction and recrystallization from methanol-water, over 50% of a white powder, m.p. 144.5-146°, $\lambda_{max}^{CHCl_3}$ 2.88 and 6.57 μ , $\lambda_{\max}^{CH_3OH}$ 335 m μ (ϵ 48) and 267 m μ (ϵ 11,500).

Anal. Calcd. for C₂₁H₃₁NS: C, 76.55; H, 9.48; S, 9.71. Found: C, 76.10; H, 9.38; S, 9.72.

N-Methylthion-O-acetylpodocarpamide (XII). N-methyl-O-acetylpodocarpamide (obtained Crude from O-acetylpodocarpic acid²⁸ by treatment of the acid chloride with methylamine in methylene chloride). after the usual reaction and recrystallization from ethanol-water, yielded only 5% of the thionamide as white needles, m.p. 184–188°; $\lambda_{max}^{CHCl_3}$ 2.88, 5.69, and 6.59 μ ; $\lambda_{\max}^{CH_3OH}$ 340 m μ (ϵ 45) and 268 m μ (ϵ 11,200).

Anal. Calcd. for C₂₀H₂₇NO₂S: C, 69.54; H, 7.88. Found: C, 69.39; H, 7.82.

N-Methylthion-3 β -acetoxy- Δ^5 -etienamide (XIII), A 20% yield was realized in the reaction of N-methyl- 3β -acetoxy- Δ^{5} -etienamide [m.p. 204° dec., white powder from methanol-water, obtained from 3β -acetoxy- Δ^5 etienic acid²⁹ by treatment of the acid chloride with methylamine in methylene chloride] to the thionamide; hair-like needles, m.p. 245° dec.; $\lambda_{max}^{CHCl_3}$ 2.92, 5.80, and 6.61 μ ; $\lambda_{max}^{CH_{3}OH}$ 333 m μ (ϵ 51) and 265 m μ (ϵ 13,100).

Anal. Calcd. for C₂₃H₃₅NO₂S: C, 70.92; H, 9.06. Found: C, 70.58; H, 9.03.

(S)-N-Methylthion-O-acetyllactamide (XIV). The reaction was performed as above with 277 mg. of (S)-N-methyl-O-acetyllactamide (low-melting solid, obtained from (-)-O-acetyllactic acid, ³⁰ $[\alpha]^{26}D$ -52.5° (c 7.05), which was synthesized³¹ from L-(+)-lactate Ca 4H₂O (California Corp. for Biochemical Research, Los Angeles, Calif.), by treatment of the acid chloride³⁰ with methylamine in methylene chloride), to give after vacuum distillation 72 mg. of an oil, b.p. 90–110° (bath, 0.25 mm.); $\lambda_{\text{max}}^{\text{CHOI}}$ 2.91, 5.68, and 6.54 μ ; $\lambda_{\text{max}}^{\text{CHOH}}$ 323 m μ (ϵ 42) and 263 m μ (ϵ 11,500).

Anal. Calcd. for C₆H₁₁NO₂S: C, 44.71; H, 6.88. Found: C, 44.63; H, 6.74.

(R)-N-(Thion- α -phenylbutyryl)morpholine (XVI). The reaction was performed as above with 395 mg. of (R)-N-(α -phenylbutyryl)morpholine [b.p. 115–125° (bath, 0.20 mm.), $[\alpha]^{27}D - 62.7^{\circ}$ (c 6.475), obtained from the (-)-acid of 68% optical purity by treatment of the acid chloride with 50% morpholine in benzene], to give 71 mg. of white crystals, m.p. 64-67°; no infrared absorption between 5 and 6.5 μ except for a small aromatic peak at 6.26 μ ; $\lambda_{max}^{CH_3OH}$ 359 (ϵ 66) and 284 $m\mu$ (ϵ 14,200).

(27) O. Jeger, O. Dürst, and G. Büchi, Helv. Chim. Acta, 30, 1853 (1947), and earlier references

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⁽²⁹⁾ C. Djerassi and J. Staunton, J. Am. Chem. Soc., 83, 736 (1961). (30) C. M. Bean, J. Kenyon, and H. Phillips, J. Chem. Soc., 303 (1936); for the enantiomeric compounds see K. Freudenberg and L. Market, Ber., 60, 2447 (1927). (31) V. Auger, Compt. rend., 140, 938 (1905).

Anal. Calcd. for C₁₄H₁₉NOS: C, 67.44; H, 7.68. Found: C, 67.70; H, 7.74.

