Reactions of Sulfenes with Schiff Bases. The Stereochemistry and Thermal Fragmentation of Thiazetidine 1,1-Dioxide

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Phenylsulfene (II) generated from benzylsulfonyl chloride (I) and triethylamine, reacted with *N*-(*p*-substituted)-benzylidene-methylamine to give 2-methyl-4-phenyl-3-(*p*-substituted-phenyl)-1,2-thiazetidine 1,1-dioxide whose *cis* and *trans* isomers were separated. Both *cis* and *trans* 3,4-diphenyl-2-methyl-1,2-thiazetidine 1,1-dioxide (IV and V) afforded *trans* stilbene and benzaldehyde on pyrolysis. This new fragmentation reaction could be explained by a stepwise decomposition because of its non-stereospecificity.

Although heterocyclic four-membered ring compounds have been well investigated,[1] little is known about 1,2-thiazetidine 1,1-dioxide due to the scarcity of synthetic examples. Whereas thermal [2+2] cycloaddition reactions for the synthesis of this four-membered saltam have been reported,[2] no stereochemical aspects are known. This report deals with reactions of sulfenes with Schiff bases and the synthesis of 1,2-thiazetidine 1,1-dioxide derivatives which sheds light on the stereochemistry and a thermal fragmentation.

Phenylsulfene (II) generated from benzylsulfonyl chloride (I) and triethylamine in tetrahydrofuran was treated with *N*-benzylidene-methylamine (III) to give 3,4-diphenyl-2-methyl-1,2-thiazetidine 1,1-dioxide whose *cis* (IV) and *trans* (V) isomers were separated by silica gel chromatography. This is the first instance of isolation of the both stereoisomers in thiazetidine 1,1-dioxide system. The other components of the reaction mixture were the starting Schiff base and stilbene which has been known to be derived from phenylsulfene.[3] Similarly substituted *N*-benzylidene-methylamine afforded the desired four-membered saltams, whose physical data are summarized in Table 1. The determination of the structures was made on the basis of NMR data which showed a typical AB type quartet due to hydrogens at 3 and 4 positions. The assignment of *cis* and *trans* isomers was also based on the coupling constants between C^3-H and C^4-H. The difference between J_{cis} and J_{trans} is relatively small (1.5—2.0 Hz), leaving the possibility of a misassignment which was pointed out by Fleming and Williams[4] in four-membered carbocyclic ring systems. The validity of these *cis* and *trans* assignments is supported by the following chemical interconversions. Heating the *cis*

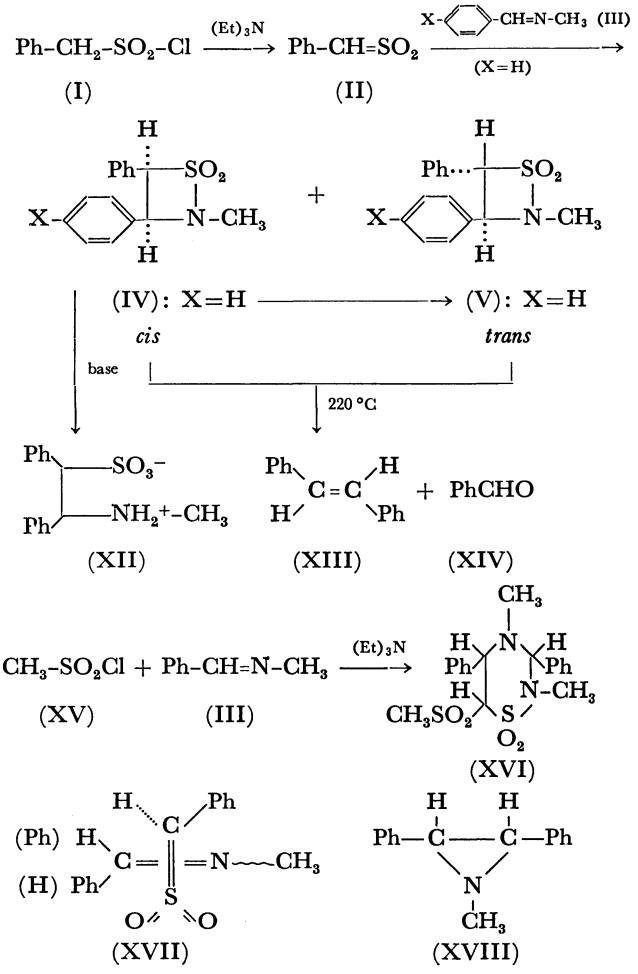

Chart 1.

