The Stereochemistry of Thioxanthene Sulfoxide and Its C-9 Methylated Analogs. The Control of Conformational Distribution in Folded Molecules by *peri* Substitution[1a]

A. L. TERNAY, JR.,[1b] L. ENS, J. HERRMANN, AND S. EVANS

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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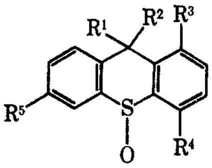
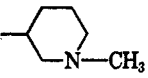
Thioxanthene 10-oxide prefers that conformation in deuteriochloroform in which the sulfinyl oxygen atom is pseudoequatorial. Similar behavior has been observed for *cis*- and *trans*-9-methylthioxanthene 10-oxides and 9,9-dimethylthioxanthene 10-oxide. 1-Methyl-4-chlorothioxanthene 10-oxide prefers that conformation in which the sulfinyl oxygen atom is pseudoaxial. Equilibration of *cis*- and *trans*-9-methylthioxanthene 10-oxide indicates that the *trans* isomer is the more stable. An initial discussion of the structural similarities and dissimilarities of *meso*-substituted 9,10-dihydroanthracenes and thioxanthenes is presented. The short wavelength (*ca.* 210 mμ) transitions in the electronic spectra of the isomeric 9-methyl-9-hydroxythioxanthene 10-oxides will allow assignment of configuration to these isomers. However, this technique cannot be applied to the isomeric 9-methylthioxanthene 10-oxides since these transitions occur at *ca.* 204 mμ in both isomers.

Thioxanthene sulfoxide (**1**) can be viewed as the progenitor of a number of conformationally restricted diaryl sulfoxides which have recently been described in the literature. All of the 9-substituted thioxanthene sulfoxides which have been reported to date,[2,3] with one exception,[4] appear to prefer that conformation in which the sulfinyl oxygen atom occupies the pseudoequatorial array (10e′). This exception is *cis*-9-[(N-methyl-3′-piperidyl)methyl]thioxanthene 10-oxide (**2**). In this compound the bulk of the substituent at C-9 is presumed[4] to control the conformational distribution. Thus, since this substituent prefers[4] the (less-hindered)[4] pseudoaxial orientation, the *cis* isomer must[4] be 9a′,10a′.

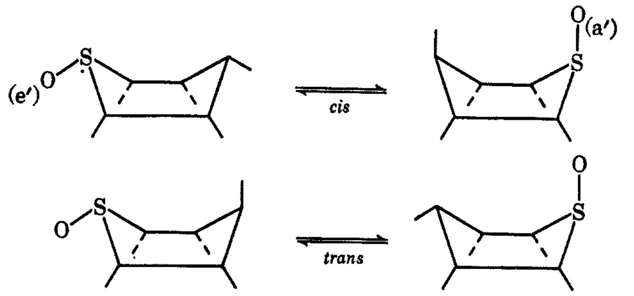


1, $R^1, R^2, R^3, R^4, R^5 = H$
2, $R^1, R^3, R^4, R^5 = H$; $R^2 = —CH_2—$ 

3, $R^1 = CH_3$; $R^2, R^3, R^4, R^5 = H$
4, $R^1, R^2 = CH_3$; $R^3, R^4, R^5 = H$
5, $R^1, R^2, R^5 = H$; $R^3 = CH_3$; $R^4 = Cl$
6, $R^1, R^2 = H$; $R^3, R^5 = Cl$; $R^4 = CH_3$
13, $R^1 = CH_3$; $R^2 = OH$; $R^3, R^4, R^5 = H$

Nuclear magnetic resonance (nmr) spectroscopy has proven valuable in studying the conformational preferences of the isomeric thioxanthen-9-ol 10-oxides and related compounds.[3] The purpose of this report is to describe the preferred conformations of thioxanthene 10-oxide (**1**), *cis*- and *trans*-9-methylthioxanthene 10-oxides (**3**), and 9,9-dimethylthioxanthene 10-oxide (**4**) in relatively noninteracting solvents as determined by nmr spectroscopy. This communication also provides evidence to illustrate the ability of a *peri* substituent to alter the conformation of a substituent in the *meso* position proximal to it within a series of 9,10-dihydroanthracene heterologs.

Finally, structural requirements necessary for the observation of differences in the ultraviolet (uv) spectra of isomeric *meso*-substituted thioxanthene sulfoxides, suggested in an earlier report,[5] are supported and expanded upon.



Results and Discussion

Conformational Analyses.—The nmr spectrum of thioxanthene sulfoxide (**1**) in deuteriochloroform consists of a complex aromatic absorption and a pair of AB doublets for the anisochronous methylene protons (Table I). Examination of the methylene region reveals that the upfield doublet is broadened (band width at half-height) relative to the downfield doublet. We have already established[3] that in this heterocyclic system such broadening results from coupling between the proton being observed and the aryl protons. That this is, indeed, the origin of the observed broadening was again[3] supported by a double-irradiation experiment. Upon irradiation of the aryl region (irradiation frequency δ 7.39) the broader signal sharpened by 41% while the less-broad (downfield) signal sharpened by only 15%. It has also been established that, in the thioxanthene system[3] and in similar systems,[6] a proton in the pseudoaxial array will couple more strongly with the aryl protons than will the corresponding pseudoequatorial proton.

The broadening of the upfield doublet observed for

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[2] A. L. Ternay, Jr., D. W. Chasar, and M. Sax, *J. Org. Chem.*, **32**, 2465 (1967).

