Optical Rotatory Dispersion Studies. CXIX. Effect of Ring Heteroatoms on the Cotton Effect of Cyclohexanones[1-3]

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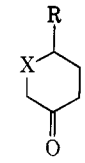
Abstract: The effects of oxygen, nitrogen, and sulfur groups on the n → π* carbonyl transition in saturated, six-membered heterocyclic systems were investigated by circular dichroism techniques. (6*S*)-6-Methyltetrahydropyran-3-one (**6**), (6*S*)-1-alkyl- or -1-acetyl-6-methyl-3-piperidone (**13**, **11**, **16**), and (6*S*)-6-methyltetrahydrothiopyran-3-one (**22**), 1-oxide (**23**), and 1,1-dioxide (**24**) were synthesized. These derivatives were selected on the basis of symmetry about the carbonyl group such that the chiral center and methyl substituent were in a nodal plane of the carbonyl group (at C-6), and such that the carbonyl group was β to the heteroatom (*i.e.*, at C-3). In both the oxygen compound, (6*S*)-6-methyltetrahydropyran-3-one (**6**) and in the nitrogen compounds, (6*S*)-1-alkyl- or -1-acetyl-6-methyl-3-piperidone (**13**, **11**, **16**), all having the heterogroup predominantly in the upper-left-rear octant, small negative Cotton effects were observed at 300 nm in all solvents investigated. In the (6*S*)-6-methyltetrahydropyran-3-one a complex solvent-dependent equilibrium was indicated. In the sulfur analogs of the same antipodal series, (6*S*)-6-methyltetrahydrothiopyran-3-one (**22**), the 1-oxide (**23**), and the 1,1-dioxide (**24**), positive Cotton effects associated with the n → π* carbonyl transition at 305 nm were observed. These effects were considerably stronger, but of opposite sign, than those encountered with the oxygen and nitrogen series. The sulfide (**22**) and the sulfoxide (**23**) both exhibited a negative Cotton effect at 250 nm, tentatively assigned to the sulfur n → σ* transition. This study has shown that the previous assumption equating a heteroatom with a methylene group in terms of its rotatory effect is not valid since such a replacement in six-member cyclic ketones gives rise to measurable Cotton effects. Thus, now knowing the sign and magnitude of the Cotton effect of these model systems, it should be possible to deduce the absolute configuration of similar heterocyclic ketones by measuring their CD curves. This correlation should be particularly useful in the structure elucidation of natural products.

Optical rotatory dispersion (ORD) and circular dichroism (CD) techniques have been widely utilized in the investigation of the stereochemistry of natural products.[4] One of the most important uses of optical rotatory dispersion and circular dichroism has been the determination of absolute configuration of chiral molecules. Previous work on cyclohexanone derivatives led to the development of the octant rule[5] which related the sign of the Cotton effect for the n → π* transition of the carbonyl chromophore to the absolute configuration of the molecule. The present investigation was undertaken to determine the rotatory effect of a heterocyclic ring system on the carbonyl chromophore.

A number of natural products contain heterocyclic ring systems incorporated in their structures (*e.g.*, tetrahydropyranone[6] and piperidone derivatives[7]). Although conclusions with regard to the stereochemistry or absolute configuration of some of these natural products were based partially on their Cotton effects, they involved the tacit assumption that in a molecule of type **1**, the rotatory contribution of a heteroatom (X = heteroatom) and a methylene group (X = CH_2) were qualitatively identical. In fact, no detailed study has yet been done on the inherent Cotton effect of such a heterocyclic system.[8]



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It was the purpose of this research to study the inherent optical properties of various heterocyclic systems of type **1** in terms of their respective CD curves. The model system (**1**, R = CH_3) chosen for this investigation was that of a chiral cyclohexanone of known absolute configuration with the C-3 methylene group replaced by a heteroatom.

This system had the advantage that much of the work had already been done on the relation of conformation of the cyclohexanone system and its ORD properties.[4] Furthermore, the methyl substituent at the single chiral center (C-6) is in a nodal plane of the carbonyl group and thus does not contribute to the rotatory strength according to the tenets of the octant rule.[5]

(1) Financial support from the National Institutes of Health (Grant No. GM 06840) is gratefully acknowledged.

(2) For previous paper see N. D. Vietmeyer and C. Djerassi, *J. Org. Chem.*, **35**, 3591 (1970).

(3) Taken in part from the Ph.D. thesis of M. M. Cook, Stanford University, 1973.

(4) See for instance (a) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, N. Y., 1960; (b) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965; (c) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Chemistry and Biochemistry; An Introduction," Academic Press, New York, N. Y., 1972; (d) G. Snatzke, Ed., "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Heyden & Son, Ltd., London, 1967.

(5) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961); see also Y.-H. Pao and D. P. Santry, *ibid.*, **88**, 4157 (1966).

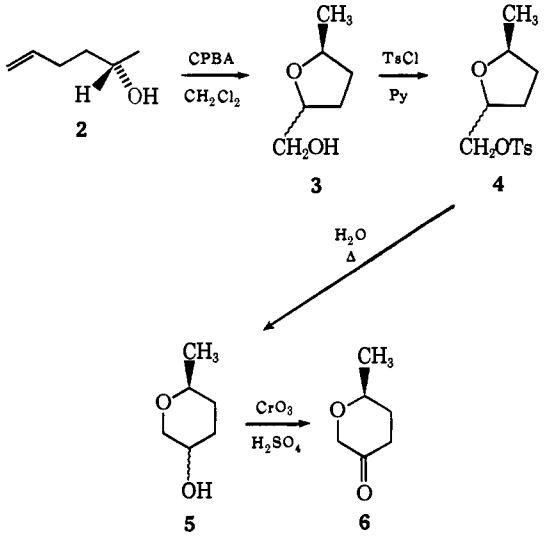
(6) (a) N. A. R. Hatam and D. A. Whiting, *J. Chem. Soc. C*, 1921 (1969); (b) C. R. Enzell, Y. Hirose, and B. R. Thomas, *Tetrahedron Lett.*, 793 (1967); (c) C. Chin, M. C. Cutter, E. R. H. Jones, J. Lee, S. Safe, and V. Thaller, *J. Chem. Soc. C*, 314 (1970); (d) S. C. Cascon, W. B. Mors, B. M. Tursch, R. T. Aplin, and L. J. Durham, *J. Amer. Chem. Soc.*, **87**, 5237 (1965); (e) J.-F. Biellman, *Tetrahedron Lett.*, 4803 (1966).

(7) (a) W. Gruber and K. Schlögl, *Monatsh. Chem.*, **80**, 499 (1959); (b) R. J. Highet, *J. Org. Chem.*, **29**, 471 (1964); (c) W. Y. Rice and J. L. Coke, *ibid.*, **31**, 1010 (1966); (d) M. Tichy and J. Sicher, *Tetrahedron Lett.*, 511 (1962), and references therein; (e) M. Spiteller-Friedmann and G. Spiteller, *Monatsh. Chem.*, **95**, 1234 (1964); (f) J. L. Coke and W. Y. Rice, *J. Org. Chem.*, **30**, 3420 (1965).

(8) The achiral thiadamantanones prepared by G. Snatzke and B. Wolfram, *Tetrahedron*, **28**, 655 (1972) encompass this moiety (**1**, X = S) but do so in a manner which elucidates the rotatory contribution of an axially oriented sulfur atom α to the carbonyl group.

Synthesis of Chiral Substituents. (6*S*)-6-Methyltetrahydropyran-3-one (**6**) was synthesized according to Scheme I. Initially 5-hexen-2-ol was resolved using

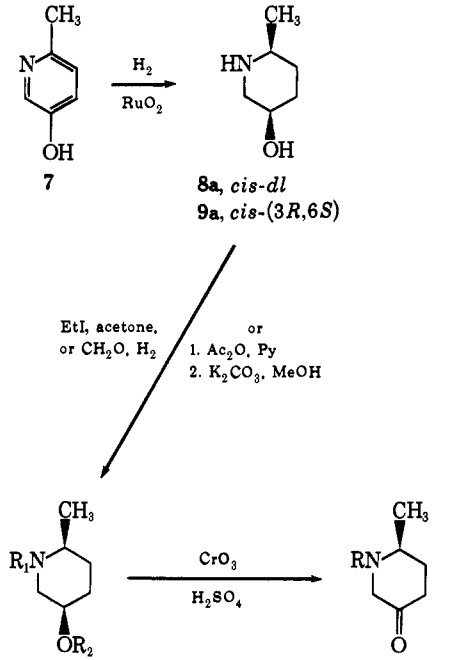
Scheme I. Synthesis of (6*S*)-6-Methyltetrahydropyran-3-one (**6**)



the method of Levene and Haller. The *S*-(+) enantiomer obtained had been previously correlated with (*S*)-(+)-lactic acid.[9-11]

The synthesis of the piperidones proceeded according to Scheme II. 3-Hydroxy-6-methylpyridine (**7**) was

Scheme II. Synthesis of 3-Piperidone Derivatives (**11**, **13**, and **16**)



