Reaction of Substituted Sulfenes with *N,N*-Disubstituted α-Aminomethyleneketones. I. Synthesis of *N,N*-Disubstituted *cis*- and *trans*-4-Amino-3,4,5,6,7,8-hexahydro-3-phenyl-1,2-benzoxathiin 2,2-Dioxides

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The polar 1,4-cycloaddition of phenylsulfene (generated *in situ* from phenylmethanesulfonyl chloride and triethylamine) to *N,N*-disubstituted *(E)*-2-aminomethylenecyclohexanones I gave in general a mixture of *N,N*-disubstituted *cis*- and *trans*-4-amino-3,4,5,6,7,8-hexahydro-3-phenyl-1,2-benzoxathiin 2,2-dioxides III and IV, which were separated by column chromatography and whose structural and conformational features were determined from uv, ir and nmr spectral data. In the case of *N,N*-diisopropylamino enaminone Ic, the cycloaddition took place with elimination of an alkyl group as propene to give the adduct III*ℓ*.

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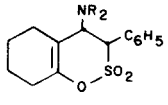
The 1,4-cycloaddition of sulfene to *N,N*-disubstituted open-chain, cyclic and heteroyclic enaminones has been long studied by us, chiefly from a synthetic viewpoint [1,2,3]. As part of our continuing study of such reaction we have undertaken an investigation concerning substituted sulfenes, also in the hope of clarifying the mechanism of the cycloaddition. We wish to report now the results obtained with the first of such sulfenes, namely phenylsulfene I, in the cycloaddition with *N,N*-disubstituted *(E)*-2-aminomethylenecyclohexanones I. The choice of enaminones I was due to their favourable configuration, already experimented in their facile cycloaddition with sulfene, especially when NR_2 was a dialkylamino group [2].

Reaction of enaminones Ia-i with phenylmethanesulfonyl chloride and triethylamine (phenylsulfene prepared *in situ*) occurred also in the case of aromatic *N*-substitution to give generally a mixture of two products III and IV, which were separated by silica gel chromatography. Compounds III and IV (with the exception of III*ℓ*, see later) corresponded both to the expected cycloadducts, namely *N,N*-disubstituted 4-amino-3,4,5,6,7,8-hexahydro-3-phenyl-1,2-benzoxathiin 2,2-dioxides, by elemental analyses and

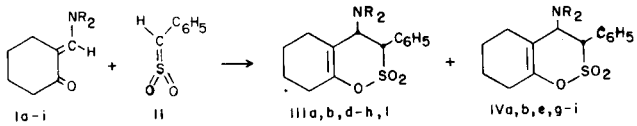
Table I

N,N-Disubstituted *cis*-4-Amino-3,4,5,6,7,8-hexahydro-3-phenyl-1,2-benzoxathiin 2,2-Dioxides IIIa,b,d-h,*ℓ* (a)



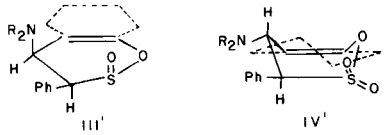
Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses% Calcd./Found C	H	N
IIIa	$N(CH_3)_2$	69	98 (b)	$C_{16}H_{21}NO_3S$	62.51	6.88	4.56
					62.45	6.87	4.48
IIIb	$N(C_2H_5)_2$	46	98 (b)	$C_{18}H_{25}NO_3S$	64.45	7.51	4.17
					64.52	7.45	4.08
IIId	$N(CH_2CH_2OCH_3)_2$	80	90 (c)	$C_{20}H_{29}NO_5S$	60.73	7.39	3.54
					60.81	7.40	3.54
IIIe	Piperidino	60	135 (b)	$C_{19}H_{25}NO_3S$	65.68	7.25	4.03
					65.70	7.19	4.00
IIIf	Morpholino	15	149 (d)	$C_{18}H_{23}NO_4S$	61.87	6.63	4.01
					61.99	6.66	3.95
IIIg	*N'*-Methylpiperazino	34	154 (b)	$C_{19}H_{26}N_2O_3S$	62.95	7.23	7.73
					62.94	7.24	7.73
IIIh	$N(CH_3)C_6H_5$	20 (e)	165 (b)	$C_{21}H_{23}NO_3S$	68.27	6.27	3.79
					68.19	6.16	3.86
III*ℓ*	$NHCH(CH_3)_2$	27	115 (c)	$C_{17}H_{23}NO_3S$	63.52	7.21	4.36
					63.74	7.14	4.41

(a) For preparation, separation and purification of these compounds, see Experimental. (b) From petroleum ether-diethyl ether 10:1. (c) From diethyl ether-acetone 5:1. (d) From acetone. (e) Still containing about 30% of IVh, as determined from the CH_3N ratio in its nmr spectrum.

