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Stereochemistry and Conformational Preferences of Meso-Alkylated Thioxanthenes by Proton Magnetic Resonance Spectroscopy[1]

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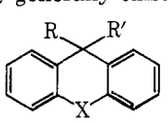
9-Alkylthioxanthenes have been shown to prefer that conformation in which the alkyl group is pseudo-axial (a′), following the pattern established for 9-alkyl-9,10-dihydroanthracenes. The central ring of 9-*tert*-butylthioxanthene is shown to be deformed (flattened). Two other series, 9-methyl-9-alkylthioxanthenes and 1,4-dimethyl-9-alkylthioxanthenes, also have been prepared and studied. Chemical shifts, NOEs, and long-range coupling phenomena have been examined with regard to their utility in conformational assignments in these compounds. Rotameric distributions for ethyl and isopropyl derivatives have been suggested on the basis of pmr parameters.

The derivatives[3] and heterocyclic analogs[4-8] of 9,10-dihydroanthracene (1) generally exist as folded structures



1, R = R′ = H; X = CH_2
2, R = R′ = H; X = S
3, R = H; R′ = Me; X = S
4, R = H; R′ = Me; X = CH_2
5, R = H; R′ = Et; X = S
6, R = H; R′ = *i*-Pr; X = S
7, R = H; R′ = *t*-Bu; X = S
12, R = Me; R′ = Et; X = S
13, R = Me; R′ = *i*-Pr; X = S
14, R = Me; R′ = *i*-Pr; X = SO_2
15, R = Me; R′ = H; X = SO

capable of displaying a substituent bound to a meso position in either the pseudo-axial (a′) or the pseudo-equatorial (e′) position. The barrier for conformational interconversion in 9,10-dihydroanthracene and structurally similar heterocycles is quite low, calculated to be on the order of 7 kcal/mol[9a] or less.[9b] Undoubtedly, the major factor responsible for establishing this low barrier is the absence of the need for atoms bonded to the meso position to pass by the peri positions and the atoms bonded to them to achieve conformational exchange. One would imagine, then, that angle deformations of the atoms at the meso positions would account for a large portion of the barrier.[10]

Beckett and Mulley[3a] have discussed the stereochemical consequences of conformational isomerism in meso-substituted 9,10-dihydroanthracenes and suggested that 9-alkyl-9,10-dihydroanthracenes should prefer that conformation in which the substituent at C_9 is a′. Recently, it has been demonstrated[3f,12] that 9-alkyl-9,10-dihydroanthracenes do, indeed, follow the conformational behavior suggested by Beckett and Mulley. Similarly, the preferred conformation of 9-methylthioxanthene (**3**)[13] is one in which the methyl group is predominately a′[14] and this result is qualitatively analogous to that for 9-methyl-9,10-dihydroanthracene (**4**).

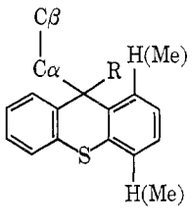
It was of interest to examine the effects of nonbonding interactions between larger alkyl groups and the ring heteroatom (sulfur) and the peri protons since a knowledge of those factors controlling the stereochemistry in these systems should contribute to an elaboration of the mode of action in these drugs.[15] The purpose of this report is to present our findings with respect to the stereochemistry of 9-alkylthioxanthenes as evaluated by pmr spectroscopy (Table I).

Results and Discussion

Preferred Conformational Assignments. First, it seems desirable to comment upon the geometry of the parent compound, thioxanthene (**2**). The presence of molecular dipole moments for both 9,10-dihydroanthracene[16] and thianthrene [17] proves that these two compounds are nonplanar in solution and viewing thioxanthene as a composite of these two systems suggests that it should also be folded in solution.

The pmr spectrum of thioxanthene in carbon disulfide, even at −90°, consists of a complex aryl absorption and a singlet for the methylene protons. Analogous results have been reported for xanthene and acridan although acridan exhibited some broadening at low temperatures.[18] This result cannot be used to distinguish between a rapidly inverting system (hence, a diastereotopomerization[19]) and a static, planar one. More direct evidence for the existence of the shallow boat conformation was obtained from the magnitude of the C_9 geminal coupling constant. It has been previously demonstrated that the angle between the nodal plane of a π system and the H–C–H bond angle of a proximal methylene group should influence J_{gem}.[20] Barfield and Grant[20a] indicate that, when the nodal plane of a double bond bisects an adjacent H–C–H angle, J_{gem} should be maximal representing a presumably negatively signed contribution to a negatively signed J_{gem}. Their argument has been employed,[12] for example, to demonstrate central ring deformation in 9-*tert*-butyl-9,10-dihydroanthracene which is also supported by X-ray studies.[21] The planar molecule, fluorene, where the π system nodal plane bisects the meth-