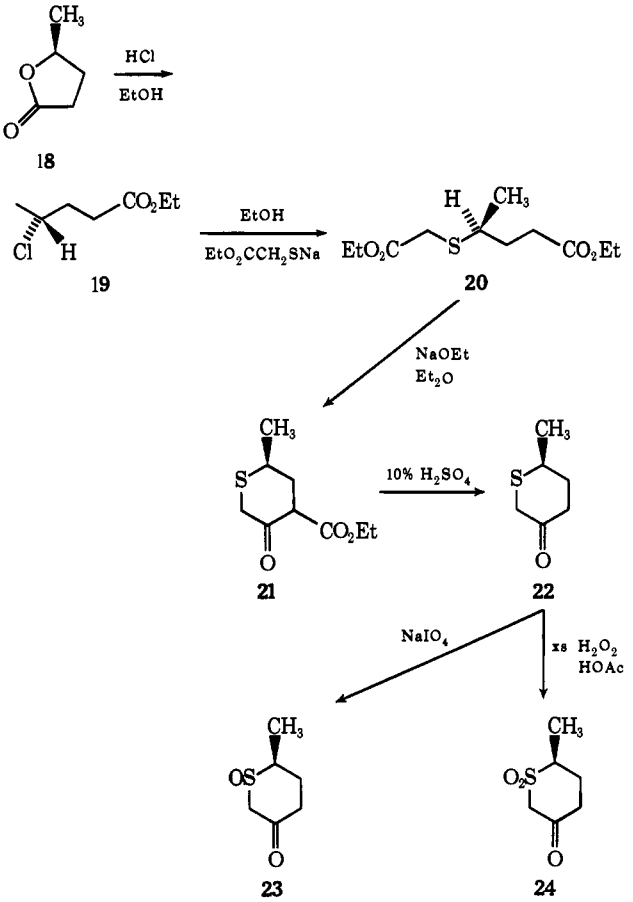
reduced to a mixture of *cis*- and *trans*-6-methyl-3-piperidinol (**8a** and **8b**, respectively, ratio of 95:5) using a ruthenium dioxide catalyst.[12] The *cis*-6-methyl-3-piperidinol (**8a**) was resolved with *d*-mandelic acid to give the (3*R*,6*S*)-6-methyl-3-piperidinol (**9a**).

The enantiomeric purity of this resolved series of piperidones was determined to be 80% (6*S*) from the proton and fluorine-19 magnetic resonance spectra of (3*R*,6*S*)-1-acetyl-6-methyl-3-piperidinyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate (**17**).[13]

The absolute configuration of the resolved (3*R*,6*S*)-*cis*-6-methyl-3-piperidinol (**8a**) was established by chemical correlation with (2*S*)-*p*-toluenesulfonyl-2-methylpiperidine,[14] which had been previously chemically correlated with D-aspartic acid.[14,15]

The synthesis of the sulfur analog (6*S*)-6-methyltetrahydrothiopyran-3-one (**22**) proceeded according to Scheme III. γ-Valerolactone was resolved,[16] and (*S*)-

Scheme III. Synthesis of (6*S*)-(+)-6-Methyltetrahydrothiopyran-3-one (**22**)



(−)-γ-valerolactone (**18**) obtained had been previously correlated with (*S*)-(+)-lactic acid.[9-11,16]

Circular Dichroism Results

Tetrahydropyranone System. (6*S*)-6-Methyltetrahydropyran-3-one (**6**) gave rise to a CD spectrum with multiple Cotton effects in the 280–320-nm region with considerable solvent dependence. In isooctane (Table I and Figure 1) a single negative band with marked

(9) (a) P. A. Levene and H. A. Haller, *J. Biol. Chem.*, **79**, 475 (1928); (b) see also A. W. Friederang and D. S. Tarbell, *J. Org. Chem.*, **33**, 3797 (1968); (c) P. A. Levene and H .A. Haller, *J. Biol. Chem.*, **69**, 165 (1926).
(10) P. A. Levene and H. A. Haller, *ibid.*, **65**, 49 (1925).
(11) P. A. Levene and H. A. Haller, *ibid.*, **67**, 329 (1926).
(12) For hydrogenation of pyridine derivatives, see M. Freifelder and G. H. Stone, *J. Org. Chem.*, **26**, 3805 (1961).
(13) Prepared according to J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
(14) H. Ripperger and K. Schreiber, *Tetrahedron*, **21**, 1485 (1965).
(15) F. E. King, T. J. King, and A. J. Worwick, *J. Chem. Soc.*, 3590 (1950).
(16) P. A. Levene and T. Mori, *J. Biol. Chem.*, **78**, 1 (1928).

Table I. Summary of CD and Uv Data

Compd	Solvent[a] (temp,[b] °C)	Uv data ϵ_{λ_1}	Uv data λ_1 (mμ)	$[\theta]\lambda_2$	λ_2 (mμ)	CD data[d] $R_0^T \times 10^{41}$ (cgs)[c] (λ_s)
(6*S*)-6-Methyltetrahydropyran-3-one (**6**)	Isooctane (25)	13.3	318	−720	329	−5.46 (316)
		16.4	307	−905	317	
		16.1	298	−694	308	
	Methanol (25)	14.4	296	−686	319	−3.69 (319)
				945	288	6.43 (288)
	EPA (25)	13.0	306	−534	327	−2.57 (320)
				−552	317	
				−221	307	
				183	282	1.46 (281)
	EPA (−196)			−989	326	−5.02 (316)
				−986	315	
				−534	302	
(6*S*)-1,6-Dimethyl-3-piperidone (**13**)	Isooctane (25)	33	297	−33	320	−0.56
				−48	308	
				−68	301	
(6*S*)-1-Ethyl-6-methyl-3-piperidone (**11**)	Isooctane (25)	34	290	−34	306	−0.32
	Methanol (25)	32	290	−32	296	−0.26
	EPA (25)			−68	305	−0.43
	EPA (−96)			−85	306	−0.66
(6*S*)-1-Acetyl-6-methyl-3-piperidone (**16**)	Isooctane (25)	38	282	−108	319	−1.64
				−177	308	
				−182	297	
	Methanol (25)	62	285	−110	295	−0.88
(6*S*)-6-Methyltetrahydrothiopyran-3-one (**22**)	Isooctane (25)	101	327	5930	329	62.8
		176	316	8710	317	
		178	305	7310	307	
		135	296			
		345	248	−9140	252	−64.1
	Methanol (25)	223	306	5760	311	43.2 (331)
		261	248	−5560	254	−37.0 (254)
	EPA (25)			8380	315	56.2 (316)
				6640	305	
				−9410	251	−80.1 (252)
	EPA (−196)	−196		10,900	324	92.5 (312)
				14,200	311	
				−21,200	248	−151 (250)
(6*S*)-6-Methyltetrahydrothiopyran-3-one 1-oxide (**23**)	Methanol (25)	362	302	9300	308	65.4 (308)
		634	240	−12,500	238	109 (253)
(6*S*)-6-Methyltetrahydrothiopyran-3-one 1,1-dioxide (**24**)	Methanol (25)	30	296	1250	305	11.1 (306)
	EPA (25)			1260	317	9.91 (305)
				1490	309	
	EPA (−196)			2030	311	15.7 (310)
				2380	302	
				1510	293	

[a] A refers to ethyl ether–isopentane–ethanol mixture (5:5:2 by volume). [b] All low temperature data have been corrected for volume contraction. [c] Rotational strength calculated for the CD curves according to the formula $R_0^T = 0.696 \times 10^{-42}[\theta]/\lambda\, d\lambda$. [d] All CD data corrected to 100% enantiomeric purity.

vibrational fine structure was centered at approximately 319 nm, while in methanol, a new band was apparent at 288 nm with a corresponding reduction in the negative band at 318 nm (Figure 1). In EPA at −196° the shorter wavelength band disappeared while the negative band at 316 nm increased in intensity.

Explanations of similar solvent effects have generally been attributed to two factors,[17] asymmetric solvation and/or variation in the conformational equilibrium.

Solvent-dependent conformational change has been demonstrated for a number of monocyclic cyclohexanone systems.[18] In the present case of compound **6**, the CD curves in the polar solvents, *i.e.*, methanol and EPA, indicated that at least two distinct species existed which gave rise to the two CD bands. The temperature dependence of the bands was consistent with a conformational equilibrium between the two chair conformers (**6a** ⇄ **6b**).[18a,19] In the case of (6*S*)-6-methyltetrahydropyran-3-one, the conformer with the pseudoequatorial methyl group (**6a**) would be expected to be the most stable at 25°,[20] and presumably gave rise to the negative Cotton effect at 317 nm (since at −196° conformer **6a** would exist at the exclusion of **6b**).

Precise assignment of the species responsible for the short wavelength CD band was difficult. Conformer **6b**, with the pseudoaxial methyl group, would be ex-

(17) (a) D. N. Kirk, W. Klyne, and S. R. Wallis, *J. Chem. Soc. C*, 350 (1970); (b) A. Moscowitz, H. M. Wellman, and C. Djerassi, *Proc. Nat. Acad. Sci. U. S.*, **50**, 799 (1963).

(18) (a) K. M. Wellman, W. S. Briggs, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 73 (1965); (b) C. Djerassi and W. Klyne, *Proc. Nat. Acad. Sci. U. S.*, **48**, 1093 (1962); (c) C. Beard, C. Djerassi, T. Elliott, and R. C. C. Tao, *J. Amer. Chem. Soc.*, **84**, 874 (1962).

(19) K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 66 (1965).

(20) Although no specific analysis of this system could be found in the literature, in a very similar system, that of 2-methyltetrahydropyran, the equatorial methyl group was conformationally preferred by 1.7 kcal/mol over the axial conformer, the same as in a cyclohexane ring; see C. B. Anderson and D. T. Sepp, *J. Org. Chem.*, **33**, 3272 (1968). Assuming this energy value could be applied to the 6-methyltetrahydropyran-3-one, one would then expect 95% of the molecules to exist with the methyl equatorial (**6a**).

pected to have a Cotton effect near 315 nm very similar in shape and rotational strength, but opposite in sign to that of **6a**, since in both conformers the 6-methyl group would be very nearly in the nodal plane of the carbonyl chromophore.[5,21] The ring oxygen would be in the same relative position, moving only from the upper-left-rear octant in **6a** to the upper-right octant in **6b**. In an "inert" solvent, assuming a ratio of **6a**:**6b** of approximately 95:5, the positive Cotton effect of **6b** would be completely masked by the negative Cotton effect of **6a**. This appeared to be the case in isooctane, where only the band at 317 nm was observed; in the polar solvents the concentration of the axial conformer **6b** appeared enhanced.

