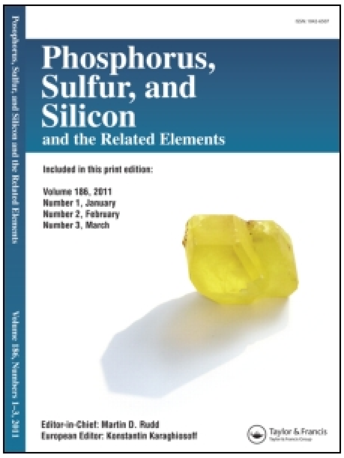

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CONFORMATIONAL PREFERENCES AND RESTRICTED RING INVERSION IN THIANTHRENIUM YLIDES

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CONFORMATIONAL PREFERENCES AND RESTRICTED RING INVERSION IN THIANTHRENIUM YLIDES

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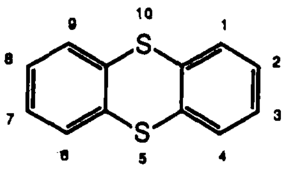
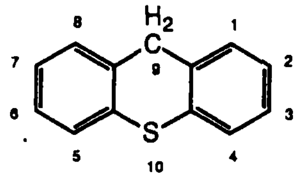
Thianthrene reacts with dialkyl diazomalonates to form, depending upon stoichiometry, both mono- and diylides. The monoylide exists perferentially in the pseudo-equatorial geometry but undergoes ring inversion at room temperature. The trans-diylide, unlike trans-thianthrene disulfoxide, does not undergo rapid ring inversion at room temperature. VT NMR indicates a barrier of 19 kcal/mole.

INTRODUCTION

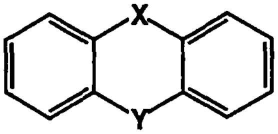
Since thianthrene, **1**, 9,10-dihydroanthracene, **2**, phenothiazine, **3**, thioxanthene, **4**, and similar systems, are folded about an imaginary line containing their two central atoms, substituents bonded to these "meso" atoms occupy either pseudo-axial (a′) or pseudo-equatorial (e′) positions. While central ring inversion[1] is relatively free in parent systems,[2] it may be inhibited by, for example, incorporating an exocyclic double bond at a meso carbon atom of thioxanthene (or similar structure)[3] or using a "peri" substituent (C1—CH_3 in 1,4,9-trimethylthioxanthene) to maintain the proximal C9 substituent (C9—CH_3) in the a′ position.[4]



thianthrene



thioxanthene



compound	X	Y
1	S	S
2	CH_2	CH_2
3	NH	S
4	CH_2	S
5	CH_2	S(O)
6	S	S-$C(CO_2C_2H_5)_2$
7	S	S(O)
8	S(O)	S(O)
9	S-$C(CO_2C_2H_5)_2$	S-$C(CO_2C_2H_5)_2$
10	S-$C(CO_2CH_3)_2$	S-$C(CO_2CH_3)_2$

Thioxanthene sulfoxide, **5**, exists preferentially in the e′ array but, like thioxanthene, undergoes facile ring inversion.[5,6] The present manuscript describes the previously unreported restricted ring inversion in an S,S′-disubstituted thianthrene whose corresponding S-monosubstituted analog undergoes rapid ring inversion at room temperature.

RESULTS AND DISCUSSION

Using thioxanthenium sulfonium ylides, we have demonstrated that when restricted ring inversion prevents an e′ malonylide fragment from occupying the a′ position, rotation about the $S^+—C^-$ bond is inhibited and its two carboalkoxy groups become diastereotopic. We now observe that thianthrenium bis(carboethoxy)methylide (**6**), while having a methylide carbon whose chemical shift (49.95 ppm)[7] is consistent[8] with an e′ geometry, does not possess disastereotopic alkoxycarbonyl groups. Therefore, thianthrenium bis(carboethoxy)methylide must (a) prefer the e′ geometry, (b) undergo rapid ring inversion at room temperature and (c) experience rapid $S^+—C^-$ bond rotation in the a′ array.[9,10]