Table I
Proton Magnetic Resonance Parameters[a] of Substituted Thioxanthenes of Type

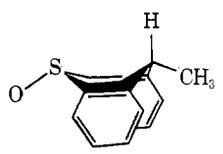


Compd	C_9 R (H or CH_3)	C_α H	C_β H
Thioxanthene (**2**)	3.80[b,c]		
9-Methyl-T (**3**)	3.97[b,d] (7.0)	1.44[e] (7.0)	
9-Ethyl-T (**5**)	3.81[b,f] (7.2)	1.73[g,h]	0.80[f] (7.2)
9-Isopropyl-T (**6**)	3.50[b,e] (10.0)	2.22[g]	0.76[e] (6.4)
9-*tert*-Butyl-T (**7**)	3.79[b,c]		0.90[c]
9,9-Dimethyl-T	1.66[c]		
cis-9-Methyl-T 10-oxide (*cis*-**15**)	3.68[b,d] (7.0)	1.90[d]	
trans-9-Methyl-T 10-oxide (*trans*-**15**)	4.26[b,d] (7.0)	1.36[d]	
9-Methyl-9-ethyl-T (**12**)	1.82[c]	1.87[d,h] (7.6)	0.54[f] (7.6)
9-Methyl-9-isopropyl-T (**13**)	1.75[c]	2.85[i] (7.0)	0.41[e] (7.0)
1,4,9-Trimethyl-T (**8**)[j]	4.47[b,d] (7.1)	1.30[e] (7.1)	
1,4-Dimethyl-9-ethyl-T (**9**)[k]	4.16[b,d]	1.43–2.04[l]	0.79[g]
1,4-Dimethyl-9-isopropyl-T (**10**)[m]	3.93[b,e] (10.2)	~2.33[g]	0.74[e,n]
1,4-Dimethyl-9-*tert*-butyl-T (**11**)[o]	4.18[b,c]		0.90[c]

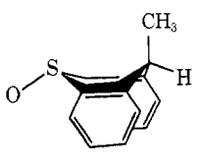
[a] Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane (TMS) and were obtained at 60 or 100 MHz (~30°); solvent is deuteriochloroform. Chemical shifts are followed by coupling constants (J) in hertz. [b] R = H. [c] Singlet. [d] Quartet. [e] Doublet. [f] Triplet. [g] Multiplet. [h] Methylene group. [i] Heptet. [j] C_1 CH_3, δ 2.43 ppm; C_4 CH_3, 2.39. [k] C_1 CH_3, δ 2.41 ppm; C_4 CH_3, 2.39. [l] Anisochronous methylene signals (see text for results of spin decoupling experiments). [m] C_1, C_4 CH_3, δ 2.39 ppm. [n] Isochronous methyl groups. [o] C_1 CH_3, δ 2.42 ppm; C_4 CH_3, 2.39.

ylene H–C–H bond angle and maximizes J_{gem}, has J_{gem} = −22.7 Hz.[22,23] We have determined J_{gem} for thioxanthene as −16.3 Hz at 40°. This observation is consistent with an π-orbital–methylene interaction that is less than that observed for fluorene and supports the view that thioxanthene is folded in solution.[24]

The chemical shift of a substituent at C_9 of the thioxanthene system is dependent on the conformational distribution [pseudo-axial (a′)/pseudo-equatorial (e′)] adopted by the molecule. For structurally similar compounds a′ substituents are generally shielded relative to their corresponding e′ counterparts, this effect being attributed, in the main, to the diamagnetic anisotropic influence of the aryl rings.[26] This proposition is supported by the relative chemical shifts of the C_9 methyl groups of the isomeric 9-methylthioxanthene 10-oxides (**15**).[14] For example, the cis diastereoisomer (*cis*-**15**)[27] exhibits its e′ methyl absorption at δ 1.90 and its a′ CH absorption at 3.68 ppm while the trans isomer (*trans*-**15**) displays an a′ methyl at δ 1.36 and



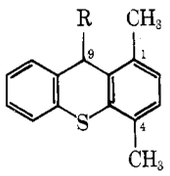
cis-(9e′,10e′)-**15**



trans-(9a′,10e′)-**15**

the corresponding CH methine at 4.26 ppm. The fact that the methyl groups of 9-methyl-T[14] and 9-methyl-9,10-dihydroanthracene[3b] become more shielded as the temperature decreases (*i.e.*, as K (= [a′]/[e′]) increases) also substantiates this view.

