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Synthesis, Stereochemistry, and Rearrangement of *N*-Tosylsulfilimines and (Bismethoxycarbonyl)methylides of 1,4-Dimethylthioxanthene and Its 9-Alkyl Derivatives

YASUMITSU TAMURA,* CHISATO MUKAI, and MASAZUMI IKEDA

Faculty of Pharmaceutical Sciences, Osaka University, 1-6,
Yamada-oka, Suita, Osaka 565, Japan

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The *N*-tosylsulfilimines and (bismethoxycarbonyl)methylides of 1,4-dimethylthioxanthene and its 9-alkyl derivatives were synthesized, and their stereochemistry was assigned on the basis of nuclear magnetic resonance spectral comparison with the corresponding 2,4-dimethylthioxanthene derivatives. Treatment of 1,4-dimethylthioxanthene *N*-tosylsulfilimine and 1,4-dimethylthioxanthene (bismethoxycarbonyl)methylide with base gave the rearranged products, 9-tosylamino- and 9-(bismethoxycarbonyl)methyl-1,4-dimethylthioxanthenes, respectively, but the 9-alkyl derivatives did not undergo this rearrangement.

Keywords—chloramine-T; *O*-mesitylenesulfonylhydroxylamine; thioxanthene *N*-tosylsulfilimine; sulfilimine; thioxanthene (bismethoxycarbonyl)methylide; ylide; stereochemistry; rearrangement

The chemistry of thioxanthene derivatives has attracted particular attention, because it provides an opportunity to explore the unique stereochemical problem of a six-membered ring held in a boat conformation. A variety of derivatives including sulfoxides (1),^{1,2} *N*-tosylsulfilimines (2),³ and sulfonium methylides (3)^{4,5} has been investigated. Among them, 2 and 3 have been shown to undergo a base-promoted rearrangement to 9-tosylamino- and 9-(bismethoxycarbonyl)methyl-thioxanthenes, 4 and 5, by way of a mechanism which involves thioxanthylum ions (6).³ The rate of the rearrangement is markedly influenced by the stereochemistry of the starting ylides as well as by the steric bulk of the 9-alkyl group. We have now prepared the *N*-tosylsulfilimines and (bismethoxycarbonyl)methylides of 1,4-dimethylthioxanthene and its 9-alkyl derivatives, in order to see how the steric crowding affects the stereochemistry and rearrangement of these thioxanthene derivatives.

Synthesis

The synthetic routes to the 1,4-dimethylthioxanthene derivatives **8a—c** and **12a—c** are illustrated in Chart 2. 1,4-Dimethylthioxanthene *N*-tosylsulfilimine (**8a**) was prepared in 38% yield by the reaction of **7a** with chloramine-T. This reaction was accompanied by the formation of **9** (40%).^{3a)} When **7b** and **7c** were treated with chloramine-T, only a complex mixture was obtained. The sulfilimines **8b, c** were prepared by a two-step procedure involving tosylation of the corresponding *S*-amine salts **10** and **11**, which in turn were synthesized by the reaction of **7b, c** with *O*-mesitylenesulfonylhydroxylamine (MSH).^{3b)} This procedure gave

Chart 1

TABLE I. NMR Data for the *N*-Tosylsulfilimines and (Bismethoxycarbonyl)-methylides derived from 1,4-Dimethylthioxanthene and Its 9-Alkyl Derivatives

