The Stereochemistry of Sulfonium Ylides Derived from 9-Alkylidenethioxanthenes--The Relationship Between Ring Inversion and S$^+$-C$^-$ Bond Rotation

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A series of sulfonium ylides has been prepared by the reaction of 9-alkylidenethioxanthenes with dimethyl diazomalonate. The e' electron pair on sulfur is more efficient than the a' in trapping the "carbenes" generated by copper(II) catalyzed decomposition of diazo compounds. Consequently, e' ylides are the kinetically-controlled reaction products. Varying the C2 substituent does not alter this.

Sulfides and sulfonium ylides containing the isopropylidene moiety do not undergo rapid ring inversion. Rotation about the S$^+$-C$^-$ bond occurs in the pseudo-axial conformation but not the pseudo-equatorial. The use of the anisochronicity of portions of the malonylide fragment as a criterion for heterocyclic ring inversion is presented. It is suggested that the sulfoxides of phenothiazine, phenoxathiin, thianthrene, and related sulfoxides, undergo rapid ring inversion.

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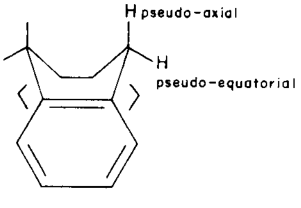
Introduction.

9,10-Dihydroanthracene (**1**) is folded about an imaginary line containing its *meso* positions (C9,C10). The same is generally true of its heterocyclic analogs. Thus most of these systems adopt a geometry in which the central ring exists in the classic "boat" form. As a consequence, substituents at the *meso* positions may occupy either the pseudo-axial (a') or the pseudo-equatorial (e') position. These two positions are diastereotopic and moieties bonded to them are expected to have different spectral properties, different chemical reactivity, and so forth. An a' bond is essentially parallel to the aryl π clouds while an e' bond is essentially orthogonal.

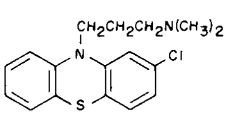


The Geometry of 9,10-Dihydroanthracene

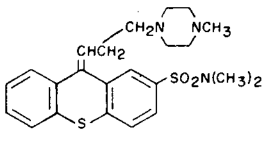
Generally, compounds of this type containing unsubstituted outer rings undergo rapid ring inversion at room temperature. It was impossible, for example, to alter the appearance of the methylene singlet of thioxanthene **2** even at −120° (at 100 MHz) [1]. It is reasonable that thianthrene **3** and thioxanthone **4** also have low barriers to ring inversion [2]. Indeed, since the thioxanthone ring system is nearly planar, its barrier to ring inversion should be quite low. The reason for these low barriers is that the major source of increased energy in the transition state for inversion is angle strain; bonds need not pass by one another during the ring inversion process.

Ring inversion in these systems exchanges e' and a' substituents.

Many sulfur-containing analogs of **1** exhibit valuable pharmacological activity. Thus chlorpromazine (a phenothiazine) and thiothixene (an alkylidenethioxanthene) are both neuroleptic agents. As part of a continuing study of the stereochemistry of such systems, and the relationships between molecular geometry and biological activity, we have begun to examine the stereochemistry and spectral properties of ylides derived from these heterocycles [3]. These studies offer among other things, the opportunity to study the effect of ring substituents upon moieties bonded to sulfur. This appears to be necessary to fully comprehend the action of such drugs since most have substituents on a ring *para* to sulfur (*i.e.*, C2 in **2-4**). While it has been suggested that these substituents alter the electronic nature of such sulfur atoms, there is a paucity of information about precisely which properties are altered--and how they are affected [4].



Chlorpromazine



Thiothixene

This report describes the synthesis and presents the conformational analysis of ylides derived from alkylidenethioxanthenes. The work addresses, among other things, the relationship between ring inversion and (a) the nature of the alkylidene fragment and (b) S$^+$-C$^-$ bond rotation in these systems. Further, it notes the greater reactivity of e' electron pairs in these systems towards copper-stabilized carbenoids prepared by the method of Ando [5].

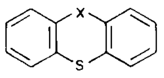
Results and Discussion.

Syntheses.

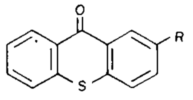
All of the thioxanthones used in this study ahve been described in the literature [6]. 2-Methylthioxanthone (**5**) and 2-methoxythioxanthone (**6**) were prepared in about 80% and 50% yield, respectively [6a,7]. This represents the range of yields. Thioxanthone, **4**, and 2-chlorothioxanthone are commercially available.

The necessary alkenes were prepared by the reaction of the appropriate thioxanthone and Grignard reagent followed by immediate dehydration of the alcohol [8]. While several dehydration procedures were tried (*eg.,* phosphorus pentoxide and thionyl chloride), the most generally successful one involved the use of cold, concentrated sulfuric acid.