[3] A. L. Ternay, Jr., and D. W. Chasar, *ibid.*, **33**, 2237 (1968).

[4] W. Michaelis, O. Schindler, and R. Signer, *Helv. Chim. Acta*, **49**, 42 (1966).

[5] A. L. Ternay, Jr., and D. W. Chasar, *J. Org. Chem.*, **33**, 3814 (1968).

[6] For example, P. T. Lansbury, J. F. Beiron, and A. J. Lacher, *J. Amer. Chem. Soc.*, **88**, 1482 (1966), and references cited therein.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA[a]

Compound	Chemical shift[b]	
	CH$_3$	C 9 H
Thioxanthene (**8**)		3.80,[c] 3.88[c,d]
9-Methylthioxanthene (**7**)	1.42,[c,e] 1.38[c,d]	3.95,[c,e] 4.13[c,d]
9,9-Dimethylthioxanthene (**9**)	1.63,[c] 1.67[c,d]	
Thioxanthene 10-oxide (**1**)		3.77,[f] 4.16[f,g]
cis-9-Methylthioxanthene 10-oxide (*cis* **3**)	1.90[h]	3.68[h]
trans-9-Methylthioxanthene 10-oxide (*trans* **3**)	1.36[h]	4.26[h]
9,9-Dimethylthioxanthene 10-oxide (**4**)	1.36, 1.98	
1-Methyl-4-chlorothioxanthene 10-oxide (**5**)	2.42	4.17,[f] 4.59[f,i]
1,6-Dichloro-4-methylthioxanthene 10-oxide	2.72	4.41,[f] 4.53[f,i]
Thioxanthene 10,10-dioxide (**10**)		4.23
9-Methylthioxanthene 10,10-dioxide (**12**)	1.78[e]	4.30[e]
9,9-Dimethylthioxanthene 10,10-dioxide (**11**)	1.86	

[a] Spectra were recorded at 60 or 100 MHz and were taken at *ca.* 35° in deuteriochloroform unless otherwise indicated. Copies of the spectra are available upon request. [b] δ, in parts per million (ppm) downfield from internal tetramethylsilane. [c] Carbon disulfide solvent. [d] −90°. [e] $J = 7$ Hz. [f] Center of the doublet, calculated from $\delta_A - \delta_B = \sqrt{(\nu_4 - \nu_1)(\nu_3 - \nu_2)}$. [g] $J = 17$ Hz. [h] $J = 7$ Hz. [i] $J = 18$ Hz.

1, considered along with the sharpening observed during the multiple-irradiation experiment, identifies the proton producing this signal as being in the pseudoaxial array (9a′). If the sulfinyl oxygen atom existed in the pseudoaxial array (10a′), the 9a′ proton might be considerably deshielded (relative to the 9e′ proton).[7] This suggests that **1** exists in the 10e′ conformation.

A derivative of thioxanthene sulfoxide possessing both a 10a′ oxygen atom *and* a 9a′ proton is required to test these hypotheses. An approach modeled after that of Michaelis, *et al.*,[4] is clearly unsatisfactory since it should create a 10a′ oxygen atom only when the 9a′ substituent is much larger than hydrogen. An alternate approach to the desired geometry rests in substituting in the thioxanthene nucleus in the position(s) *peri* to the sulfinyl group. Examination of space-filling models (Stuart–Briegleb) suggests that a substituent at C-4 would interact quite severely with a 10e′ oxygen atom. If the oxygen atom is "larger" than is the lone pair of electrons on sulfur, the result would be that the oxygen atom would now prefer the 10a′ array. To confirm this effect of a *peri* substituent and thereby obtain a substance possessing a 10a′ oxygen atom, 1-methyl-4-chlorothioxanthene 10-oxide (**5**) and 1,6-dichloro-4-methylthioxanthene 10-oxide (**6**) have been synthesized and their spectra compared with that of **1**.

The nmr spectrum (deuteriochloroform) of **5** possesses a complex aryl absorption and a pair of AB doublets centered at δ 4.38 [δ_A 4.59, δ_B 4.17 ($J = 18$ Hz)]. As with **1**, the band widths at half-height of the wings of the quartet are not identical. However, in **5** it is the low field doublet that is broadened. We have already noted that the broadened signal in this system corresponds to a proton at C-9 in the pseudoaxial array. This deshielding of the pseudoaxial proton is taken as confirmation of the change in the conformation of the sulfinyl group from that found in **1** to that containing a pseudoaxial sulfinyl oxygen atom. Similarly, the nmr spectrum (deuteriochloroform) of **6** also possesses a pair of AB doublets. Although $|\delta_A - \delta_B|$ (Table I) is much smaller in **6** than it is in **5**, the downfield doublet occurs at nearly the same position in both **5** and **6**; the upfield doublet in **6** has been deshielded relative to the upfield doublet in **5**. This is consistent with the assigned conformations (*i.e.*, pseudoaxial oxygen atom) since the upfield signal in **5** and **6** is assigned to the 9e′ proton and a chlorine atom *peri* to an e′ proton would be expected[8] to deshield this proton.

These data are taken as confirmation of (a) the efficacy of *peri* substituents in altering the conformation of these (and related) systems, (b) the deshielding effect of the sulfinyl group upon a substituent (here a proton) in the 9a′ array when the oxygen atom is 10a′ (compared with that geometry in which the sulfur *n* electrons are 10a′), (c) the larger steric requirement of the oxygen atom of the sulfinyl group relative to the sulfur *n* electrons in diaryl sulfoxides, (d) the assignment of **1** as preferring the oxygen 10e′ conformation in a chloroform solution,[9] and (e) the relative insensitivity of the chemical shift of a pseudoequatorial substituent at C-9 to the disposition of the sulfinyl oxygen atom.