N-(Thioncholanyl)morpholine (XVII). The usual reaction with 264 mg. of N-(cholanyl)morpholine [m.p. 134.5–136°, white crystals from ethanol-water, $[\alpha]^{26}D$ $+24^{\circ}$ (c 0.891), obtained from cholanic acid²⁴ by treatment of the acid chloride²⁵ with 50% morpholine in benzene] gave 75 mg. of yellow plates, m.p. 182.5-185°, no infrared absorption between 5 and 6.65 μ . $\lambda_{\max}^{\text{dioxane}}$ 353 m μ (ϵ 53) and 280 m μ (ϵ 14,700).

Anal. Calcd. for C₂₈H₄₇NOS: C, 75.46; H, 10.63. Found: C, 75.04; H, 10.61.

Optical Rotatory Dispersion Studies. XCVIII.¹ The Conformation of the 17-Acetyl Group in Steroids and Its Correlation with Variable-Temperature Circular Dichroism²

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The conformation of the 17-acetyl side chain in several 20-keto steroids has been examined by conformational analysis and a correlation has been made with the observed temperature-dependent circular dichroism. In general, it has been found that the acetyl group has two preferred orientations: one exhibiting a strong positive Cotton effect, the other a negative one. The presence or absence of β -substituents at C-13 and C-16 alters the conformational preference of the acetyl side chain in a predictable manner for the substances examined.

Although the octant rule⁴ has been applied to configurational and conformational problems mainly in substituted cyclohexanones where spatial relationships are either well established or can be deduced from the resulting Cotton effect, there is no a priori reason why the rule cannot be applied to acyclic carbonyl compounds as well. Presumably the hesitancy to use the octant rule in open-chain systems arises from the lack of conformational homogeneity in these substances, as well as the inherent difficulties in making a clear-cut assignment of the preferred conformation in an acyclic system. Nevertheless, a start in this direction has been made by several investigators.5,6

17-Acetyl steroids seemed a likely candidate for such a study for two reasons. First, the system is simple in the sense that conformational changes will be localized mainly in rotation about the C-17-C-20 bond and, second, 17-acetyl steroids are of interest both chemically and biologically. In an early piece of work, Djerassi⁷ successfully employed optical rotatory dispersion (O.R.D.) measurements to determine the configuration

- (1) Paper XCVII: J. V. Burakevich and C. Djerassi, J. Am. Chem. Soc., 87, 51 (1965).
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- (3) National Institutes of Health Postdoctoral Research Fellow, 1962-1963
- (4) W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. (5) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, Book Co., Inc., New York, N. Y., 1960, p. 128.
- (6) (a) M. J. T. Robinson, Chem. Ind. (London), 932 (1964); (b) J. C. Danilewicz and W. Klyne, J. Chem. Soc., in press.
- (7) C. Djerassi, Bull. soc. chim. France, 741 (1957).

of 17-acetyl groups. Thus, a strongly positive Cotton effect signified a 17β -acetyl substituent, whereas a negative Cotton effect was associated with a 17α grouping. This early work was confirmed and further extended by Struck and Hautman⁸ to a series of substituted pregnan-20-ones. These authors noted vicinal interactions in certain cases between C-16 substituents and the C-20 keto group. Crabbé has utilized O.R.D.9 and circular dichroism^{9, 10} (C.D.) methods in a study of cis- and trans-16-substituted 17-acetyl steroids and suggested that the amplitude changes caused by C-16 substituents were probably due to a combination of effects including steric factors (such as the conformation of the acetyl side chain, ring D, and the C-16 substituent) as well as electronic effects introduced by the C-16 group. Snatzke and his group¹¹ recently reported upon the contributions of C-15 and C-11 substituents to the rotational strengths of C-20 ketones. Interestingly, Snatzke, as did Crabbé,10 noted a striking effect on the Cotton effect of 17β -acetyl steroids when a 16 β -methyl was introduced into the system, the Cotton effect actually inverting from strongly positive to weakly negative. This transformation was attributed to a conformational change of the 20-keto side chain. Dipole moments have been used by Allinger and DaRooge to investigate the conformational preference of a 17-acetyl group.¹² These authors concluded that a conformation similar to VIIa (see Figure 1) prevailed at room temperature. A detailed conformational analysis of the 17-acetyl conformers was not provided by the authors. Rakhit and Engel have also commented upon the conformation of the 20keto side chain and its relationship to the observed reduction pattern of 20-ketones to give either 20α or 20β -alcohols.¹³ In general, the latter authors

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