Compd.	X	R	Preferred conformn.	H-9	9-R
8a	NTs	H	ax-X	4.10 4.58 ^{a)} (ABq)	—
15a	NTs	H	ax-X	3.86 4.80 ^{a)} (ABq)	—
8b	NTs	Me	D	4.34 (q)	1.88 (3, d)
<i>cis</i> - 15b	NTs	Me	D	4.15 (q)	1.89 (3, d)
<i>trans</i> - 15b ^{b)}	NTs	Me	B	5.14 (q)	1.81 (3, d)
8c	NTs	Et	D	4.00 (dd)	2.25 (2, quintet) 0.98 (3, t)
<i>cis</i> - 15c	NTs	Et	D	3.78 (t)	2.35 (2, quintet) 0.98 (3, t)
<i>trans</i> - 15c	NTs	Et	B	4.51 (t)	2.02 (2, quintet) 1.00 (3, t)
12a	C (CO ₂ Me) ₂	H	ax-X	4.00 4.66 ^{a)} (ABq)	—
16a ^{b)}	C (CO ₂ Me) ₂	H	ax-X	3.96 5.03 ^{a)} (ABq)	—
12b ^{b)}	C (CO ₂ Me) ₂	Me	A	4.51 (q)	1.30 (3, d)
<i>cis</i> - 16b	C (CO ₂ Me) ₂	Me	C or D ^{c)}	4.11 (q)	1.99 (3, d)
<i>trans</i> - 16b	C (CO ₂ Me) ₂	Me	A	4.39 (q)	1.39 (3, d)
12c	C (CO ₂ Me) ₂	Et	A	4.38 (t)	1.60 (2, quintet) 0.76 (3, t)
<i>trans</i> - 16c ^{b)}	C (CO ₂ Me) ₂	Et	A	4.13 (t)	1.60 (2, quintet) 0.76 (3, t)

a) Broadened by allylic coupling with C₈-H (and C₁-H).

b) Stereochemistry has been confirmed by an X-ray analysis. [*trans*-**15b**, ref. 13; **16a**, ref. 7; **12b**, ref. 8; *trans*-**16c**, ref. 4b].

c) Probably C.

In principle, the 9-alkylthioxanthene derivatives (*e.g.*, **1**—**3**, R≠H) can exist in four possible configurational and conformational structures, *i.e.*, A—D. The preferred conformations of these derivatives are determined by a combination of the following three factors: (1) the steric interference between the equatorial S⁺—X[−] group and the peri-hydrogens (H-4 and H-5) and/or 4-methyl group (see structures A and C), (2) the steric interference between the equatorial 9-alkyl group and the peri-hydrogens (H-1 and H-8) and/or 1-methyl group (see structures B and C), and (3) the non-bonded interaction between two boat-axial substituents in structure D.

Previous studies indicated that the orders of stability of the sulfoxides and *N*-tosylsulfilimines are very similar, and in the 2,4-dimethylthioxanthene series (**14** and **15**), D>B>A or C when R=Me and Et,^{3d,10)} and D>A>B or C when R=iso-Pr.¹¹⁾ The present work showed that the most stable structure of 1,4-dimethyl-9-alkylthioxanthene *N*-tosylsulfilimines **8b**, **c** is also D: the factors 1 and 2 become very important, making the structures A, B, and C unfavorable.

On the other hand, the most stable structure of the methylides *trans*-**16** (R=Me,^{4b)} Et,^{4b)} iso-Pr¹¹⁾ and **12b**, **c** is always structure A, in which the (bismethoxycarbonyl)methylide group is equatorial, in spite of the fact that unfavorable interaction between this and the 4-methyl group (factor 1) can be expected. Such a preference for the equatorial position of S⁺—C[−]—(CO₂Me)₂ group¹²⁾ has been rationalized by Ternay *et al.*^{5b)}: the axial conformer would be destabilized either by steric interaction between one of the ester group and the axial 9-substituent (see structure E) or by electron-electron repulsion between the sulfur lone pair and the *p*-orbital of the methylide carbon (see structure F). Such interactions are not present in the sulfoxides and *N*-tosylsulfilimines. In addition, the longer bond length of S⁺—C[−] (*ca.* 1.74

$X = O, NTs, C(CO_2Me)_2$

Chart 3

$\text{\AA}^{4b,5b})$ than of S^+-O^- (*ca.* 1.50 $\text{\AA}^{10})$ and S^+-N^- (*ca.* 1.64 $\text{\AA}^{13})$ may also contribute to the decrease of the unfavorable interaction between the equatorial $S^+-C^-(CO_2Me)_2$ and 4-methyl group.

