(s, 3 H, $CH_3C(O)$, 1.42 (t, 3 H, CH_3); M^+ 185. Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56; S, 17.31. Found: C, 51.88; H, 6.06; N, 7.35; S, 17.18.

Ethyl 4-Ethoxy-3-thiophenecarbamate (20). 4-Ethoxy-3-thiophenecarbonyl azide (**17**, 1.97 g, 0.010 mol) was refluxed overnight in ethanol (25 mL), filtered hot to remove a trace of insoluble material, and concentrated to dryness, and the residue was crystallized from petroleum ether at −78 °C to give the yellow crystalline product: 1.85 g, 86%; mp 62.5–63 °C; IR 3250, 1710 cm^{-1}; UV 260, 205 nm; ^1H NMR δ 7.32 (br s, 1 H), 6.14 (d, 1 H, both thiophene), 6.92 (br s, 1 H, NH), 4.10 (dq, 4 H, CH_2O), 1.35 (dt, 6 H, CH_3); M^+ 215. Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.21; H, 6.09; N, 6.51; S, 14.90. Found: C, 50.20; H, 5.92; N, 6.46; S, 15.18.

1,3-Bis(4-ethoxy-3-thienyl)urea (21). 4-Ethoxy-3-thiophenecarbonyl azide (**17**, 1.97 g, 0.010 mol) was refluxed in water (25 mL) for 1 h. After being cooled, the product was collected by filtration and dried in vacuo to give a yellow solid: 1.20 g (80%), which was purified by sublimation (bath 250 °C, pressure 0.05 mmHg); mp 298–299 °C; IR 3300, 1660 cm^{-1}; ^1H NMR δ 8.82 (s, 2 H, NH), 7.37 (d, 2 H), 6.54 (d, 2 H, all thiophene), 4.12 (q, 4 H, CH_2O), 1.40 (t, 6 H, CH_3). Anal. Calcd for $C_{13}H_{16}N_2O_3S_2$: C, 49.98; H, 5.16; N, 8.97; S, 20.53. Found: C, 50.03; H, 5.08; N, 8.63; S, 20.16.

***N*-(4-Hydroxy-3-thienyl)acetamide (22).** *N*-(4-Ethoxy-3-thienyl)acetamide (**19**, 2.96 g, 0.016 mol) in methylene chloride (75 mL) was added to boron tribromide (8.0 g, 3.1 mL, 0.032 mol) in methylene chloride (30 mL) and stirred overnight. After quenching the reaction with water (50 mL) for 0.5 h, the layers were separated, and the aqueous layer extracted with ether (2×). The organic layer was filtered through magnesium silicate and eluted with ethyl acetate which provided, after concentration, 1.03 g (41%) of a tan solid. The analytical sample was prepared by sublimation: mp 148.5–149 °C as a yellow crystalline solid; IR 3000, 1660 cm^{-1}; UV 266, 215 nm; ^1H NMR δ 9.70 (br s, 1 H, OH), 9.10 (br s, 1 H, NH), 7.31 (d, 1 H), 6.18 (d, 1 H, both thiophene), 2.11 (s, 3 H, CH_3); M^+ 157. Anal. Calcd for $C_6H_7NO_2S$: C, 45.54; H, 4.49; N, 8.91; S, 20.40. Found: C, 45.83; H, 4.52; N, 8.93; S, 19.92.

4-Ethoxy-3-thiopheneamine (23). A mixture of 15.4 g (0.09 mol) of *N*-(4-ethoxy-3-thienyl)formamide (**18**) in 50 mL of 2 N ethanolic hydrogen chloride and 90 mL of ethanol was refluxed for 2 h and filtered, and the filtrate was evaporated. Water was added to the residue, and the solution was cooled and made alkaline with 5 N sodium hydroxide. The mixture was extracted with methylene chloride, the extracts were dried ($MgSO_4$) and filtered, and the filtrate was evaporated to give 12.7 g (98%) of the product as a dark amber oil. A 1-g sample was distilled to give a colorless liquid: bp 69 °C (0.4 mmHg); IR 3400, 3330 cm^{-1}; UV 270, 213 nm; ^1H NMR δ 5.98 (dd, 2 H, thiophene H), 3.93 (q, 2 H, CH_2), 3.60 (br s, 2 H, NH_2), 1.32 (t, 3 H, CH_3); M^+ 143. Anal. Calcd for C_6H_9NOS: C, 50.34; H, 6.34, N, 9.79; S, 22.36. Found: C, 49.92; H, 6.49; N, 9.93; S, 22.39.