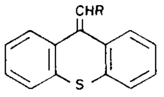
The ylides were prepared by reaction of the appropriate sulfides with dimethyl diazomalonate using anhydrous copper(II) sulfate as a catalyst and toluene as the "solvent". This process, based upon the work of Ando [5], afforded the ylides in 60-98% yields (isolated). The isomeric cyclopropanes were not detected by nmr but these might have been present at concentrations of less than about 5%. The ylides, once separated from insoluble (inorganic) materials, were recrystallized from any of several solvents (including ethanol *and* a benzene-hexane mixture). There was no evidence for decomposition or isomerization during recrystallizations. However, traces of ethanol sometimes had to be removed with the aid of an Abderhalden drying pistol (charged with phosphorus pentoxide and warmed to 40-50°).



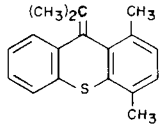
2, X = CH2
3, X = S
4, X = C=O



5, R = CH3
6, R = OCH3



7, R = H
8, R = CH3
9, R = C2H5



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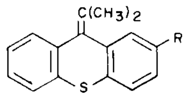
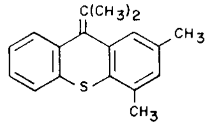


10, R = H
13, R = CH3
14, R = Cl
15, R = Br
16, R = OCH3



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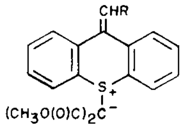
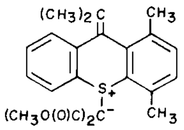


17, R = H
18, R = CH3
19, R = C2H5



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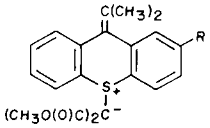
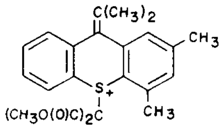


22, R = H
23, R = CH3
24, R = Cl
25, R = Br
26, R = OCH3



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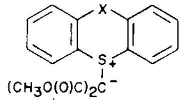
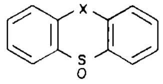


27, X = C=O
28, X = CH2

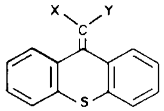


29, X = S
30, X = O
31, X = S(O)
32, X = NH

Table 1 summarizes the synthetic results for methylidenethioxanthene (**7**), ethylidenethioxanthene (**8**), propylidenethioxanthene (**9**), and isopropylidenethioxanthene (**10**). The syntheses, described in detail in the experimental section, are derived from the work of Sindelar [9] and of Tamura [10].

Table 1

Synthesis of 9-Alkylidenethioxanthenes



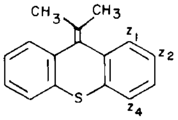
Compound	X	Y	% Yield	Mp, (°C)
7	H	H	92	oil
8	H	CH_3	74	oil
9	H	C_2H_5	82	oil
10	CH_3	CH_3	75	85-87

It is convenient to consider separately the aryl-substituted isopropylidenethioxanthenes prepared for this study. A summary of pertinent synthetic information is found in Table 2 for 1,4-dimethyl-9-isopropylidenethioxanthene (**11**), 2,4-dimethyl-9-isopropylidenethioxanthene (**12**), 2-methyl-9-isopropylidenethoxanthene (**13**), 2-chloro-9-isopropylidenethioxanthene (**14**), 2-bromo-9-isopropylidenethioxanthene (**15**), and 2-methoxy-9-isopropylidenethioxanthene (**16**).

Finally, pertinent data for the following ylides is found in Table 3; 9-methylidenethioxanthenium bis(carbomethoxy)methylide (**17**), 9-ethylidenethioxanthenium bis(carbomethoxy)methylide (**18**), 9-propylidenethioxanthenium bis(carbomethoxy)methylide (**19**), 9-isopropylidenethioxanthenium bis(carbomethoxy)methylide (**20**), 1,4-dimethyl-9-isopropylidenethioxanthenium bis(carbomethoxy)-methylide (**21**), 2,4-dimethyl-9-isopropylidenethioxanthenium bis(carbomethoxy)methylide (**22**), 2-methyl-9-isopropylidenethioxanthenium bis(carbomethoxy)methylide (**23**), 2-chloro-9-isopropylidenethioxanthenium bis(carbomethoxy)methylide (**24**), 2-bromo-9-isopropylidenethioxanthenium bis(carbomethoxy)methylide (**25**), 2-methoxy-9-isopropylidenethioxanthenium bis(carbomethoxy)methylide (**26**).