TABLE 1. 1,2-THIAZETIDINE 1,1-DIOXIDE

Compound X			Mp (°C)	NMR spectra[a] N-CH_3	C_3-H	C_4-H	$J_{3,4}$(Hz)	aromatic H
H	IV	*cis*	147—148	2.89	4.75(d)	5.74(d)	8.5	6.98—7.28(m)
	V	*trans*	81— 82	2.80	4.28(d)	5.22(d)	7.0	7.12—7.60(m)
Cl	VI	*cis*	154—155	2.88	4.72(d)	5.73(d)	8.8	7.10—7.32(m)
	VII	*trans*	89— 90	2.78	4.24(d)	5.16(d)	7.5	7.33—7.52(m)
OCH_3	VIII	*cis*	132—133	2.88[b]	4.73(d)	5.68(d)	8.5	6.62—7.32(m)
	IX	*trans*	oil	2.74[c]	4.22(d)	5.18(d)	7.0	6.78—7.58(m)
NO_2	X	*cis*	179—180	2.94	4.81(d)	5.82(d)	9.0	7.10—8.18(m)
	XI	*trans*	170—171	2.85	4.37(d)	5.18(d)	7.0	7.43—8.39(m)

a) ppm in $CDCl_3$. b) OCH_3 3.70. c) OCH_3 3.78.

isomer(IV) in tetrahydrofuran in the presence of triethylamine for 15 hr gave a mixture of the *cis* (IV) and *trans* isomer (V) in a ratio of 4 : 1, whereas the same treatment of the *trans* compound (V) afforded the unchanged starting material together with a trace amount of the *cis* isomer (IV).

The yields of these 1,2-thiazetidine 1,1-dioxides changed significantly depending on the reaction conditions. The best result was obtained when two equivalents of Schiff base and one equivalent of benzylsulfonyl chloride were used without triethylamine or another base (Table 2).

Table 2. Formation of 1,2-thiazetidine 1,1-dioxides from benzylsulfonyl chloride and Schiff bases in THF

Schiff base	Reaction conditions	Yield[c]	Ratio[d] *cis* : *trans*
Ph-CH=N-CH_3	A[a]	17.5%	64 : 36
	B[b]	80.0%	61 : 39
p-Cl-Ph-CH=N-CH_3	A	14.6%	62 : 38
	B	88.3%	58 : 42
p-CH_3O-Ph-CH= N-CH_3	A	16.7%	68 : 32
	B	79.7%	64 : 36
p-NO_2-Ph-CH= N-CH_3	A	12.3%	60 : 40
	B	51.7%	52 : 48

a) Molar ratio of benzylsulfonyl chloride-Schiff base-triethylamine=1 : 1 : 1, −78 °C, 5 hr, then, allowed to warm slowly to room temperature and kept at this temperature overnight. b) Molar ratio of benzylsulfonyl chloride-Schiff base=1 : 2, room temperature, 42 hr. When the reaction was stopped after 18 hr, 10—30% decrease of yields was observed. c) Otained from NMR data. The reactions were carried out using 0.05 equivalents of hexamethylbenzene as an internal standard for NMR analysis. The isolated yields were given in experimental part. d) Calculated from NMR data.