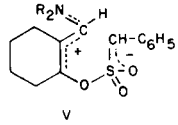


Ia-i II IIIa,b,d-h,l IVa,b,e,g-i

a $N(CH_3)_2$
b $N(C_2H_5)_2$
c $N[CH(CH_3)_2]_2$
d $N(CH_2CH_2OCH_3)_2$
e Piperidino
f Morpholino
g N'-Methylpiperazino
h $N(CH_3)C_6H_5$
i $N(C_6H_5)_2$
l $NHCH(CH_3)_2$



III' IV'



V

spectral data (Tables I-IV) and clearly were stereoisomers. Compounds III can be represented as isomers where both CH-3 and CH-4 are *cis*, and IV as isomers where the same protons are *trans*. A better stereochemical picture of compounds III and IV is that of formulas III', in which the hydrogenated 1,2-oxathiin ring has a near half-chair less stable conformation with near planarity of C=C-O-SO_2 group, and IV', where the same ring has a near boat conformation.

These results arise from the following spectral remarks. Whereas aliphatic *N,N*-disubstituted compounds IV showed in their uv spectra only an end-absorption as a shoulder at 230 nm (Table IV), the related compounds III showed in addition a conjugation band at 310-330 nm (Table II), a fact that we attribute to a near planarity of C=C-O-SO_2 grouping.

An interesting feature appeared also in the ir spectra. Compounds IV showed a regular, *i.e.* very strong, symmetrical stretching of the SO_2 group in the 1175 cm^{-1} region, whereas the same band was weak in the case of compounds III (*cf.* Tables II, IV and Figures 1,2). These data are ex-

Table II

UV, IR and NMR Spectral Data of Compounds IIIa,b,d-h,ℓ

Compound	UV, λ max nm (log ε)	IR, cm^{-1} C=C	IR, cm^{-1} O=S=O		NMR, δ
IIIa	230 sh (3.50) 309 (3.25)	1690	1366	1175	1.50-1.95 (m, CH_2-6 + CH_2-7), 2.0-2.5 (m, CH_2-5 + CH_2-8), 2.15 (s, 2 CH_3N), 4.17 (mc, CH-4), 4.74 (d, J = 6.6, CH-3), 7.41 (mc, C_6H_5)
IIIb	237 sh (3.38) 307.5 (2.86) 321 sh (2.78)	1688	1360	1182	0.83 (t, J = 7, 2 CH_3), 1.5-2.7 (m, 4 CH_2), 2.27 (q, J = 7, 2 CH_2Me), 4.26 (mc, CH-4), 4.63 (d, J = 6.6, CH-3), 7.37 (mc, C_6H_5)
IIId	330 (2.12)	1690	1365	1175	1.74 (mc, CH_2-6 + CH_2-7), 2.0-2.5 (m, CH_2-5 + CH_2-8), 2.62 (near t, J = 5.4, 2 CH_2N), 3.13 (near t, J = 6, 2 CH_2O), 3.20 (s, 2 CH_3O), 4.38 (mc, CH-4), 4.80 (d, J = 6.6, CH-3), 7.43 (mc, C_6H_5)
IIIe	230 sh (3.43) 332 (3.35)	1687	1363	1173	1.30 (mc, 3 CH_2 pip), 1.72 (mc, CH_2-6 + CH_2-7), 2.33 (mc, CH_2-5 + CH_2-8 + 2 CH_2N), 4.08 (mc, CH-4), 4.64 (d, J = 6, CH-3), 7.45 (mc, C_6H_5)
IIIf	230 sh (3.55) 320 (2.20)	1695	1367	1185	1.72 (mc, CH_2-6 + CH_2-7), 2.0-2.8 (m, CH_2-5 + CH_2-8 + 2 CH_2N), 3.44 (t, J = 4.8, 2 CH_2O), 3.86 (mc, CH-4), 4.58 (d, J = 6, CH-3), 7.38 (mc, C_6H_5)
IIIg	230 sh (3.54) 305 sh (2.93) 328 sh (2.71)	1692	1368	1175	1.5-1.9 (m, CH_2-6 + CH_2-7), 2.16 (near s, CH_3N), 2.00-2.75 (m, CH_2-5 + CH_2-8 + 4 CH_2N), 3.98 (mc, CH-4), 4.59 (d, J = 6, CH-3), 7.45 (mc, C_6H_5)
IIIh	249.5 (4.36) 295 (3.55)	1690	1368	1175	1.5-2.5 (m, 4 CH_2), 2.32 (s, CH_3N), 4.82 (near d, J = 6.6, CH-3), 5.22 (mc, CH-4), 6.53 (mc, C_6H_5N), 7.16 (mc, C_6H_5) (a)
IIIℓ	327 (3.41)	1695	1365	1175	0.61 (d, J = 6, CH_3), 0.92 (d, J = 6, CH_3), 1.25 (broad s, NH; disappears with deuterium oxide), 1.76 (mc, CH_2-6 + CH_2-7), 2.0-2.8 (m, CH_2-5 + CH_2-8 + $CHMe_2$), 4.05 (mc, CH-4), 4.77 (d, J = 6.6, CH-3), 7.47 (near s, C_6H_5)