Table 2

The Synthesis of 9-Isopropylidenethioxanthenes



Compound	Z_1	Z_2	Z_4	% Yield	Mp (°C)
11	CH_3	H	CH_3	91	90-92
12	H	CH_3	CH_3	86	119-120
13	H	CH_3	H	86	61-63
14	H	Cl	H	50 [a]	98-99
15	H	Br	H	51 [a]	92-94
16	H	OCH_3	H	91	78-79

[a] The yield is based upon a single synthesis.

NMR Spectra.

The proton magnetic resonance spectra of the sulfonium ylides and their progenitor sulfides are summarized in Tables 4 and 5.

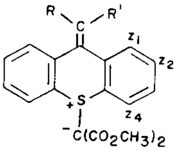
The most striking characteristic of these spectra is the appearance of the methoxy resonance(s) and their relationship to the substituent at C9. Thus, when C9 is methylidene, ethylidene or propylidene (**17-19**, respectively), the two methoxy groups are isochronous, appearing as a sharp singlet near 3.6 ppm. This resonance is not very sensitive to the nature of the alkylidene group in the series **17-19**. These values are close to the methoxy resonance for thioxanthonium bis(carbomethoxy)methylide (**27**) reported under conditions of rapid S^+-C^- bond rotation [11]. These results suggest, among other things, that these systems all have approximately the same geometry.

It has already been demonstrated that the C-13 chemical shift of the methylide carbon of ylides derived from thioxanthenes (and related heterocycles) can be used to assigned conformation to the malonylide fragment [3]. Thus, e′ ylides containing e′ malonylide fragments were found to resonate near 50 ppm while structurally-related a′ malonylide fragments exhibited their methylide resonance at over 60 ppm. The ylides examined in this study exhibit their methylide resonance at 50-55 ppm, suggesting that they are e′ rather than a′.

Those ylides which have an isopropylidene fragment at C9 show, in dramatic contrast, *two* methoxy resonances in the ^1H nmr. Thus increasing the size of the 9-alkylidene group has rendered the methoxy groups of the malonylide

Table 3

The Synthesis of Thioxanthenium Ylides

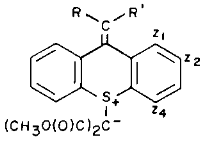


Compound	R	R′	Z_1	Z_2	Z_4	Temp [a]	Time [b]	% Yield	Mp (°C)
17	H	H	H	H	H	85-86	3	63	190-191
18	H	CH_3	H	H	H	90-95	3	84	228-230
19	H	C_2H_5	H	H	H	78-92	3.5	71	201-203
20	CH_3	CH_3	H	H	H	85-87	4	81	197-200
21	CH_3	CH_3	CH_3	H	CH_3	95-98	4	84	165-167
22	CH_3	CH_3	H	CH_3	CH_3	90-94	4	62	150-152
23	CH_3	CH_3	H	CH_3	H	97-102	3	92	154-156
24	CH_3	CH_3	H	Cl	H	98-100	3	98	197-198
25	CH_3	CH_3	H	Br	H	95-99	3	59	187-189
26	CH_3	CH_3	H	OCH_3	H	98-102	3	95	185-187

[a] Reaction temperature (°C). [b] Reaction time (hours) includes approximately 15 minutes for reaction mixture to reach designated temperature.

Table 4

^{1}H-NMR Spectra of Alkylidenethioxanthene bis(Carbomethoxy)methylides [a]

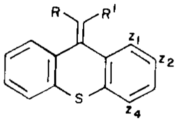


Compound	R, δ	R′, δ	Z_1, δ	Z_2, δ	Z_4, δ	CO_2CH_3	Ar-H
17	H, 1.8	H, 1.8	H	H	H	3.6 [b]	7.4-7.7
18	H, 6.3 [c]	CH_3, 2.1 [d]	H	H	H	3.6 [b]	7.3-7.7
19	H, 6.2 [e]	CH_2, 2.5 [f] CH_3, 1.2 [g]	H	H	H	3.6 [b]	7.3-7.7
20	CH_3, 2.0	CH_3, 2.0	H	H	H	3.4, 3.8 [h]	7.3-7.6
21	CH_3, 1.7 [i]	CH_3, 1.9 [i]	CH_3, 2.3 [i]	H	CH_2, 2.5 [i]	3.4, 3.8 [h]	6.9-7.6
22	CH_3, 2.0 [i]	CH_3, 1.9 [i]	H	CH_3, 2.3 [i]	CH_3, 2.4 [i]	3.3, 3.7 [h]	6.8-7.6
23	CH_3, 2.0 [j]	CH_3, 2.0 [j]	H	CH_3, 2.3	H	3.3, 3.6 [h]	6.9-7.5
24	CH_3, 2.1 [h]	CH_3, 2.1 [j]	H	Cl	H	3.4, 3.8 [h]	7.2-7.8
25	CH_3, 2.0	CH_3, 2.0	H	Br	H	3.4, 3.8 [h]	7.1-7.8
26	CH_3, 2.0 [i]	CH_3, 2.1 [i]	H	OCH_3, 3.8	H	3.4, 3.8 [h,k]	6.8-7.6