Like thianthrenium bis(carboethoxy)methylide, thianthrene monosulfoxide (**7**) exhibits six carbon resonances whose chemical shifts are rather independent of temperature.[11] Furthermore, variations[12] in the conditions used to oxidize thianthrene to its monoxide have failed to produce a "second" monoxide. Therefore, we conclude that the monosulfoxide of thianthrene, like the monoylide, undergoes rapid ring inversion at room temperature. cis-Thianthrene disulfoxide, **cis-8**, is reported to exist in the e′, e′ array.[13] Its ^{13}C nmr spectrum contains three signals (138 (quat), 131 and 124 ppm) and we believe that, like thianthrene monosulfoxide, it undergoes rapid ring inversion.[14] Since trans-thianthrene disulfoxide, **trans-8**, also exhibits only three ^{13}C resonances (143 (quat), 131 and 128 ppm) it also must undergo rapid ring inversion.

In addition to the above, we now report the preparation, configuration and conformation of trans-thianthrenium di(bis(carboethoxy)methylide), **trans-9**. To our knowledge, this is the first observation of restricted central-ring inversion in any 6,6,6-system[15] where substituents are present only at the meso position and where the *mono*substituted analog undergoes rapid ring inversion. It also is unusual to encounter a system where the sulfoxide and sulfonium ylide behave so differently.

Our assignment of configuration to this diylide[16] is based upon its exhibiting *six* distinct ^{13}C aryl resonances, consistent only with a noninverting, trans geometry. Furthermore, the existence of two distinctly different methylide carbon resonances (66.0 and 48.3 ppm) is inconsistent with either (a) a cis diylide or (b) a rapidly ring inverting trans diylide. Based upon our studies in the thioxanthene system, the resonance at 66.0 ppm is assigned to the a′ malonylide fragment and the 48.3 ppm signal to the e′ fragment. The appearance of the ethoxy region in the ^1H nmr spectrum ($CDCl_3$) confirms both the assigned stereochemistry *and* the presence of restricted ring inversion. The ethoxy region contains *three* sets of methylene quartets: 4.32 ppm (2H); 3.87 ppm (2H); and 4.11 ppm (4H). Furthermore, three sets of methyl triplets are present: 1.36 ppm (3H); 0.78 ppm (3H); 1.19 ppm (6H). Decoupling and two-dimensional (COSY) experiments indicate that the signals at

0.78 and 3.87 ppm represent one ethyl group and those at 1.36 and 4.32 ppm represent another. These are assigned to the e′ malonylide fragment since, being locked in this position, they cannot exchange. The remaining methyl and methylene signals correspond to the two a′ ethyl groups which are exchanging rapidly by rotation about the $S^+—C^-$ bond.

In order to establish that the ethyl derivative was not unique, trans-thianthrenium di(bis(carbomethoxy)methylide), **trans-10**, has been prepared. It behaves similarly, exhibiting six aryl ^{13}C signals.

The magnitude of the barrier to ring inversion was determined by conducting a VT proton nmr study of trans-thianthrenium 5,10-di(bis(carboethoxy)methylide) over the range +25°C to + 140°C[17] in DMSO-d_6. At 25°C the aliphatic region exhibits three well-defined triplets and three well-defined quartets. Coalescence occurs at approximately 129°C.[18] When the sample was cooled to +25°C the original spectrum was obtained, indicating the absence of significant decomposition or isomerization. Using the Eyring equation[19] leads to a calculated energy of activation of 19 kcal/mol.

While the details of the origin of the barrier to ring inversion are not fully understood, we believe that at least two factors contribute to this unusual situation. One involves an attractive interaction between a carbonyl oxygen of the a′ malonylide fragment and the positively charged sulfur at the other meso position. A second factor is entropic, related to the need to orient both (planar) malonylide fragments in a common plane (which also contains the imaginary line containing the two sulfur atoms) in order for ring inversion to occur.