It seemed unlikely that the variation of the proportion of the axial conformer present at 25° could be solely responsible for the observed curve since this would imply that the equatorial to axial conformer ratio varied from approximately 95:5 in isooctane to approximately 45:55 in methanol. A more reasonable explanation would be that in addition to conformational equilibrium, a solvent dependence of the CD curves of (6*S*)-6-methyltetrahydropyran-3-one (**6**) existed, arising from asymmetric solvation of the ring oxygen as a result of the adjacent methyl group. It can be argued that the conformer with the methyl group in the pseudoaxial position would have a larger Cotton effect due to this dissymmetric arrangement of solvent molecules.[17a] For instance, in the case of the conformer **6a** the pseudoequatorial methyl group would have a relatively small steric effect on the approach of solvent molecules, whereas the axial methyl adjacent to the ring oxygen could selectively restrict the approach of solvent molecules on one side of the ring. While in both cases the associated solvent molecules would act as additional perturbing groups on the carbonyl n → π^* transition,[17a] the solvent arrangement would be more dissymmetric in the axial methyl case, leading to a relatively larger contribution to the CD band from the solvated conformer **6b**. This contention is consistent with the relatively large rotational strength of the 280-nm band in methanol.

It would be rather difficult to separate these two effects, and therefore no definite conclusions could be reached as to the extent each effect accounts for the observed CD curves in the polar solvents investigated.

In summary, the detailed investigation of the Cotton effects of (6*S*)-6-methyltetrahydropyran-3-one shows that introduction of a ring oxygen in the upper-left-rear octant results in a negative Cotton effect with a rotational strength smaller than that of 3-methylcyclohexanone.[4] The complex solvent dependence of this compound in polar media was best explained in terms of a dissymmetric solvation of the two chair conformers.

3-Piperidone Series. In the solvents investigated, all three compounds, (6*S*)-1,6-dimethyl-3-piperidone (**13**), (6*S*)-1-ethyl-6-methyl-3-piperidone (**11**), and (6*S*)-1-acetyl-6-methyl-3-piperidone (**16**), exhibited weakly negative Cotton effects in the CD bands centered at 305 nm (see Figure 2 and Table I).

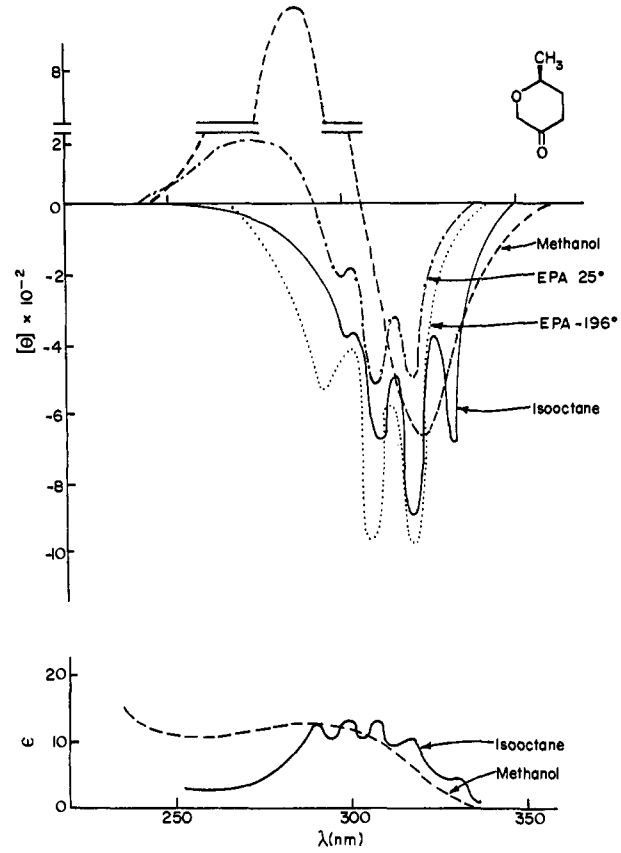


Figure 1. Uv and CD spectra of (6*S*)-6-methyltetrahydropyran-3-one (**6**) (corrected to 100% enantiomeric purity).

This study indicated that nitrogen in the upper-left-rear octant in 3-piperidone derivatives gave rise to negative Cotton effects for the n → π^* carbonyl transition. Yamada had previously made similar observation in the quinolizone series.[22]

Although the signs of the Cotton effects for this nitrogen series were the same as those of the oxygen analog, the magnitude of the curves was significantly smaller (see Table I). This was due in part to the fact that more than one species could be present, thus giving rise to multiple Cotton effects. Since ring flipping and nitrogen inversion both occur at room temperature,[23] it is apparent that four isomers would be in equilibrium.[24] Low-temperature measurements showed that the rotational strength of the CD band increased by more than 50% on going to −196° in the case of the

(21) The prediction of the Cotton effect of compound 6 was based on the tacit assumption that very little ring distortion was caused by replacement of the methylene group by an oxygen atom in a cyclohexanone ring. The replacement of a methylene by oxygen in similar ring systems has been shown to produce only very slight changes in the shape[a] or Bayer strain[b] of the ring. In 1,4-dioxane the C–O bond length = 1.42 Å, COC bond angle = 112.4° *vs.* C–C bond length = 1.52 Å, C–C–C bond angle = 111.5° in cyclohexane.[c] (a) J. B. Lambert, *J. Amer. Chem. Soc.*, 89, 1836 (1967); (b) H. C. Brown, J. H. Brewster, and H. Schechter, *ibid.*, 76, 467 (1954); (c) M. Davis and O. Hassel, *Acta Chem. Scand.*, 17, 1181 (1963).

(22) S. Yamada and T. Kunieda, *Chem. Pharm. Bull.*, 15, 490 (1967).

(23) J. M. Lehn and J. Wagner, *Chem. Commun.*, 415 (1970).

(24) The discussion of this Cotton effect is based on the tacit assumption that little ring distortion is caused by introduction of the nitrogen for a methylene group in the cyclohexanone ring. The piperidine and piperidone ring systems have been shown to exist predominantly in the chair configuration with only slight changes in shape;[a,b] in 1,4-piperazine the C–N bond length = 1.47 Å, CNC bond angle = 112.6° *vs.* CC bond length = 1.52 Å, and CCC bond angle = 111.5° in cyclohexane.[c] X-Ray studies confirmed that the chair form was the preferred conformation for the piperidine ring in a number of compounds.[d] (a) J. B. Lambert, R. G. Keske, and D. K. Weary, *J. Amer. Chem. Soc.*, 89, 5923 (1967); (b) A. R. Katritzky, "Topics in Heterocyclic Chemistry," R. N. Castle, Ed., Wiley-Interscience, New York, N. Y., 1969, Chapter 2, p 35; (c) M. Davis and O. Hassel, *Acta Chem. Scand.*, 17, 1181 (1963); (d) M. Przybylska and W. H. Barnes, *Acta Crystallogr.*, 6, 377 (1953); J. W. Visser, J. Manassen, and J. L. DeFries, *ibid.*, 7, 288 (1954).

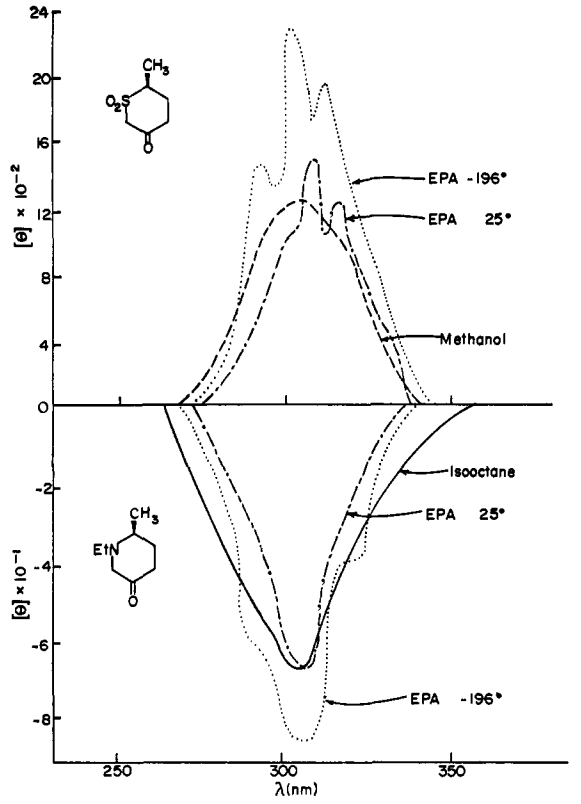


Figure 2. CD spectra of (6*S*)-6-methyltetrahydrothiopyran-3-one 1,1-dioxide (**24**) (upper half) and (6*S*)-1-ethyl-6-methyl-3-piperidione (**11**) (lower half) (corrected to 100% enantiomeric purity).

