respectively. The mass spectrum of I was also obtained by introduction through the heated inlet system of the CEC 21-110B at 280°.

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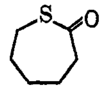
Syntheses and Optical Rotatory Dispersion Studies of Asymmetric Thiepan-2-ones

C. G. Overberger[1a] **and Jurgen K. Weise**[1b]

Contribution from the Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, New York 11201. *Received July 24, 1967*

Abstract: Optically pure (*R*)-(−)-4-methylthiepan-2-one and (*R*)-(+)-5-methylthiepan-2-one were prepared from pulegone. Racemic 5-methylthiepan-2-one was independently prepared from 4-methylcyclohexanone. The two optically pure thiolactones have complex optical rotatory dispersion spectra in dioxane and in methanol. Between 200 and 620 mμ two Cotton effects were observed for each compound. They are centered around 234 and 298 mμ, respectively, but only the lower wavelength transitions are definitely observed in the ultraviolet spectra. Solvent effects indicate that the former transition is of type π–π^* and the latter of type n–π^*. The relation between the absolute configuration of the asymmetric center and the sign of the low-wavelength Cotton effect is discussed in terms of cyclic *vs.* linear molecular structure. The conformation of the thiolactone ring appears to be the same in both isomers studied.

Several thiolactones with five- and six-membered rings have been known for some time.[2] A number of β-thiolactones (four-membered rings) have also been reported in the past.[3,4] In a recent paper from this laboratory[5] the synthesis and polymerization of thiepan-2-one (ϵ-thiocaprolactone, I), containing a seven-membered ring, were described. It is the parent compound of the methyl-substituted, asymmetric thiolactones presented in this paper. These optically active thiepan-2-ones were synthesized from an optically active natural product. Their preparation served a double purpose. First, an investigation of the ultraviolet and optical rotatory dispersion spectra was effected. No such study of cyclic thiol esters had yet been undertaken, and little was known of the optical properties of thiolactones. Secondly, these compounds proved to be the most suitable monomers for the preparation of linear, structurally homogeneous poly(thiol esters).[6]



I

Results

Since Eisenbraun and McElvain[7] converted (+)-pulegone into (−)-α-methylglutaric acid, which Fredga[8] has previously correlated with (−)-lactic acid, the terpene has been known to be optically pure and of *R* configuration. (*R*)-(+)-Pulegone (II) was therefore a suitable starting material. Throughout the syntheses, care was taken to avoid reaction conditions that might cause racemization, and no transformations were used which involved the asymmetric carbon or the carbon atoms in α position to it.

(*R*)-(+)-Citronellic acid (III) was prepared from pulegone (II) according to a modified procedure of Plesek[9] (Figure 1). Compound III was esterified with methanol in the presence of a catalytic amount of sulfuric acid. The ozonide of (*R*)-(+)-methyl citronellate (IV) was prepared at −30° in methanol and reduced with sodium borohydride at 0° to give (*R*)-(+)-methyl 6-hydroxy-3-methylhexanoate (V). By bromination of V with phosphorus tribromide, VI was obtained in 43% yield. Esters V and VI were prepared in preference to the corresponding acids because a stable and distillable product which does not undergo cyclization and polymerization was desired after each step. Bromo ester VI was converted to the mercapto acid VII with thiourea according to a general method.[10]

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(1) (a) Author to whom inquiries should be sent at The University of Michigan, Ann Arbor, Mich. 48104. (b) This paper comprises a portion of the dissertation submitted by J. K. Weise in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry) to the Graduate School of the Polytechnic Institute of Brooklyn, 1966.

(2) K. Fries and H. Mengel, *Ber.*, **45**, 3408 (1912).

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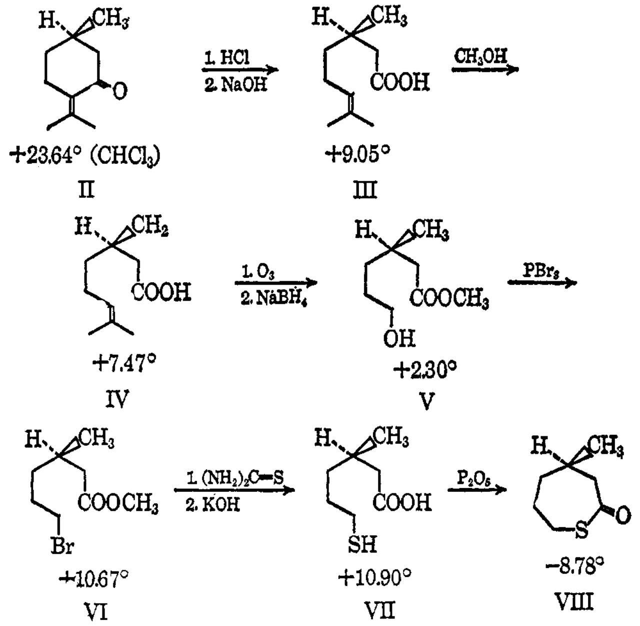

Figure 1. Synthesis of (*R*)-(−)-4-methylthiepan-2-one (VIII). Unless otherwise indicated, the specific rotations $[\alpha]^{25}D$ were measured in methanol.

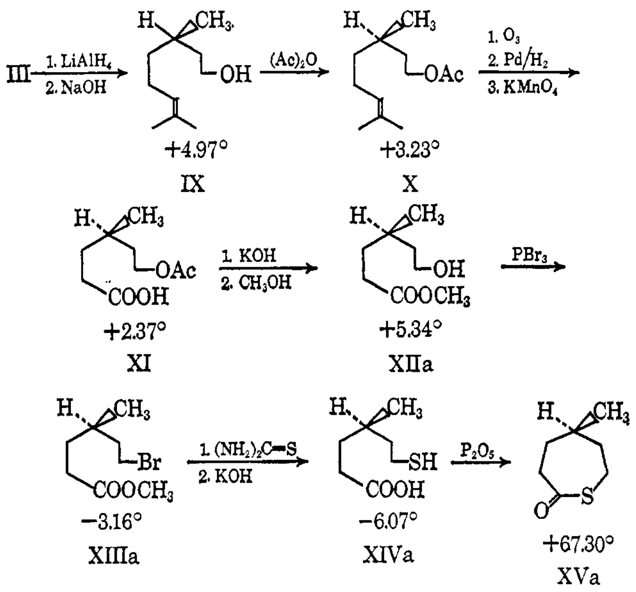

Figure 2. Synthesis of (*R*)-(+)-5-methylthiepan-2-one (XVa). The specific rotations $[\alpha]^{25}D$ were measured in methanol.

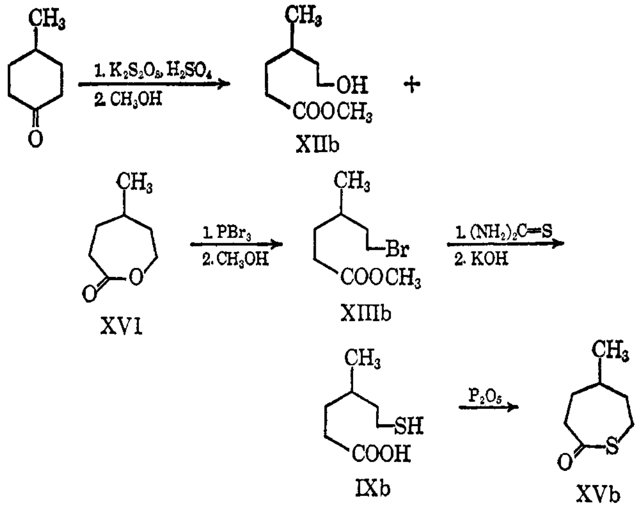

Figure 3. Synthesis of racemic 5-methylthiepan-2-one (XVb).