The preferred formation of the *cis* isomer over the *trans* isomer in the reaction of the sulfene with the Schiff base suggests that the reaction would be a concerted $[{}_\pi 2_s + {}_\pi 2_s]$ cycloaddition (depicted as XVII) with some secondary effects.[5]

Treatment of the saltam (IV) with sodium methoxide in methanol and subsequent work-up with hydrochloric acid gave 1,2-diphenyl-2-methylamine-ethanesulfonic acid (XII). This ring cleavage presents a striking contrast with a base-catalyzed ring opening of four-membered saltam, in which 2—3 bond fission took place.[2b,2c]

According to the literature[3] the structures of the products obtained by the reactions of sulfene with Schiff bases have not been established. In our experiments only phenylsulfene afforded a four-membered sulfonamide, and alkyl sulfenes gave many products whose structures could not be clarified at this time. In the case of unsubstituted sulfene the reaction proceeded in a different way. Methanesulfonyl chloride was treated with *N*-benzylidene-methylamine in tetrahydrofuran in the presence of triethylamine to yield a crystalline substance, mp 181—182 °C. The NMR spectrum of this compound exhibited peaks at 1.87 (3H, singlet), 2.84 (3H, singlet), 2.85 (3H, singlet), 4.39 (1H, doublet, J=9.0Hz), 4.83 (1H, doublet, J=9.0Hz), and 5.30ppm (1H, singlet), in addition to aromatic hydrogen peaks (10H, multiplet). This fact suggests that 2 mol of sulfene and 2 mol of Schiff base were incorporated into the product. The molecular ion peak at *m/e* 394 in the mass spectrum supported this inference. When this reaction was carried out in acetonitrile instead of tetrahydrofuran the yield of the product increased appreciably, suggesting the involvement of a dimeric sulfene: similarly Optiz[6] observed O_2S=CH-SO_2-CH_3 was formed from methanesulfonyl chloride and triethylamine in acetonitrile. Degradation of this product with hydrochloric acid gave methylamine hydrochloride, and treatment with sodium hydroxide afforded benzylalcohol, which was not helpful in the elucidation of the structure. From these facts we propose the structure (XVI) *i.e.* 2,4-dimethyl-3,5-diphenyl-6-methylsulfonyl-tetrahydro-1,2,4-thiadiazine 1,1-dioxide for the reaction product from methanesulfonyl chloride and *N*-benzylidene-methylamine. The measurement of nuclear Overhauser effect of XVI in NMR also suported this structure. This NOE results are shown in Fig. 1, together with the stereochemistry.

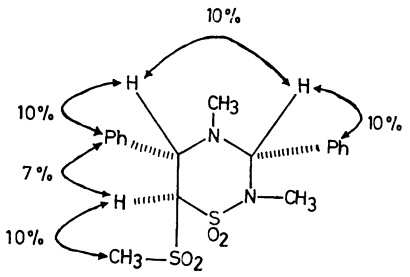

Fig. 1. Nuclear Overhauser effect of XVI.

Next our attention was directed towards thermal fragmentation reaction of such four-membered saltams. Pyrolysis of the *cis* saltam (IV) at 220 °C in nitrogen atmosphere yielded *trans*-stilbene (XIII) (37% yield) and benzaldehyde (XIV) (5% yield) together with the unchanged starting material (*ca* 10%). Analogously heating the *trans* isomer (V) at the same temperature afforded also *trans*-stilbene (XIII) and benzaldehyde (XIV) in 7% and 8% yield, respectively, in addition to the starting *trans* compound (V) (*ca* 7%) and polymeric substance. Recovery of a part of the unchanged *cis* (IV) and the *trans* saltam (V) indicates no interconversions between the two isomers during pyrolysis. Under these reaction conditions (220 °C, 2 hr) *cis*-stilbene gave a mixture of *cis* and *trans* stilbene (3 : 2), whereas *trans*-stilbene isomerized to a negligible amount of *cis*-stilbene (vpc analysis). Thus the formation of *trans*-stilbene from both *cis*-and *trans*-thiazetidine dioxide took place non-stereospecifically. This thermal fragmentation exhibits a striking contrast to that of β-lactams wherein cleavage leading to an olefinic compound proceeded with total retention of stereochemistry.[7] The concerted fragmentation of a four membered ring is only symmetry allowed in the case of $[{}_\sigma 2_s + {}_\sigma 2_a]$ pathway,[5] which is not apparently applicable to the present cleav-