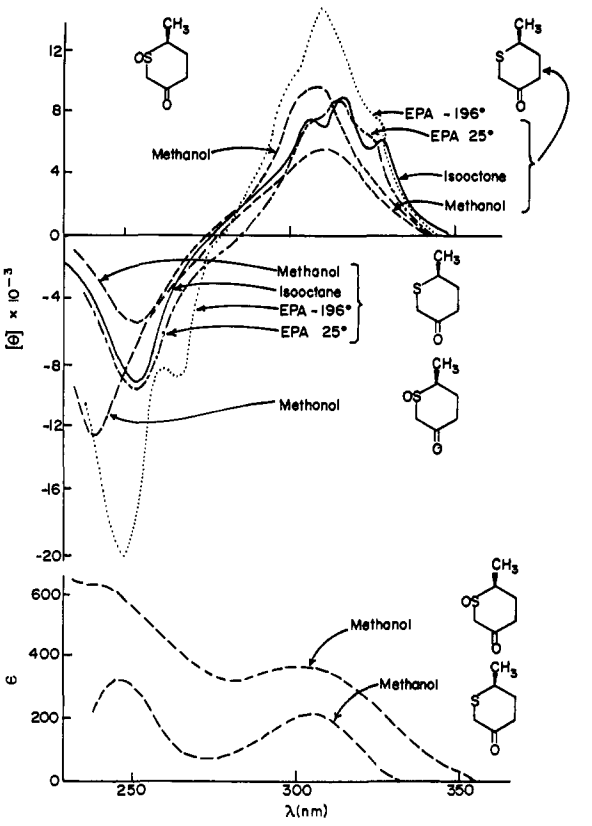
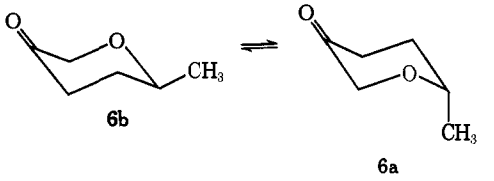


Figure 3. Uv and CD spectra of (6*S*)-6-methyltetrahydrothiopyran-3-one (**22**) and (6*S*)-6-methyltetrahydrothiopyran-3-one 1-oxide (**23**) (corrected to 100% enantiomeric purity).

N-ethyl compound (**11**). The amount of each isomer present at room temperature could only be qualitatively estimated. Since the diequatorial conformer should predominate at room temperature, it would be primarily responsible for the observed negative Cotton effect.



6b ⇌ 6a

Tetrahydrothiopyranone System. (6*S*)-6-Methyltetrahydrothiopyran-3-one (**22**) and (6*S*)-6-methyltetrahydrothiopyran-3-one 1-oxide (**23**) gave rise to two Cotton effects centered at approximately 315 and 250 nm and 308 and 240 nm, respectively, in all solvents investigated (see Figure 3 and Table I). These CD bands closely corresponded with the observed ultraviolet absorption maxima. In the CD spectrum of compound **22** the intensities of both bands increased at −196° in EPA. This increase in rotational strength at lower temperature was presumably due to a shift of the equilibrium toward the more stable pseudoequatorial methyl conformer.

The positive CD band in the β-keto sulfide (**22**) *and the β-keto sulfoxide* (**23**) *due to the* $n \rightarrow \pi^*$ *carbonyl transition was opposite in sign to that of the oxygen and nitrogen analogs, even though all three were of the same antipodal series (see Figure 4).*

The Cotton effect at 315 nm was also much more intense for the tetrahydrothiopyran-3-one system than

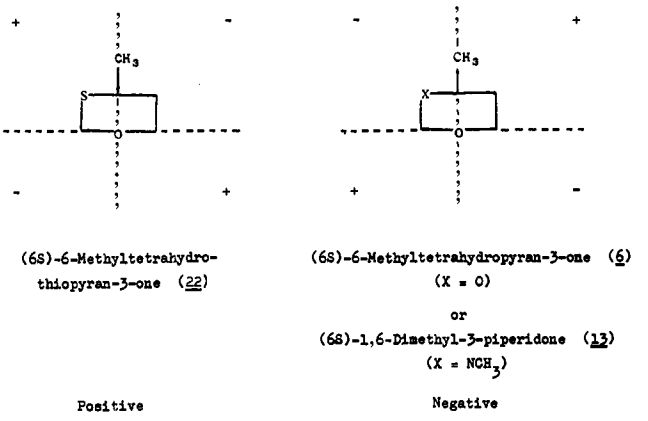


Figure 4. Octant projection and sign of the Cotton effect at 315 mμ.

the nitrogen or oxygen analogs. This larger effect is also apparent in the ultraviolet spectrum [ϵ_{305} 178 (isooctane)], the value for cyclohexanone being approximately one-tenth as large [ϵ_{295} 15.8 (isooctane)].[25] Such considerable bathochromic and hyperchromic shifts have also been observed in the ultraviolet spectrum of other β-keto sulfides.[26]

The negative CD band in the β-keto sulfide (**22**) and β-keto sulfoxide (**23**) at 250 and 240 nm, respectively, is the result of a sulfur electronic transition. Rosenfield and Moscowitz have recently assigned the three lowest-lying electronic transitions of the sulfide chromophore

(25) C. N. R. Rao, G. K. Goldman, and J. Ramachandran, *Tetrahedron Lett.*, No. 2, 1 (1960).

(26) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, 71, 84 (1949).

in various acyclic and cyclic systems and their calculations agreed well with the sign of the observed Cotton effect.[27] The 240-nm band of the sulfide and sulfoxide chromophores has been assigned to an n → σ* transition involving a nonbonding 3p sulfur orbital and C–S antibonding orbital.[28] In the present case of β-keto sulfide **22** the chromophore, presumably the sulfur n → σ* transition, exhibits a small hyperchromic effect and a bathochromic shift to 250 nm compared with the sulfoxide (**23**) which absorbs at 240 nm.

(6*S*)-6-Methyltetrahydropyran-3-one 1,1-dioxide (**24**) showed only a positive Cotton effect at 305 nm (Figure 2, Table I) with considerably reduced rotational strength; similarly, the uv extinction coefficient was much smaller compared with that of **22**. There was no absorption below 270 nm in either the CD or uv curves. The 305-nm band can be assigned to the n → π* carbonyl transition. The CD curves in all solvents were similar in intensities at 25°, but at −196° in EPA significant enhancement was noted consistent with an increase in the proportion of the pseudoequatorial methyl conformer. The sulfone chromophore, transparent in this region of the spectrum,[28] showed no shorter wavelength bands.

In summary, all three compounds (the β-keto sulfide **22**, the β-keto sulfoxide **23**, and the β-keto sulfone **24**) give rise to positive Cotton effects for the n → π* carbonyl transition in the 300-nm region. The β-keto sulfide **22** and the β-keto sulfoxide **23** carbonyl bands are more intense than that of the sulfone **24**. The n → π* Cotton effects of all three sulfur-containing compounds are significantly stronger and opposite in sign to those of the oxygen or nitrogen analogs. Further theoretical work is indicated to elucidate the reasons for this sign inversion when sulfur replaces oxygen or nitrogen, but qualitatively and somewhat crudely one could summarize the situation by stating that two effects are likely to operate. One is the normal consequence of the octant rule (dissymmetric perturbation of the intrinsically symmetrical carbonyl chromophore) arising from the replacement of a methylene group by the heteroatom. The other is the electrostatic coupling of the carbonyl chromophore with the heteroatoms. Since the electronic transitions available to oxygen and nitrogen are of considerably higher energy than those of the sulfur analog, it appears that in the latter the electrostatic coupling plays the dominant role, whereas the normal octant type perturbation is primarily responsible for the sign of the Cotton effect in the nitrogen and oxygen examples.

The Cotton effects for the β-keto sulfide **22** and β-keto sulfoxide **23** clearly indicate an electronic interaction between the sulfur and carbonyl chromophores which is absent in the β-keto sulfone **24**. Such interactions have previously been noted in other systems; however, this was the first investigation of such phenomena in β-keto sulfide and sulfoxide systems by circular dichroism techniques.

Experimental Section

The melting points are uncorrected. The infrared spectra were determined in chloroform or as a thin film on either a Perkin-Elmer 421 grating spectrophotometer or a Perkin-Elmer 700 infrared spectrophotometer. Optical rotations were done on a Perkin-Elmer 141 polarimeter. Circular dichroism measurements (Durrum JASCO ORD-CD-5 spectropolarimeter) and ultraviolet absorptions (Cary recording spectrophotometer, Model 14M) were determined by Mrs. R. Records. Nmr spectra were determined on a Varian T-60 nmr spectrometer or on a Varian HA-100 nmr spectrometer by Dr. Louis Durham and associates. Mass spectra were determined on the A.E.I. MS-9 mass spectrometer [with a heated inlet (150°), at a source temperature of 190° and 100 μA filament current] by Mr. R. G. Ross.

Gas–liquid phase chromatography (glpc) was performed with 10 ft × 0.25 in. stainless steel columns with the appropriate liquid phase (SE-30 or Carbowax 20M) on Chromosorb W at 100–255° on a Varian Aerograph Model 200 (dual column) gas chromatograph. All microanalyses are by Messrs. E. Meier and J. Consoloy.

(5*S*)-(+)-5-Methyltetrahydrofurfuryl Alcohol (3). A dichloromethane solution (500 ml) of *m*-chloroperoxybenzoic acid (49.08 g, 0.285 mol, 99%) was added over 30 min to a solution of 23.78 g (0.238 mol) of (2*S*)-5-hexen-2-ol (**2**) [$[\alpha]^{24}D$ 31.2° (*c* 0.915, Et_2O), optical purity 98%][9] in 40 ml of dichloromethane, kept below 20°. After the solution was stirred for 8 hr at 25°, the precipitated *m*-chlorobenzoic acid was removed by filtration and the filtrate washed with saturated sodium sulfate solution (1 × 40 ml) and sodium bicarbonate solution (2 × 40 ml). The aqueous extracts were combined and continuously back extracted with ether (24 hr). The combined organic layers were dried ($MgSO_4$), and the solvent was removed at atmospheric pressure. The resulting liquid was distilled, bp 101–102° (60 mm) (lit.[29] bp 72° (12 mm) of racemic compound), yielding 23.2 g (0.200 mol. 84%) of (5*S*)-5-methyltetrahydrofurfuryl alcohol (**3**).