With this rather large disparity in chemical shift between the a′ and e′ methyl groups of the preferred conformers of the isomeric sulfoxides, it was clear to us that the preferred conformations of 9-methyl-T (**3**), 9-ethyl-T (**5**), 9-isopropyl-T (**6**), and 9-*tert*-butyl-T (**7**) could be convincingly established by comparing the pmr parameters of these compounds with those of appropriate models. It is also clear from an examination of Dreiding and Stuart–Briegleb molecular models that a methyl group at C_1 (peri position) would destabilize the equatorial position for any alkyl group. The model compounds chosen for this study were 1,4,9-trimethyl-T (**8**), 1,4-dimethyl-9-ethyl-T (**9**), 1,4-dimethyl-9-isopropyl-T (**10**), and 1,4-dimethyl-9-*tert*-butyl-T (**11**). The assignment of the a′ conformation to all



R = Me (**8**); Et (**9**); *i*-Pr (**10**); *t*-Bu (**11**)

the monoalkyl thioxanthenes reported herein was confirmed by comparison of the chemical shifts of the alkyl groups. Thus, the methyl group of 9-ethyl-T and its conformationally homogeneous (anancomeric[29]) counterpart[30] **9** absorb at δ 0.80 and 0.76, respectively.[31]

While these peri-substituted thioxanthene derivatives serve as structural models, only the chemical shift of the alkyl group is directly extrapolable between 9-alkyl-T and 1,4-dimethyl-9-alkyl-T. The chemical shift of C_9 H is deshielded in the model compounds presumably because of van der Waals steric compression.[32]

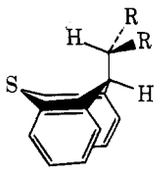
While the chemical shift of the C_9 proton proved to be of dubious value regarding conformational assignments, we chose to exploit the angular dependence documented for allylic couplings[33] hoping to gain further insight into conformational preferences in these systems which might be inaccessible from chemical shift correlations.

A proton bonded to C_9 and occupying the a′ conformation is properly oriented for strong long range coupling with the aryl protons. It has already been demonstrated[34] that the greatest effect results when the benzylic C–H bond lies perpendicular to the aromatic ring, thus allowing for efficient σ–π overlap. The coupling is identified by an increased broadening of the a′ proton absorption relative to the e′ and confirmation of this effect is obtained by multi-

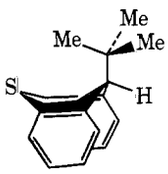
ple irradiation techniques.[34] For example, it has been observed that the a′ proton in thioxanthene 10-oxide (**16**) sharpened by 41% during irradiation of the aryl protons while the e′ proton sharpened only 15%.[35] To a first approximation, it seemed reasonable to assume that an examination of the broadness (and sharpening) of the C_9 proton absorption for a number of 9-substituted thioxanthenes would indicate the position of that proton. The appropriate data for several 9-substituted thioxanthenes are summarized in Table II.[36,37]

It can be seen that the change in the band width at half height of the C_9 proton decreases in going from 9-methyl-T to 9-ethyl-T to 9-isopropyl-T but then increases to a value approximating that of **3** for 9-*tert*-butyl-T.

These data are interpreted in the following fashion. The methyl derivative **3** as already shown,[14] is quite clearly a mixture of a′ and e′ conformers, the half bandwidth of the C_9 proton reflecting this distribution. As the larger alkyl groups increasingly favor the a′ position, the half bandwidth decreases, thus reflecting the anticipated decrease in long range coupling to the aryl proton by the (now) e′ C_9 proton. In the *tert*-butyl derivative **7** transannular repulsion between the alkyl group and the sulfur atom may result in a flattening of the central ring.[38] Only in **7** (as compared to **3, 5,** and **6**) must a methyl group be proximal to the sulfur atom; in **3, 5,** and **6** a hydrogen atom may occupy this position.



3, **5**, and **6**



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This flattening of the central ring in 9-*tert*-butyl-T causes a displacement of the C_9 H to a position which is more a′ in character with an apparent concommitant increase in its half bandwidth.

Zurcher[39] has suggested that methyl groups may be better conformational probes than single protons because of decreased sensitivity of methyl groups to minor geometric (and solvation) changes. With these points in mind we have prepared and examined the pmr spectra of 9-methyl-9-ethyl-T (**12**) and 9-methyl-9-isopropyl-T (**13**) to evaluate the efficacy of the chemical shift of the C_9 methyl group to serve as a conformational probe. Moreover, determination of the stereochemistry of these compounds will permit a testing of our conclusion that the larger alkyl group occupies the a′ conformation. Estimates of the anticipated chemical shifts of a′ and e′ C_9 methyl groups can be garnered from the pmr spectra of *cis*- and *trans*-9-methyl-T 10-oxides (**15**). These data suggest that a chemical shift of δ ~1.90 ppm may be considered representative of the e′ methyl group.