EXPERIMENTAL

Thianthrenium Bis(carboethoxy)methylide (7)[20]: Into a 100 ml flask there was placed 4.50 g (208 mmol) of thianthrene, 150 mg (0.940 mmol) of anhydrous copper sulfate and 22 ml of toluene. After being heated to 90–95°C, a mixture of 8 ml of anyhdrous toluene and 4.1 g (21 mmol) of diethyl diazomalonate were added over 40 min. The temperature then was raised to 105–108°C and maintained there for 3 h. Hot chloroform (70 ml) then was added and the mixture filtered (hot) through Celite. The Celite pad was washed with hot chloroform (30 ml), the wash combined with the original filtrate, the chloroform removed, hexane (50 ml) added and the resulting mixture filtered. The resulting solid was washed with hexane and recrystallized (benzene-chloroform, 1/1) to afford 6.82 g (18.2 mmol, 87.5%) of thianthrenium bis(carboethoxy)methylide, mp 218–220°C.

The MS[21] showed major peaks at 375.0 (M+1, 15), 373.9 (27), 330.0 (20), 329.0 (100), 302.0 (13), 301.0 (36), 273.3 (17), 228.9 (13), 218.0 (15), 217.0 (16), 216.0 (69), 196.9 (13), 184.1 (33) and 161.7 (13). The IR (KBr) showed absorptions at 1689, 1650, 1440, 1370, 1314, 1292, 1230 and 1069 cm^{-1}. The ^{1}H NMR showed resonances at δ 7.62 (m, 4H), 7.46 (m, 4H), 4.10 (q, J = 7.0 Hz, 4H) and 1.10 (t, J = 7.0 Hz, 6H). The ^{13}C NMR exhibited resonances at δ 165.8 (quat), 130.4, 130.2, 129.1, 128.2, 126.1, 59.7, 49.9 (quat) and 14.48.

Anal. Calcd. for $C_{19}H_{18}O_4S_2$: C, 60.94; H, 4.85. Found: C, 61.01; H, 4.56.

Trans-Thianthrenium 5,10-Di(bis(carboethoxy)methylide) (**trans-9**): Into a 50 ml flask there was placed 1.50 g (7.00 mmol) of thianthrene, 50.0 mg (0.313 mmol) of anhydrous copper sulfate and 7.5 ml of anhydrous toluene. After being heated to 95°C, a solution of 2.50 g (0.0160 mol) of diethyl diazomalonate in 2.5 mL of anhydrous toluene was added over 8 min. The mixture then was heated to 110°C and maintained there for 3 h.[22] Upon cooling to room temperature the resulting solid was removed and washed sequentially with 5 ml of toluene and of hexane. The solid then was "dissolved" in 30 ml of chloroform and the turbid suspension filtered through Celite. Concentration of the filtrate yielded a solid (3.00 g) whose TLC showed two spots.

A flash column[23] was used to separate 0.700 g of the mixture. The first fraction (2 L) afforded 230 mg (0.615 mmol, 8.78%) of monoylide, mp 215–217°C. The second fraction (eluent chloroform-methanol [95/5, v/v]; 900 ml) ultimately afforded 420 mg (0.788 mmol, 11.3%) of *trans*-thianthrenium 5,10-

di(bis(carboethoxy)methylide) as a white solid, mp 203–205°C. The sample was homogeneous on HPLC.[24]

The MS showed major peaks at 533 (M + 1, 48), 487 (30), 403 (18), 375 (70), 343 (18) and 329 (100). The IR (KBr) contained absorptions at 1697, 1646, 1368, 1311, 1283, 1231, 1167, 1078 and 1018 cm^{-1}. The ^{1}H NMR contained resonances at δ 7.87 (m, 4H), 7.66 (m, 4H), 4.32 (q, J = 7.2 Hz, 2H), 4.11 (q, J = 7.2 Hz, 4H), 3.87 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 6H), 0.78 (t, J = 7.2 Hz, 3H). The ^{13}C NMR contained resonances at δ 166.8 (quat), 165.9 (quat), 163.1 (quat), 131.9, 131.6 (quat), 131.2, 129.1, 126.6 (quat), 126.2, 66.0 (quat), 60.5, 60.0, 59.6, 48.3 (quat), 14.6, 14.5, and 13.9.