Decomposition of the intermediate thiouronium salt with potassium hydroxide also resulted in hydrolysis of the ester function. Cyclization of VII to (*R*)-(−)-4-methylthiepan-2-one (VIII) was carried out as has already been described in the case of the unsubstituted analog I.[5]

The optically active γ-substituted thiepan-2-one (XVa) was also prepared from pulegone *via* citronellic acid (Figure 2). The latter (III) was reduced to citronellol (IX), which was then esterified to X before the double bond was oxidized. The synthesis of XI was found to proceed most readily if a three-step procedure was used, *i.e.*, ozonization of X at −78° followed by catalytic hydrogenation to afford a mixture of alcohol and aldehyde, which was then oxidized to the ester acid XI with potassium permanganate. Once XI was prepared, the acetate group was hydrolyzed and the molecule reesterified at its other (acid) functional group to afford the hydroxy ester XIIa. This was converted in successive steps to XIIIa, XIVa, and XVa in the same manner as were the β-methyl isomers of these compounds. The structures of these products were confirmed by nuclear magnetic resonance. (*R*)-(+)-5-Methylthiepan-2-one (XVa) was obtained by cyclization of XIVa in 60% yield; this is a higher yield than could be obtained either with I (48%) or with VIII (51%). Compound XVa was purified by preparative vpc. The over-all yields of the thiepan-2-ones VIII and XVa from pulegone were 6.1 and 2.3%, respectively.

Racemic 5-methylthiepan-2-one (XVb) was prepared from 4-methylcyclohexanone (Figure 3) *via* Baeyer–Villiger oxidation of the ketone and subsequent esterification with methanol to give a mixture consisting of approximately equal amounts of ester XIIb and lactone XVI. This mixture was subjected to bromination and again treated with methanol and sulfuric acid before distillation. Compound XIIIb was easily purified and transformed into XIVb and racemic 5-methylthiepan-2-one (XVb) in the same way as were their optically active forms XIVa and XVa.

The reactions used to convert pulegone to mercapto acids VII and XIVa are known to proceed without racemization, and mild reaction conditions were chosen for all steps. However, the cyclization of these acids to the thiolactones VIII and XVa required drastic conditions. To determine whether this reaction resulted in racemization or not, a sample of polymer[6] prepared from VIII was hydrolyzed to afford mercapto acid VII. The specific rotation of the acid obtained by hydrolysis of the polymer is 2.8% smaller than that of the original VII. The former is only 98% pure as indicated by vpc. Therefore, within experimental error, no racemization took place.

The chemical purity of the thiepan-2-ones VIII, XVa, and XVb was established by vpc analysis on two or more columns. Their structures were proved by their spectroscopic properties, by their syntheses, and by their chemical compositions, as well as by subsequent chemical reactions (polymerization, hydrolysis)[6] and by the similarity of their physical properties with those of

Table I. Ultraviolet Absorption Spectra of Thiepan-2-one (I)

Solvent	Absorptions
Cyclohexane	$\lambda_{\max}$ 188 mμ; $\lambda_{\max}$ 232 mμ (ϵ 4160)
Dioxane	$\lambda_{\max}$ 235 mμ (ϵ 3830)
Methanol	$\lambda_{\max}$ 237 mμ (ϵ 3850)

Table II. Optical Rotatory Dispersion and Ultraviolet Absorption Data of (*R*)-(−)-4-Methylthiepan-2-one (VIII)

Measurement and solvent	π–π^* transition[a]			n–π^* transition[a]	
	Trough	λ_0	Peak	Trough	Peak
ORD					
Dioxane	214 mμ (−7020 ± 150°)	232 mμ	242 mμ (+3940 ± 150°)	282 mμ (−19°)	306 mμ (+174°)
Methanol	216 mμ (−6760 ± 150°)	234 mμ	247 mμ (+4410 ± 150°)	281 mμ (−312°)	307 mμ (+44°)
Uv					
Cyclohexane[b]	$\lambda_{\max}$ 233 mμ (ϵ 4190)				
Dioxane	$\lambda_{\max}$ 235 mμ (ϵ 4020)				
Drude analysis[c]	Complex in dioxane, chloroform, tetrahydrofuran, and methanol (Figure 6)				

[a] This assignment is tentative; see text for discussion. [b] A second absorption band was observed in cyclohexane; $\lambda_{\max}$ 188 mμ. [c] Only data recorded with a Rudolph spectrophotometer, Model 80, were evaluated. The data were plotted according to Yang and Doty (λ^2[M] *vs.* [M]) and the results checked by Lowry plots (λ^2 *vs.* 1/[M]) in all cases.

Table III. Optical Rotatory Dispersion and Ultraviolet Absorption Data of (*R*)-(+)-5-Methylthiepan-2-one (XVa)

Measurement and solvent	π–π^* transition[a]			n–π^* transition[a]	
	Trough	λ_0	Peak	Trough	Peak
ORD					
Dioxane	217 mμ (−5520 ± 150°)	231 mμ	242 mμ (+6900 ± 150°)	[295–298 mμ] (+551°)	306 mμ (+564°)
Methanol	222 mμ (−6400 ± 150°)	234 mμ	248 mμ (+6910 ± 150°)	291 mμ (+469°)	305 mμ (+543°)
Uv					
Cyclohexane[b]	$\lambda_{\max}$ 233 mμ (ϵ 3900)				
Dioxane	$\lambda_{\max}$ 234 mμ (ϵ 4190)				
Drude analysis[c]	λ_c 223 mμ (dioxane)				

[a] This assignment is tentative; see text for discussion. [b] A second absorption band was observed in cyclohexane; $\lambda_{\max}$ 188 mμ. [c] Only data recorded with a Rudolph spectropolarimeter, Model 80, were evaluated. The data were plotted according to Yang and Doty (λ^2 [M] *vs.* [M]) and the results checked by Lowry plots (λ^2 *vs.* 1/[M]) in all cases.

I. The configurational purity of the thiepan-2-ones has an effect on their ability to crystallize. Whereas VIII and XVa crystallize at −16 and +14°, respectively, XVb cannot be crystallized.[11]

Ultraviolet and Optical Rotatory Dispersion Spectra Discussion

In each of the three solvents in which the ultraviolet spectrum of thiepan-2-one (I) was studied, I exhibited a single broad peak (Table I). The variation of the extinction coefficient is small; the absorption maximum, on the other hand, shows small but reproducible bathochromic shifts with increasing solvent polarity. Methanol is a hydrogen-donor solvent and therefore different from dioxane and cyclohexane. The maximum is shifted toward higher wavelengths in both dioxane and methanol as compared to the maximum observed in cyclohexane. Similar spectra and the same solvent dependencies of $\lambda_{\max}$ were observed for the two thiolactones VIII and XVa (Tables II and III). Ultraviolet absorption bands of very similar shape, intensity, and wavelength were observed for poly(thiol esters) and their model compounds in this laboratory[6] and have been observed for other thiolactones[12] and for thiol acetates.[13] These spectra are therefore typical of thiol esters. The observed bathochromic shifts and the high intensity of this absorption strongly indicate that it is due to a π–π^* transition. This assignment has been proposed by Djerassi and coworkers[14] on the grounds of intensity alone.