[a] Recorded at 200 MHz in deuteriochloroform at 25°. Chemical shifts, in ppm and relative to TMS, are given to the nearest 0.1 ppm. Integrated intensities are consistent with assignments. Assignments of isomeric groups (*eg.*, R and R′ in **21**) may be exchanged. [b] Isochronous under these conditions. [c] Quartet, J = 7.5 Hz. [d] Doublet, J = 7.5 Hz. [e] Multiplet. [f] Sextet, J = 7.3 Hz. [g] Triplet, J = 1.2 Hz. [h] Anisochronous. Based upon variable temperature studies of **27** (unpublished results), the upfield methoxy resonance is assigned the "endo" position (within the dihedral angle formed by the aryl planes) carbomethoxy group. [i] Assignments may be exchanged. [j] Chemical shifts differ only very slightly and are indistinguishable at 60 MHz (deuteriochloroform, 34°). [k] Signals slightly broadened.

Table 5

^{1}H-NMR Spectra of Alkylidenethioxanthenes [a]



Compound	R, δ	R′, δ	Z_1, δ	Z_2, δ	Z_4, δ	Ar-H
7	H, 5.33	H, 5.33	H	H	H	7.1-7.4
8	H, 5.95 [b]	CH_3, 1.94 [c]	H	H	H	7.1-7.4
9	H, 5.82 [d]	CH_2, 2.38 [e] CH_3, 1.04 [f]	H	H	H	7.1-7.4
10	CH_3, 1.99	CH_3, 1.99	H	H	H	7.1-7.5
11	CH_3, 1.88	CH_3, 1.69	CH_3, 2.40	H	CH_3, 2.30	6.9-7.5
12	CH_3, 1.97 [g]	CH_3, 1.97 [g]	H	CH_3, 2.31	CH_3, 2.40	6.8-7.5
13	CH_3, 1.99	CH_3, 1.97	H	CH_3, 2.32	H	6.8-7.6
14	CH_3, 1.99	CH_3, 2.01	H	Cl	H	7.1-7.5
15	CH_3, 2.00	CH_3, 2.00	H	Br	H	7.0-7.6
16	CH_3, 1.98	CH_3, 2.03	H	OCH_3, 3.78	H	6.7-7.5

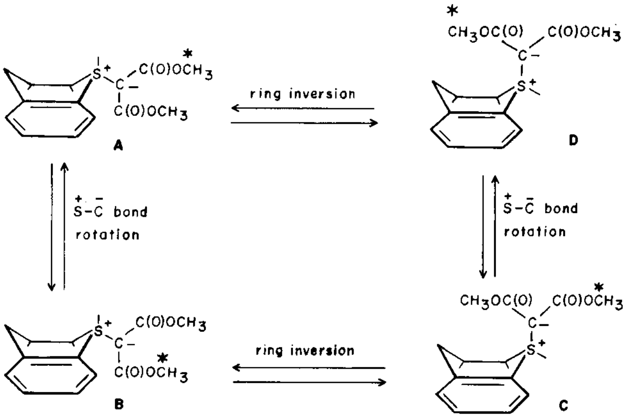
[a] Spectra recorded at 200 MHz in deuteriochloroform at 25°. Chemical shifts, in ppm are reported relative to TMS. All integrations match the assignments shown. [b] Quartet, J = 7.1 Hz. [c] Doublet, J = 7.1 Hz. [d] Triplet, J = 7.4 Hz. [e] Quintet, J = 7.4 Hz. [f] Triplet, J = 7.4 Hz. [g] Unresolvable.

fragment anisochronous. This pattern does not appear to be very sensitive to the C2 substituent [12]. The diastereotopic nature of the two carbomethoxy groups in **20-26** is further supported by the anisochronous C-O resonances occurring at approximately 165 and 168 ppm. The methyl carbons of the carbomethoxy groups appear at approximately 50 and 51 ppm--also anisochronous. Like the other ylides, the methylide carbon resonates at 50-55 ppm. This suggests that all of the ylides in this study have essentially the same conformation, *i.e.*, pseudo-equatorial.

It is possible to group ylides derived from various thioxanthene-like systems into three groups. These groups, of course, represent points along a spectrum of behavior; however, they correspond to the types of behavior of greatest interest to stereochemistry. First, there are molecules such as thioxanthenium bis(carbomethoxy)methylide (**28**), as well as **17-19**, which exhibit rapid rotation around the S^+-C^- bond. Second, there are the thioxanthonium bis(carbomethoxy)methylides (*eg.*, **27**) which show a slowed rotation about the S^+-C^- bond (25°). Finally, there are the 9-isopropylidenethioxanthenium bis(carbomethoxy)methylides (*eg.*, **24**) which exhibit essentially "frozen" S^+-C^- bond rotation under comparable conditions.