Bis(4-ethoxy-3-thienyl)amine (24). 4-Ethoxy-3-thiopheneamine (0.5 g, 0.0035 mol) was heated at 135–140 °C for 28 h, at which time no more starting amine was present by TLC analysis. The mass was cooled, dissolved in CH_2Cl_2, and filtered through a cake of magnesium silicate. The filtrate was evaporated to give 0.3 g (60%) of the solid product. The pure sample melted at 131–133 °C: IR 3350 cm^{-1}; UV 282, 215 nm; ^1H NMR δ 9.50 (br s, 1 H, NH), 6.51 (d, 2 H), 6.18 (d, 2 H, both thiophene), 4.08 (q, 4 H, CH_2), 1.35 (t, 6 H, CH_3); M^+ 269. Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.50; H, 5.61; N, 5.20; S, 23.81. Found: C, 53.50; H, 5.55; N, 5.22; S, 23.17.

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Registry No. 1, 2689-68-1; **2**, 65369-32-6; **3**, 65369-31-5; **4**, 71050-37-8; **5**, 71050-38-9; **6**, 71050-39-0; **7**, 65369-21-3; **8a**, 65369-22-4; **8b**, 70437-99-9; **10a**, 71050-40-3; **10b**, 70438-00-5; **11a**, 65369-29-1; **11b**, 71050-41-4; **12**, 71050-42-5; **13**, 70438-26-5; **14**, 71050-43-6; **15**, 50624-50-5; **16**, 71050-44-7; **17**, 71050-45-8; **18**, 71050-46-9; **19**, 71050-47-0; **20**, 71050-48-1; **21**, 71050-49-2; **22**, 71050-50-5; **23**, 71050-51-6; **24**, 71050-52-7.

Stereochemistry and Base-Catalyzed Rearrangement of 9-Phenylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimine

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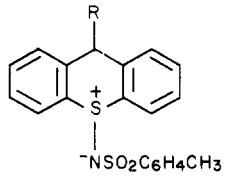
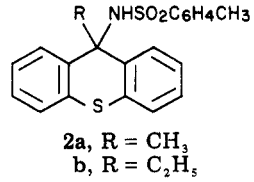
cis- and *trans*-9-phenylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimines were synthesized. The stereochemical assignment was made by careful examination of the NMR spectra and thermodynamic considerations. The sulfilimines underwent base-catalyzed rearrangement to 9-(*N*-*p*-toluenesulfonamido)-9-phenylthioxanthene.

In a previous publication[1] we reported the base-catalyzed rearrangement of *cis*- and *trans*-9-alkylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimines (**1**) to 9-alkyl-9-(*N*-*p*-toluenesulfonamido)thioxanthenes (**2**). The rate of the rearrangement was found to be markedly affected by the stereochemistry of the starting sulfilimines as well as by the steric bulk of the 9-alkyl group. It was of interest in this connection to synthesize *cis*- and *trans*-9-phenylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimines in order to see the effect of the 9-phenyl substituent on the rate of the rearrangement as compared with the rate of the 9-alkyl derivatives **1**.