The optical rotatory dispersion curves of (*R*)-(−)-4-methylthiepan-2-one (VIII) in methanol (Table II and Figure 4)[15] consists of two different Cotton effects. The larger one is centered around λ_0 234 mμ[16] and is positive; the other appears to be positive and to be centered around λ_0 297 mμ. The latter Cotton effect is shown in Figure 5 with the scale of rotatory power enlarged. Figure 6 shows the rotatory dispersion curves in four solvents as measured with a Rudolph spectropolarimeter. It is evident from this figure that the curves in tetrahydrofuran and methanol are complex. A plot of $\lambda^2[M]_\lambda$ *vs.* $[M]_\lambda$ shows strong curvature in all four solvents and reveals that none of them follows the single-term Drude equation.

The optical rotatory dispersion curve of (*R*)-(+)-5-methylthiepan-2-one (XVa) in methanol (Table III and

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(11) It does not freeze after having been kept at −75° for 1 hr. At −195° it still shows no evidence of crystallinity but becomes a clear brittle glass.

(12) F. Korte and K. H. Buchel, *Angew. Chem.*, **71**, 719 (1959).

(13) B. Sjöberg, *Z. Physik. Chem.*, **52**, 209 (1942); J. I. Cunneen, *J. Chem. Soc.*, 134 (1947).

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

(15) The optical rotations are shown as molar rotations $[M]_\lambda^{26}$ = $[\alpha]_\lambda^{26}$ × mol wt/100 and have units of degrees centimeter/decimole. The $[M]_\lambda$ values of the polymers refer to one structural unit.

(16) λ_0 refers to the wavelength at which the rotation is zero.

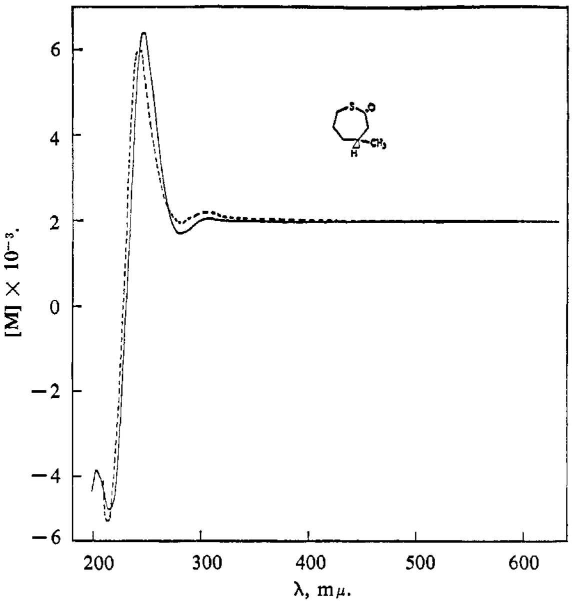

Figure 4. Optical rotatory dispersion of (*R*)-(−)-4-methylthiepan-2-one (VIII) in methanol (solid line) and dioxane (broken line).

Figure 7) has features very similar to those of VIII. Two Cotton effects are visible: the stronger one is positive and centered around λ_0 234 mμ;[16] the weaker one is shown enlarged in Figure 5. It too may be positive and appears to be centered around 298 mμ. In this case the data measured with the Rudolph instrument (350–610 mμ) follow the single-term Drude equation.

In dioxane the extrema of the large (low wavelength) Cotton effects are shifted to lower wavelengths as compared to the observations made in methanol. These shifts are analogous to those seen in the ultraviolet spectra. Apparently both this Cotton effect and the strong ultraviolet absorption band are the result of the same electronic transition, which is most likely a π–π^* transition.

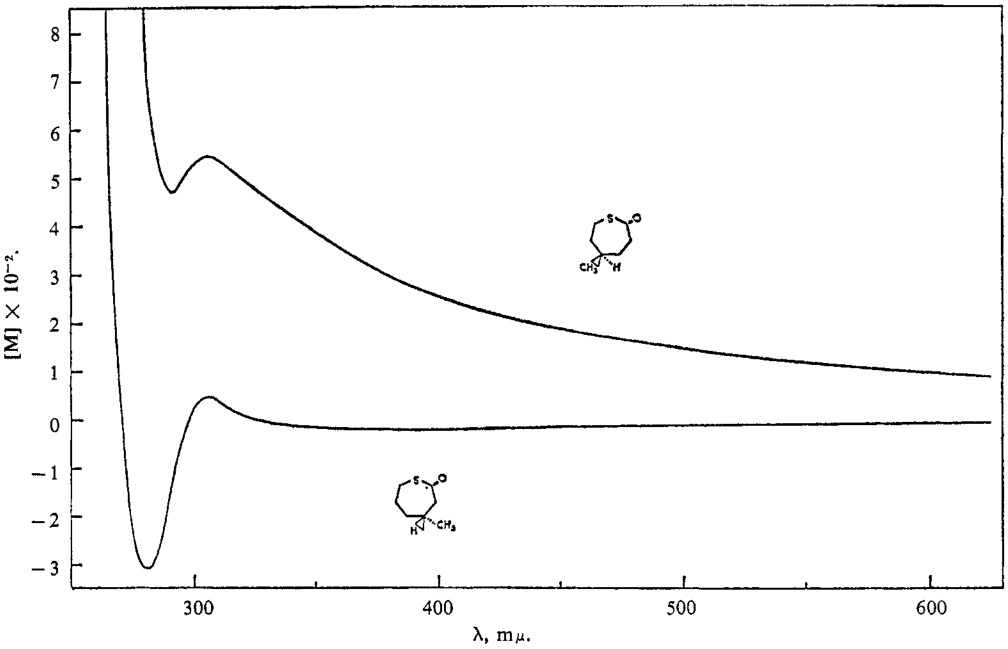

Figure 5. High wavelength Cotton effects (n–π^*) of (*R*)-(−)-4-methylthiepan-2-one (VIII) and (*R*)-(+)-5-methylthiepan-2-one (XVa) in methanol.

The high-wavelength Cotton effects are drastically affected by the solvent: for the β-methyl isomer VIII the amplitude is 356°[15] in methanol, but only 193° in dioxane, for XVa the amplitudes are 74° (methanol) and 13° (dioxane). These Cotton effects are small compared to the low-wavelength Cotton effects which have amplitudes of more than 11,000°. The dramatic solvent dependence of the high-wavelength Cotton effects is, nevertheless, clearly established, since the rotations at 280 mμ were found to be reproducible within ±23°, and the reproducibilities at higher wavelengths are much better. Therefore, these Cotton effects appear to arise from lone-pair transitions that are strongly affected by the hydrogen-bonding power of the solvent. Because of its apparent lone-pair character, its low intensity, and its occurrence at higher wavelength than the π–π^* transition, the second transition is very probably of type n–π^*.[17] In the case of steroidal thiol acetates, Djerassi[14] drew this conclusion solely on the basis of considerations concerning intensity and wavelength. It would seem that this n–π^* transition causes the high-wavelength tail of the π–π^* transition observed in all ultraviolet spectra of thiepan-2-ones.[18] Whether this weak, high-wavelength Cotton effect is the result of a single optically active transition or of

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(17) Solvent dependent shifts of the extrema were also observed for this Cotton effect (Tables II and III). They are mostly blue shifts for the more polar solvent and therefore consistent with the n–π^* designation. However, the shifts are small and the extrema ill defined because of the strong background curves.