An analytical sample of each isomer was separated by means of glpc (15% Carbowax 20M) and showed the following characteristics. Cis: $[\alpha]^{25}D$ 11.1° (*c* 9.335, EtOH); ir (film) 3450–3370 (OH), 3000 (CH_3), 2970, 2900, 1450 (CH_3), 1090 cm^{-1} ($CHOCH_2$); nmr (T-60) ($CDCl_3$) δ 1.24 (d, 3, *J* = 6 Hz, CH_3), 1.32–2.33 (m, 4, CH_2CH_2), 2.75 (s, 1, OH, confirmed by D_2O exchange), 3.58 (m, 2, CH_2OH, confirmed by $Cl_3CCONCO$ addition), 4.00 (m, 2, $CHOCH_3$, $OCHCH_2OH$); mass spectrum (70 eV) *m/e* 85 (100%) ($M^+ - CH_2OH$). Trans: $[\alpha]^{25}D$ 33.7° (*c* 11.525, EtOH); ir (film) 3450–3380 (OH), 2970 (CH_3), 2940, 2870, 1440 (CH_2), and 1080 cm^{-1} ($CHOCH_2$); nmr (T-60) ($CDCl_3$) δ 1.22 (d, 3, *J* = 6.0 Hz, CH_3), 1.35–2.30 (m, 4, CH_2CH_2), 2.90 (s, 1, OH, confirmed by D_2O), 3.40, 3.70 (m, 2, CH_2OH), 4.10 (m, 2, CHOCH); mass spectrum (70 eV) *m/e* 85 (100%) ($M^+ - CH_2OH$).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found (cis): C, 62.04; H, 10.38. Found (trans): C, 61.81; H, 10.34.

The 3,5-dinitrobenzoate derivative, recrystallized from EtOH (lit.[29] mp 79° no mention of cis/trans isomerism), had mp 85–86° (cis), mp 75–76° (trans).

(6*S*)-(+)-6-Methyltetrahydropyran-3-ol (5). *p*-Toluenesulfonyl chloride (41.9 g, 0.22 mol) in 100 ml of pyridine was added over 30 min to a cooled solution of 22.7 g (0.197 mol) of the (5*S*)-*cis*,*trans*-5-methyltetrahydrofurfuryl alcohol (**3**) in 50 ml of pyridine (0°). The solution was stored at 0° for 48 hr.

Work-up was effected by addition of 30 ml of cold water and 100 ml of ether. The ether solution was separated, extracted with 1:1 cold hydrochloric acid (3 × 75 ml), and 5% sodium carbonate solution (1 × 20 ml), washed with saturated sodium chloride solution, dried ($MgSO_4$), and the solvent removed under reduced pressure (5° (20 mm)), leaving a light yellow oil. The crude toluenesulfonate (**4**) (51.0 g, 95%) [ir ν_{max}^{film} no OH 3020 (CH_3), 2950 (CH_2), 1200, 1180 (SO_2), and 1110 cm^{-1} (COC)], used without further purification, was dissolved in 500 ml of water and heated under reflux for 24 hr.[30] The aqueous solution was made basic (pH 9) and then continuously extracted with ether for 24 hr. The ether layer was dried ($MgSO_4$) and the ether removed by distillation. The residue was distilled (bp 70–80° (15 mm)) yielding 10 g of liquid. Glpc analysis (15% Carbowax 20M) showed three peaks associated with the *cis*- and *trans*-5-methyltetrahydrofurfuryl alcohols (**3a** and **3b**) and the 6-methyltetrahydropyran-3-ol (**5**), respectively. The desired pyranol made up approximately 30% of the total sample.

Spinning band distillation yielded 2.5 g (12%) of (6*S*)-6-methyltetrahydropyran-3-ol (**5**) and 6.0 g of (5*S*)-*cis*,*trans*-5-methyltetra-

(27) J. S. Rosenfield and A. Moscowitz, *J. Amer. Chem. Soc.*, 94, 4797 (1972).

(28) M. Procházka and M. Palaček, *Collect. Czech. Chem. Commun.*, **32**, 3049 (1967).

(29) J. Cologne and A. Girantet, *C. R. Acad. Sci.*, 254, 498 (1962).

(30) According to the method of D. Gagnaire, *ibid.*, 248, 420 (1959), on tetrahydrofurfuryl alcohol.

hydrofurfuryl alcohol (**3a** and **3b**) (the rotation of which had not changed).

An analytical sample of the pyranol separated by glpc (15% Carbowax 20M) showed the following characteristics: $[\alpha]^{25}D$ 10.5° (*c* 11.33, EtOH); ir ν_{max}^{film} 3300–3250 (OH), 2960 (CH_3), 2940, 2860, 1450 (CH_2), and 1090 cm^{-1} ($CHOCH_2$); nmr (HA-100) ($CDCl_3$) δ 1.17 (d, 3, J = 6.0 Hz, CH_3), 1.20–2.20 (m, 4, CH_2CH_2), 2.64 (s, 1, OH), 3.10 (t, 1, J = 10 Hz, OCH_aH_eCHOH), 3.40 (m, 1, $CHOH$, confirmed by $Cl_3CCONCO$), 3.83 (m, 1, CH-CH_3), 3.95 (m, 1, J = 5 Hz, 10 Hz, OCH_aH_eCHOH); mass spectrum (70 eV) *m/e* (rel intensity) 116 (10) (M^+), 101 (18) ($M^+ - CH_3$), 99 (11) ($M^+ - OH$), 98 (13) ($M^+ - H_2O$), 44 (100); (12 eV) 116 (55) (M^+), 101 (91) ($M^+ - CH_3$), 99 (44) ($M^+ - OH$), 98 (100) ($M^+ - H_2O$).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.97; 10.35. The 3,5-dinitrobenzoate derivative (recrystallized from ethanol) had mp 164–166°. *Anal.* Calcd for $C_{13}H_{14}N_2O_7$: C, 50.33; H, 4.55; N, 9.03. Found: C, 50.31; H, 4.50; N, 9.20.

(6*S*)-6-Methyltetrahydropyran-3-one (6). (6*S*)-6-Methyltetrahydropyran-3-ol (**5**) (2.1 g, 18.1 mol) was dissolved in acetone and cooled to 10°. A 50% excess of Jones reagent (prepared according to Djerassi, *et al.*)[31] was added dropwise over 10 min, and the reaction was stirred for 2 hr at 25°.

The acetone layer was removed and 100 ml of ether was added. The solution was then washed with 5% sodium bicarbonate solution (2 × 20 ml) and water (4 × 20 ml). The organic layer was dried ($MgSO_4$) and the solvent removed at atmospheric pressure, leaving 1.5 g (75%) of a clear liquid. Glpc (15% Carbowax 20M) showed only one peak in addition to the solvent.

The chiral ketone (**6**) separated by glpc (15% Carbowax 20M) showed the following characteristics: $[\alpha]^{25}D$ 27.3° (*c* 13.39, EtOH); uv and CD (see table); ir ν_{max}^{film} 2980, 1282 (CH_3), 2940, 2860, 1448 (CH_2), 1726 (C=O), and 1098 cm^{-1} (COC); nmr (HA-100) ($CDCl_3$) δ 1.29 (d, 3, J = 6 Hz, CH_3), 1.6–2.3 (m, 2, CH_2 at C-5), 2.52 (m, 2, $CH_2CH_2C{=}O$), 3.84 (m, 1, $CHCH_3$), 3.97, 4.11 (AB pattern, 2, $J_{H_aH_b}$ = 16–17 Hz, $OCH_2C{=}O$); mass spectrum(70 eV) *m/e* (rel intensity) 114 (82) (M^+), 56 (100) ($C_4H_8^+$ and $C_3H_4O^+$).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.24; H, 8.80. The 2,4-dinitrophenylhydrazone (recrystallized from ethanol) had mp 246°. *Anal.* Calcd for $C_{12}H_{14}O_5N_4$: C, 48.98; H, 4.80; N, 19.04. Found: C, 48.90; H, 4.73; N, 19.10.

6-Methyl-3-piperidinol (8a).[12] 3-Hydroxy-6-methylpyridine (**7**) (20 g, 0.183 mol) was dissolved in 70 ml of anhydrous ethanol containing 1.5 of ruthenium dioxide. The reaction was stirred under a hydrogen atmosphere (1600 psi) for 6 hr at 75°. The catalyst was recovered by filtration and the ethanol removed by distillation at atmospheric pressure. The residue was distilled at reduced pressure to yield 17.3 g (0.151 mol), 82%, bp 70° (0.8 mm), of the 6-methyl-3-piperidinol (**8**).

Glpc analysis (10% SE-30) of the oil showed two peaks corresponding to the cis and trans isomers (**8a** and **8b**) in a 95:5 ratio. An analytical sample of the cis isomer **8a** showed the following characteristics: ir ν_{max}^{film} 3450–3250, 1650 (OH, NH), and 2940, 2870 cm^{-1} (CH_2); nmr (HA-100) ($CDCl_3$) δ 1.05 (d, 3, J = 6 Hz, CH_3), 1.27–1.95 (m, 4, CH_2CH_2), 2.32 (s, 2, NH and OH, confirmed by D_2O), 2.62 (6-line pattern, 1, J = 6 Hz, CH_3CHNH), 2.87 (doublet of doublets, 1, $J_{H_{2a}H_{2e}}$ = 12 Hz, $J_{H_{2a}H_{3e}}$ = 2 Hz, CH_eH_aN), 3.01 (triplet of doublets, 1, $J_{H_{2a}H_{2e}}$ 12 Hz, $J_{H_{2e}H_{4e}}$ = 2 Hz, CH_aH_eN), and 3.78 (5-line pattern, 1, J = 2 Hz, CH_eO); mass spectrum (70 eV) *m/e* (rel intensity) 115 (14) (M^+), 100 (100) ($M^+ - 15$); (12 eV) 115 (21), 100 (100).