1a, R = CH_3
b, R = C_2H_5



2a, R = CH_3
b, R = C_2H_5

Results and Discussion

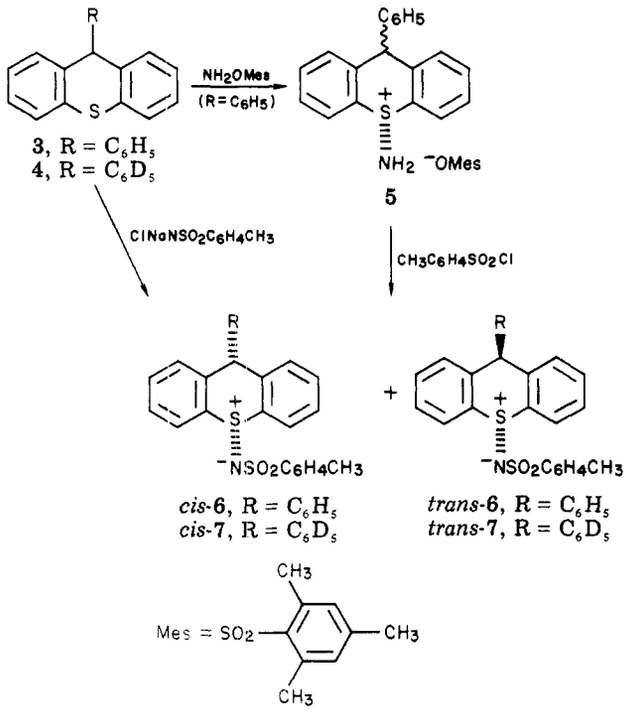
Reaction of 9-phenylthioxanthene (**3**) with *O*-mesitylenesulfonylhydroxylamine (MSH)[2] gave a mixture

(1) Tamura, Y.; Nishikawa, Y.; Muka, C.; Sumoto, K.; Ikeda, M.; Kise, M. *J. Org. Chem.* **1979**, *44*, 1684.

(2) Tamura, Y.; Matsuchima, H.; Minamikawa, J.; Ikeda, M.; Sumoto, K. *Tetrahedron* **1975**, *31*, 303.

0022-3263/79/1944-3296$01.00/0

Scheme I



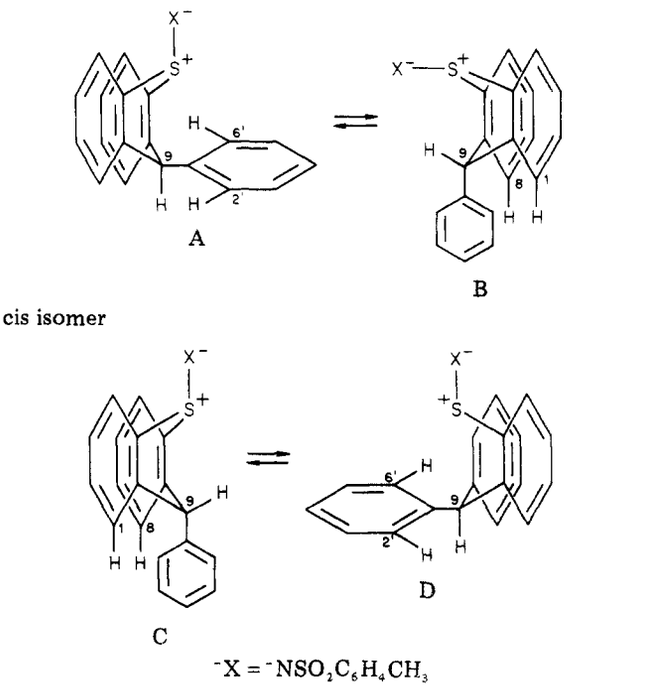
of cis and trans isomers of the *S*-amine salts **5** (Scheme I) The mixture was directly converted to a mixture of two isomeric *N*-(*p*-toluenesulfonyl)sulfilimines **6**, which was separated by preparative TLC on silica gel to give pure *cis*- and *trans*-**6** each in 20% overall yield. More conveniently, treatment of **3** with 2 equiv of chloramine T followed by separation by column chromatography on silica gel afforded pure *cis*- and *trans*-**6** in 41 and 40% yields, respectively.[3]

The stereochemical assignment of **6** was made on the basis of careful examination of the NMR spectra and thermodynamic considerations. In the NMR spectrum of *cis*-**6**, the H-1 and H-8 appear at higher field (δ 7.0–7.2) than the remaining aromatic protons, while the H-2′ and H-6′ of *trans*-**6** occur at higher field (δ 6.8–7.0) than the other aromatic protons. The assignment of these signals was confirmed by comparison with the NMR spectra of the corresponding 9-perdeuteriophenyl derivatives **7** prepared from 9-(perdeuteriophenyl)thioxanthene (**4**) and chloramine T.