Of particular interest is the signal of the two methoxyl groups in the NMR spectra (Table II): *trans*-3 ($R=Me$) and *trans*-16 ($R=Me, Et$) show a sharp singlet, whereas *trans*-3 ($R=Et, iso-Pr$), *trans*-16 ($R=iso-Pr$),¹²⁾ and 12b, c show a broad signal or split signals.¹⁴⁾ This means that rotation about the S^+-C^- bond is free for the first three compounds but hindered for the latter five compounds. The presence of a bulky 9-alkyl group and/or introduction of a 1-methyl group appear to increase the energy barrier for rotation, but the 4-methyl group does not have a significant influence. The change of the dihedral angle between the planes of the two benzene rings might be responsible for these phenomena. However, a precise conclusion must await a more detailed investigation, particularly by X-ray studies.

TABLE II. Splitting Pattern of the equatorial-Methoxycarbonyl Group of 9-Alkylthioxanthanium (Bismethoxycarbonyl)methylides at 34°C

Compd.	9-R		
	Me	Et	iso-Pr
<i>trans</i> -3	3.59 (6H, sharp s)	3.59 (6H, br s)	3.82 (3H, s)
<i>trans</i> -16	3.64 (6H, sharp s)	3.54 (6H, sharp s)	3.26 (3H, s)
<i>trans</i> -12	4.1—3.1 (6H, br)	3.86 (3H, s) 3.26 (3H, s)	4.1—2.9 (6H, br)

s = singlet; br = broad.

Rearrangement

Treatment of **8a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at room temperature gave the rearranged product **9** in 71% yield. The structure of **9** was apparent

from its spectral data (see "Experimental"). Refluxing of **12a** in toluene in the presence of DBU for 2 h afforded the rearranged product **13** in 81% yield. However, **8b**, **c** and **12b**, **c** were stable under the reaction conditions which we used for the rearrangement of **8a** and **12a**. Prolonged refluxing of **12b** in toluene (for more than 20 h) resulted in decomposition. Non-bonded interaction between the 9-alkyl group and 1-methyl group in the transition state leading to the thioxanthylum ion **17** may increase the activation energy of the rearrangement.¹⁵⁾

Experimental¹⁶⁾

1,4-Dimethylthioxanthene *N*-Tosylsulfilimine (8a) and 9-(*N*-Tosylamino)-1,4-dimethylthioxanthene (9)—Chloramine-T·3H₂O (1.4 g, 5 mmol) was added all at once to a stirred solution of **7a** (1.13 g, 5 mmol) in methanol (25 ml) and methylene chloride (12 ml) containing AcOH (0.05 ml) at room temperature. After 30 min, CHCl₃ (30 ml) was added to the reaction mixture and the solution was washed with a saturated NaHCO₃ solution and H₂O, then dried (MgSO₄), and concentrated. The residual oil was chromatographed on silica gel with benzene–AcOH (5:1) to give **9** (745 mg, 38%) and **8a** (785 mg, 40%).

Compound **9** gave mp 163–164°C (from benzene–*n*-hexane). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3370 (NH), 1340, and 1160 (SO₂). NMR (CDCl₃) δ : 7.4–6.8 (m, 10H, aromatic protons), 5.90 (d, 1H, *J* = 8 Hz, H-9), 5.16 (br d, 1H, *J* = 8 Hz, NH), 2.47 (s, 3H, CH₃), and 2.30 (s, 6H, 2 × CH₃). Anal. Calcd for C₂₂H₂₁NO₂S₂: C, 66.80; H, 5.35; N, 3.54. Found: C, 67.10; H, 5.25; N, 3.60.