The chemical shift of the C_9 methyl group in 9-methyl-9-ethyl-T and 9-methyl-9-isopropyl-T correlate satisfactorily with the e′ methyl group of the cis sulfoxide **15** and this was considered a distinctive feature of an e′ conformation. This conclusion supports the view that the larger alkyl group prefers the a′ conformation.

A final, and direct, evaluation of the steric environment of the C_9 methyl group was obtained by establishing the presence of a spin-lattice relaxation mode between the C_9 methyl and the peri protons employing the nuclear Overhauser effect (NOE).[40]

The intensity enhancement measurements of the aryl absorptions while irradiating the C_9 methyl group clearly established the C_9 methyl as being proximal to the $C_{1,8}$ peri protons and therefore e′. Thus, while saturating the C_9 methyl absorption (δ 1.82 ppm) and observing the aromatic absorptions of 9-methyl-9-ethyl-T, a 21% increase in the integrated intensity of the low field aryl protons was observed.[41] In a similar experiment with 9-methyl-9-isopropyl-T, a 19% increase was observed.

Table II
Long Range Spin-Spin Decoupling of 9-Alkyl Thioxanthenes[a]

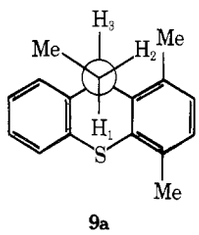
Compd	ω_2[b]	W_H[c]	W_H[d]	% change[e]
9-Methyl-T (**3**)	7.26–7	1.73	1.37	21 (±1.5)
9-Ethyl-T (**5**)	7.21–2	1.54	1.30	16 (±1.5)
9-Isopropyl-T (**6**)	7.16–8	1.62	1.40	14 (±1.5)
9-*tert*-butyl-T (**7**)	7.18–9	1.38	1.08	22 (±1.5)

[a] Decoupling experiments were performed at ambient temperature (~32°) at 100 MHz with deuteriochloroform as solvent. [b] Irradiating frequency, generated from an H.P. Model 200 CD wide range oscillator, in parts per million downfield from internal tetramethylsilane. [c] Band width at half height [hertz before irradiation of aryl region. Values are an average of 8 to 14 traces (sweep width 100 Hz, sweep time 100 sec)]. [d] Band width at half height during irradiation of the aryl region. Values are an average of 10 to 15 traces (sweep width 100 Hz, sweep time 100 sec). [e] Calculated from $\% = |(W_H{}^d - W_H{}^c)/W_H{}^c| \times 100$.

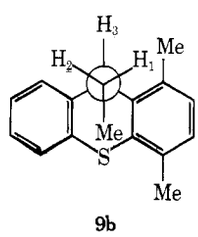
Rotameric Distribution. Although this report has centered upon the disposition of the C_9 meso substituent, the ethyl and isopropyl groups possess additional features which allow for an assessment of a preferred rotamer. Even though eclipsing interactions cannot be safely extrapolated from substituted ethanes to this system, it seems reasonable to assume that gauche conformers are lower in energy than eclipsed forms.

The C_9 proton of 1,4-dimethyl-9-ethyl-T appeared as a quartet reminiscent of unequal coupling from nearby vicinal methylene protons. The quartet pattern was consistent with vicinal coupling constants of 6.2 and 9.0 Hz.[42]

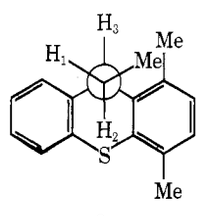
The relative magnitudes of the nonidentical vicinal coupling constants suggest (with the assistance of the Karplus relationship[43]) that a rotamer energetically similar to **9a** is favored. This also makes intuitive sense since in conformer **9b** transannular interactions between sulfur and the "inside" methyl group would be unfavorable and in **9c** methyl–



9a



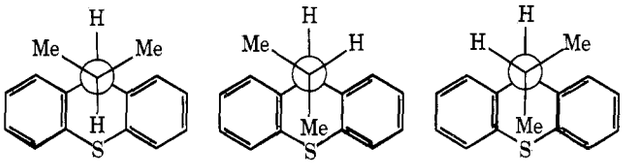
9b



9c

methyl interactions (Dreiding molecular models) would afford considerable steric hindrance to this rotamer. Assuming 9-ethyl-T exists predominantly as rotamer **9a** or **9c** (without the 1,4-methyl groups),[44] conversion to the 9-ethyl-9-methyl derivative **12** should destabilize rotamer **9a** because of the extra methyl–methyl gauche interaction. The net observable effect should be an upfield shift of the methyl group (CH_3CH_2) since its average environment over the diamagnetic region of the aryl rings has increased. Thus, the methyl triplet of **12** occurs 0.25 ppm to higher field than the methyl triplet of 9-ethyl-T. Similarly, the deshielding of the methylene protons may be accounted for by removal of the methylene group from the shielding region of the aryl rings.[45]