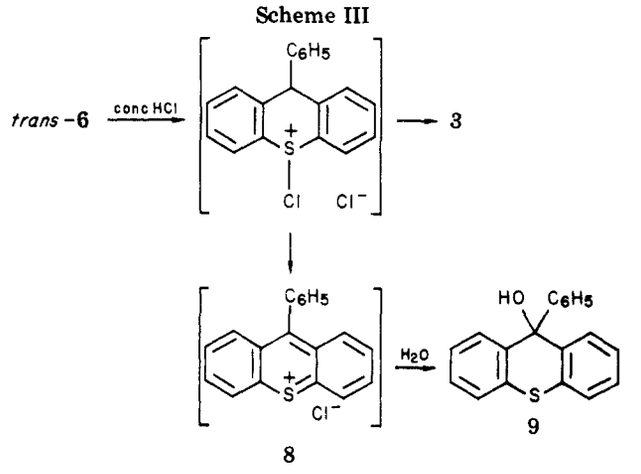
Examination of molecular models indicates that the equatorial 9-phenyl group in the conformers B and C is oriented almost perpendicular to the folded thioxanthene molecule to releave steric interference with the peri hydrogens at the 1 and 8 positions (Scheme II). Consequently both the H-1 and H-8 protons lie over the 9-phenyl ring and should be diamagnetically shielded relative to the other aromatic protons. On the other hand, the H-2′ and H-6′ of the axial 9-phenyl ring in conformers A and D are situated over two benzene rings of the thioxanthene molecule and should occur at higher field than the other aromatic protons.

Another distinguishing feature of the NMR spectra of *cis*- and *trans*-**6** is the H-9 signal, which appears at δ 4.95 and 5.56, respectively. This large difference in the chemical shift may be attributed mainly to the diamagnetic anisotropic effect of two benzene rings in the thioxanthene molecule;[4] the shielding of the axial H-9 and the deshielding of the equatorial H-9 by the two benzene rings are mutually reinforcing. In addition, the signal of the H-9 in *cis*-**6** shows slight broadening (23% increase in the band width at half-height compared with that in *trans*-**6**). It is known that such broadening results from the long-range coupling with the H-1 and H-8 of the thioxanthene ring and occurs if the H-9 occupies an axial position.[5]

Scheme II



Scheme III



Final confirmation of the stereochemistry of *cis*- and *trans*-**6** was made on the basis of thermodynamic considerations. When *cis*- or *trans*-**6** was refluxed in benzene for 10 h, an equilibrium mixture consisting of *cis*- and *trans*-**6** in a ratio of ~1:3 was obtained. Considering that the S^+–$N^-SO_2C_6H_4CH_3$ group favors the equatorial position,[1] whereas the 9-substituent prefers the axial position,[5] the stable isomer (*trans*-**6**) must be conformer A and thus the less stable isomer (*cis*-**6**) should be conformer C. These conclusions are in good agreement with the results of Hori and co-workers[6] who investigated in detail the stereochemistry of 9-arylthioxanthene 10-oxides by NMR spectroscopy.

(3) In contrast to the case of 9-alkylthioxanthenes,[1] the corresponding sulfoxides were not formed.

(4) Ternay, A. L., Jr.; Evans, S. A. *J. Org. Chem.* **1974**, *39*, 2941.

(5) Ternay, A. L., Jr.; Ens, L.; Evans, S. *J. Org. Chem.* **1969**, *34*, 940.

(6) Hori, M.; Kataoka, T.; Shimizu, H. *Chem. Lett.* **1974**, 1073; Hori, M.; Kataoka, T.; Shimizu, H.; Ohno, S. Abstracts of the 10th Congress of Heterocyclic Chemistry, Tsukuba, Japan, 1977, 266.