The stereoisomeric 9-methylthioxanthene 10-oxides (*cis* and *trans* **3**) were prepared by the oxidation of 9-methylthioxanthene (**7**). Since uv spectroscopy could not readily distinguish between the isomers of **3** (presented under "Absorption Spectra"), the single crystal X-ray technique was employed[10] to assign unequivocally the *cis* configuration (9e′, 10e′ conformation) to that isomer of **3** melting at 206–207°.

Examination of the nmr spectra of *cis* and *trans* **3** reveals that the methine signal of *cis* **3** is considerably broadened relative to the methine signal of *trans* **3**. Moreover, using the inner (and more intense) signals of the methine quartet as our probe, we have observed that, while the band width at half-height of the methine

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(7) See, for example, A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *Chem. Commun.*, 881 (1967).

(8) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, Chapter 4.

(9) We have observed that **1** can crystallize in two forms, having strikingly different infrared (ir) spectra in the S–O stretching region (1100–1000 cm^{-1}). The possibility that these may represent the alternative conformers of **1** is being investigated. Moreover, the nmr spectrum of **1** in trifluoroacetic acid-*d* (TFA-*d*) possesses a pair of AB doublets in which the broadened signal (a′ proton) occurs downfield of the sharper signal (e′ proton). This suggests that in TFA-*d* the sulfinyl oxygen atom is strongly hydrogen bonded and, as a result of complexing, may now occupy the pseudoaxial array. These observations will be detailed in a future publication.

(10) M. Sundaralingam and J. Jackobs, submitted for publication.

signal of *trans* **3** sharpened by *ca.* 10%, the methine signal of *cis* **3** sharpened by *ca.* 35% during the double-irradiation experiment (irradiation frequency δ 7.61). Furthermore, the band widths at half-height of the methine signals for both *cis* and *trans* **3** were essentially the same during the double-irradiation experiment. This behavior, coupled with arguments already presented in this and an earlier report,[3] indicates that the C-9 H proton of *cis* **3** is pseudoaxially oriented while the C-9 H proton of *trans* **3** is pseudoequatorially oriented.

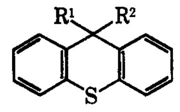
This assignment is supported by the chemical shift of the methine and methyl protons in these isomers. Thus, in *cis* **3** the methine signal occurs upfield of the methine signal of *trans* **3** (δ 3.68 *vs.* 4.26). This behavior is similar to that of **1** where the 9a′ proton occurs upfield from the 9e′ proton (δ 3.77 *vs.* 4.16). Furthermore, examination of the methyl signals of *cis* and *trans* **3** reveals that the *cis* isomer (assigned a pseudoequatorial methyl group) displays its resonance downfield from that of the *trans* isomer (δ 1.90 *vs.* 1.36). This, again, follows the pattern established for the methylene protons of **1**.

Thus, it is concluded on the basis of both long-range coupling behavior and the chemical shifts of the protons associated with the C-9 position, that *cis* **3** is 9e′,10e′ while *trans* **3** is 9a′,10e′. It is noteworthy that the conformation of *cis* **3** is the same in both the solid phase[10] and in solution (chloroform). Similar behavior has also been noted for *trans*-thioxanthen-9-ol 10-oxide, where the conformation is 9a′,10e′ both in the solid state[2] and in solution.[3]

Slight broadening of the e′ methyl resonance of 9,9-dimethylthioxanthene 10-oxide (**4**) (relative to the a′ methyl group) is observed. The resonances observed for the methyl groups of **4** are almost identical in chemical shift with the signals arising from the 9e′ and 9a′ methyl groups of *cis* and *trans* **3**, respectively. This constitutes compelling evidence to assign the oxygen 10e′ conformation to **4**. Moreover, this conformation is quite reasonable in light of the preferred conformation of the sulfinyl oxygen atom in both *cis* and *trans* **3**.

For the compounds under discussion, and to the extent that *cis* **3** and *trans* **3** are conformationally homogeneous,[11] the equilibrium constant between *cis* and *trans* **3** should provide a measure of the relative stability of the 9e′ *vs.* the 9a′ methyl group. These isomers were equilibrated and the equilibrium was found to favor the *trans* isomer, *i.e.*, the a′ methyl group, with K_{equil} ([*trans* **3**]/[*cis* **3**]) = 2.3. It has already been noted[3] that equilibration of the acetates of thioxanthen-9-ol 10-oxide also favors the *trans* isomer.