Employing similar arguments, the most acceptable rotamer for 9-isopropyl-T appears to be **6a** since the populations of **6b** and its mirror image are presumably diminished by the sulfur–methyl interaction. Indeed, the isopropyl



6a **6b** **6c**

methyl resonance of **13** is 0.35 ppm upfield from the methyl signal of **6.** This is consistent with a rotamer whose average lifetime over the aryl rings has increased.

Additional, although indirect, information about the rotameric distribution of the isopropyl moiety was obtained by examining the pmr spectrum of 9-methyl-9-isopropyl-T 10,10-dioxide (**14**). In deuteriochloroform the pmr spectrum of **14** exhibited a singlet for the single methyl (δ 1.77 ppm), a multiplet for the isopropyl methine (2.84), and a doublet at 0.70 for the isopropyl methyls. The chemical shifts of the C_9 methyl and isopropyl methine are virtually equivalent in sulfide **13** and sulfone **14;** however, the isopropyl methyls are deshielded in the sulfone ($\Delta\delta$ = 0.29 ppm) relative to the disubstituted sulfide **13.** The conclusion is that both **13** and **14** exist in the a′ conformation and populate that rotamer in which the isopropyl methyls are proximal to the heteroatom (S and SO_2, respectively).

The temperature dependence of the pmr spectrum of 9-isopropyl-T has been examined and the results support these views. As the temperature is decreased (carbon disulfide solution) from +35 to −90° the vicinal coupling constant between the proton and the isopropyl methine changes from 9.52 ± 0.02 Hz to 10.24 ± 0.02 Hz, suggesting a small but increasing population of **6a.** As the temperature increases (tetrachloroethylene solution) from +35 to +120°, J_{vic} decreases from 9.33 Hz to 8.86 Hz, suggesting a decrease in the mole fraction of **6a.**

Experimental Section[46]

The preparation of thioxanthene (**2**), 9-methyl-T (**3**), and the *cis-* and *trans*-9-methyl-T 10-oxides (**15**) has been described elsewhere.[14]

9-Methyl-9-ethyl-T (12). A suspension of 9-methyl-T (4.10 g, 19.3 mmol) in 100 ml of anhydrous ether was cooled to 0–5° (ice bath) and then treated with 7.47 ml of a 22.3% solution of *n*-butyllithium in hexane. The resulting red suspension was allowed to warm to room temperature and then treated with a solution of ethyl iodide (3.10 g, 19.9 mmol) in 25 ml of ether; the heat resulting from the dropwise addition of the ethyl iodide solution was used to reflux the reaction mixture. The resulting suspension was stirred for ~12 hr and then diluted with water (100 ml). The ethereal solution was separated, washed with water (two 50-ml portions), dried ($MgSO_4$), and concentrated to 4.50 g of a yellow oil.

This yellow oil was column chromatographed (silica gel, hexane eluent), a procedure which served as a "rough" purification technique, to afford 4.26 g of crude product. Vacuum distillation gave 2.97 g (12.4 mmol, 66.2% yield) of the desired dialkyl sulfide **12,** bp 111–112° (0.33 mm).

Anal. Calcd for $C_{16}H_{16}S$: C, 79.84; H, 6.71; S, 13.34. Found: C, 79.82; H, 6.73; S, 13.23.

9-Methyl-9-isopropyl-T (13). A suspension of 9-methyl derivative **3** (3.50 g, 16.5 mmol) in 100 ml of ether was cooled to 0–5° (ice bath) and then treated with 6.75 ml of a 22.3% solution of *n*-butyllithium in hexane. After stirring for 10 min at room temperature, a solution of isopropyl bromide (2.01 g, 16.4 mmol) in 25 ml of ether was added to the suspension of the carbanion of **3.** The resulting suspension was stirred at room temperature for 10 hr and then diluted with water (100 ml). The ethereal layer was separated, washed with water (two 100-ml portions), dried ($MgSO_4$), and concentrated (stream of nitrogen gas) to afford an orange, viscous oil. Molecular distillation (60° at 0.1 mm) of this material afforded **13** as a clear light yellow liquid (4.10 g, 16.2 mmol, 99% yield). Thin layer chromatography indicated this material to be essentially homogeneous.