Scheme IV

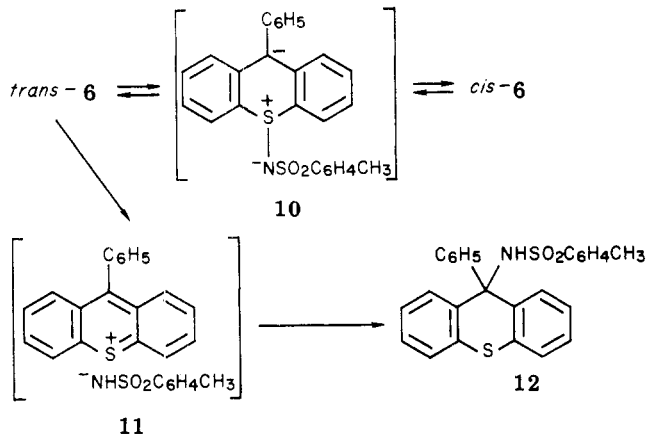


Table I. The Half-lives of 9-Substituted Thioxanthene *N*-(*p*-Toluenesulfonyl)sulfilimines in $CDCl_3$ Containing Piperidine as Base at 34 °C

compd	$t_{1/2}$, min	compd	$t_{1/2}$, min
trans-6	<1[a]	*cis*-8	~45
trans-1a	<1[a]	*cis*-1a	~85
trans-1b	~5	*cis*-1b	no reaction[b]

[a] After 30 s, *trans*-6 completely disappeared but small amounts of *trans*-1a still remained. [b] This compound rearranged by using DBU as base at room temperature.

Before discussing the base-catalyzed rearrangement, the behavior of *N*-(*p*-toluenesulfonyl)sulfilimine 6 toward concentrated hydrochloric acid should be mentioned. Thus, upon treatment with concentrated hydrochloric acid in dioxane, *trans*-6 afforded 9-phenylthioxanthene (3) and 9-hydroxy-9-phenylthioxanthene (9) in 61 and 32% yields, respectively. Apparently, reduction of 6 by chloride ion can compete with the formation of thioxanthylium ion 8, which is attacked by water to give 9 (Scheme III). This result is in contrast to the case of the 9-alkyl congeners 1, which were reduced exclusively to the corresponding 9-alkylthioxanthenes.[1] This differing behavior may be attributed to the conformational flexibility of the 9-phenyl group, which can minimize nonbonding interaction with the peri hydrogens by adopting the orthogonal geometry with respect to the thioxanthene molecule in conversion to the possible intermediate thioxanthylium ion 8.

When treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at room temperature, the sulfilimines *cis*- and *trans*-6 were smoothly converted to 9-phenyl-9-(*N*-*p*-toluenesulfonamido)thioxanthene (12) (Scheme IV). When the reaction was carried out in $CDCl_3$ containing piperidine as base and monitored using ^1H NMR spectroscopy, *trans*-6 ($t_{1/2}$ < 1 min) was found to rearrange much faster than *cis*-6 ($t_{1/2}$ = ~45 min).

As stated earlier, one purpose of this study was to determine the effect of the phenyl substituent at C-9 on the rate of the rearrangement as compared with 9-alkyl derivatives 1. The relevant data are summarized in Table I. A discussion of the effects of the alkyl group in these sulfilimines has already been presented in terms of the intermediacy of thioxanthylium ions 11 (9-CH_3 or C_2H_5 instead of 9-C_6H_5).[1] The faster rearrangement of *trans*-**1a,b** than the corresponding *cis*-**1a,b** has been rationalized by assuming that the trans isomers undergo syn 1,4-elimination[7] through less stable conformer B (9-CH_3 or C_2H_5 instead of 9-C_6H_5), while the cis isomers undergo prior isomerization via C-9 carbanions to the trans isomers and then rearrange to 12 (9-CH_3 or C_2H_5 instead of 9-C_6H_5).