Stereochemistry.

Ylides such as **28** have already been shown [3] to prefer the e′ conformation in both the solid state as well as in solution. Variable temperature experiments (−50° to +50°, 200 MHz) on **28** have not indicated any broadening of the OCH_3 resonance which would signal a decrease in the rate of S^+-C^- bond rotation. The equivalence of the methoxy resonances in **29** and in **18-20** can be explained in several different ways. The manifold which encompasses these is shown in Scheme 1.



Scheme 1

Alternate Methods for Producing Equivalence in Methoxy Resonances. Conversion of **A** to **B** by simple bond rotation is disfavored by steric hindrance. The alternate route, **A** → **D** → **C** → **B**, is more likely in systems which can ring invert and which lack bulky a′ substituents at the other *meso* position.

In order to evaluate the alternate pathways in Scheme 1 it is necessary to examine the behavior of ylides such as **25**. In these it is believed that ring inversion is prevented at 25° (200 MHz, nmr time scale). The higher barrier to ring inversion is a result of steric repulsions between the methyl groups of the isopropylidene moiety and the hydrogens at C1 and C8. (Drieding models suggest that in a planar activated complex for ring inversion, the C1, C8 protons and the protons of the methyl groups will approach one another within 0.3 Å.)

The ^{13}C nmr spectra, as already noted, suggest that the molonylide moiety in ylides such as **20** exists in the e′ array. This establishes that in the e′ geometry rotation about the S^+-C^- bond of bis(carboalkoxy)methylides of this variety is severely hindered. The high barrier to rotation in the e′ position undoubtedly results from steric repulsions generated as the planar [13] malonylide fragment attempts to rotate past C4-H and C5-H. Thus systems such as **20**, where the a′ conformation is unattainable because ring inversion is prevented, possess diastereotopic groups bonded to the methylide carbon.

This analysis proves that ylides such as **28**, where the preferred conformation is e′, must undergo facile ring inversion. It is in the less favored a′ conformation that the groups bonded to the methylide carbon become equivalent by bond rotation. These results also demonstrate that ring inversion occurs rapidly in compounds such as **17-19**. In summary, the isochronicity exhibited in these systems results from a combination of ring inversion and bond rotation in the a′ position and suggests that nonequivalence of this type may be an extremely useful probe of rates of ring inversion in sulfur-containing heterocycles.

Rapid rotation occurs easily in the ylide derived from 4,5-dimethyl-9-isopropylidenethioxanthene. This is evidenced by the singlet which is observed for the two methoxylcarbonyl groups in this ylide. Examination of both Dreiding and space-filling (Stuart-Brieglib) models support the view that in this ylide the two methyl groups *peri* to the sulfur force the methylide carbon into the pseudoaxial position--where it is free to rotate rapidly. That this ylide fragment is a′ also is supported by the chemical shift of the carbanionic carbon (67 ppm) falling where we have already demonstrated that a′ carbons occur.

Ylides derived from thioxanthones usually exhibited an intermediate rate of rotation about the S^+-C^- bond. Thus, at 60 MHz (34°) the ^1H nmr of the methoxy region of **27** consists of an extremely broadened singlet [11]. If the temperature is lowered (or the operating frequency raised to 200 MHz) then this becomes two singlets. This intermediate behavior is explained by a difference in the dihedral angle ("angle of fold") of systems such as **27** compared to the other under discussion [14]. As the central ring approaches planarity the differences between the a′ and e′ positions disappears. Indeed, in a completely planar system the distinction between a′ and e′ should not exist (discounting distortions, and so forth). As these folded rings become more planar the e′ position moves away from C4-H, C5-H while the a′ position moves toward them. (Simplistically, the a′ position is becoming more e′ and *vice versa.*) In the more planar thioxanthonium bis(carbomethoxy)-methylides (*eg.*, **27**) the malonylide fragment is moved somewhat away from C4-H, C5-H (compared to **20** or **28**) and, as a result, can rotate more freely about the S$^+$-C$^-$ bond than in **20** (or the e′ conformation of **28**). Undoubtedly ring inversion in **27** is quite rapid. However, inversion in **28** does not move the methylide carbon to the "traditional" a′ position found in the more folded systems (*eg.*, **29**). Rather, ring inversion in **27** moves the methylide carbon from one rather hindered environment to another. The net result is a slower rate of S$^+$-C$^-$ bond rotation.