Anal. Calcd for $C_{17}H_{18}S$: C, 80.26; H, 7.13; S, 12.60. Found: C, 80.30; H, 7.19; S, 12.42.

9-Ethyl-T (5). A suspension of **2** (10.0 g, 50.0 mmol) in 200 ml of ether was cooled to 0–5° (ice bath) and then treated with 21 ml of a 22.3% solution of *n*-butyllithium in hexane. A solution of ethyl iodide (7.8 g, 50 mmol) in 25 ml of ether was added to the above suspension at 0–5°. The reaction mixture was refluxed for 13 hr and then diluted with water (50 ml). The organic phase was separated, washed with water (three 100-ml portions), and dried ($MgSO_4$) to afford a yellow liquid. This liquid was distilled to afford a light yellow oil which was essentially homogeneous to tlc: bp 133–141° (0.2 mm).[47] The results of several reactions indicate an average yield of ~90%.

Anal. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.23; S, 14.16. Found: C, 79.42; H, 6.21; S, 13.92.

9-Isopropyl-T (6). A suspension of **2** (19.8 g, 100 mmol) in 400 ml of ether was cooled to 0–5° (ice bath) and then treated with 65 ml of 15.2% solution of *n*-butyllithium in hexane. This mixture was refluxed for 10 min then quenched with a solution of isopropyl bromide (12.3 g, 100 mmol) in 50 ml of ether. The resulting suspension was refluxed for 28 hr and then diluted with water (100 ml). The organic layer was separated, washed with water (two 100-ml portions), dried ($MgSO_4$), and concentrated (steam of nitrogen gas) to afford a red, viscous oil. This liquid was distilled (molecular distillation at 40–45° and 0.05 mm) to afford 17.3 g (72.2 mmol, 72% yield) of a white, crystalline solid, mp 50–51°.

Anal. Calcd for $C_{16}H_{16}S$: C, 79.94; H, 6.71; S, 13.34. Found: C, 79.75; H, 6.80; S, 13.18.

9-*tert*-Butyl-T (7). A solution of *tert*-butyllithium (10.7 ml of a 1.24 *M* solution) was added to a suspension of thioxanthylium perchlorate[48] (4.00 g, 13.5 mmol) in 150 ml of ether at 0–5°. The reaction mixture was stirred for 2 hr and then at room temperature for 7 hr. Water (20 ml) was added to this suspension and the organic layer separated. The organic layer was dried ($MgSO_4$) and concentrated (rotary evaporator) to afford 2.92 g of an oily solid. Glpc[49] indicated the presence of two components, one of which (35%) was identified as thioxanthene[50] by comparison with an authentic sample. Column chromatography (silica gel, hexane eluent) of this oily material afforded 1.23 g (48.4 mmol, 35.9%) of the desired product, mp 156–157°.

Anal. Calcd for $C_{17}H_{18}S$: C, 80.26; H, 7.13; S, 12.60. Found: C, 80.40; H, 7.27; S, 12.30.

1,4-Dimethylthioxanthone. *o*-Xylene (1.00 kg, 9.43 mol) was added, dropwise and with stirring, to a cold (0–5°) suspension of 300 g (1.98 mol) of thiosalicylic acid in 900 ml of concentrated sulfuric acid. Stirring was continued for ~1 hr at room temperature after which the reaction mixture was refluxed for ~5 hr. The resulting dark red suspension was stirred for ~14 hr at room temperature. The acidic suspension was poured, in 300-ml portions, over ice (~2 kg per portion) and each resulting suspension was further diluted with ~3 l. of water. Filtration of each suspension afforded a yellow solid which was then suspended in a saturated solution of sodium bicarbonate (~150 ml). The resulting suspensions were extracted with chloroform and the combined organic phase dried ($MgSO_4$) and concentrated to afford a yellow solid, mp 103–106°.

Recrystallization of the crude product from 95% ethanol afforded 382 g (1.59 mol, 83.5% yield) of product, mp 112.5–113.0° (lit.[51] mp 112°).

1,4-Dimethyl-T.[52] Diborane, produced by the reaction of 5.10 g (135 mmol) of sodium borohydride with 28.5 g (200 mmol) of boron trifluoride etherate, was passed through a suspension of 1,4-dimethylthioxanthone (48.1 g, 223 mmol) in 350 ml of tetrahydrofuran cooled to 0–5° (ice bath). The resulting solution was poured over ~1.5 kg of ice, mixed, and then allowed to stand overnight. The resulting solid was extracted with chloroform; the chloroform solution was separated, dried, and then concentrated (rotary evaporator) to afford an off-white solid. This material was sublimed (70° at 0.1 mm) to afford 36.6 g (181 mmol, 82%) of 1,4-dimethylthioxanthene, mp 80–81°.