(18) No second maximum was observed in any of these spectra, and from the ultraviolet data alone the existence of a second transition cannot be inferred. But the spectra generally have extinction coefficients of ϵ 50–100 in the range of 265–300 mμ.

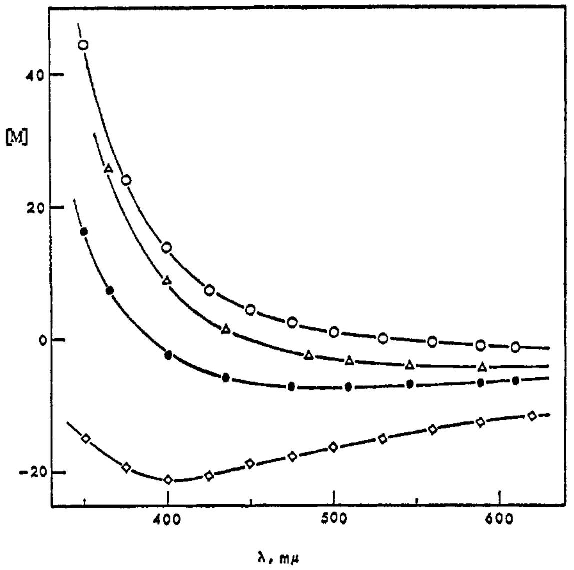

Figure 6. Optical rotatory dispersion of (*R*)-(−)-4-methylthiepan-2-one (VIII) in dioxane (○), chloroform (△), tetrahydrofuran (●), and methanol (◇), as measured by Rudolph spectropolarimeter.

several cannot be decided at this time. Moreover, these Cotton effects are quite unsymmetrical because of the strong background curves from the π–π^* Cotton effects. It is therefore not certain that the n–π^* Cotton effects are positive.

The optical rotatory dispersions of the two thiolactones resemble each other. The γ-substituted isomer XVa has rotations which are, on the whole, more positive, but the over-all shapes of the two curves and the locations of the extrema are very similar. Moreover, in both cases the π–π^* Cotton effects are positive, and the n–π^* effects appear to be of the same sign as well. These similarities may indicate that the two thiepan-2-ones have a similar preferred conformation or a similar equilibrium of corresponding conformations. This suggested conformational analogy becomes more plausible if viewed in terms of the absolute configuration and if correlated with the rotatory dispersions of the corresponding noncyclic compounds.

In spite of the fact that the configurational symbol according to the proposal of Cahn, Ingold, and Prelog[19] is *R* for both optically active thiepan-2-ones, they are not of the same configuration. This is indicated in Figures 4 and 7, and it will be understood if it is realized that both compounds were prepared from (*R*)-pulegone (or D-pulegone). The double bond of pulegone was ultimately converted in the one case to a CH_2–SH group and in the other to the carboxyl of the mercapto acids from which the thiolactones VIII and XVa were prepared.

If the terminology used for cyclohexane has any relevance to the seven-membered rings under discussion, it must be concluded that, in a given conformation of the ring system, the β-methyl group in the pseudo-equatorial position has the same configuration as the γ-methyl substituent in the pseudo-axial position. Since the β-methyl and the γ-methyl thiolactones are of opposite configuration, the same conformation of the ring system for the two compounds leads to a pseudo-equatorial arrangement for the methyl group in both.

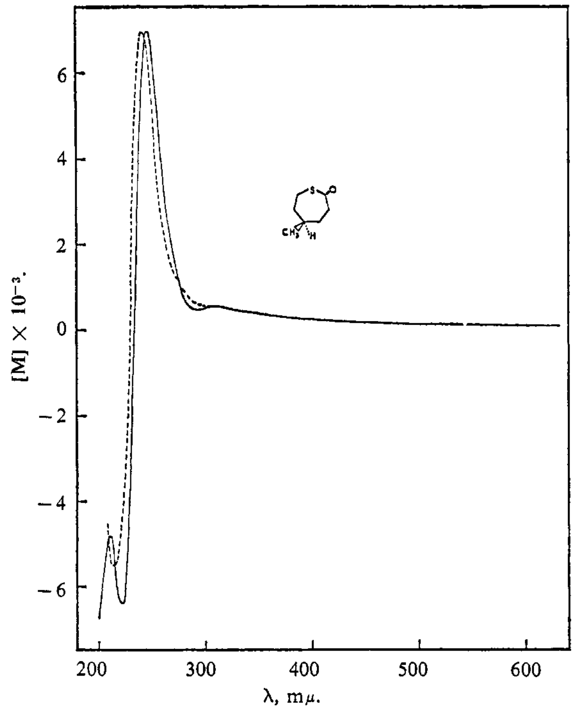

Figure 7. Optical rotatory dispersion of (*R*)-(+)-5-methylthiepan-2-one (XVa) in methanol (solid line) and dioxane (broken line).

With the corresponding linear compounds, however, this is not the case. As is demonstrated elsewhere,[6] the linear polymers prepared from thiepan-2-ones may be considered, to a first approximation, to consist of zig-zag chains. Hence, asymmetric β- and γ-carbon atoms would be expected to perturb the inherently symmetric chromophore in a similar manner. As the β-carbon of the linear poly(thiol ester) prepared from VIII is of opposite configuration to that of the γ-carbon in the poly(thiol ester) prepared from XVa, the two polymers will be expected to exhibit Cotton effects of opposite sign. This is in fact observed from the π–π^* Cotton effect, which is positive in the one case and negative in the other.[6] Because of the strong background curves, the n–π^* Cotton effects are too unsymmetrical to be definitely identified as positive or negative by optical rotatory dispersion. A comparison of the influence of cyclic and linear molecular structure on the sign of this Cotton effect is therefore not feasible.

Although it is realized that six- and seven-membered rings are conformationally very different, the conformational effect discussed above fully accounts for the experimental observations. Therefore an effect related to the above argument may well determine which conformers are the main contributors of optical rotation. However, the optical rotations of the various conformers may differ greatly, and the conformer which mainly determines the optical rotatory dispersion need be neither the only one present at room temperature in solution nor even the more present in highest concentration.