age reaction. A mechanistic possibility might be the extrusion of sulfur dioxide from the four-membered saltam to give an aziridine derivatives, which will subsequently afforded stilbene by a cheletropic reaction.[5] This route seems reasonable since thietane has been known to lose sulfur dioxide to give a cyclopropane derivatives.[8] However, to our knowledge, no aziridine derivative produces an olefinic compound without its conversion to the corresponding *N*-oxide.[9] In order to clarify this point *cis*-2,3-diphenyl-1-methylaziridine (XVIII) was prepared according to the literature.[10] The compound (XVIII) was pyrolyzed under the same conditions as in the case of IV and V to afford an unidentified mixture with a trace amount of *trans*-stilbene (XIII), thus excluding the intermediacy of XVIII. At present, the fragmentation of IV and V could be explained by a stepwise decomposition as in the case of cyclobutane derivatives.[11] An intermediate leading to benzaldehyde is not clear at present time.

The mass spectra of IV and V are interesting in connection with their thermal reactions. The peak due to (M^+–SO_2) appeared in medium intensity, and (M^+–SO_2–H) peak constituted a base peak. A fragment corresponding to stilbene was not observed, whereas a peak assignable to Ph–C≡N^+–CH_3 was very strong.

Experimental

All melting points were determined in open capillaries and are uncorrected. IR spectra were measured with a Hitachi IRA-2 spectrophotometer. NMR spectra were recorded on a Varian D-60 spectrometer.

General Procedure for Reactions of Sulfonyl Chlorides with N-p-*substituted-Benzylidene-methylamine.* A stirred solution of 0.01 mol of the *N-p*-substituted-benzylidene-methylamine and 0.01 mol of triethylamine in 25 ml of a dry solvent, under slight pressure of dry nitrogen, was maintained at −78 °C while a solution of 0.01 mol of a sulfonyl chloride in 5 ml of a dry solvent was slowly added over a period of 30 min. Usually triethylamine hydrochloride separated immediately. The resulting suspension was allowed to warm slowly to room temperature and was then stirred overnight. The solid (triethylamine hydrochloride) was removed by filtration and washed with a small amount of a solvent. The filtrate and washings were combined and concentrated under reduced pressure. The residue, oil or crystals, was purified by column chromatography using silica gel or alumina. Recrystallization from a suitable solvent gave a desired compound.

*2-Methyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide (*cis *IV and* trans *V).* Under the general procedure with THF as solvent, *N*-benzylidene-methylamine (1.19 g) and benzylsulfonyl chloride (1.91 g) in the presence of triethylamine (1.01 g) gave a mixture of IV and V. The mixture was purified by column chromatography using silica gel (solvent: benzene) to give 222 mg (after recrystallization from isopropyl ether) of *cis*-isomer IV and 70 mg (after recrystallization from ethanol) of *trans*-isomer V; 10.7% yield, *cis*-isomer (IV): mp 147—148 °C; IR (Nujol) 1142 and 1303 (SO_2) cm^{-1}; NMR see Table 1. (Found: C, 65.78; H, 5.59; N, 5.21; S, 11.67%. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12; S, 11.73%), *trans*-isomer (V): mp 81—82 °C; IR (Nujol) 1160 and 1303 (SO_2) cm^{-1}; NMR see Table 1. (Found: C, 66.11; H, 5.52; N, 5.29; S, 11.76%. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12; S, 11.73%).