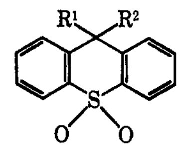
There are three likely geometries for this type of ring system: (a) a static, planar array, (b) a static, folded array, or (c) a folded array, rapidly equilibrating ("flapping") through a planar (or nearly planar) array. The nmr spectra (Table I) of thioxanthene (**8**), 9-methylthioxanthene (**7**), and 9,9-dimethylthioxanthene (**9**) are consistent with either a static, planar geometry or with a rapidly equilibrating system. For reasons that have been presented by several authors,[12] we prefer the latter interpretation. The change in the nmr spectrum that is observed in going from +35 to −90° is greater for **7** than for either **8** or **9** (Table I). The increased shielding of the methyl signal at −90° may be interpreted, with the aid of the Johnson–Bovey treatment,[13] as signifying a change in population distribution favoring a 9a′ methyl group at the lower temperature. This is also consistent with the observations already made for those sulfoxides which possess the sulfinyl oxygen atom in that orientation (10e′) which is remote from the substituents at C-9. Thus, in all of those compounds (**1**, **3**, and **4**) a 9a′ substituent (CH or CCH_3) occurs upfield relative to the corresponding 9e′ substituent. The pseudoaxial array has also been suggested as the more stable conformation of 9-methyl-9,10-dihydroanthracene.[14]



7, $R^1 = H$; $R^2 = CH_3$
8, $R^1, R^2 = H$
9, $R^1, R^2 = CH_3$

The nmr spectrum of thioxanthene 10,10-dioxide (**10**) exhibits a single, sharp resonance for the methylene group. This precludes a static, folded geometry and suggests that **10** is undergoing rapid conformational interchange at room temperature. Similarly, a static, folded geometry for 9,9-dimethylthioxanthene 10,10-dioxide (**11**) is precluded by its nmr spectrum since one would again predict that the substituents at C-9 would be anisochronous. The two remaining alternatives, *i.e.*, rapid conformational interchange *or* a static, planar geometry, are both possible. The former explanation is supported by precedent.[12] The latter cannot be ruled out since it has been shown[15] that 9,9,10,10-tetrachloro-9,10-dihydroanthracene, which is also tetrasubstituted at the *meso* positions, is planar in the solid state. Low temperature (< −90°) spectra have not been obtainable thus far because of the low solubility of **10** and **11**. However, we are attempting to resolve this question.

The nmr spectrum of 9-methylthioxanthene sulfone (**12**) suggests that its preferred conformation is one in which the methyl group is pseudoaxial (9a′). Thus, the methine proton sharpens up *ca.* 20% during a double-irradiation experiment. This is not inconsistent with a geometry which places this proton in the pseudoequatorial array. If this proton were pseudo-



10, $R^1, R^2 = H$
11, $R^1, R^2 = CH_3$
12, $R^1 = H$; $R^2 = CH_3$

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[11] The nmr spectra of **1**, **3**, and **4** were virtually unchanged at −90° (carbon disulfide).

[12] For leading references, see ref 3.

[13] C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

[14] M. L. Caspar, J. N. Seiber, and K. Matsumoto, The 146th National Meeting of the American Chemical Society, Denver, Colo., 1964, Abstracts, p 30C.

[15] N. F. Yannoni and J. Silverman, *Acta Cryst.*, **21**, 390 (1966).

axial one would expect marked deshielding by the S–O bond. However, the relatively minor deshielding of the C-9 proton observed in going from *trans* **3** to **12** (δ 0.04) is more consistent with the change in the inductive/resonance effect resulting from the oxidation at sulfur. In contrast to this minor deshielding, the methyl signal is deshielded by δ 0.42 relative to the methyl group of *trans* **3**. This deshielding is consistent with the C-9–CH_3 bond being parallel to the S–O bond, *i.e.*, 9a′,10a′.

The work of Beckett, *et al.*,[16] on the preferred conformations of *meso*-substituted 9,10-dihydroanthracenes led to the conclusion that a 9-substituted 9,10-dihydroanthracene would probably prefer that conformation in which the substituent is pseudoaxial. This, it was suggested, would remove the repulsive interactions between a pseudoequatorial substituent and the aryl protons *peri* to it. The tendency for a methyl group bonded to a *meso* atom to occupy the pseudoaxial array in both the thioxanthene system and the 9,10-dihydroanthracene system does, indeed, suggest that the a′ position is less hindered for small, nonpolar substituents than is the e′ position.

Recently, Carruthers and Hall[17a] and Nicholls and Szwarc[17b] concluded that the pseudoequatorial position is preferred when the *meso* substituent of a 9-alkyl 9,10-dihydroanthracene increases in size from methyl to *t*-butyl. These conclusions are in conflict with the suggestions of Beckett[16] although their data[17] may be open to an alternate interpretation.[18]

In addition to repulsive interactions between an e′ substituent and the positions *peri* to it, interactions (attractive or repulsive) between an a′ substituent and the aryl π cloud may also dictate conformational preferences in this type of structure. This latter consideration may account, at least in part, for the preferred conformation of the sulfinyl group in **1**, **3**, and **4** as well as in other *meso*-substituted thioxanthene sulfoxides.[3,19] In this instance the dipolar repulsive interaction between the sulfinyl oxygen atom and the aryl π cloud would destabilize the oxygen 10a′ conformation.

The analogy between the geometries of the thioxanthene system and the 9,10-dihydroanthracene system is not without flaw. For example, the C–S(O)C bond is longer than is the C–CH(OH)C bond in *trans*-thioxanthen-9-ol 10-oxide (~1.80 Å *vs.* ~1.50 Å).[2] One result of this is that the *peri* protons at C-1 and C-8 are closer to one another than are the *peri* protons at C-4 and C-5. This, in turn, suggests that there is less room for an e′ substituent at C-9 than there is at S. Moreover, there is no evidence extant which will aid in estimating the tendency for the thioxanthene ring system to become planar to relieve strain. There are, of course, still further differences.

The results, cited earlier, of Michaelis, *et al.*,[4] that **2** prefers the 9a′ conformation implies, *to the extent that all*[4,17] *of the germane conformational analyses are correct*, that a strict analogy may not exist between all *meso*-substituted 9,10-dihydroanthracenes and their heterologs. We are attempting to clarify these points.