The polymers mentioned above and the analogous low molecular weight model compounds[6] may be considered as open-chain models of the thiepan-2-ones VIII and XVa. For these linear compounds the same two Cotton effects were observed, but the ratio of their amplitudes is very different from that of the thiepan-2-

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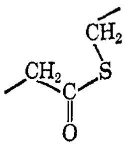
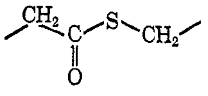
(19) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

ones. Whereas the amplitudes of the n–π^* Cotton effects in dioxane are smaller in the cyclic monomers (VIII and XVa) than in the polymers, the π–π^* Cotton effects of the two thiepan-2-ones have amplitudes ten times greater than those of the corresponding acyclic compounds. It seems that this enhancement of the rotatory power in the cyclic compounds, which reflects a stronger interaction of the center of asymmetry with the chromophore, must be related to the spatial separation between them and to their steric position relative to each other. Huisgen and Ott[20] have shown that oxepan-2-one has a *cis*-ester group, whereas in linear esters this moiety has a *trans* configuration. Molecular models indicate that thiolactones VIII and XVa must possess a conformation in which the thiol ester group is of a *cis* type. It follows (as can also be observed in models) that the asymmetric center in a cyclic system



cis



trans

with a *cis*-ester conformation will be located above or below the plane formed by the three bonds of the carbonyl carbon atom, whereas in an extended linear polymer the asymmetric center will be located in this plane or close to it. According to the octant rule,[21] substituents in the corresponding plane of cyclohexanone do not contribute appreciably to the optical rotation. In addition, the asymmetric carbon atom may be located slightly behind the carbonyl carbon atom (in a direction opposite to that of the oxygen atom) in the thiepan-2-ones, but it will be nearly on a normal to the carbon–oxygen double bond in the polymers. Therefore the asymmetric perturbation of the orbitals of the double bond can be much stronger in the case of the monomeric thiolactones. Molecular models also indicate that the spatial separation between the inherently symmetrical carbonyl chromophore and the center of asymmetry, which induces its optical activity, is smaller in the monomer than in the polymer. This is especially the case in the γ-substituted compounds.

The carbonyl stretching vibrations of thiepan-2-ones I, VIII, XVa, and XVb occur at $\bar{\nu}_{\max}$ 1665 cm^{-1}, but those of the acyclic model compounds[5] mentioned above occur at $\bar{\nu}_{\max}$ 1687 cm^{-1}. The corresponding bands of the polymers are broad but are also centered around $\bar{\nu}_{\max}$ 1685–1690 cm^{-1}. In the cyclic compounds this band is thus shifted to a wave number about 22 cm^{-1} smaller than what it is in the linear ones. This shift may indicate increased resonance in the monomers, or it may stem from the probable *cis*-ester conformation discussed above. However, it seems that the structural factors which cause the carbonyl frequency shifts in normal esters do not have the same effect in thiol esters,[22] and such conclusions would therefore be speculative.

The oxygen analogs of VIII and XVa are described in a separate paper from this laboratory.[23] Whereas the thiepan-2-ones (VIII and XVa) exhibit positive π–π^* and apparently positive n–π^* Cotton effects, the oxepan-2-ones apparently have negative π–π^* and positive n–π^* Cotton effects. Thus, the two oxepan-2-ones also have Cotton effects of the same sign, although they are of opposite configuration. As in the case of the thiepan-2-ones described here, this is to be understood as the effect of ring structure discussed above.

A conformational description of cycloheptane in solution is far more complex and uncertain than that of cyclohexane. The energy differences between various conformers of cycloheptanone are so small that "it seems likely that the compound will exist as a conformation mixture."[24] Two different attempts[25,26] to adapt the octant rule to six-membered steroidal lactones, conformationally far less ambiguous, have led to conflicting rules.[27] Moreover, the extent to which resonance effects enforce planarity of the ester or thiol ester group in solution is unknown. If resonance is pronounced, the carbonyl carbon atom, the sulfur atom, and the α- and ϵ-carbon atoms of VIII and XVa would all lie in one plane. In this case the β-, γ-, and δ-carbon atoms might all be above or below the plane formed by the other four ring atoms. On the other hand, if steric and resonance effects are small, the molecule will be quite flexible. Thus no detailed conformational analysis of these flexible seven-membered thiolester rings in dilute solution is possible on the basis of optical rotatory dispersion studies. However, it was found that the spectral changes in the optical rotatory dispersions of the thiepan-2-ones and of analogous noncyclic compounds can be explained in terms of cyclic *vs.* linear molecular structure, if the two thiepan-2-one rings have the same conformation. Therefore the predominant conformers of VIII and XVa in dioxane solution appear to be the same.

Experimental Section[28]

(*R*)-(+)-Citronellic Acid (III). The procedure of Plesek[9] was modified. (*R*)-Pulegone (II) [Givaudan, $[\alpha]^{25}\mathrm{D}$ +23.64° (*c* 0.077 g/ml, chloroform), $n^{25}\mathrm{D}$ 1.4843, chemical purity 90% as indicated by vpc on silicone oil (Dow Corning 200, retention time 8 min at 180°)], 760 g (5.0 mol), was saturated with 190 g (5.2 mol) of hydrogen chloride at +5–10° and allowed to stand overnight. Instead of using a large volume of 5 *M* sodium hydroxide solution, the ring-opening reaction was carried out as follows. A 3-l., three-necked flask, equipped with two dropping funnels, mechanical stirrer, and

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[20] R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).

[21] W. A. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

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[28] Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are corrected. Elemental analyses were performed by Bernhardt Mikroanalytisches Laboratorium, Mulheim, Germany. Optical rotatory dispersions were measured with a Rudolph photoelectric spectropolarimeter, Model 80, and with a Cary 60 spectropolarimeter; infrared spectra were recorded on Perkin-Elmer spectrophotometers, Models 21 or 521 and the wave numbers reported are the $\bar{\nu}_{\max}$ of strong and medium bands, or important shoulders. Nmr spectra of dissolved samples were taken with a Varian HR-60 spectrometer. A Perkin-Elmer vapor fractometer, Model 154-D, was used for analytical vpc and a Wilkins Aerograph Model A-700 for preparative work. The reported retention times are for samples of 1 μl at pressures of 15 psi on the Perkin-Elmer instrument, with helium as carrier gas.

thermometer, was charged with 1 l. of water and 50 ml of sodium hydroxide solution (280 g of sodium hydroxide in 750 ml of solution). The remaining sodium hydroxide solution and 475 g (2.5 mol) of pulegone hydrochloride were added simultaneously, at a steady rate, over a period of 3 hr. Thus, although the solution remained alkaline throughout, the base was not concentrated at any time. During addition the mixture was agitated vigorously and maintained at 10–15°. It was stirred overnight without cooling and residual pulegone was extracted with three portions of ether. The aqueous phase was added slowly to an agitated solution of 250 g of sulfuric acid and 1 kg of ice. Citronellic acid was extracted with ether, and the combined extracts were washed with water and dried. Slow fractional distillation (Podbielniak column) gave 220 g (57%) of product which was found to be 100% pure by vpc (silicone oil Dow Corning 200), retention time 6 min (200°) and 10.5 min (180°), bp 96–97° (0.2 mm), $n^{25}\text{D}$ 1.4522, $[\alpha]^{25}\text{D}$ +9.05° (*c* 0.032 g/ml, methanol) (lit.[29] bp 112–113° (0.6 mm), $n^{20}\text{D}$ 1.4540, $[\alpha]^{20}\text{D}$ +8.40° (neat)).