*3-*p*-Chlorophenyl-2-methyl-4-phenyl-1,2-thiazetidine 1,1-Dioxide (*cis *VI and* trans *VII).* Analogously *N-p*-chlorobenzylidene-methylamine (1.54 g) and benzylsulfonyl chloride (1.91 g) in THF with triethylamine (1.01 g) gave a mixture of VI and VII. The mixture was purified by column chromatography using silica gel (solvent: benzene) to give 199 mg (after recrystallization from isopropyl ether) of *cis*-isomer VI and 117 mg (after recrystallization from ethanol) of *trans*-isomer VII; 10.2% yield, *cis*-isomer (VI): mp 154—155 °C; IR (Nujol) 1120 and 1308 (SO_2) cm^{-1}; NMR see Table 1. (Found: C, 58.77; H, 4.54; N, 4.67; S, 10.51; Cl, 11.58%. Calcd for $C_{15}H_{14}NO_2SCl$: C, 58.53; H, 4.58; N, 4.55; S, 10.42; Cl, 11.52%), *trans*-isomer (VII): mp 89—90 °C; IR (Nujol) 1092 and 1298 (SO_2) cm^{-1}; NMR see Table 1. (Found: C, 58.73; H, 4.58; N, 4.78; S, 10.56; Cl, 11.64%. Calcd for $C_{15}H_{14}NO_2SCl$: C, 58.53; H, 4.58 N, 4.55; S, 10.56; Cl, 11.64%).

*3-*p*-Methoxyphenyl-2-methyl-4-phenyl-1,2-thiazetidine 1,1-Dioxide (*cis *VIII and* trans *IX).* According to the general procedure, *N-p*-methoxybenzylidene-methylamine (1.49 g) and benzylsulfonyl chloride (1.91 g) with triethylamine (1.01 g) afforded a mixture of VIII and IX. The mixture was purified by column chromatography using silica gel (solvent: benzene) to give 204 mg (after recrystallization from isopropyl ether) of *cis*-isomer VIII and 115 mg (oil) of *trans*-isomer IX; 10.5% yield, *cis*-isomer (VIII): mp 132—133 °C; IR (Nujol) 1142 and 1320 (SO_2) cm^{-1}; NMR see Table 1. (Found: C, 63.85; H, 5.60; N, 4.69; S, 10.74%. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62; S, 10.57%), *trans*-isomer (IX): oil; IR (Nujol) 1160 and 1302 (SO_2) cm^{-1}; NMR see Table 1. (Found: C, 63.72; H, 5.82; N, 4.55; S, 9.94%. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62; S, 10.57%).

*2-Methyl-3-*p*-nitrophenyl-4-phenyl-1,2-thiazetidine 1,1-Dioxide (*cis *X and* trans *XI).* As described in the general procedure, *N-p*-nitrobenzylidene-methylamine (1.64 g) and benzylsulfonyl chloride (1.91 g) in the presence of triethylamine (1.01 g) in THF gave a mixture of X and XI. The mixture was purified by column chromatography using silica gel (solvent: benzene) to give 114 mg (after recrystallization from ethanol–ethyl acetate) of *cis*-isomer X and 73 mg (after recrystallization from ethanol) of *trans*-isomer XI; 5.9% yield, *cis*-isomer (X): mp 179—180 °C; IR (Nujol) 1142 and 1309 (SO_2), 1346 and 1520 (NO_2) cm^{-1}; NMR see Table 1. (Found: C, 56.53; H, 4.36; N, 8.86; S, 10.27%. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80; S, 10.07%), *trans*-isomer (XI): mp 170—171 °C; IR (Nujol) 1162 and 1315 (SO_2), 1350 and 1512 (NO_2) cm^{-1}; NMR see Table 1. (Found: C, 56.68; H, 4.40; N, 8.81; S, 10.27%. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80; S, 10.07%).

2,4-Dimethyl-3,5-diphenyl-6-methylsulfonyl-tetrahydro-1,2,4-thiadiazine 1,1-Dioxide (XVI). Under the general procedure with THF as solvent, *N*-benzylidene-methylamine (1.19 g) and methanesulfonyl chloride (1.15 g) in the presence of triethylamine (1.01 g) gave a solid. The solid was purified by column chromatography using alumina (solvent: benzene–ethyl acetate 7 : 1) to give 378 mg (after recrystallization from ethyl acetate–ethanol) of XV; 19.3% yield. When the reaction was carried out in acetonitrile 28.0% yield of XV was obtained: mp 181—182 °C; IR (Nujol) 1140 and 1300 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 1.87 (3H, s, N–C**H**$_3$), 2.84 (3H, s, SO_2–C**H**$_3$), 2.85 (3H, s, SO_2–N–C**H**$_3$), 4.39 (1H, d, Ph–C**H**–N, J=9.0 Hz), 4.83 (1H, d, SO_2–C**H**–SO_2, J=9.0 Hz), 5.30 (1H, s, Ph–C**H**(N)–N), 7.21–7.83 (10H, m, aromatic H). (Found: C, 54.88; H, 5.51; N, 7.17; S, 16.32%. Calcd for $C_{18}H_{22}N_2O_4S_2$: C, 54.80;

H, 5.62; N, 7.10; S, 16.26%).