These data force us to conclude, therefore, that: (a) ring inversion is comparatively rapid in simple, unhindered ylides derived from thioxanthene; (b) S$^+$-C$^-$ bond rotation occurs freely in the a′ conformation of ylides such as **28**; (c) ylides such as **20** are not undergoing rapid ring inversion; (d) ylides such as **17** are undergoing rapid ring inversion. It is suggested that sulfides such as **7-9**, like **1** and **4**, also undergo rapid ring inversion but that sulfides such as **15** exist an enantiomerically-stable species in solution.

Our earlier efforts have shown a striking similarity in the stereochemistry of related sulfoxides and sulfonium ylides in these types of heterocycles [15]. Based upon these similarities and the results presented in this report, it seems clear that thianthrene monosulfoxide (**29**) [3b], phenoxathiin sulfoxide (**30**) [16], the isomeric disulfoxides of thianthrene (**31**) [17] and phenothiazine sulfoxide (**32**) [18] all undergo rapid ring inversion in solution.

Since the rings with 9-isopropylidene substituents are not ring inverting rapidly, the conformation (a′ *vs* e′) of the sulfonium ylides will be kinetically controlled. (The products are, we believe, also thermodynamically favored.)

These results demonstrate that, at least in the systems under discussion, the e′ electron pair on sulfur is more reactive towards carbenes than is the a′ electron pair. This suggests that an electronic effect rather than a steric effect is important in controlling the relative rates of nucleophilicity of these diastereotopic electron pairs. A simple "steric hindrance" argument would have favored attack at the a′ position due to hindrance of the e′ pair by C4-H and C5-H. Interactions between the a′ electron pair and the aryl pi cloud may reduce the relative reactivity of the a′ pair.

There is an alternate explanation, one which has a certain appeal to these authors. The e′ electron pair is much more hindered than is the a′ pair. It is suggested that the *apparent* greater reactivity of the e′ pair may be simply "apparent". The ylides are made by decomposing dimethyl diazomalonate in the presence of anhydrous copper(II) sulfate. If the copper coordinates to the (perhaps) more reactive a′ electron pair then this leaves only the e′ pair for trapping by the carbenoid. In this manner, the less reactive electron pair on sulfur could lead to the observed final product. We are currently attempting to determine whether the directing of the ylide fragment to the e′ position is due to prior coordination of the a′ electron pair.

EXPERIMENTAL [19]

Thioxanthones.

All thioxanthones corresponding to alkylidenes described below have been described in the literature [6,20].

9-Alkylidenethioxanthenes--Unsubstituted Aryl Rings.

All of the alkenes were prepared by the following generalized route. Specific yields (isolated) are included in Table 1. Magnesium (1.2 g, 0.05 g-atom) was suspended in 20 ml of anhydrous ether and a crystal of iodine added. The appropriate alkyl halide (either bromide or iodide, 0.060 *M*) was added dropwise over about 10 minutes. After addition was complete the reaction mixture was refluxed for 15 minutes and then cooled to room temperature.

Table 6

		Analyses %			
		Calcd.		Found	
Compound	Formula	C	H	C	H
10	$C_{16}H_{14}S$	80.63	5.92	80.13	5.90
11	$C_{18}H_{18}S$	81.15	6.81	81.09	6.48
12	$C_{18}H_{18}S$	81.15	6.81	81.40	7.16
13	$C_{17}H_{16}S$	80.90	6.39	80.55	6.01
14	$C_{16}H_{13}ClS$	70.45	4.80	70.85	4.80
15	$C_{16}H_{13}BrS$	60.57	4.13	60.49	4.05
16	$C_{17}H_{16}OS$	76.08	6.01	76.15	5.94
17	$C_{19}H_{16}O_4S$	67.04	4.74	66.93	4.50
18	$C_{20}H_{18}O_4S$	67.78	5.12	67.84	5.25
19	$C_{21}H_{20}O_4S$	68.46	5.47	68.46	5.40
20	$C_{21}H_{20}O_4S$	68.46	5.47	68.22	5.21
21	$C_{23}H_{24}O_4S$	69.67	6.10	69.28	6.00
22	$C_{23}H_{24}O_4S$	69.67	6.10	69.91	6.22
23	$C_{22}H_{22}O_4S$	69.08	5.80	68.92	5.66
24	$C_{21}H_{19}ClO_4S$	62.60	4.75	62.45	4.70
25	$C_{21}H_{19}BrO_4S$	56.38	4.28	56.70	4.51
26	$C_{22}H_{22}O_5S$	66.31	5.67	66.35	5.99