Anal. Calcd. for $C_{26}H_{28}O_8S_2$: C, 58.63; H, 5.30; S, 12.04. Found: C, 58.62; H, 5.39; S, 11.97.

Trans-Thianthrenium 5,10-Di(bis(carbomethoxy)methylide) (**trans 10**): Into a 100 ml flask there was placed thianthrene (3.0 g, 1.4 mmol), anhydrous copper sulfate powder (225 mg, 1.4 mmol) and anhydrous toluene (22 ml). After being heated to 95°C, 5.5 g (35 mmol) of dimethyl diazomalonate dissolved in 4 ml of anhydrous toluene was added over 6 min. Following 3.5 h of reflux, the mixture was cooled to room temperature and the resulting solid separated, washed with hexane (230 ml), and then suspended in water (120 ml). The washed solid was dried *in vacuo* to afford 4.7 g of a white solid, mp 231–232°C, whose TLC[25] showed two spots. Recrystallization from methylene chloride yielded 4.5 g (9.4 mmol, 67%) of *trans*-thianthrenium 5,10-du(bis(carbomethoxy)methylide), mp 239–240°C, which was homogeneous on TLC.

The MS exhibited major peaks at 477.0 (M + 1, 14), 445.0 (16), 357.0 (35), 356.1 (14), 353.1 (14), 326.1 (19), 325.0 (100), 324.1 (21), 315.0 (18), 216.0 (18), 101.0 (11), 85.0 (35) and 83.0 (53). The IR (KBr) showed absorptions at 1719, 1690, 1625, 1435, 1331, 1241, 1091 and 1076 cm^{-1}. The ^{1}H NMR exhibited resonances at δ 7.85 (m, 4H), 7.65 (m, 4H), 3.83 (s, 3H), 3.67 (s, 6H) and 3.46 (s, 3H). The ^{13}C NMR showed resonances at δ 166.9 (quat), 166.3 (quat), 163.9 (quat), 132.0, 131.5, 131.2 (quat), 129.0, 126.1 (quat), 126.0, 65.6 (quat), 51.6, 51.5, 51.3 and 48.7.

ACKNOWLEDGEMENT

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FOOTNOTES AND REFERENCES

1. A boat-to-boat interconversion.
2. In these unsubstituted systems ring inversion does not require bonds to pass by one another. Thus, bond angle distortions are assumed to be the significant contributors to the barriers. For example, we have been unable to significantly reduce the rate of ring inversion of thioxanthene even at −100°C, as studied by variable temperature nmr; unpublished results.
3. M. Kluba, J. Harwood, P. K. Casey and A. L. Ternay, Jr., *J. Heterocyclic Chem.*, **22**, 1261 (1985), and references cited therein.
4. A. L. Ternay, Jr. and S. A. Evans, *J. Org. Chem.*, **39**, 2941 (1974).
5. Its preferred conformation can be altered to a′ by hydrogen bonding: A. L. Ternay, Jr., J. Herrmann, B. A. Hayes and P. Joseph-Nathan, *J. Org. Chem.*, **45**, 189 (1980).
6. Substitution peri to sulfur can force substituents bonded to sulfur into the a′ array and inhibit ring inversion: A. L. Ternay, Jr., L. Ens, J. Herrmann and S. Evans, *J. Org. Chem.*, **34**, 940 (1969).
7. Deuteriochloroform; 25°C.
8. Typically e′ methylide carbons resonate near 50 ppm while a′ counterparts are found near 70 ppm: 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), and references cited therein.
9. Additionally, the proton and ^{13}C nmr spectra of thianthrenium bis(carboethoxy)methylide are rather independent of temperature over the range from −25 to +100°C, further supporting a rather rapid ring inversion at room temperature.
10. Thianthrenium bis(carboethoxy)methylide is e′ in the solid state: A. L. Ternay, Jr., J. C. Baack, S. S. C. Chu, V. Napoleone, G. Martin and C. Alfaro, *J. Heterocyclic Chem.*, **19**, 833 (1982).
11. Probe temperature range −10 to +60°C.
12. Oxidants include (a) dinitrogen tetroxide (0°C); (b) m-chloroperoxybenzoic acid (−20 to +25°C); (c) ceric ammonium nitrate; and (d) hydrogen peroxide/acetic acid.
13. For a presentation of X-ray results see (a) S. Hosoya and R. G. Wood, *Chem. and Ind.*, 1042 (1957); (b) S. Hosoya, *ibid.*, 159 (1958).