Anal. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.23; S, 14.16. Found: C, 79.83; H, 6.43; S, 14.18.

1,4,9-Trimethyl-T (8). A solution of 1,4-dimethyl-T (5.00 g, 24.7 mmol) in ether (200 ml) was cooled to 0–5° (ice bath) and treated with 10.33 ml of a solution containing 25 mmol of *n*-butyllithium in *n*-hexane. To the resulting red suspension there was then added, at 0–5°, a solution of methyl iodide (3.55 g, 25 mmol) in 10 ml of ether. The resulting light orange solution was stirred at

25° for 24 hr and then diluted with 100 ml of water. The organic layer was separated, dried ($MgSO_4$), and then concentrated to 5.25 g of a light yellow oil (rotary evaporator). This oil was chromatographed (silica gel, hexane eluent) to afford 5.17 g (24.2 mmol, 98%) of the desired product.

The pmr spectrum was completely consistent with the assigned structure. The mass spectrum (70 eV) displayed the molecular ion at *m/e* 240 (calcd 240 for $C_{16}H_{16}S$).

1,4-Dimethyl-9-ethyl-T (9). A solution of 1,4-dimethyl-T (5.00 g, 24.7 mmol) in 150 ml of ether was cooled to 0–5° (ice bath) and treated with 10.33 ml of a solution of *n*-butyllithium (25 mmol) in *n*-hexane. To the resulting red suspension there was added (at 0–5°) a solution of 3.87 g (24.8 mmol) of ethyl iodide in ether (15 ml). After ~0.5 hr at 0–5° the reaction mixture was warmed to 25° and then maintained at this temperature for 22 hr. The reaction mixture was then diluted with water (~50 ml) and the organic layer separated. The organic layer was washed with water, dried ($MgSO_4$), and concentrated (rotary evaporator) to afford a 5.57 g of an orange oil. This oil was chromatographed (silica gel, *n*-hexane eluent) to afford the desired product (5.49 g, 24.2 mmol, 98%) as a colorless oil.

Anal. Calcd for $C_{17}H_{18}S$: C, 80.26; H, 7.13; S, 12.60. Found: C, 80.25; H, 7.17; S, 12.30.

1,4-Dimethyl-9-isopropyl-T (10). A solution of 1,4-dimethyl-T (5.00 g, 24.7 mmol) in ether (150 ml) was cooled to 0–5° (ice bath) and treated with 10.33 ml of a solution of 25 mmol of *n*-butyllithium in hexane. To the resulting red suspension there was added, after ~10 min a solution of isopropyl bromide (3.00 g, 24.4 mmol) in ether (25 ml). After stirring for 20 min at 0–5°, the reaction mixture was stirred for 3 days at 25°. The resulting yellow solution was diluted with water (80 ml) and the organic layer separated and dried ($MgSO_4$). Concentration (rotary evaporator) of this solution afforded 5.89 g of an orange oil. "Sublimation" of this oil at 45–50° (0.03 mm) gave 5.80 g (24 mmol, 98% yield) of the desired product as a white, crystalline solid, mp 59–60°.

Anal. Calcd for $C_{18}H_{20}S$: C, 80.55; H, 7.51; S, 11.94. Found: C, 80.75; H, 7.70; S, 12.16.

1,4-Dimethyl-9-*tert*-butyl-T (11). The title compound was prepared in a manner similar to that used to prepare **7**. The product was obtained in low yield (<15%), mp 115–116°. This material was homogeneous on thin layer chromatography and exhibited a pmr spectrum totally consistent with the assigned structure.

Anal. Calcd for $C_{19}H_{22}S$: S, 11.35. Found: S, 11.19.

9-Methyl-9-isopropyl-T 10,10-Dioxide (14). Oxidation of sulfide **13** with an excess of hydrogen peroxide (30%) in refluxing acetic acid gave sulfone **14** in 90% yield, mp 82–83°. This material was homogenous on tlc and possessed a pmr spectrum totally consistent with the assigned structure. The ir spectrum (Nujol) exhibited strong absorptions at 1297 and 1161 cm^{-1} (SO_2) and other strong bands at 779, 760, and 731 cm^{-1}.

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Registry No. 2, 261-31-4; **3,** 16860-11-0; **5,** 28612-38-6; **6,** 28612-39-7; **7,** 28612-40-0; **8,** 51966-06-4; **9,** 51966-07-5; **10,** 51966-08-6; **11,** 51966-09-7; **12,** 51966-10-0; **13,** 51966-11-1; **14,** 51966-12-2; *cis*-**15,** 19018-80-5; *trans*-**15,** 19018-81-6; thioxanthylium perchlorate, 2567-20-6; 1,4-dimethyl-T, 17394-13-7; 1,4-dimethylthioxanthone, 25942-61-4; 9,9-dimethyl-T, 19019-10-4.