To the resulting Grignard reagent there was added, dropwise and with stirring, 0.024 mole of the appropriate thioxanthone dissolved (or suspended) in 40 ml of ether. Addition was carried out at 0-5° (ice bath). After addition, the reaction mixture was refluxed for 3 hours and then cooled to 0-5°. A saturated solution of ammonium chloride was added until the *p*H was 6-7. The resulting organic layer was washed with water (15 ml), dried (magnesium sulfate) and the solvent removed under reduced pressure to afford an oil [21]. This oil was dissolved in methanol (approximately 40 ml) and the solution cooled in an ice bath (0-5°). To this was added, dropwise, 5 ml of concentrated sulfuric acid. The resulting reaction mixture was refluxed for 30 minutes, diluted with water (40 ml), neutralized with 10% aqueous sodium hydroxide and then extracted with chloroform (3 × 25 ml). The extract was dried (magnesium sulfate) and the solvent removed under reduced pressure to afford the desired alkene.

Sulfides were shown to be homogeneous by tlc and had nmr spectra (proton and carbon) consistent with the assigned structures.

9-Alkylidenethioxanthenes--Substituted Aryl Rings.

All of the compounds shown in Table 2 were prepared by this same general route.

Isopropylmagnesium bromide was prepared by reacting 2-bromopropane (0.060 mole) with magnesium turnings (0.050 g-atom) in 20 ml of freshly distilled butyl ether at 65-70°. Addition required approximately 0.5 hour. The resulting Grignard reagent was diluted with an additional 20 ml of butyl ether. After cooling in an ice bath (0-5°), the appropriate thioxanthone was added, in small portions, over ten minutes. Following this addition, the reaction mixture was heated for 7 hours at 100-105°.

The reaction mixture then was treated, in an ice bath, with saturated aqueous ammonium chloride until the pH went below 7.

The organic layer was separated, washed with water (2 × 10 ml) and then concentrated under reduced pressure. The resulting residue [21] was dissolved in ethyl ether (40 ml) and, upon cooling to 0-5°, was treated, dropwise, with 4 ml of concentrated sulfuric acid [22]. The reaction mixture was then refluxed for 0.5 hour and then cooled to 0-5°. To this there then was added 30 ml water and sufficient 10% aqueous sodium hydroxide to bring the solution to pH 8. The ethereal solution was separated, washed with water (2 × 10 ml), dried (magnesium sulfate) and the solvent removed under reduced pressure. This work up sometimes yielded an oil and sometimes a solid. In either instance the crude product was recrystallized from 95% ethanol. Specific yields and melting points of products are contained in Table 2. Products had nmr (proton and carbon) spectra consistent with the assigned structures.

9-Alkylidenethioxanthenium bis(Carbomethoxy)methylides.

All of the compounds shown in Table 3 were prepared by the same general route.

The appropriate alkene (0.010 mole), dimethyl diazomalonate (1.6 g, 0.010 mole), anhydrous copper(II) sulfate (100 mg) and toluene (20 ml) were mixed together and stirred, for 3-4 hours at 85-102° (see Table 3). The reaction was, in general, continued until bubbles of nitrogen no longer were produced. The reaction mixture was filtered while still hot to remove copper(II) sulfate and other impurities [23]. When reaction mixtures containing **17-21** were cooled to room temperature they deposited crystals of the desired ylides. Reaction mixtures containing **22-25** afforded a light yellow oil after the solvent was removed under reduced pressure. These oils were crystallized using 95% ethanol (and were also crystallizable from 1:1 benzene-hexane mixtures) [24]. Evaporation of the toluene afforded solid **26** which was recrystallized from a 1:1 benzene-hexane mixture.

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REFERENCES AND NOTES

[1] Unpublished results.

[2a] There is no evidence extant in the literature to suggest that these parent heterocycles have high barriers to ring inversion. Moreover, 2-chlorothioxanthone has been shown to have geometry which is nearly planar: S. S. C. Chu and H. T. Yang, *Acta Cryst.*, **B32**, 2248 (1976); [b] A. K. Chandra, *Tetrahedron,* **19**, 471 (1963); P. T. Lansbury, *Acc. Chem. Res.*, **2**, 210 (1969); D. M. Wieland and C. G. McCarty, *J. Org. Chem.*, **37**, 4285 (1972).

[3] See, for example, [a] M. A. Abbady, S. Askari, M. Morgan, A. L. Ternay, Jr., J. Galloy and W. H. Watson, *J. Heterocyclic Chem.*, **19**, 1473 (1982); [b] A. L. Ternay, Jr. J. C. Baack, S. S. C. Chu, V. Napoleone, G. Martin and C. Alfaro, *J. Heterocyclic Chem.*, **19**, 833 (1982); [c] A. L. Ternay, Jr. D. Craig and H. R. O'Neal, *J. Org. Chem.*, **45**, 1520 (1980); [d] J. Galloy, W. H. Watson, D. Craig, C. Guidry, M. Morgan, R. McKellar, A. L. Ternay, Jr. and G. Martin, *J. Heterocyclic Chem.*, **20**, 399 (1983).