Anal. Calcd for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.56; H, 11.29; N, 12.09.

Resolution of *cis*-6-Methyl-3-piperidinol (8a). *cis*-6-Methyl-3-piperidinol (**8a**) (16.2 g, 0.141 mol) and *d*-mandelic acid (20.8 g, 0.141 mol) were dissolved in 60 ml of anhydrous methanol at 40°. Ether was added until the solution became slightly turbid (*ca.* 40 ml). The solution was slowly cooled to 5° and stored at 0° for 10 hr, during which time some crystallization took place. The resulting salt was recrystallized three times from 1:1 methanol–ether, yielding 16 g, mp 106–107°, $[\alpha]^{20}D$ 54.9° (*c* 1.27, 95% EtOH).

This salt (15 g) was dissolved in water 30 ml), basified with solid potassium hydroxide, and heated 15 min on the steam bath. The aqueous layer was extracted with dichloromethane (3 × 40 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed at reduced pressure (30° (20 mm)). The residue was distilled (bp 70° (1 mm)), yielding 6.1 g (0.053 mol) of *cis*-(3*R*,6*S*)-6-methyl-3-piperidinol (**9a**). An analytical sample separated by glpc (10% SE-30) showed the identical physical characteristics as the racemic material (**8a**), except for the rotation: $[\alpha]^{20}D$ 5.50 (*c* 1.62, 95% EtOH).

(6*S*)-1-Ethyl-6-methyl-3-piperidinol (10). *cis*-(6*S*)-6-Methyl-3-piperidinol (**9a**) (375 mg, 3.26 mmol) in 20 ml of acetone was treated with 1.0 g (6.3 mmol) of ethyl iodide. The solution was heated under reflux 4 hr. Excess ethyl iodide and acetone were removed under reduced pressure, yielding a semisolid residue. The residue was taken up in water, made basic with ammonium hydroxide, and extracted with dichloromethane. The extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure yielding a yellow oil (430 mg, 3.02 mmol, 95%), identified as (6*S*)-1-ethyl-6-methyl-3-piperidinol (**10**).

An analytical sample separated glpc (10% SE-30) showed the following characteristics: $[\alpha]^{20}D$ 7.41° (*c* 2.94, EtOH); ir ν_{max}^{film} 3300 (OH), 2970, 2940, 2870 (CH_3,CH_2); nmr (T-60) ($CDCl_3$) δ 0.93 (t, 3, J = 6 Hz, CH_2CH_3), 1.03 (d, 3, J = 6 Hz, $CHCH_3$), 1.3–1.9 (m, 4, CH_2CH_2), 2.3–2.9 (m, 5, $CH_2N(CH)CH_2$), 2.94 (s, 1, OH, confirmed by D_2O exchange), 3.8–3.9 (m, 1, $CHOH$); mass spectrum (70 eV) *m/e* (rel intensity) 143 (10) (M^+), 128 (100) ($M^+ - 15$); (12 eV) 143 (24), 128 (100).

Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.95; H, 12.01; N, 9.82.

(6*S*)-1-Ethyl-6-methyl-3-piperidone (11). (6*S*)-1-Ethyl-6-methyl-3-piperidinol (**10**) (200 mg, 1.4 mmol) was dissolved in 15 ml of acetone at 10°. Chromic acid solution (Jones' reagent) (3 ml) was added over 10 min. The reaction was stirred 4 hr, during which time it warmed to 25°. Excess saturated sodium bisulfite solution (4 ml) was added, and the acetone removed at reduced pressure (30° (20 mm)). The solution was basified with ammonium hydroxide and extracted with chloroform (3 × 20 ml). The combined chloroform extracts were dired (Na_2SO_4), and the solution was concentrated at atmospheric pressure. The piperidone (**11**) was collected by preparative glpc (15% SE-30), yielding 45 mg of pure material. The sample was sealed under helium and stored at 0° in the dark until use. It had the following properties: uv and CD (see table; ir $\nu_{max}^{CHCl_3}$ (no OH) 2970, 2940, 2800 (CH_3,CH_2), and 1725 cm^{-1} (C=O); nmr (T-60) ($CDCl_3$) δ 0.95 and 1.03 (t, J = 6 Hz, CH_2CH_3; d, J = 6 Hz, CH_3, 6 protons total), 1.15–1.85 (m, 2, CH_2CH), 1.09–3.20 (complex m, 7, $CH_2COCH_2N(CH_2)CH$); mass spectrum (70 eV) *m/e* (rel intensity) 141 (25) (M^+), 126 (12) ($M^+ - CH_3$), 98 (100).

(6*S*)-1,6-Dimethyl-3-piperidinol (12). *cis*-(6*S*)-6-Methyl-3-piperidinol (**9a**) (435 mg, 3.8 mmol), 150 mg of 10% palladium on carbon, and 7 ml of 30% formaldehyde were dissolved in 30 ml of ethanol. The solution was stirred under a hydrogen atmosphere for 4 hr. The catalyst was removed by filtration, and the filtrate was acidified with 1 *N* hydrochloric acid. The ethanol was removed at reduced pressure (30° (20 mm)), and the resulting solution was extracted with ether and the aqueous layer then basified with ammonium hydroxide. This solution was extracted with chloroform (3 × 10 ml). The combined chloroform extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure (35° (20 mm)), leaving the dimethylpiperidinol (**12**) (430 mg, 3.3 mmol, 87%) as the only product (by glpc, 10% SE-30). The spectral properties were as follows: $[\alpha]^{20}D$ 12.2° (*c* 2.3, 95% EtOH); ir ν_{max}^{film} 3350 (OH), 2950, 2890 (CH_3,CH_2), and 2800 cm^{-1} (NCH_3); nmr (T-60) ($CDCl_3$) δ 1.03 (d, 3, J = 6 Hz, $CHCH_3$), 1.25–2.5 (m, 9, CH_2CH_2, $CHN(CH_3)CH_2$), 2.22 (s, CH_3N), 2.22 (m, $J_{H_{2a}H_{2e}}$ = 12 Hz, $J_{H_{2a}H_3}$ = 2 Hz, NCH_aH), 2.8 (broadened doublet, 1, $J_{H_{2a}H_{2e}}$ = 12 Hz, $J_{H_{2e}H_{3e}}$ = 4 Hz, NCH_aH_e), 2.85 (s, 1, OH, confirmed by D_2O exchange), and 3.8 (broad m, 1, $HOCH$); mass spectrum (70 eV) *m/e* (rel intensity) 129 (15) (M^+), 114 (100) ($N^+ - CH_3$); (12 eV) 129 (24), 114 (100).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.95; H, 11.65; N, 10.91.

(6*S*)-1,6-Dimethyl-3-piperidone (13). (6*S*)-1,6-Dimethyl-3-piperidinol (**12**) (200 mg, 1.55 mmol) was dissolved in 15 ml of acetone at 10°. A slight excess of Jones' reagent (0.75 ml) was added and the mixture was stirred 4 hr at 25°. Saturated sodium bisulfite solution (1 ml) was added and the acetone removed at reduced pressure. The solution was basified with ammonium hydroxide and extracted with chloroform (3 × 5 ml). The combined chloroform extracts were dried (Na_2SO_4), and the solution was concentrated. A sample of the pure material (**13**) (45 mg) was isolated by glpc (10% SE-30) and sealed under helium and stored at 0° in the dark. The spectral properties of an analytical sample separated

(31) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 21, 1547 (1956).

by glpc (10% SE-30) were as follows: uv and CD (see table); ir ν_{max}^{film} 2960, 2940 (CH_3), 2850 (CH_2), 2770 (CH_3N), 1726 cm^{-1} (C=O); nmr (T-60) ($CDCl_3$) δ 1.00 (d, 3, J = 6 Hz, CH_3), 2.2–3.2 (complex, 9 protons) including 2.3 (s, NCH_3), 2.53 and 3.02 (AB, J = 14 Hz, CH_2N); mass spectrum (70 eV) m/e (rel intensity) 127 (30) (M^+), 112 (10) ($M^+ - CH_3$), 84 (100).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.62; H, 10.15; N, 10.95.