(*R*)-(+)-Methyl Citronellate (IV). To a solution of 431 g (2.53 mol) of (*R*)-(+)-citronellic acid (III) in 1600 ml of methanol was added 1.68 g (17 mmol) of sulfuric acid. The mixture was kept at 60° for 17 hr, cooled, and neutralized by addition of a solution of 1.91 g (34 mmol) of potassium hydroxide in methanol. Distillation gave 423 g (91%) of the product which was homogeneous as indicated by vpc on silicone oil (Dow Corning 200), retention time 10.5 min (160°) and 6.2 min (186°), bp 80° (4.2 mm), $n^{25}\text{D}$ 1.4391, $[\alpha]^{25}\text{D}$ 7.47° (*c* 0.033 g/ml, methanol) (lit.[29] bp 78° (3 mm), $n^{20}\text{D}$ 1.4415, $[\alpha]^{20}\text{D}$ +5.45° (neat)).

(*R*)-(+)-Methyl 6-Hydroxy-3-methylhexanoate (V). (*R*)-(+)-Methyl citronellate (IV), 36.85 g (0.20 mol), was dissolved in 100 ml of methanol and saturated with ozone (Welsbach Ozonator) during 2.5 hr at *ca.* −30°. A magnetic stirrer was introduced, and sodium borohydride, 12 g, was added in small portions. During the strongly exothermic reaction which took 2 hr, the temperature was held between −20 and +10°. The coolant was removed and the mixture allowed to warm to 20° under stirring. Most of the methanol was distilled at 10°, and the remaining slurry was diluted with 250 ml of chloroform. This mixture was added, at 0°, to a rapidly stirred solution of 400 g of sulfuric acid and 1 kg of ice, and the stirring was continued for 1 hr. The chloroform layer was washed once with aqueous sodium carbonate and with water, respectively. The dried combined extracts of several experiments were distilled after the solvent was removed at room temperature, 72%.

A vpc analysis on silicone oil (Dow Corning 200) showed that the product was contaminated; on poly(propylene glycol) at 190° two overlapping peaks with retention times of 16 min (~80%) and 17.5 min (~8%) were observed. An analytical sample was prepared by vpc [on poly(propylene glycol) at 172°] followed by redistillation. It has 98% pure as determined by vpc on silicone oil (Dow Corning 200 and 710), retention times 5 min (190°) and 9.4 min (112°), respectively, bp 85° (1 mm), $n^{25}\text{D}$ 1.4389, $[\alpha]^{25}\text{D}$ +2.30° (*c* 0.028 g/ml, methanol); $\bar{\nu}_{\max}$ 3445 (broad), 2940, 2865, 1740, 1435, 1290, 1205, 1165, and 1010 cm^{-1}.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.95; H, 10.07. Found: C, 6014; H, 9.98.

(*R*)-(+)-Methyl 6-Bromo-3-methylhexanoate (VI). (*R*)-(+)-Methyl-6-hydroxy-3-methylhexanoate (V), 80.1 g (0.50 mol), was placed in a 500-ml, two-necked flask, equipped with a stirrer, a thermometer, and a dropping funnel. It was cooled to 0 ± 5°, and this temperature was maintained, while phosphorus tribromide, 216 g, was added dropwise, with stirring. The reaction mixture was allowed to come to room temperature and stirred for 2 hr. The reaction product was then poured over ice and extracted four times with ether. The combined extracts were quickly washed with excess sodium carbonate solution, and then with water until the latter remained neutral. The ether solution was dried over magnesium sulfate and fractionally distilled through a Podbielniak column to yield 53.5 g (45%) of the bromo ester. The product was homogeneous as shown by vpc on silicone oil (Dow Corning 200, retention time 8.5 min at 174°), bp 62° (0.4 mm), $n^{25}\text{D}$ 1.4606, $[\alpha]^{25}\text{D}$ +10.67° (*c* 0.047 g/ml, methanol); $\bar{\nu}_{\max}$ 2960, 2875, 2850, 1735, 1432, 1370, 1250, 1195, 1008, 638, and 650 cm^{-1}.

Anal. Calcd for $C_8H_{15}BrO_2$: C, 43.06; H, 6.78; Br, 35.82. Found: C, 42.85; H, 6.86; Br, 35.75.

(*R*)-(+)-6-Mercapto-3-methylhexanoic Acid (VII). (*R*)-(+)-Methyl-6-bromo-3-methylhexanoate (VI), 51.5 g (0.23 mol) dissolved in 30 ml of ethanol, was added dropwise to a hot, stirred solution of 17.6 g (0.23 mol) of thiourea in 150 ml of water, and the mixture was heated at reflux for 3 hr. A few milliliters of benzene was added to avoid oxidation; potassium hydroxide, 33 g in 150 ml of water, was then added with stirring, and heating was continued for 2 more hr. The mixture was cooled, acidified by addition of 85 g of sulfuric acid dissolved in 250 g of ice, and then saturated with ammonium sulfate. The mercapto acid was separated and the solution extracted with three portions of ether. The combined extracts were dried over magnesium sulfate and distilled through a Podbielniak column, 79%. Vpc on silicone oil showed that the product was 99% pure; retention times 1.5 min (Dow Corning 710, at 210°) and 9 min (Dow Corning 200, at 190°), bp 96° (0.1 mm), $n^{25}\text{D}$ 1.4789, $[\alpha]^{25}\text{D}$ +10.90° (*c* 0.37 g/ml, methanol); $\bar{\nu}_{\max}$ 3050 (broad), 2955, 2925, 2870, 2560, 1705, 1405, 1375, 1285, 930, and 600 cm^{-1}; τ −0.98 (1 H, singlet), 7.41–7.81 (4 H, multiplet), 7.98–8.55 (5 H, multiplet), 8.64 (1 H, triplet), and 9.02 (2 H, doublet).

Anal. Calcd for $C_7H_{14}O_2S$: C, 51.82; H, 8.70; S, 19.76. Found: C, 51.69; H, 8.56; S, 19.67.

Hydrolysis of (*R*)-(+)-Poly-β-methyl-ε-thiocaprolactone. A sample of polymer[6] (600 mg) was placed in a 50-ml flask equipped with a nitrogen inlet, a magnetic stirrer, and a reflux condenser. Sodium hydroxide, 0.9 g in 10 ml of water, and 10 ml of tetrahydrofuran were added, and the mixture was stirred for 2 hr at 60°. The tetrahydrofuran was removed under vacuum; the mixture was diluted with water, treated with charcoal, and filtered. After acidification of the filtrate with sulfuric acid, the solution was extracted with ether. When the extracts had been dried, the ether was completely removed under vacuum and the crude acid vacuum distilled in a one-piece microapparatus specially prepared for the purpose. The distillate was analyzed by vpc and was found to be 98% pure; retention time 4 min on silicone oil (Dow Corning 710) at 168°, $n^{25}\text{D}$ 1.4782, $[\alpha]^{25}\text{D}$ +10.59° (*c* 0.037 g/ml, methanol). The infrared spectrum proved to be identical with that of (*R*)-(+)-6-mercapto-3-methylhexanoic acid (VII).

Anal. Calcd for $C_7H_{14}O_2S$: C, 51.82; H, 8.70; S, 19.76. Found: C, 52.03; H, 8.66; S, 19.64.