[4] See, for example, C. Kaiser and P. E. Setler, "Antipsychotic Agents", In Burger's Medicinal Chemistry, 4th Edition, Part III, M. E. Wolff, ed, J. Wiley and Sons, New York, 1981, esp. pp 871-952. See, also, D. M. Gallant and M. P. Bishop in "Psychopharmacology", D. H. Efon, ed, Public Health Service Pub. No. 1836, 1968.

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[6] In addition to citations in ref [3], and references contained therein, see also, [a] W. G. Prescott and S. Smiles, *J. Chem. Soc.*, **99**, 645 (1911) [7]; [b] V. G. Kharchenko, T. I. Krupina and A. F. Blinokhvatov, "Thioxanthenes, Hydrothioxanthene and Their Derivatives", Saratova University Press, 1979.

[7] We observed that using 85% sulfuric acid, rather than the concentrated acid employed by Smiles, improved the yield of 2-methoxythioxanthone produced from the reaction of thiosalicyclic acid with anisole. It is suggested that sulfonation accompanies the use of concentrated acid and reduces the overall yield.

[8] Attempts to isolate the intermediate alcohols were generally unsuccessful since they often were accompanied by varying amounts of alkene. Alcohols sometimes appeared to dehydrate, at least partially, during the work up of the Grignard reaction.

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[10] Y. Tamura, Y. Takebe, C. Mukai and M. Okeda, *J. Org. Chem.*, **45**, 2970 (1980).

[11] A. L. Ternay, Jr. M. A. Abbady, G. E. Martin, W. H. Watson and J. Galloy, *Chem. Commun.*, 846 (1980). At 200 MHz these compounds must be heated to approximately 50-60° in order to observe a sharp singlet. However, the chemical shift of the singlet is essentially at the center of the diastereotopic methoxyl signals as they appear at 25° (200 MHz).

[12] One interesting, and as yet unexplained, variation is the behavior of **23**, where the two methoxy proton resonances are somewhat closer than in related systems (*eg.*, **20**).

[13] The malonylide fragment has been shown to be essentially planar in all single crystal X-ray analyses of these systems [3]. This stems from the delocalization of the electron pair of the methylide carbon on to the carbomethoxy carbonyl groups. Whether planar or not, this group sweeps through a large volume during rotation about the S^+-C^- bond.

[14] Both thioxanthone and 2-chlorothioxanthone are nearly planar [2]. The angle of fold in **27** is 168.4° while that in 2-chlorothioxanthonium bis(carbomethoxy)methylide is 173.5° [3d].

[15] A. L. Ternay, Jr., in "IUPAC Organic Sulfur Chemistry", R. Kh. Freidlina and A. E. Skorova, eds, Pergamon Press, New York, 1981.

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[18] Phenothiazine sulfoxide exists, preferentially, in the a' conformation both in the solid state and in solution (manuscript in preparation).

[19] Melting points are uncorrected. 60 MHz ^{1}H nmr Spectra were recorded on a Varian Model T-60 and a Varian Model EM-360L. ^{1}H and ^{13}C nmr Spectra were obtained using an NT-200 wide-bore spectrometer operating at 25°. All nmr spectra were recorded in chloroform-d using internal TMS as a chemical shift standard. Melting points of known compounds agreed with values reported in the literature [6]. All new compounds gave satisfactory elemental analyses (C and H) and these are collected in Table 6.

[20] Our impression is that, all other things being equal, the condensation of thiosalicyclic acid and with a monosubstituted benzene in the presence of concentrated sulfuric acid is not the method of choice for these syntheses. This stems from the long times required for work up as much as from the presence of minor amounts (usually < 10%) of C4-substituted thioxanthone produced during the condensation.

[21] Infrared and proton nmr spectra revealed that these oils contained varying amounts of alkene as well as alcohol. In general, attempts to isolate alcohol free of alkene proved to be difficult and were ultimately abandoned in favor of direct dehydration.

[22] Attempted dehydration of this series using methanol/sulfuric acid led to significant amounts of etherification (equivalent to methanol adding to the alkene) and was rejected for routine use. Dehydration using phosphorus pentoxide suspended in benzene provided an alternate scuccessful route to alkene *via* dehydration. However, convenience of work up and so forth, led to the use of sulfuric acid.

[23] Small amounts of relatively insoluble, polymeric (?) materials were removed in this manner. If reaction mixtures were allowed to cool substantially, then they tended to deposit the desired ylides before the copper(II) sulfate could be removed.

[24] These oils were often noted to solidify on standing.