Compound **8a** gave mp 153–157°C (from MeOH–AcOEt). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1290, 1140, 1095 (SO₂), and 960 (S⁺–N⁻). NMR (CDCl₃) δ : 7.7–6.9 (m, 10H, aromatic protons), 4.58, 4.10 (ABq, 1H each, *J* = 18 Hz, H-9), and 2.42, 2.39, 2.33 (all s, 3H each, 3 × CH₃). Anal. Calcd for C₂₂H₂₁NO₂S₂: C, 66.80; H, 5.35; N, 3.54. Found: C, 66.87; H, 5.23; N, 3.58.

General Procedure for the Preparation of 10-Amino-9-alkyl-1,4-dimethylthioxanthanium Mesitylenesulfonates (10 and 11)—A solution of MSH (4.2 mmol) in CH₂Cl₂ (15 ml) was added to an ice-cooled solution of **7b** or **7c** (4 mmol) in CH₂Cl₂ (15 ml) with stirring. The reaction mixture was stirred at room temperature for 2.5 h and then ether (30 ml) was added. The precipitated crystals were collected by filtration and recrystallized from MeOH–AcOEt.

Compound **10** (85%) gave mp 171–173°C. Anal. Calcd for C₂₅H₂₉NO₃S₂: C, 65.90; H, 6.42; N, 3.07. Found: C, 65.53; H, 6.49; N, 3.35.

Compound **11** (89%) gave mp 191–193°C. Anal. Calcd for C₂₆H₃₁NO₃S₂·1/2H₂O: C, 65.24; H, 6.74; N, 2.93. Found: C, 65.04; H, 6.91; N, 2.87.

General Procedure for the Preparation of *cis*-9-Alkyl-1,4-dimethylthioxanthene *N*-Tosylsulfilimines (8b, c)—Tosyl chloride (2 mmol) and K₂CO₃ (2.5 mmol) were added all at once to a solution of **10** or **11** (2 mmol) in dimethylformamide (DMF) (20 ml) at 0°C. The reaction mixture was stirred at room temperature for 3 h, then concentrated *in vacuo* at below 30°C, and CHCl₃ (30 ml) was added to the residue. The solution was washed with H₂O, dried (MgSO₄), and concentrated. The residual oil was chromatographed on silica gel with benzene–AcOEt (4:1).

Compound **8b** (31%) gave mp 247.5–248.5°C (from CHCl₃–MeOH). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1290, 1140, 1090 (SO₂), and 950 (S⁺–N⁻). NMR (CDCl₃) δ : 7.8–7.0 (m, 10H, aromatic protons), 4.34 (q, 1H, *J* = 7.5 Hz, H-9), 2.43, 2.41, 2.36 (s each, 3H each, 3 × CH₃), and 1.88 (d, 3H, *J* = 7.5 Hz, 9-CH₃). MS *m/z*: 409 (M⁺). Anal. Calcd for C₂₃H₂₃NO₂S₂: C, 67.45; H, 5.66; N, 3.42. Found: C, 67.24; H, 5.57; N, 3.44.

Compound **8c** (45%) gave mp 223–224°C (from benzene). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1290, 1140, 1090 (SO₂), and 950 (S⁺–N⁻). NMR (CDCl₃) δ : 7.8–6.9 (m, 10H, aromatic protons), 4.00 (dd, 1H, *J* = 11 and 6 Hz, H-9), 2.25 (m, 2H, CH₂CH₃), 2.40 (s, 6H, 2 × CH₃), 2.35 (s, 3H, CH₃), and 0.98 (t, 3H, *J* = 7 Hz, CH₂CH₃). MS *m/z*: 423 (M⁺). Anal. Calcd for C₂₄H₂₅NO₂S₂: C, 68.05; H, 5.95; N, 3.31. Found: C, 67.91; H, 5.86; N, 3.32.