Table I shows that both *trans*-6 and *cis*-6 rearrange at faster rates than *trans*-1a and *cis*-1a, respectively. These results are most likely a reflection of the ability of the 9-phenyl group to minimize the nonbonding interaction with peri hydrogens in the process to 11 as well as in the cis–trans isomerization step. In addition, the presence of an electron-withdrawing phenyl group at C-9 is expected to increase the acidity of the benzylic proton, so that isomerization of *cis*-6 to *trans*-6 would be facilitated.

Experimental Section

Melting points are uncorrected. NMR spectra were determined with a Hitachi R-22 (90 MHz) spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded with a Hitachi EPI-G2 spectrophotometer. Low- and high-resolution mass spectra were obtained with a Hitachi RMU-6MG and a JEOL-JMS-OI56 instrument with a direct inlet system at 70 and 75 eV, respectively, unless otherwise stated.

***cis*- and *trans*-10-Amino-9-phenylthioxanthenium Mesitylenesulfonates (5).** A solution of MSH (215 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added to an ice-cooled and stirred solution of 3 (274 mg, 1 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 2 h and then ether (20 mL) was added. The precipitated crystals were collected and recrystallized from methanol–AcOEt to give a mixture of *cis*- and *trans*-5 (395 mg, 81%), mp 161–164 °C.

Anal. Calcd for $C_{28}H_{27}NO_2S_2$: C, 68.68; H, 5.56; N, 2.86. Found: C, 68.32; H, 5.64; N, 3.14.

***cis*- and *trans*-9-Phenylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimines (6). Method A.** To a stirred solution of crude 5 (200 mg, 0.41 mmol; as a mixture of cis and trans isomers) in dimethylformamide (5 mL) was added all at once *p*-toluenesulfonyl chloride (78 mg, 0.41 mmol) and K_2CO_3 (57 mg, 0.41 mmol). The mixture was stirred at room temperature for 2 h and concentrated in vacuo, and $CHCl_3$ (50 mL) was added to the residue. The solution was washed with water, dried ($MgSO_4$), and concentrated. The residue was separated by preparative TLC on silica gel with AcOEt–benzene (1:4) as solvent to give *cis*-6 (46 mg, 25%) and *trans*-6 (46 mg, 25%).

cis-6 had: mp 186–188 °C [from benzene–petroleum ether (bp 60–80 °C)]; IR ($CHCl_3$) 1300, 1142, 1085 (SO_2), 970 (S^+–N^-) cm^{-1}; NMR ($CDCl_3$) δ 7.2–8.1 (m, 15, aromatic protons), 7.0–7.2 (m, 2, aromatic protons), 4.95 [s, 1, H(9)], 2.42 (s, 3, toluene ring CH_3); mass spectrum (20 eV) *m/e* (rel intensity) 443 (6.9, M^+), 366 (0.8), 273 (100), 272 (4.6), 271 (12.4), 197 (4.4).

Analysis was carried out by high-resolution mass spectrometry: calcd for $C_{26}H_{21}NO_2S_2$, 443.1013; found, 443.0995.

trans-6 had: mp 167–170 °C [from benzene–petroleum ether (bp 60–80 °C)]; IR ($CHCl_3$) 1300, 1145, 1090 (SO_2), 970 (S^+–N^-) cm^{-1}; NMR ($CDCl_3$) δ 7.0–8.0 (m, 15, aromatic protons), 6.8–7.0 (m, 2, aromatic protons), 5.56 [s, 1, H(9)], 2.39 (s, 3, toluene ring CH_3); mass spectrum (20 eV) *m/e* (rel intensity) 443 (7.1, M^+), 366 (0.7), 273 (100), 272 (5.8), 271 (16.5), 197 (4.9).

Analysis was carried out by high-resolution mass spectrometry: calcd for $C_{26}H_{21}NO_2S_2$, 443.1013; found, 443.1040.

Method B. To a stirred solution of methanol (20 mL) and CH_2Cl_2 (10 mL) containing acetic acid (0.04 mL) was added all at once 3 (1.0 g, 3.65 mmol) and chloramine T·$3H_2O$ (2.08 g, 7.38 mmol) at room temperature. After 60 min, CH_2Cl_2 (30 mL) was added to the reaction mixture and the solution was washed with a saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on silica gel with benzene–AcOEt (4:1) to afford *cis*-6 (675 mg, 41%), mp 186–188 °C, and *trans*-6 (649 mg, 40%), mp 167–170 °C.