(6*S*)-1,3-Diacetyl-6-methyl-3-piperidinol (14). Acetic anhydride (10 ml) and sodium acetate (0.1 g) were heated along with 500 mg (5.2 mmol) of (6*S*)-6-methyl-3-piperidinol (**9a**) at 100° for 60 min and then cooled. Potassium bicarbonate solution (1 *N*, 75 ml) was added, and the mixture was stirred 8 hr. The solution was extracted with chloroform (3 × 45 ml), and the combined extracts were washed with 1 *N* hydrochloric acid and dried (Na_2SO_4). The solvent was removed at reduced pressure (25° (20 mm)), leaving the diacetyl compound (**14**) (20 mg, 4.1 mmol, 80%). The material was approximately 95% pure as indicated by glpc analysis (10% SE-30). An analytical sample separated by glpc (10% SE-30) showed the following characteristics: $[\alpha]^{20}D$ 8.61° (*c* 1.63, 95% EtOH); ir ν_{max}^{film} 2940, 2860 (CH_3,CH_2), 1730, 1640 (C=O), and 1250 cm^{-1} (C–O); nmr (T-60) ($CDCl_3$) δ 1.2 (d, 3, J = 6H z, CH_3), 1.4–2.2 (complex, 10, CH_2CH_2, $NCOCH_3$, $OCOCH_3$) including 2.06 and 2.08 (two singlets 6, $NCOCH_3$ and $OCOCH_3$), 2.6–3.2 (complex, 1, CNH), 3.8–4.0 (complex, 1, HC*H*N), and 4.2–4.8 (complex, 2, NCH*HCH*OAc); mass spectrum (70 eV) m/e (rel intensity) 199 (5 × 30) (M^+), 139 (43) ($M^+ - CH_3CO_2H$), 43 (100); (12 eV) 199 (10 × 30), 139 (100).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.32; H, 8.54; N, 6.97.

(6*S*)-1-Acetyl-6-methyl-3-piperidinol (15). The diacetyl compound (**14**) (710 mg, 3.6 mmol) was dissolved in 20 ml of methanol containing 1.25 g of potassium carbonate and heated under reflux 50 min. The methanol was removed at reduced pressure (30° (20 mm)), and the residue was dissolved in an ether–water mixture. The aqueous layer was extracted with ether (3 × 10 ml), the combined ether layers were dried (Na_2SO_4), and the solvent was removed at reduced pressure (20° (20 mm)), leaving 1-acetyl-6-methyl-3-piperidinol (**15**) (530 mg, 3.5 mmol, 96%). An analytical sample, separated by glpc (10% SE-30), showed the following characteristics: $[\alpha]^{20}D$ 13.0° (*c* 0.86, 95% EtOH); ir ν_{max}^{film} 3350 (OH), 2930, 2850 (CH_3,CH_2), and 1620 cm^{-1} (C=O); nmr (T-60) ($CDCl_3$) δ 1.21 (d, 3, J = 6 Hz, $CHCH_3$), 1.35–2.2 (complex, 7, CH_2CH_2, $O{=}CCH_3$), including 2.02 (s, $O{=}CCH_3$), 5.02 (s, 1, OH, confirmed by D_2O exchange), 2.5–4.2 (complex, 4 protons, $CHCH_2$, NCH); mass spectrum (70 eV) m/e (rel intensity) 157 (37) (M^+), 142 (32) ($M^+ - CH_3$), 100 (100) ($M^+ - CH_3$ and $CH_2{=}C{=}O$); (12 eV) 157 (100), 142 (53).

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.08; H, 9.59, N, 8.95.

(6*S*)-1-Acetyl-6-methyl-3-piperidone (16). The alcohol (**15**) (210 mg, 1.3 mmol) was dissolved in 20 ml of acetone at 10°. Excess chromic acid solution (Jones' reagent) (0.75 ml) was added and the solution stirred 4 hr at 25°. Saturated sodium bisulfite solution was added (1.5 ml) and the acetone was removed under reduced pressure (20° (20 mm)). The residue was dissolved in a water–chloroform mixture, the aqueous layer was extracted with chloroform (3 × 5 ml) and dried (Na_2SO_4), and the solution was concentrated. An analytical sample of the ketone (**16**) (sealed under helium and stored at 0° in the dark) showed the following characteristics: uv and CD (see table); ir ν_{max}^{film} 2990, 2980, 2940 (CH_3,CH_2), and 1726, 1637 cm^{-1} (C=O); nmr (T-60) ($CDCl_3$) 1.25 (d, 3, J = 6 Hz, CH_3), 1.4–1.9 (complex, *ca.* 2 protons, CH_2CH), 2.12 (s, $COCH_3$), 1.9–2.5 (complex, 5 protons), 3.75 and 4.8 (broadened AB, *ca.* 2 protons, J = 18 Hz, $O{=}CCH_2N$), and 3.6–4.3 (*ca.* 1 proton, CHN); mass spectrum (70 eV) m/e (rel intensity) 155 (28) (M^+), 113 (18), 112 (74) ($M^+ - COCH_3$), 70 (100); (12 eV) 155 (49), 116 (29), 112 (100).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.85; H, 8.50; N, 8.97.

***cis*-(6*S*)-1-Acetyl-6-methyl-3-piperidinyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (17).** Anhydrous pyridine (300 μl, 300 mg) was injected into a dry 10 × 75 mm test tube stoppered with a septum cap. (*R*)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl)[32] (39.5 mg, 0.16 mmol) was introduced in the same manner. Carbon tetrachloride (350 μl) and 24 mg (0.15 mmol) of analytically pure *cis*-(+)-1-acetyl-6-methyl-3-piperidinol (**39**) in 50 μl of carbon tetrachloride were introduced in the same manner. The reaction was shaken and allowed to stand at 25° for 30 min. 3-Dimethylaminopropylamine[32] (0.10 mmol, 10 mg, 12 μl) was added and allowed to stand for 5 min.

The mixture was diluted with ether (5 ml) and washed with cold 0.1 *N* hydrochloric acid, and cold saturated sodium carbonate solution, and the ether layer was dried ($MgSO_4$). The filtered ether solution was evaporated to dryness and the residue was dissolved in carbon tetrachloride and the solvent reevaporated. This procedure was repeated yielding 48 mg (0.13 mmol, 87%) of the MTPA derivative (**17**): nmr (HA-100) (CCl_4) 1.0–2.2 (complex, 10 protons, including 1.21, d, J = 6 Hz, CH_3CH; 2.02, CH_3CO; and CH_2CH_2), 2.6–3.1 (complex, 1, CHN), 3.40 and 3.49 (two singlets, 3, together, OCH_3), 3.5–4.5 (complex, 2, CH_2N), 3.76 (complex, 1, CHO), 7.0–7.6 (complex, 5, C_6H_5); (XL-100) (CCl_4) (^{19}F nmr, 94.1 MHz; lock at ^2H, 15.4 MHz) (2 broad groups due to the two diastereoisomers present, integration ratio: 2.5 implies diastereoisomeric ratio of 80:20).

1,3-Bis(*p*-toluenesulfonyl)-*cis*-(6*S*)-6-methyl-3-piperidinol. *p*-Toluenesulfonyl chloride (2.2 g, 11.5 mmol) was added to *cis*-(6*S*)-6-methyl-3-piperidinol (**9a**) (485 mg, 4.25 mmol) dissolved in 5 ml of anhydrous pyridine at 0°. The reaction was stirred 3 hr at 0° and stored at 0° for 72 hr, during which time pyridine hydrochloride precipitated. The mixture was poured into 40 ml of ice–water and extracted with ether (3 × 40 ml). The combined extracts were washed with cold 1 *N* hydrochloric acid until the washings were at pH 1, and then washed with 5% sodium bicarbonate solution (1 × 10 ml). The ether layer was dried (Na_2SO_4) and the ether removed at reduced pressure (15° (20 mm)), leaving 1.30 g (3.01 mmol) (71%) of the ditoluenesulfonate with the following properties: $[\alpha]^{20}D$ 30.6° (*c* 0.87, $CHCl_3$); ir ν_{max}^{film} 2970, 2940, 2860 (CH_3,CH_2), 1600 (aromatic), and 1360, 1340, 1180, 1170, 1150 cm^{-1} (SO_2N,SO_3); nmr (T-60) (CCl_4) δ 0.99 (d, 3, J = 6 Hz, CH_3), 1.16–1.90 (complex, 4, CH_2CH_2), 2.37 and 2.40 (two singlets, 6, $CH_3C_6H_4$), 2.42–4.3 (complex, 4 protons, CH_2NH, CHO), and 6.9–7.7 (complex, 8, C_6H_4).

(6*S*)-1-*p*-Toluenesulfonyl-6-methylpiperidine. The ditoluenesulfonate (1.0 g, 2.31 mmol) was dissolved in 35 ml of anhydrous tetrahydrofuran and 300 mg (7.9 mmol) of lithium aluminum hydride was added. The mixture was heated under reflux under dry nitrogen 20 hr. Saturated ammonium chloride solution was added and the solution was filtered, and the filtrate was concentrated to dryness at reduced pressure (30° (20 mm)). The crude material was purified by column chromatography using Activity 2 aluminum oxide (Al_2O_3) (30 g), and the material eluted with *n*-hexane–benzene (50:50). The material (250 mg, 0.99 mmol, 42%) was crystallized from *n*-hexane: mp 65–66°; $[\alpha]^{26.2}D$ (*c* 1.23, EtOH), lit.[14] mp 68–70°, $[\alpha]D$ 47° (*c* 0.98, EtOH); ir $\nu_{max}^{CHCl_3}$ 2980, 2950, 2870 (CH_3,CH_2), 1600 (aromatic), 1330, 1160, 1145 cm^{-1} (SO_2N); nmr (T-60) (CCl_4) δ 0.95 (d, 3, J = 6 Hz, CH_3), 1.1–1.9 (complex, 6, $CH_2CH_2CH_2$), 2.35 (s, 3, $CH_3C_6H_4$), 2.70–3.3 (complex, 3, CH_2NCH), 7.25 and 7.6 (AB, 4, J = 8 Hz, C_6H_4).

Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.62; H, 7.56; N, 5.53; S, 12.68. Found: C, 61.90; H, 7.72; N, 5.42; S, 12.52.

(*R*)-(−)-Ethyl 4-Chloropentanoate (19). (*S*)-(−)-γ-Valerolactone (**22S**) ($[\alpha]^{22}D$ −16.8° (neat), lit.[16] $[\alpha]^{22}D$ −27.75° (neat) (100% enantiomeric purity)) (2.6 g, 25 mmol) was dissolved in 20 ml of absolute ethanol. The solution of 0° was saturated with dry hydrogen chloride and the reaction mixture was stored at 0° for 48 hr and at 25° for 72 hr.