Absorption Spectra.—We have recently demonstrated the utility of ir and uv spectroscopy in assigning configurations to the isomeric thioxanthen-9-ol 10-oxides and to the corresponding trimethylsilyl and acetyl derivatives.[2,3,5] It was observed that the uv spectra of both stereoisomers possess intense (ϵ *ca.* 40,000) short wavelength transitions, the position of the absorption maximum serving to distinguish between the stereoisomers. Thus, those isomers assigned the *cis* configuration exhibit this transition at *ca.* 10 mμ to shorter wavelength than do the corresponding *trans* isomers (~205 *vs.* ~215 mμ, respectively).

We have previously suggested[5] that the differences in these uv spectra arise from the different orientations of the S–O and C–O bonds relative to the aryl planes. The assumption that *two* dipolar functional groups are required at the *meso* positions implied that the replacement of the hydroxyl group by a simple alkyl group (*e.g.*, methyl) should result in a pair of stereoisomers with similar uv spectra. To test this hypothesis, we have examined the electronic spectra of *cis* and *trans* **3**.

The uv spectra of the stereoisomers of **3** were found to be nearly identical, both isomers exhibiting an intense (ϵ *ca.* 40,000) short wavelength transition at ~204 mμ. This, then, supports the ideas presented earlier.

If this hypothesis (concerning the origin of the differences *or* lack of differences in the uv spectra of *meso*-substituted thioxanthene sulfoxides) is correct, then the stereoisomeric 9-methyl-9-hydroxythioxanthene 10-oxides (**13**) should possess uv spectra with strikingly different short wavelength characteristics. The desired sulfoxides were synthesized by the oxidation of 9-methyl-9-hydroxythioxanthene. One of the stereoisomers exhibited its short wavelength maximum at *ca.* 205 mμ (ϵ *ca.* 41,000), while the second exhibited its maximum at *ca.* 215 (*ca.* 42,000). It is apparent that replacement of the methine hydrogen by a hydroxyl group in the isomers of **3** *does* regenerate the spectroscopic differences already noted. On the basis of these uv spectra we have tentatively assigned that isomer of **13** possessing the shorter wavelength transition the *cis* (sulfinyl, hydroxyl) configuration.

In our attempts to assign configurations to the isomers of **3**, the ir spectra of these compounds were also studied. It has been found[2] that the ir spectrum (Nujol) of *trans*-thioxanthenol sulfoxide is more complex in the 1100–1000-cm^{-1} region than is the spectrum of the *cis* isomer. However, the ir spectra of *cis* and *trans* **3** were not sufficiently different[2] (Nujol) in this region to allow configurational assignment. Thus, *cis* **3** possessed absorptions at 1092, 1060, 1038, and 1028 cm^{-1}, while *trans* **3** possessed absorptions at 1086, 1048, and 1036 cm^{-1}.

Experimental Section[20]

***cis*- and *trans*-9-Methylthioxanthene 10-Oxides** (**3**).—A solution of 2.48 g (0.0123 mol assuming 85% purity) of *m*-chloro-

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[16] A. H. Beckett and B. A. Mulley, *Chem. Ind.* (London), 146 (1955); *J. Chem. Soc.*, 4159 (1955); and other papers in this series.

[17] (a) W. Carruthers and G. E. Hall, *J. Chem. Soc.*, *B*, 861 (1966); (b) D. Nicholls and M. Szwarc, *Proc. Roy. Soc.*, **A 301**, 231 (1967), and other papers in the series.

[18] The nmr spectrum of 9-*t*-butyl-9,10-dihydroanthracene[17] may be consistent with an a′ *t*-butyl group if the *t*-butyl group deshields the 10a′ methylene proton *via* van der Waals deshielding: unpublished results with A. Brinkmann.

[19] It has been reported that phenoxanthiin sulfoxide exists with the sulfinyl oxygen atom in the pseudoequatorial position: H. Lumbroso and G. Montando, *Bull. Soc. Chim. Fr.*, 2119 (1964).

perbenzoic acid in methylene chloride (100 ml) was added to a cold (0–5°) solution of 3.00 g (0.0141 mol) of 9-methylthioxanthene (**7**)[21] in methylene chloride (150 ml). The reaction mixture was stirred at 0–5° for 16.5 hr and then washed with 10% sodium bicarbonate solution. The organic layer was dried (magnesium sulfate) and concentrated (stream of nitrogen) to afford 3.24 g of a light yellow solid, mp 92–165°. Extensive recrystallization from methanol eventually afforded yields of *ca.* 20% of one isomer (mp 206–207°) and the other isomer could not be isolated.[22]

Anal. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.30; S, 14.04. Found: C, 73.88; H, 5.45; S, 14.05.

Slow crystallization of mixtures of *cis* and *trans* **3** from ethyl acetate afforded two types of crystals ("needles" and "diamonds"). These could be separated with the aid of a microscope and, after one subsequent recrystallization from benzene, the diamondlike crystals afforded the other isomer, mp 170–171°.

Anal. Found: C, 73.47; H, 5.29; S, 13.90.

The needlelike crystals represented the higher melting isomer. Using this method yields of *ca.* 35% of each of the isomers were achieved.