(a) Extrapolated data.

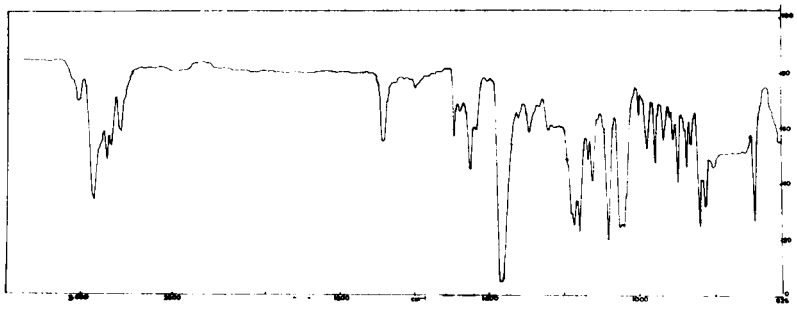


Figure 1. IR Spectrum of IIIa.

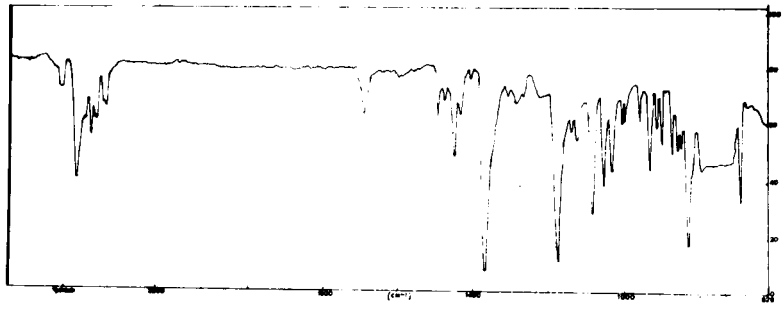
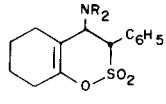


Figure 2. IR Spectrum of IVa.

Table III

N,N-Disubstituted *trans*-4-Amino-3,4,5,6,7,8-hexahydro-3-phenyl-1,2-benzoxathiin 2,2-Dioxides IVa,b,e,g-i (a)



Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses% Calcd./Found C	H	N
IVa	$N(CH_3)_2$	30	171 (b)	$C_{16}H_{21}NO_3S$	62.51	6.88	4.56
					62.65	6.85	4.61
IVb	$N(C_2H_5)_2$	17	141 (b)	$C_{18}H_{25}NO_3S$	64.45	7.51	4.17
					64.51	7.44	4.10
IVe	Piperidino	30	143 (b)	$C_{19}H_{25}NO_3S$	65.68	7.25	4.03
					65.94	7.28	4.10
IVg	*N'*-Methylpiperazino	8	147 (c)	$C_{19}H_{26}N_2O_3S$	62.95	7.23	7.73
					62.98	7.20	7.89
IVh	$N(CH_3)C_6H_5$	50	195 (b)	$C_{21}H_{23}NO_3S$	68.27	6.27	3.79
					67.98	6.22	3.78
IVi	$N(C_6H_5)_2$	19	175 (d)	$C_{26}H_{25}NO_3S$	72.36	5.84	3.24
					72.46	5.91	3.29

(a) For preparation, separation and purification of these compounds, see Experimental. (b) From diethyl ether-acetone 5:2. (c) From acetone-chloroform 2:1. (d) From petroleum ether.