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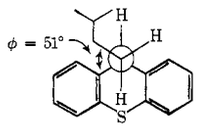

(45) It is recognized that other factors may also contribute to these changes in relative chemical shifts (*vide supra*).
(46) All melting points were obtained in a Mel-Temp apparatus (open capillary) and are corrected. Pmr spectra were recorded on Varian Models HA-100 and A-60 nmr spectrometers in deuteriochloroform unless otherwise indicated. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Crobaugh Laboratories, Cleveland, Ohio. All compounds were shown to be a homogeneous by thin layer chromatography (silica gel substrate) on glass plates using ethyl acetate or chloroform as eluents and with uv and iodine vapor for visualization. Mass spectra were obtained on a Varian Model M-66 mass spectrometer. Ir spectra were recorded using a Beckman Model IR-8 spectrophotometer. All alkylation reactions were carried out in a nitrogen atmosphere.
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Syntheses of Cyclic Bisthioacylals. 1,3-Dithiane-4,6-diones and 1,3-Dithiolane-4,5-dione[1]

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Reaction of bisthiomalonic acids **1a,b** with isopropenyl acetate gave thietanediones **3a,b** and thioacetone *via* Grob fragmentation (Scheme I, path a). When bisthio acid **1a** was treated with carbonyl compounds (acetone, acetaldehyde, acetophenone, and benzophenone) and boron trifluoride etherate, **3a** was again obtained (path a) except in the case of *p*-anisaldehyde, where path b was competitive and the 1,3-dithiane-4,6-dione **4c** was also obtained. Treatment of the pyridinium salt of **1a** with methylene iodide or dichlorodiphenylmethane also gave **3a**. The title compounds (**7a, 8c,d,f–i**) were alternately prepared by condensation of oxalyl, malonyl, and certain substituted malonyl halides with *gem*-dithiols. Selective methylation of compounds **8d, 8e,** and **8g** at C-2 and/or C-5 was achieved.

Although 1,3-dioxane-4,6-diones such as Meldrum's acid (**8a**) and a number of its derivatives have received considerable attention,[2] the 1,3-dithio analogs have not been studied. Herein we report the results of investigations into synthetic approaches to these sulfur heterocycles.

Reaction of dimethylmalonic acid with isopropenyl acetate catalyzed by sulfuric acid is known to give 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**8b**).[2a] In contrast, we have observed that reaction of dimethylbisthiomalonic acid (**1a**) or cyclobutane-1,1-bisthiodicarboxylic acid (**1b**) with isopropenyl acetate under similar conditions afforded the thietanes **3a** and **3b,** respectively, plus thioacetone. This apparently occurs *via* Grob fragmentation[3,4] of the expected intermediates **2a** and **2b** (Scheme I, path a) rather than ring closure to the 1,3-dithiane-4,6-diones (**4a, 4b,** path b). The latter compounds have been synthesized alternately (*vide infra*) and are stable both thermally and toward sulfuric acid, thus excluding them as intermediates to the thietanediones. The possibility that the thietanediones **3a** and **3b** might form directly by acid-catalyzed loss of hydrogen sulfide from the bisthio acids was also ruled out. Thus, the bisthio acids **1a** and **1b** underwent only slow loss of carbonyl sulfide in the presence of sulfuric acid.

Reaction of dimethylbisthiomalonic acid with *p*-anisaldehyde and boron trifluoride etherate in refluxing methylene chloride solution[5] again provided the thietanedione **3a;** however, it was accompanied by 2-(*p*-anisyl)-5,5-dimethyl-1,3-dithiane-4,6-dione (**4c**) in 26% yield. In this case reaction *via* **2c** (Scheme I, path b) apparently competes with Grob fragmentation (path a) and both products are observed. Since **4c** was thermally stable at its melting point (119–124°) it was considered an unlikely precursor to the thietanedione.

Formation of the bisthioacylal **4c** from dimethylbisthiomalonic acid and anisaldehyde–boron trifluoride prompted us to examine such reactions with other carbonyl compounds. Reaction of the bisthio acid with benzophenone or acetone and boron trifluoride gave only thietanedione accompanied by thiobenzophenone or thioacetone, respectively. Similar reactions with acetophenone and with acetaldehyde also netted some thietanedione **3a** (glpc, nmr) but again none of the bisthioacylals (**4f, 4g**). When