9,9-Dimethylthioxanthene 10-Oxide (**4**).—9-Methylthioxanthene (**7**)[21] (20.0 g, 0.094 mol) was oxidized with 20.4 g of *m*-chloroperbenzoic acid (80% minimum assay) dissolved in methylene chloride (750 ml). Standard reaction conditions and work-up (as in the preparation of **3**) afforded a quantitative yield of a mixture (nearly equimolar) of *cis*- and *trans*-9-methylthioxanthene 10-oxides (**3**).

To a stirred solution of 11.8 g (0.105 mol) of potassium *t*-butoxide in 300 ml of *t*-butyl alcohol there was added 12.0 g (0.0526 mol) of the oxide mixture described above. After stirring for 1.5 hr at 60°, a solution of methyl iodide (30 g, 0.21 mol) in *t*-butyl alcohol (50 ml) was added (over 20 min) to the reaction mixture. This mixture was stirred for 0.5 hr at 60° and then filtered. The solvent was removed to afford 12.8 g (0.0529 mol) of crude **4**. A sample of this material (2.50 g) was chromatographed on silica gel[23] (88 g) using benzene and benzene–chloroform mixtures as the eluent. Combining fractions upon the basis of their tlc behavior yielded 1.24 g of the desired compound, mp 120–121°. Recrystallization from ethyl acetate afforded the analytical sample, mp 121–122°.

Anal. Calcd for $C_{15}H_{14}OS$: C, 74.34; H, 5.82; S, 13.23. Found: C, 74.30; H, 5.90; S, 13.14.

The results of several experiments indicate an average, isolated yield of *ca.* 30–40%.[24]

9,9-Dimethylthioxanthene (**9**).—A solution of **4** (0.80 g, 3.3 mmol) in 25 ml of tetrahydrofuran was reduced with 0.13 g (3.4 mmol) of lithium aluminum hydride. The reaction mixture was stirred at room temperature for 2 hr and then taken to the reflux temperature. After the mixture was cooled to room temperature, ethyl acetate was added to destroy any unreacted lithium aluminum hydride. The resulting mixture, after removal of the solvent, was treated with 25 ml of a 20% solution of hydrochloric acid and extracted with chloroform. The extract was dried (magnesium sulfate) and concentrated to afford 0.69 g of a light yellow oil. Distillation using a Hickman still (0.003 mm of Hg, 50–55°) afforded a white solid, mp 26–27°.

Anal. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.23; S, 14.17. Found: C, 79.80; H, 6.25; S, 13.96.

The results of several experiments indicate an isolated yield of *ca.* 85%.

9-Methylthioxanthene 10,10-Dioxide (**12**).—A solution of 9-methylthioxanthene (2.50 g, 0.0118 mol) and 15 ml of 30% hydrogen peroxide in glacial acetic acid (15 ml) was refluxed for 2.5 hr. The reaction mixture was diluted with water and the resulting solid was washed with a solution (5% w/v) of sodium bicarbonate and then with water. The resulting solid was dried (vacuum desiccator, sodium hydroxide) to afford 2.37 g (0.00972 mol, 82% yield) of crude product, mp 239–241°. Recrystallization (ethyl acetate) afforded pure **12**, mp 241–242°.

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.82; H, 4.95; S, 13.13. Found: C, 68.74; H, 5.03; S, 12.89.

9,9-Dimethylthioxanthene 10,10-Dioxide (**11**).—To a stirred solution of 6.25 g (0.0558 mol) of potassium *t*-butoxide in *t*-butyl alcohol (150 ml) there was added 6.25 g (0.0256 mol) of 9-methylthioxanthene 10,10-dioxide (**12**). The mixture was stirred at 60° for 7.5 hr and was then treated with a solution of methyl iodide (16.3 g, 0.115 mol) in *t*-butyl alcohol (10 ml); addition required 25 min. After being stirred for 4 hr at 60°, the white precipitate (potassium iodide) was removed and the solution was concentrated (stream of nitrogen) to afford 6.7 g (0.026 mol, 100% yield) of an off-white, crystalline solid, mp 164–167°. Recrystallization from 95% ethanol afforded an analytical sample of **11**, mp 169–170°.

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.64; H, 5.43; S, 12.50.

1-Methyl-4-chlorothioxanthene 10-Oxide (**5**). A. **1-Methyl-4-chlorothioxanthene.**—A slurry of 1-methyl-4-chlorothioxanthone[25] (1.0 g, 0.0039 mol) in tetrahydrofuran was cooled to 0–5° and treated with diborane prepared from the reaction of 3.45 g of boron trifluoride etherate with 0.34 g (0.00895 mol) of sodium borohydride.[26] After the addition of diborane was completed (1 hr), the reaction mixture was stirred for 45 min. Ice (50 g) was then added and the resulting precipitate was removed by filtration to afford 0.85 g of crude 1-methyl-4-chlorothioxanthene. Recrystallization from *n*-hexane yielded 0.60 g (0.0024 mol, 63% yield) of 1-methyl-4-chlorothioxanthene, mp 99–100°.

Anal. Calcd for $C_{14}H_{11}ClS$: C, 68.10; H, 4.49; S, 12.99. Found: C, 68.33; H, 4.37; S, 13.25.

B. **1-Methyl-4-chlorothioxanthene 10-Oxide** (**5**).—1-Methyl-4-chlorothioxanthene (0.50 g, 0.0020 mol) was oxidized with 0.4 g of *m*-chloroperbenzoic acid (80% minimum assay) in a total of 55 ml of methylene chloride. The standard reaction conditions and work-up afforded 0.40 g of crude **5**, mp 172–176°. The material was chromatographed on silica gel (40 g) using a chloroform–ethyl acetate mixture (9:1 v/v) as the eluent. There resulted 0.33 g (0.0012 mol, 60% yield) of **5**, mp 188–189°.