***cis*- and *trans*-9-(Perdeuteriophenyl)thioxanthene-*N*-(*p*-Toluenesulfonyl)sulfilimines (7).** 9-(Perdeuteriophenyl)thioxanthene (4) was prepared from thioxanthene and Grignard reagent derived from bromobenzene-d_5 by application of the method of Price and co-workers.[8] Treatment of 4 (279

(7) Hill, R. K.; Bock, M. T. *J. Am. Chem. Soc.*, **1978**, *100*, 637; and references cited therein.

(8) Price, C. C.; Hori, M.; Prasaran, T.; Polk, M. *J. Am. Chem. Soc.* **1963**, *85*, 2278.

mg, 1 mmol) with chloramine T·3H_2O (564 mg, 2 mmol) as described above for the preparation of **6** gave *cis*-**7** (162 mg, 36%) and *trans*-**7** (132 mg, 29%).

cis-**7** had: mp 179–181 °C [from $CHCl_3$–petroleum ether (bp 60–80 °C)]; IR ($CHCl_3$) 2270 (C–D), 1300, 1140, 1085 (SO_2), 968 (S^+–N^-) cm^{-1}; NMR ($CDCl_3$) δ 7.2–8.1 (m, 10, aromatic protons), 7.0–7.2 (m, 2, aromatic protons), 4.96 [s, 1, H(9)], 2.42 (s, 3, toluene ring CH_3); mass spectrum m/e 448 (M^+).

trans-**7** had: mp 169–172 °C (from benzene); IR ($CHCl_3$) 2270 (C–D), 1300, 1143, 1088 (SO_2), 968 (S^+–N^-) cm^{-1}; NMR ($CDCl_3$) δ 7.1–8.0 (m, 12, aromatic protons), 5.55 [s, 1, H(9)], 2.38 (s, 3, toluene ring CH_3); mass spectrum m/e 448 (M^+).

Thermal Isomerization of *cis*- and *trans*-6. A solution of *cis*-**6** (30 mg) in benzene (3 mL) was refluxed for 10 h. Evaporation of the solvent gave a mixture of *cis*- and *trans*-**6** in a ratio of ~1:3 (by NMR spectroscopy).

Similar treatment of *trans*-**6** gave a mixture of *cis*- and *trans*-**6** in the same ratio.

Reaction of *trans*-6 with Concentrated HCl in Dioxane. A solution of *trans*-**6** (100 mg, 0.23 mmol) in dioxane containing concentrated HCl (0.1 mL) was refluxed for 2 h. The reaction mixture was concentrated, neutralized with 5% NaOH solution, and extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on silica gel with benzene to give **3** (38 mg, 61%) and 9-hydroxy-9-phenylthioxanthene (**9**; 20 mg, 32%).[8]

Rearrangement of *cis*- and *trans*-6 with DBU in Benzene. To a stirred suspension of *cis*-**6** (100 mg, 0.23 mmol) in benzene (5 mL) was added DBU (34 mg, 0.23 mmol). After stirring at room temperature for 10 min, the reaction mixture was washed with 10% HCl and water and concentrated. The residual oil was purified by preparative TLC on silica gel with benzene as solvent to give 9-phenyl-9-(*N*-*p*-toluenesulfonamido)thioxanthene (**12**; 94 mg, 94%): mp 219–222 °C (from benzene–*n*-hexane); IR ($CHCl_3$) 3350 (NH), 1325, 1150, 1090 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 6.8–7.5 (m, 17 aromatic protons), 5.11 (s, 1, NH), 2.29 (s, 3, toluene ring CH_3).

Analysis was carried out by high-resolution mass spectrometry: calcd for $C_{26}H_{21}NO_2S_2$, 443.1013; found, 443.1061.

Similar treatment of *trans*-**6** (100 mg) gave **12** (85 mg, 85%).