Table IV

UV, IR and NMR Spectral Data of Compounds IVa,b,e, g-i

Compound	UV, λ max nm (log ε)	IR, cm^{-1} C=C	O=S=O		NMR, δ
IVa	230 sh (3.44)	1695	1368	1175	1.50-1.95 (m, CH_2-6 + CH_2-7), 2.14 (s, 2 CH_3N), 2.0-2.5 (m, CH_2-5 + CH_2-8), 4.10 (near d, J = 10.2, CH-4), 4.64 (d, J = 10.2, CH-3), 7.36 (mc, C_6H_5)
IVb	230 sh (3.36)	1693	1368	1174	0.81 (t, J = 7.2, 2 CH_3), 1.68 (mc, CH_2-6 + CH_2-7), 1.9-2.7 (m, CH_2-5 + CH_2-8 + 2 CH_2Me), 4.06 (d, J = 10.2, CH-4), 4.44 (d, J = 10.2, CH-3), 7.37 (mc, C_6H_5)
IVe	230 sh (3.48)	1693	1372	1173	1.25 (mc, 3 CH_2 pip), 1.65 (mc, CH_2-6 + CH_2-7), 2.17 (mc, CH_2-5 + CH_2-8 + 2 CH_2N), 3.98 (near d, J = 10.2, CH-4), 4.54 (d, J = 10.2, CH-3), 7.36 (mc, C_6H_5)
IVg	230 sh (3.06)	1695	1367	1173	1.74 (mc, CH_2-6 + CH_2-7), 2.19 (s, CH_3N), 2.26 (mc, CH_2-5 + CH_2-8 + 4 CH_2N), 4.14 (d, J = 10.2, CH-4), 4.68 (d, J = 10.2, CH-3), 7.39 (mc, C_6H_5)
IVh	250 (3.98) 294 (3.10)	1693	1373	1176	1.69 (mc, CH_2-6 + CH_2-7), 1.91 (mc, CH_2-5), 2.34 (mc, CH_2-8), 2.67 (s, CH_3N), 4.71 (d, J = 10.2, CH-3), 5.00 (near d, J = 10.2, CH-4), 6.71 (mc, C_6H_5N), 7.35 (near s, C_6H_5)
IVi	220 sh (3.98)	1693	1377	1177	1.69 (mc, CH_2-6 + CH_2-7), 2.27 (mc, CH_2-5 + CH_2-8), 4.93 (d, J = 10.8, CH-3), 5.30 (near d, J = 10.8, CH-4), 6.55-7.20 (m, 2 C_6H_5N), 7.29 (near s, C_6H_5)

plainable by an electron shift toward the positive center of O=S=O dipole, effective only in the symmetrical stretching and when the C=C-O-SO_2 group is near planar.

In the nmr spectra of IIIa,b,e, the signals of CH-3 and CH-4 appeared as a doublet at δ 4.65-4.75 (J = 6-6.5 Hz) and as a multiplet at δ 4.1-4.3, respectively, whereas the same protons appeared as two doublets at δ 4.45-4.65 and 4.0-4.1 (J = 10.2 Hz), respectively, in the case of IVa,b,e (Tables II ane IV). The apparent exception of *N*-methyl-*N*-phenyl adducts IIIh and IVh is due to a normal inversion of δ values for CH-3 and CH-4 (*cf.* [2,4]).

By applying the modified Shoolery rules [5], namely an increment of 1.3 for phenyl group to the δ values of CH_2-3 group in the related *N,N*-disubstituted 4-amino-3,4-dihydro-6-phenyl-1,2-oxathiin 2,2-dioxides already described [2], the calculated values agree better with those found in the case of compounds III rather than with those of compounds IV. In any case, compounds III showed a downward shift of δ 0.1-0.2 in comparison with the related compounds IV, a fact that is consistent with a better electron availability and a consequent deshielding effect.