(*R*)-(−)-4-Methylthiepan-2-one (VIII). The cyclization was effected as has been described for theipan-2-one (I).[5] After (*R*)-(+)-6-mercapto-3-methylhexanoic acid (VII), 7.5 g, has been mixed with 1.7 g of phosphorus pentoxide and slowly distilled (at oil bath temperatures of 190–220°), the resulting crude thiolactone was isolated as described previously, 51%. The colorless product was shown by vpc to be homogeneous; retention times 11 min on silicone oil (Dow Corning 200) at 170° and 13.8 min on Apiezon L at 250°, bp 76° (1.1 mm), $n^{25}\text{D}$ 1.5153, $[\alpha]^{25}\text{D}$ −8.78° (*c* 0.036 g/ml, methanol), $[\alpha]^{25}\text{D}$ −0.81° (*c* 0.041 g/ml, dioxane), $[\alpha]^{25}\text{D}$ −4.51° (*c* 0.039 g/ml, tetrahydrofuran), $[\alpha]^{25}\text{D}$ −2.97° (*c* 0.045 g/ml, chloroform); $\lambda_{\max}^{\text{dioxane}}$ 235 mμ (ε 4020); $\lambda_{\max}^{\text{cyclohexane}}$ 233 mμ (ε 4190); $\bar{\nu}_{\max}$ 2964, 2930, 2877, 2855, 1665, 1450, 1442, 1225, 1165, 1127, 1102, 1071, 678, and 603 cm^{-1}; τ 7.29–7.65 (4 H, multiplet), 7.69–8.80 (5 H, multiplet), and 9.10 (3 H, doublet).

Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.26; H, 8.35; S, 22.04.

(*R*)-(+)-Citronellol (IX). The procedure of Lukes, Zobacova, and Plesek[29] was modified. More concentrated solutions were employed and the reaction mixture was hydrolyzed with aqueous sodium hydroxide instead of being worked up with acid,[30] yield 79%. The product gave a single peak on a gas chromatogram; retention time 12.5 min on silicone oil (Dow Corning 200) at 162°, bp 81° (1.8 mm), $n^{25}\text{D}$ 1.4541, $[\alpha]^{25}\text{D}$ +4.97° (*c* 0.231 g/ml, methanol) (lit.[29] bp 110° (10 mm), $n^{20}\text{D}$ 1.4558, $[\alpha]^{25}\text{D}$ +5.37° (neat)).

(*R*)-(+)-Citronellyl acetate (X) was prepared from IX, 416 g (2.67 mol), and acetic anhydride, 343 g (3.35 mol), with 2.2 g (0.027 mol) of sodium acetate, 98%. Vpc on silicone oil (Dow Corning 200) at 175° showed the product to be homogeneous, retention time 15.5 min, bp 69° (1.0 mm), $n^{25}\text{D}$ 1.4409, $[\alpha]^{25}\text{D}$ +3.23° (*c* 0.218 g/ml, methanol) (lit.[31] bp 87–88° (4 mm), $n^{20}\text{D}$ 1.4430, $[\alpha]^{20}\text{D}$ +2.59°).

(R)-(+)-Acetoxy-4-methylhexanoic Acid (XI). (*R*)-(+)-Citronellyl acetate (X), 20.7 g (0.103 mol), was dissolved in 100 ml of methanol and saturated with ozone at −78° (Welsbach Ozonator). Excess ozone and oxygen were replaced by nitrogen, and the cold solution was transferred to a pressure bottle. Palladium catalyst

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(29) R. Lukes, A. Zobacova, and J. Plesek, *Croat. Chem. Acta*, **29**, 201 (1957).

(30) The method used is analogous to the procedure of C. G. Overberger and T. Takekoshi for the reduction of methyl citronellate to citronellol: *Macromolecules*, **1**, 1 (1968).

(31) Y. R. Naves and P. Tullen, *Helv. Chim. Acta*, **44**, 1870 (1961).

(5% on charcoal, 0.5 g) was added and the ozonide hydrogenated within a few minutes on a Parr pressure reaction apparatus (0.11 mol of H_2). The catalyst was filtered and methanol was removed with a rotary evaporator. The crude product has an infrared band at 2720 cm^{-1} (aldehyde C–H).

The product was then mixed with 800 ml of water, and enough acetone was added to produce a homogeneous solution. The solution was heated to reflux, while potassium permanganate, 15 g, was added in small portions and carbon dioxide was bubbled through the stirred solution. When the oxidation was completed, the slurry was filtered through Celite and the precipitate washed several times with acetone. The solvent was removed from the combined filtrate with a rotary evaporator and the aqueous solution extracted with ether. The acid was in turn extracted from the ether with sodium carbonate solution. The precipitate from the oxidation was also washed repeatedly with sodium carbonate solution and the combined alkaline solutions were subsequently acidified and once more extracted with ether. Distillation of the dried solution gave 10.9 g (56%) of product, which was found to be homogeneous by vpc on silicone oil (Dow Corning 710); retention time 28 min at 212°, bp 107–108° (0.06 mm), $n^{25}\mathrm{D}$ 1.4423, $[\alpha]^{25}\mathrm{D}$ +2.37° (*c* 0.351 g/ml, methanol); $\bar{\nu}_{\max}$ 3050 (broad), 2960, 2930, 2870, 1740, 1708, 1458, 1370, 1240, 1170, and 1050 cm^{-1}.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.31; H, 8.39.

(*R*)-(+)-Methyl 6-Hydroxy-4-methylhexanoate (XIIa). (*R*)-(+)-6-Acetoxy-4-methylhexanoic acid (XI), 5.8 g, and potassium hydroxide, 5.1 g, were dissolved in 50 ml of water. The solution was stirred overnight at 50° and heated to reflux for 1 hr, then acidified and extracted with ether. The ether was removed completely with a rotary evaporator. Methanol, 80 ml, and sulfuric acid (0.9 mmol) were added, and the solution was kept at 50° overnight. It was cooled, and potassium hydroxide (1.8 mmol) dissolved in methanol was added. The methanol was distilled at 10° and the remaining slurry was dissolved in ether and washed with water. Distillation of the dried product afforded 2.8 g (55%); vpc on silicone oil (Dow Corning 710) at 174° (11 min) showed the product to be 99% pure, bp 75–76° (0.2 mm), $n^{25}\mathrm{D}$ 1.4393, $[\alpha]^{25}\mathrm{D}$ +5.34° (*c* 0.083 g/ml, methanol); $\bar{\nu}_{\max}$ 3570 (broad), 2950, 2925, 2870, 1745, 1435, 1377, 1250, 1197, 1168, 1100, 1056, and 1006 cm^{-1}.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.95; H, 10.07; OCH_3, 19.35; mol wt, 160.2. Found: C, 59.83; H, 9.87; OCH_3, 19.07; mol wt, 157.