Anal. Calcd for $C_{14}H_{11}ClOS$: C, 64.00; H, 4.22; Cl, 13.49; S, 12.20. Found: C, 63.92; H, 4.24; Cl, 13.30; S, 12.50.

1,6-Dichloro-4-methylthioxanthene 10-Oxide (**6**). A. **2-Carboxy-2′-methyl-5,5′-dichlorodiphenyl sulfide** was prepared according to the method of Archer and Suter.[25]

B. **1,6-Dichloro-4-methylthioxanthone** was prepared, in 70% yield, according to the procedure of Archer and Suter.[25] The product was homogeneous to tlc: mp 196–197° (lit.[25] mp 196–197°).

C. **1,6-Dichloro-4-methylthioxanthene** was prepared by the diborane reduction of the ketone described above (B). The conditions and quantities were similar to those described in the preparation of **5**. The product was purified by column chromatography [silica gel, 9:1 (v/v) chloroform–ethyl acetate eluent] and resulted in a 100% yield of 1,6-dichloro-4-methylthioxanthene, mp 115–117°.

Anal. Calcd for $C_{14}H_{10}Cl_2S$: C, 59.80; H, 3.55; Cl, 25.22; S, 11.40. Found: C, 60.80; H, 3.44; Cl, 24.99; S, 11.62.

D. **1,6-Dichloro-4-methylthioxanthene 10-Oxide** (**6**).—Oxidation of 1,6-dichloro-4-methylthioxanthene (1.0 g, 3.6 mmol) was accomplished with *m*-chloroperbenzoic acid (0.72 g, 80% minimum assay) in 80 ml of methylene chloride under the usual conditions. After the standard work-up there resulted 0.80 g of crude product. Column chromatography of 0.52 g of this material on silica gel (40 g) using a 9:1 (v/v) chloroform–ethyl acetate mixture as the eluent afforded 0.51 g (1.7 mmol, 47% yield) of **6**, mp 166–167°.

Anal. Calcd for $C_{14}H_{10}Cl_2OS$: C, 56.58; H, 3.39; Cl, 23.76; S, 10.79. Found: C, 56.67; H, 3.39; Cl, 23.85; S, 10.95.

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[20] Melting points were obtained in a Mel-Temp apparatus and are corrected. Nmr spectra were recorded on a Varian Model A-60 or a Varian Model HA-100. Ultraviolet spectra were obtained on a Cary Model 15 from 95% ethanol solutions. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Thin layer chromatographies (tlc) were performed employing glass plates coated with silica containing a fluorescent indicator. Development was achieved with ethyl acetate, chloroform, or chloroform–ethyl acetate mixtures (9:1 v/v). Ultraviolet light and/or iodine vapor were used for visualization.

[21] C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.*, **85**, 2278 (1963).

[22] The nmr spectra of the crude reaction product indicated the presence of *ca.* 20% sulfone and *ca.* 80% sulfoxides. Moreover, the isomeric sulfoxides were apparently present in approximately equimolar amounts.

[23] Will Scientific Inc., grade 950, 60–200 mesh.

[24] Professor K. K. Andersen (University of New Hampshire) has kindly informed us of his preparation of **4** *via* the oxidation of **9** with iodobenzene dichloride. The product, mp 116–117°, was obtained in *ca.* 70% yield and had an nmr spectrum similar to that reported here.

[25] S. Archer and C. M. Suter, *J. Amer. Chem. Soc.*, **74**, 4296 (1952), and references cited therein.

[26] H. C. Brown and B. C. Subba Rao, *J. Org. Chem.* **22**, 1135 (1957).

Equilibration of *cis*- and *trans*-9-Methylthioxanthene 10-Oxides (3).—Typically, 0.10 g of either *cis* or *trans* **3** was treated with 8 ml (at 0–5°) of dry (phosphorus pentoxide) dinitrogen tetroxide. After 3 hr at 0°, the excess dinitrogen tetroxide was removed under reduced pressure and the residue was analyzed by nmr spectroscopy. The product was essentially free of decomposition products (as determined by nmr) and consisted of a mixture of 30% *cis* **3** and 70% *trans* **3**.[27]

***cis*- and *trans*-9-Methyl-9-hydroxythioxanthene 10-Oxides (13).**—A solution of *m*-chloroperbenzoic acid (2.84 g, 0.0131 mol assuming 80% purity) in methylene chloride (100 ml) was added to a cold (0–5°) solution of 9-methylthioxanthen-9-ol (3.00 g, 0.0132 mol) in 200 ml of methylene chloride. The resulting mixture was stirred for 18 hr and then washed with saturated sodium bicarbonate solution. The organic layer was dried (magnesium sulfate) and the solvent was removed (stream of nitrogen) to afford 3.20 g of a light yellow oil that solidified upon standing. Thin layer chromatography indicated the presence of two major and one minor component.

This solid was extracted with hot benzene (200 ml) and the benzene solution was cooled to 25°. The benzene-insoluble material and the substance which precipitated upon cooling of the benzene solution were combined and recrystallized from ethyl acetate to afford 0.79 g (0.0032 mol, 25% yield) of α **13**, mp 199.5–202.5 dec. This material was homogeneous to tlc.

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.82; H, 4.95; S, 13.13. Found: C, 68.61; H, 4.81; S, 13.31.