General Procedure for the Preparation of 1,4-Dimethylthioxanthanium and *trans*-9-Alkyl-1,4-dimethylthioxanthanium (Bismethoxycarbonyl)methylides (12a–c)—A mixture of **7a–c** (5 mmol), dimethyl diazomalonate (5.5 mmol), and anhydrous cupric sulfate (50 mg) was heated with vigorous stirring at 90°C for 3 h, then cooled. CHCl₃ (50 ml) was added to the reaction mixture and the whole was filtered and concentrated to give a yellow oil, which was chromatographed on silica gel with benzene–AcOEt (1:1).

Compound **12a** (65%) gave mp 184–185°C (from benzene–*n*-hexane). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1660 and 1640 (C=O). NMR (CDCl₃) δ : 7.8–6.9 (m, 6H, aromatic protons), 4.66, 4.00 (ABq, 1H each, *J* = 20 Hz), 3.61 (s, 6H, 2 × OCH₃), and 2.53, 2.39 (s each, 3H each, 2 × CH₃). Anal. Calcd for C₂₀H₂₀O₄S: C, 67.39; H, 5.66. Found: C, 67.35; H, 5.65.

Compound **12b** (79%) gave mp 178–179°C (from benzene–*n*-hexane). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1650 (C=O); NMR (CDCl₃) δ : 7.8–6.9 (m, 6H, aromatic protons), 4.51 (q, 1H, *J* = 7.5 Hz, H-9), 3.9–3.1 (br, 6H, 2 × OCH₃), 2.51, 2.47 (s each, 3H each, 2 × CH₃), and 1.30 (d, 3H, *J* = 7.5 Hz, 9-CH₃). MS *m/z*: 370 (M⁺). Anal. Calcd for C₂₁H₂₂O₄S: C, 68.08; H, 5.99. Found: C, 67.91; H, 6.05.

Compound **12c** (62%) gave mp 175–176°C (from AcOEt). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1650 (C=O). NMR (CDCl_3) δ : 7.8–6.9 (m, 6H, aromatic protons), 4.38 (t, 1H, $J=7$ Hz, H-9), 3.86, 3.26 (s each, 3H each, $2 \times \text{OCH}_3$), 2.52, 2.48 (s each, 3H each, $2 \times \text{CH}_3$), 1.60 (quint, 2H, $J=7$ and 7 Hz, CH_2CH_3), and 0.76 (t, 3H, $J=7$ Hz, CH_2CH_3). MS m/z : 384 (M^+). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_4\text{S}$: C, 68.73; H, 6.29. Found: C, 68.65; H, 6.32.

Rearrangement of 8a to 9—A solution of **8a** (100 mg, 0.25 mmol) and DBU (20 mg, 0.13 mmol) in benzene (8 ml) was stirred at room temperature for 30 min. Benzene (10 ml) was added to the reaction mixture and the benzene solution was washed with 10% HCl and H_2O , then dried (MgSO_4), and concentrated. The residual solid was recrystallized from benzene–*n*-hexane to give **9** (71 mg, 71%), mp 163–164°C.

Rearrangement of 12a to 13—A solution of **12a** (120 mg, 0.34 mmol) and DBU (50 mg, 0.33 mmol) in toluene (9 ml) was refluxed for 2 h and then benzene (20 ml) was added. The reaction mixture was washed with 10% HCl and H_2O , dried (MgSO_4), and concentrated. The residual oil was chromatographed on silica gel with benzene to give **13** (97 mg, 81%), mp 122–122.5°C (from MeOH). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1750 and 1730 (C=O). NMR (CDCl_3) δ : 7.6–6.9 (m, 6H, aromatic protons), 5.23 (d, 1H, $J=11$ Hz), 4.34 (d, 1H, $J=11$ Hz), 3.50, 3.34 (both s, 3H each, $2 \times \text{OCH}_3$), and 2.48, 2.41 (both s, 3H each, $2 \times \text{CH}_3$). Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{O}_4\text{S}$: C, 67.40; H, 5.66. Found: C, 67.25; H, 5.58.

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