1,2-Diphenyl-2-methylamino-ethanesulfonic Acid (XII). A stirred suspension of compound IV (136 mg, 0.0005 mol) in 5 ml of 1 M-sodium methoxide-methanol was heated under reflux in an atomosphere of nitrogen. The solution was allowed to cool to room temperature and then treated with 1M-aqueous hydrochloric acid solution until the pH reached 1.0. The separated white solid was collected by filtration and recrystallized from acetone-water to give 104 mg (yield 60.9%) of 1,2-diphenyl-2-methyl-amino-ethanesulfonic acid (XII).: mp >300 °C: IR (Nujol) 2750 and 2520 (N^+H_2), 1618 (benzene), 1249 and 1050 (SO_3^-) cm^{-1}; NMR (DMSO-d_6) δ 2.46 (3H, s, N-C**H**$_3$), 4.56 (1H, d, C**H**-SO_3^- or C**H**-NH_2^+, $J=11.0$ Hz), 4.98 (1H, d C**H**-SO_3^- or C**H**-NH_2^+, $J=11.0$ Hz), 6.99—7.54 (10H, m, aromatic H). (Found: C, 61.92; H, 5.65; N, 5.06; S, 11.06%. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81; S, 11.00%).

Isomerization of cis- *and* trans-*2-Methyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide (IV and V).* *cis-* or *trans*-2-Methyl-3,4-diphenyl-1,2-thiazetidine 1,1-dioxide (IV or V, 91.0 mg, 0.3 m mol) was dissolved in 10 ml of dry THF, followed by the addition of 10 ml (0.14 mol) of triethylamine. The solution was heated on an oil bath (80 °C) for 3 hr under dry nitrogen. Thin layer chromatography indicated no interconversion between *cis*-isomer IV and *trans*-isomer V. Then the solution was further refluxed for 15 hr. The resulting solution was evaporated under reduced pressure. The residue was dissolved in deuteriochloroform and examined by NMR. In the case of the *cis* compound IV, 80% *cis*-20% *trans* mixture was established, whereas *trans*-isomer V was unchanged under these reaction conditions.

Thermal Fragmentation of cis- *and* trans-*2-Methyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide (IV and V).* *cis-* or *trans*-2-Methyl-3,4-diphenyl-1,2-thiazetidine 1,1-dioxide (IV and V, 100 mg) was placed in a 30 ml flask equipped with a Dimroth-type condenser. A stirred sample was then heated at 220 °C under slight pressure of dry nitrogen for 3 hr. The cooled sample was dissolved in 10 ml of chloroform which was washed with 5 ml of water. The organic layer was evaporated under reduced pressure and the residue was checked by VPC and NMR.

Similarly *cis-* and *trans*-stilbene were heated at 220 °C for 3 hr and analysis of the products was carried out using VPC.

The compound IV was completely recovered on heating at 200 °C for 2 hr.

We wish to thank Mr. H. Kuwano for NOE measurement.

Starting compound	Products distribution (%)				
	(IV)[a]	(V)[a]	*cis*-stilbene[b]	*trans*-stilbene[b]	benzaldehyde[c]
(IV)	10	0	0	37	5
(V)	0	7	0	7	8

a) Determined by NMR. b) Determined by vpc, column SE-30, 140 °C. c) Determined by vpc, column SE-30, 60 °C.

Starting compound	Products distribution (%)[a]	
	cis-stilbene	*trans*-stilbene
cis-Stilbene	30	19
trans-Stilbene	2	51

a) Determined by vpc, column SE-30, 140 °C.

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