14. This view stems from the rather minor effects of temperature change upon the nmr spectrum (−20°C to +120°C).
15. Derivatives of such heterocycles are important in psychopharmacology and often are cataloged by the number of atoms in their fused ring systems.
16. Our syntheses have inevitably produced the trans diylide in *very* large excess. However, we have a preliminary single crystal X-ray analysis of the corresponding cis-diylide (unpublished results) which shows that this isomer is e',e' (like the corresponding disulfoxide) and not a',a'.
17. This represents the upper operating limit of the spectrometer.
18. The VT experiment was done in duplicate and results were reproducible within 1°C. Copies of these spectra are available upon request.
19. Oki, M. in *Applications of Dynamic NMR Spectroscopy to Organic Chemistry,* VCH: Florida, 1985, p. 407. Tc was taken as 402 K and ν_{max} as 115 Hz (the difference between the center peaks of the more downfield (1.17 ppm) and more upfield (0.60 ppm) triplets at 25°C in DMSO-d_6.
20. Melting points are uncorrected. IR spectra were obtained on a BIO-RAD FTS-40 FTIR spectrometer over a range of 4000–400 cm^{-1}. Mass spectra were obtained on a Finnigan MAT TSQ 70 spectrometer operating in the chemical ionization (CI) mode using methane gas. Spectra were obtained using either a gas chromatography (GC) inlet or a solid probe (SP). NMR spectra were acquired using a Nicolet NT-200 spectrometer operating at approximately 200.067 MHz for ^1H and 50.31 MHz for ^{13}C observation. All non-VT spectra were acquired using a 12 mm probe operating at 25 ± 1°C employing 100–300 mg of compound/3 ml of $CDCl_3$. Typical 90° pulses for ^1H and ^{13}C were 38 and 21.5 μs, respectively. Chemical shifts are reported relative to tetramethylsilane, using either the protiochloroform signal set to 7.26 ppm as internal reference for proton, or the center peak of the deuteriochloroform signal set to 77.00 ppm as internal reference for ^{13}C spectra.
21. m/z (relative intensity).
22. Bubbles of gas (presumed to be nitrogen) evolved during the course of heating. A white precipitate was observed after heating at 110°C for 15 min.
23. The flash column (4.5 cm) was packed with 90 g of 200–235 mesh silica gel using chloroform.
24. Separation was achieved with a Varian Model 5000 and the following: Alltech C8 column; methanol eluent; solvent flow rate: 1.0 and 0.5 mL/min; λ max: 254 nm; recorder: 1 au/mv; chart speed: 2 cm/min; chart input: 10 mv.
25. 4" Silica plate; (acetonitrile/methylene chlorida, 5/95) eluent; UV visualization; Rf 0.28 (minor) and 0.13 (major).