(*R*)-(−)-Methyl 6-Bromo-4-methylhexanoate (XIIIa). (*R*)-(+)-Methyl-6-hydroxy-4-methylhexanoate (XIIa), 40 g (0.25 mol), was treated with phosphorus tribromide, 81 g (0.3 mol), and worked up as described above for isomer VI. Distillation yielded 25.1 g (43%). The product was homogeneous as determined by vpc on silicone oil (Dow Corning 710, retention time 7.5 min at 195°); bp 72° (0.8 mm), $n^{25}\mathrm{D}$ 1.4632, $[\alpha]^{25}\mathrm{D}$ −3.16° (*c* 0.107 g/ml, methanol), (lit. for the racemic compound[32] bp 125° (15 mm), $n^{22}\mathrm{D}$ 1.4654); $\bar{\nu}_{\max}$ 2960, 2930, 2865, 1735, 1432, 1378, 1258, 1190, 1170, 640, and 560 cm^{-1}; τ 6.38 (3 H, singlet), 6.58 (2 H, triplet), 7.67 (2 H, triplet), 8.03–8.56 (5 H, multiplet), and 9.08 (3 H, doublet).

Anal. Calcd for $C_8H_{15}BrO_2$: C, 43.06; H, 6.78; Br, 35.82. Found: C, 42.84; H, 6.87; Br, 35.68.

(*R*)-(−)-6-Mercapto-4-methylhexanoic Acid (XIVa). (*R*)-(−)-Methyl 6-bromo-4-methylhexanoate (XIIIa), 72 g (0.32 mol), was allowed to react with 25 g (0.32 mol) of thiourea as reported above in the case of 6-mercapto-3-methylhexanoic acid (VII). The thiouronium salt and ester functions were hydrolyzed with 46 g of potassium hydroxide. The product was distilled in 71% yield and was found to be 98% pure by vpc on Carbowax 1540 (retention time 10 min at 180°) and silicone oil (Dow Corning 200, retention time 9 min at 196°, 29 min at 157°); bp 107° (0.2 mm), $n^{25}\mathrm{D}$ 1.4816, $[\alpha]^{25}\mathrm{D}$ −6.07° (*c* 0.046 g/ml, methanol); $\bar{\nu}_{\max}$ 3050 (broad), 2960, 2930, 2870, 2570, 1455, 1412, 1377, 1280, 1220, and 935 cm^{-1}; τ 7.32–7.79 (4 H, multiplet), 7.96–8.60 (5 H, multiplet), 8.67 (1 H, triplet), and 9.00 (3 H, doublet).

Anal. Calcd for $C_7H_{14}O_2S$: C, 51.82; H, 8.70; S, 19.76. Found: C, 51.80; H, 8.68; S, 19.73.

(*R*)-(+)-5-Methylthiepan-2-one (XVa). (*R*)-(−)-6-Mercapto-4-methylhexanoic acid (XIVa), 8.0 g (49 mmol), was mixed with 1.8 g of phosphorus pentoxide. The mixture was distilled slowly at 190–220° (oil bath temperature) and worked up as has been described for thiepan-2-one (I).[5] Fractional distillation gave 60% yield of a colorless product. It was purified by vpc on Carbowax 1540 at 215° and redistilled; it was then found to be homogeneous on Carbowax 1500 (retention time 3 min at 180°), poly(propylene glycol) (23 min at 186°), and silicone oil (Dow Corning 200; 15.5 min at 160°); bp 74° (1.0 mm), $n^{25}\mathrm{D}$ 1.5135, $[\alpha]^{26}\mathrm{D}$ +67.30° (*c* 0.016 g/ml, methanol), $[\alpha]^{25}\mathrm{D}$ +68.35° (*c* 0.039 g/ml, dioxane); $\lambda_{\max}^{\mathit{cyclohexane}}$ 233 mμ (ϵ 3900); $\lambda_{\max}^{\text{dioxane}}$ 234 mμ (ϵ 4190); $\bar{\nu}_{\max}$ 2955, 2930, 2875, 2850, 1665, 1458, 1445, 1378, 1293, 1210, 1133, 1097, 1053, 1028, 857, and 605 cm^{-1}; τ 6.86–7.28 (4 H, multiplet), 7.54–8.77 (5 H, multiplet), and 9.10 (3 H, doublet).

Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.28; H, 8.35; S, 22.11.

(±)-Methyl 6-Hydroxy-4-methylhexanoate (XIIb). The procedure employed was similar to that of Robinson and Smith[33] for the Baeyer–Villiger oxidation of cyclohexanone. Potassium persulfate, 300 g (1.1 mol), was gradually added to a well-stirred solution of sulfuric acid, 426 ml (8 mol), and water, 144 ml (8 mol). It was maintained at 5 ± 5° while ethanol, 600 ml (13 mol), was added. 4-Methylcyclohexanone (Eastman), 65.2 g (0.58 mol), dissolved in 180 ml of ethanol was added dropwise at 5 to 10°, and the mixture was stirred without cooling for 4 hr. It was filtered from the excess salt, diluted to 4 l. and saturated with ammonium sulfate. The combined ether extracts were washed with a solution of ammonium sulfate and sodium sulfite until the ethereal solution gave a negative test with starch iodide paper. The solution was dried over excess magnesium sulfate and the ether removed with a rotary evaporator.

The crude product of two oxidations was dissolved in 2 l. of methanol and 5.5 ml (0.1 mol) of sulfuric acid and the solution was kept at 50° for 2 days. The catalyst was neutralized with 11.2 g (0.2 mol) of potassium hydroxide dissolved in methanol. The solution was filtered from the precipitated salt and concentrated on a rotary evaporator. It was diluted with ether and washed with water, aqueous sodium carbonate, and again with water until the latter remained neutral. Distillation through a Podbielniak column afforded a 50:50 mixture of the methyl ester (XIIb) and 5-methyloxepan-2-one (XVI) (combined yield 52%). An analytical sample was prepared by vpc on Carbowax. The purified product was 99% pure by vpc on silicone oil (Dow Corning 710) at 192°, retention time 17 min, bp 84–85° (0.6 mm), $n^{25}\mathrm{D}$ 1.4385; the infrared spectrum was identical with that of the (*R*)-(+) enantiomer XIIa.

(±)-Methyl-6-bromo-4-methylhexanoate (XIIIb). The bromination of the mixture of methyl 6-hydroxy-4-methylhexanoate (XIIb) and 5-methyl oxepan-2-one (XVI) was carried out as described above for (*R*)-(−)-methyl-6-bromo-4-methylhexanoate (XIIIa), but in addition the crude product was treated again with methanol and sulfuric acid before distillation. The product was found to be homogeneous by vpc, bp 72° (0.7 mm), $n^{25}\mathrm{D}$ 1.4624; retention times and infrared spectrum are identical with those of the optically active isomer XIIIa.

(±)-6-Mercapto-4-methylhexanoic Acid (XIVb). The compound was prepared in the same way as its optically active isomer XIVa and obtained in 79% yield. It was 99% pure as determined by vpc (conditions and retention times as above), bp 120° (0.7 mm), $n^{25}\mathrm{D}$ 1.4804; infrared and nmr spectra were identical with those of XIVa.

(±)-5-Methylthiepan-2-one (XVb). The cyclization of mercapto acid XIVb was carried out as has been described in the case of thiepan-2-one (I)[5] (*cf.* also preparation of XVa above). Vpc on Carbowax 1540 and silicone oil showed the product to be homogeneous after two vacuum distillations, bp 75° (1.0 mm), $n^{25}\mathrm{D}$ 1.5129; ultraviolet, infrared, and nmr spectra as well as retention times (vpc) were the same as for the (*R*)-(+) enantiomer (XVa).

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