Work-up was effected by addition of 30 ml of water and 40 ml of ether. The aqueous layer was basified by addition of potassium carbonate. After separation of the two layers, the aqueous layer was continuously extracted with ether for 24 hr. The combined ether layers were dried ($MgSO_4$), and the solvents were removed under reduced pressure (0° (20 mm)). The concentrated layer contained 2.3 g (14 mmol) (54%) of ethyl 4-chloropentanoate (**19**), based on glpc analysis (15% Carbowax 20M).

The mixture was used without further purification for the next step. An analytical sample separated by glpc (15% Carbowax 20M) showed the following spectral characteristics: $[\alpha]^{25}D$ −14.6° (*c* 0.792 Et_2O), lit.[16] $[\alpha]^{20}D$ −19.7° (*c* 1.23 Et_2O) (90% enantiomeric purity); ir ν_{max}^{film} 2995, 2960 (CH_2), and 1730 cm^{-1} (C=O, ester); nmr (T-60) (CCl_4) δ 1.24 (t, 3, J = 7 Hz, CH_3), 1.50 (d, 3, J = 6 Hz, CH_3), 1.70–2.20 (m, 2, $ClCHCH_2$), 2.10–2.6 (m, 2, CH_2COO), 4.08 (m, 1, ClCH), 4.10 (q, 2, J = 7 Hz, CH_2CH_2), mass spectrum (70 eV) m/e (rel intensity) 164 (6 (× 30)) (M^+), 119 (66), 101 (69), 88 (100) ($M^+ - C_3H_5Cl$).

(32) A sample of the MTPA-Cl and 3-dimethylaminopropylamine were provided by Professor H. S. Mosher of this department; the (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid is available from Aldrich Chemical Co.

Anal. Calcd for $C_7H_{13}O_2Cl$: C, 51.07; H, 7.96; Cl, 21.54. Found: C, 51.76; H, 8.02; Cl, 21.17.

Ethyl (4*S*)-4-(Carboethoxymethylthio)pentanoate (20). A dry flask was charged with 15 ml of absolute ethanol and 0.38 g (16.5 g-atom) of sodium all under nitrogen. After 40 min the flask was cooled (0°) and 1.8 g (15 mmol) of ethyl 2-mercaptoacetate was added, forming a white precipitate. After 1 hr 2.0 g (12 mmol) of chloroester (**19**) was added. The resulting mixture was stirred 3 hr at 25° and heated under reflux 5 hr.

The precipitated sodium chloride was removed by filtration and washed with ethanol. From the combined filtrate and washings the ethanol was removed at reduced pressure (30° (20 mm)), leaving a light yellow oil. This oil was dissolved in ether (25 ml), washed with water, and then dried ($MgSO_4$). Removal of the ether at reduced pressure yielded 2.4 g of an oil. Glpc analysis (15% Carbowax 20M) showed that this oil consisted of approximately 60% ethyl 2-mercaptoacetate and 25% of the desired thioester **20**. From the mixture, 600 mg (2.6 mmol) (23%) of the thioester **20** could be isolated by preparative gas chromatography.

An analytical sample of the thioester **20**, separated by glpc (15% Carbowax 20M) had the following characteristics: $[\alpha]^{22}D$ 1.86° (*c* 0.750, EtOH); ir ν_{max}^{film} 2990, 2940 (CH_2), 1730 (C=O), 1270, 1160, 1030 cm; nmr (T-60) ($CDCl_3$) 1.26 (t, 3, J = 7 Hz, CH_3), 1.24 (t, 3, J = 7 Hz, CH_3), 1.30 (d, 3, J = 6 Hz, CH_3), 1.6–2.2 (m, 2, $SCHCH_2CH_2$), 2.2–2.6 (m, CH_2CH_2C=O), 2.95 (m, 1, CHS), 3.24 (s, 2, O_2CCH_2S), 4.12 (q, 2, J = 7 Hz, CH_2CH_3), 4.19 (q, 2, J = 7 Hz, CH_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 248 (10) (M^+), 117 (100).

Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12; S, 12.91. Found: C, 53.54; H, 8.09; S, 12.92.

(6*S*)-(+)-6-Methyltetrahydrothiopyran-3-one (22). An alcohol-free sodium ethoxide suspension in anhydrous ether (15 ml) was prepared in a nitrogen atmosphere using 350 mg (0.015 g-atom) of sodium and 700 mg (15 mmol) of anhydrous ethanol. The thioester (**20**) (600 mg, 2.42 mmol) was added over 20 min and stirred 4 hr at 25° and heated 1 hr under reflux conditions. Anhydrous ether was added when necessary to facilitate stirring. A mixture of 2 ml of acetic acid and 10 ml of ice–water was added to this suspension. The organic layer was separated and the aqueous layer was continuously extracted with ether. The combined organic layers were dried ($MgSO_4$), and the solvents were then removed under reduced pressure (30° (20 mm)). The oily residue showed a positive ferric chloride test. Without further purification, this material was hydrolyzed and decarboxylated by addition of 10 ml of 10% sulfuric acid and heating under reflux 6 hr.

An analytical sample showed the following spectral characteristics: $[\alpha]^{23}D$ 8.4° (*c* 1.47, $MeOH_3$); uv and CD (see table); ir ν_{max}^{film} 2960, 2940 (CH_2), and 1715 cm^{-1} (C=O); nmr (T-60) ($CDCl_3$) 1.29 (d, 3, J = 6 Hz, CH_3), 1.7–2.8 (m, 4, CH_2CH_2CO), 3.0 and 3.44 (AB q, 2, J = 12 Hz, SCH_2C=O), 2.8–3.4 (m, 1, CHS); mass spectrum (70 eV) *m/e* (rel intensity) 130 (85) (M^+), 87 (29), 75 (100) ($C_3H_7S^+$); (12 eV) 130 (100), 75 (62).

Anal. Calcd for $C_6H_{10}OS$: C, 55.34; H, 7.74; S, 24.63. Found: C, 55.34; H, 7.78; S, 24.56. 2,4-Dinitrophenylhydrazone derivative; mp 140–141° (methanol). *Anal.* Calcd for $C_{12}H_{14}N_4O_4S$: C, 46.44; H, 4.55; N, 9.05; S, 10.33. Found: C, 45.92; H, 4.50; N, 9.91; S, 10.33.

(6*S*)-6-Methyltetrahydrothiopyran-3-one 1-Oxide (23). (6*S*)-6-Methyltetrahydrothiopyran-3-one (**22**) (65 mg, 0.5 mmol) was added to 1.1 ml of 0.5 *M* aqueous sodium periodate solution (0.55 mmol) at 0°. The solution was stirred 8 hr and the solid was removed by filtration. The aqueous solution was extracted with chloroform (3 × 5 ml). The combined chloroform extracts were dried ($MgSO_4$) and concentrated to approximately 1 ml at atmospheric pressure.

The desired (6*S*)-6-methyltetrahydrothiopyran-3-one 1-oxide (**23**) was isolated by preparative gas chromatography (15% Carbowax 20M), yielding 33 mg (0.228 mmol) (45%) of material. An analytical sample of the compound was separated by glpc (15% Carbowax 20M) and showed the following characteristics: uv and CD (see table); ir $\nu_{max}^{CHCl_3}$ 2980, 2800 (CH_3), 1725 (C=O), and 1045 cm^{-1} (S=O); nmr (T-60) ($CDCl_3$) 1.31 (d, 3, J = 6 Hz, CH_3), 1.6–2.9 (m, 4, CH_2CH_2CO), 3.52 and 3.95 (AB q, 2, J = 12 Hz, $OSCH_2C$=O), 3.0–3.5 (m, 1, CHSO); mass spectrum (70 eV) *m/e* (rel intensity) 146 (25) (M^+), 55 (100).

Anal. Calcd for $C_6H_{10}SO_2$: C, 49.31; H, 6.90; S, 21.90. Found: C, 49.12; H, 6.80; S, 22.01.

(6*S*)-6-Methyltetrahydrothiopyran-3-one 1,1-Dioxide (24). Hydrogen peroxide (30%, 0.040 ml) was added to a solution of 60 mg (0.46 mmol) of (6*S*)-6-methyltetrahydrothiopyran-3-one (**24**) in 0.5 ml of acetic acid and 0.5 ml of acetic anhydride at 0°. The solution was stirred 8 hr at 25° and then diluted with acetone. The solution was dried ($MgSO_4$) and concentrated to approximately 1 ml at atmospheric pressure. The product (**24**) (30 mg) was obtained by preparative glpc (15% Carbowax 20M).

An analytical sample separated by glpc (15% Carbowax 20M) showed the following characteristics: uv and CD (see table); ir $\nu_{max}^{CHCl_3}$ 2950, 2880 (CH_2), 1715 (C=O), and 1340 cm^{-1} (SO_2); nmr (T-60) ($CDCl_3$) 1.47 (d, 3, J = 6 Hz, CH_3), 1.8–2.9 (m, 4, CH_2CH_2CO, 3.2 (m, 1, CHS), 3.58 and 5.04 (AB q, 2, O_2SCH_2C=O); mass spectrum (70 eV) *m/e* (rel intensity) 162 (23) (M^+), 55 (100); (15 eV) 162 (44), 43 (100).

Anal. Calcd for $C_6H_{10}SO_3$: C, 44.44; H, 6.22; S, 19.74. Found: C, 44.38; H, 6.26; S, 19.83.