The benzene solution which remained was concentrated (steam bath) to 35 ml. Two types of crystals deposited upon cooling and these were separated mechanically. This procedure afforded 0.40 g (0.0016 mol, 13%) of crude β **13**, mp 195–197° dec. Thin layer chromatography indicated that this material was essentially homogeneous. One recrystallization from acetone afforded β **13**, mp 201.5–202.5°.

Anal. Found: C, 68.60; H, 4.88; S, 12.98.

While the melting points of α **13** and β **13** are quite similar, their electronic spectra prove that they are not the same material.[28]

Registry No.—**1**, 10133-81-0; **3** (*cis*), 19018-80-5; **3** (*trans*), 19018-81-6; **4**, 19019-06-8; **5**, 19019-07-9; **6**, 19019-08-0; **7**, 16860-11-0; **8**, 261-31-4; **9**, 19019-10-4; **10**, 3166-16-3; **11**, 19019-12-6; **12**, 19019-13-7; α **13**, 19018-82-7; β **13**, 19018-83-8; 1-methyl-4-chlorothioxanthene, 19019-14-8; 1,6-dichloro-4-methylthioxanthene, 19019-15-9.

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[27] Attempted equilibration using a dioxane–hydrochloric acid mixture resulted in some decomposition; however, the use of morpholine led to the clean equilibration of *cis* and *trans* **3**. The results were similar to those obtained with dinitrogen tetroxide.

[28] On the basis of their electronic spectra (see above), we have tentatively assigned the *cis* (sulfoxide-alcohol) configuration to α **13** and the *trans* configuration to β **13**.

The Mass Spectra of Pseudoguaianolides Related to Helenalin

L. Tsai,[2] R. J. Highet,[2] and W. Herz[3]

National Heart Institute, Bethesda, Maryland 20014,
and Department of Chemistry, Florida State University, Tallahassee, Florida 32306

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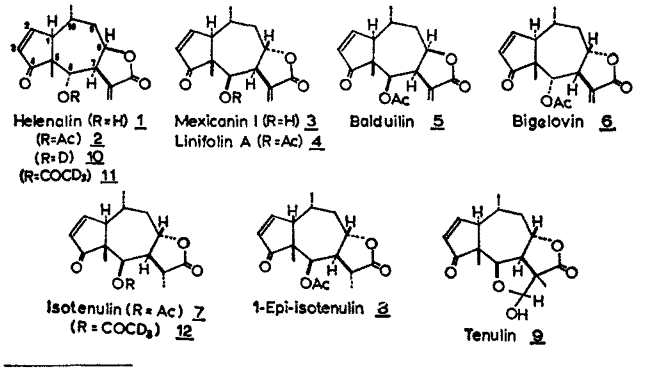
Examination of the mass spectra of 11 pseudoguaianolide sesquiterpenoid lactones bearing oxygen substituents at the 4, 6, and 8 positions reveal characteristic peaks at *m/e* 95, 96, 122, 123, and 124, compositions of which have been determined by high-resolution studies. Fragmentation mechanisms leading to these peaks are postulated and supported by the mass spectra of four deuterated derivatives.

The mass spectrometric study of fragmentation patterns of organic compounds under electron impact can yield fundamental information and also provide a diagnostic tool for the structural study of related compounds. Pseudoguaianolide sesquiterpenoid lactones[4] whose spectra have not been previously described[5] constitute an extensive series of closely related compounds which is eminently suitable for such studies. In this initial communication we report studies on pseudoguaianolides bearing the 4-, 6-, and 8-oxygenation pattern which occurs frequently within this family. Most significantly, peaks of *m/e* 95, 96, 122, 123, and 124 are common to this group of spectra. These peaks appear to be of diagnostic value and also seem capable of being interpreted rationally. [The complete spectra of the compounds **1–9** (Chart I) are shown in Figures 1–9.[6]]

Chart I



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[1] Constituents of *Helenium* Species. XXII. Previous paper: W. Herz, C. M. Gast, and P. S. Subramaniam, *J. Org. Chem.*, **33**, 2780 (1968). Studies at Florida State University were supported by grants from the National Institutes of Health (GM-05814) and the National Science Foundation (GP-6362).

[2] National Heart Institute.

[3] Department of Chemistry, Florida State University.

[4] *Cf.* W. Herz, Abstracts of the 19th Symposium on Organic Chemistry, Tempe, Ariz., 1965, pp 67–75.

[5] Mass spectrometric studies of other sesquiterpene lactones have been reported: (a) santonin and related compounds by D. G. B. Boocock and E. S. Waight, *Chem. Comm.*, 90 (1960), and by T. Tsuchiya, E. Yoshii, and T. E. Watanabe, *Tetrahedron*, **23**, 4623 (1967); (b) elephantopin and its relatives by S. M. Kupchan, Y. Aynehchi, J. M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **88**, 3674 (1966); (c) gaillardin and its derivatives by S. M. Kupchan, J. M. Cassady, J. E. Kelsey, H. K. Schnoes, D. H. Smith, and A. L. Burlingame, *ibid.*, **88**, 5292 (1966); (d) achillin by S. J. Smolenski, C. L. Bell, and L. Bauer, *Lloydia*, **30**, 144 (1967).

[6] For Figures 1–15 and Table II, order document NAPS-00178 from ASIS-National Auxiliary Publications Service, c/o CCM Information Sciences, Inc., 22 West 34th Street, New York, N. Y. 10001, remitting $1.00 for microfiche or $3.00 for photocopies.