Determination of the Half-life of *cis*- and *trans*-6 in $CDCl_3$ Containing Piperidine as Base at 34 °C. The samples (0.25 M in substrate) were made up in NMR tubes from weighed amounts of *cis*- and *trans*-**6** in $CDCl_3$ with tetramethylsilane as internal standard. The NMR spectrum was then recorded and piperidine (8.5 mg, 0.1 mmol) was added. The spectrum was immediately recorded again at intervals, the temperature being held at 34 °C. The reaction was followed by electronic integration of the H(9) signals. The product was free of decomposition products or byproducts.

Registry No. *cis*-**1a**, 6931-68-6; *trans*-**1a**, 69381-65-3; *cis*-**1b**, 69381-69-7; *trans*-**1b**, 69381-66-4; **3**, 35500-04-0; **4**, 71031-54-4; *cis*-**5**, 71001-68-8; *trans*-**5**, 71001-70-2; *cis*-**6**, 71001-71-3; *trans*-**6**, 71001-72-4; *cis*-**7**, 71001-73-5; *trans*-**7**, 71001-74-6; **9**, 6630-80-4; **12**, 71001-75-7; thioxanthene, 261-31-4; bromobenzene-d_5, 4165-57-5.

Ring Conformations of Proline. Solution Studies Based on Lanthanide Nuclear Magnetic Resonance Shifts and Molecular Mechanics

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Previous studies of ring conformational equilibria of proline based on molecular mechanics computations show the presence of two shallow energy minima: A is a half chair with C^γ up and C^β down with respect to the average plane of the ring and with the carboxyl group up; B is an envelope with C^γ down. Evaluation of available X-ray data showed that in the solid state the reported conformations cluster about one or the other of these conformations of the theoretical minimum energy. The present study concerns the conformational states of the proline ring in solution in $CDCl_3$ and is based on lanthanide NMR shift studies. The shift reagents Yb(fod)$_3$ and Eu(fod)$_3$ gave 25 usable shift values with Ac-L-Pro-OCH_3 and 29 with Bz-Pro-OCH_3.[1] The shift results are consistent with a conformational mixture of roughly 60 parts of A and 40 of B. Assumption of a planar average ring conformation gives a poorer account of the data and the data are inconsistent with a ring having a single intermediate conformation derived from either A or B. In the present study the lanthanide shift data were processed by a molecular mechanics program modified so as to permit simultaneous adjustment of lanthanide parameters, substrate geometry, and conformer mole fractions. Minor adjustment of substrate geometry gave dramatic improvement in the agreement factor between observed and calculated induced shift values, and the observed values have been reproduced to within experimental error. We provide a probable explanation of the variable and unrealistically long lanthanide–oxygen distances commonly reported in LIS studies. This is a consequence of representing a physical system made up of many complexes in rapid equilibrium by one single mathematically averaged complex. The geometry of the substrate is reproduced well by the mathematical model, although this may not closely resemble any individual complex with respect to the lanthanide position nor with respect to the properties of the magnetic tensor.

A previous theoretical evaluation of the conformational energy map for the proline ring based on molecular mechanics calculations showed two shallow minima located at $a_0 = 37°$, $t = 13.3$ (A) and at $a_0 = -36°$, $t = 177.3$ (B).[2] A corresponds to a half chair conformation with C^β down and C^γ up with respect to the average plane of the ring. B corresponds roughly to an envelope with C^γ down. The carboxyl is up. Analysis of the available X-ray data for about 40 proline rings showed that the ring conformations

(1) (a) IUPAC-IUB Conventions as published in "Amino Acids, Peptides, and Proteins", Vol. 4, G. T. Young, Sr. Reporter, The Chemical Society, London, 1972, p 441; (b) fod is the complexing group derived from 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione; dpm is derived from 2,2,6,6-tetramethyl-3,5-heptanedione; (c) LIS, lanthanide induced shift.

(2) D. F. DeTar and N. P. Luthra, *J. Am. Chem. Soc.*, **99**, 1232 (1977).

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