The nmr spectral data (Tables II and IV) seem to substantiate conformations III′ and IV′, with CH-3 near axial in both stereoisomers and CH-4 near equatorial in III′ and near axial in IV′. As a matter of fact, by applying Karplus rules to the molecular models, a J value of about 10 Hz is consistent with a dihedral angle of about 180° between C-3 and C-4 protons found in compounds IV when both protons are near axial, whereas a J value of 6-7 Hz is consistent with a dihedral angle of about 30° found in compounds III when the C-3 proton is near axial and C-4 proton is near equatorial. Another feature concerns CH-4, that in conformers III appears as a broad multiplet. This is due to an homoallylic coupling between CH-4 and CH_2-8, possible only when CH-4 is located in the near half-chair conformation III′, not coplanar with the endocyclic double bond.

Some peculiarities of the above cycloaddition deserve a comment. In the reaction of phenylsulfene with the diisopropylamino synthon Ic, a product was isolated in low yield which was proven by elemental analysis and nmr spectral data (Tables I and II) to be the isopropylamino adduct IIIℓ. In this case the bulky dialkylamino group eliminates an alkyl group as propene, in order to allow the cycloaddition to occur. Apparently, the mixture of cycloadducts III and IV was not always obtained. In the case of synthon Id [NR_2 = $N(CH_2CH_2OCH_3)_2$] we obtained in high yield only the cycloadduct IIId, whereas we were able to isolate in low yield only the cycloadduct IVi starting from synthon Ii (NR_2 = diphenylamino). In the latter case we observed a better reactivity of phenylsulfene in comparison with sulfene, that usually does not cycloadd to such enaminones (cf. [2,4]). Morpholinoenaminone If gave a mixture of adducts IIIf and IVf, plus another unidentified compound (nmr spectral data); from this mixture, only IIIf could be obtained pure. Also IIIh could not be obtained

pure. In conclusion, it appears that the lack of stereospecificity in the 1,4-cycloaddition of phenylsulfene to *N,N*-disubstituted *(E)*-2-aminomethylenecyclohexanones supports the existence of a dipolar intermediate such as V, similar to that suggested by us in the case of sulfene [6].

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. The ir spectra were taken in chloroform on a Perkin-Elmer Model 398 spectrophotometer; the nmr spectra were recorded in deuteriochloroform on a Perkin-Elmer Model R-12 instrument (60 MHz, TMS as internal standard, J in Hz). The purity of compounds was checked by tlc (silica gel plates; eluant petroleum ether (bp 40-60°)-diethyl ether 8:2, except adducts h,i where the eluant was petroleum ether-acetone 8:2; spray reagent 0.1 *N* iodine-10% sulfuric acid 2:1). Melting points were determined with a Fisher-Johns apparatus.

N,N-Disubstituted *(E)*-2-Aminomethylenecyclohexanones (Ia-i).

Enaminones Ia [7], Ib,e,f,g [8] and Ic,h,i [2,9] were prepared according to the literature.

Enaminone Ig [8] solidified after distillation *in vacuo*, mp 49° from petroleum ether-diethyl ether 1:1; uv: λ max nm (log ε) 330.5 (4.34); ir (tetrachloromethane): ν max 1652, 1545 cm^{-1}; nmr (tetrachloromethane): δ 1.51 (mc, CH_2-4 + CH_2-5), 2.09 (s, CH_3N), 2.22 (mc, CH_2-6 + CH_2-7 + 2 CH_2N), 3.31 (t, J = 4.8, 2 CH_2N), 7.18 (near s, =CHN).

Enaminone Id was prepared according to a general procedure already described [8], yield, 74%, bp 185°/0.2 mm; uv: λ max nm (log ε) 331 (4.29); ir (tetrachloromethane): ν max 1652, 1535 cm^{-1}; nmr (tetrachloromethane): δ 1.70 (mc, CH_2-4 + CH_2-5), 2.19 (mc, CH_2-3), 2.59 (mc, CH_2-6), 3.36 (s, 2 CH_3O), 3.53 [s, 2 $(CH_2)_2N$], 7.24 (s, =CHN).

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.44; H, 9.54; N, 5.92.

General Procedure for *N,N*-Disubstituted *cis*- and *trans*-4-Amino-3,4,5,6,-7,8-hexahydro-3-phenyl-1,2-benzoxathiin 2,2-Dioxides III and IV.

A solution of phenylmethanesulfonyl chloride (4.19 g, 22 mmoles) in anhydrous benzene (20 ml) was slowly added under nitrogen and with stirring, to a solution of I (20 mmoles) and triethylamine (2.23 g, 22 mmoles) in the same solvent (100 ml) at room temperature. The reaction mixture was stirred for 30 minutes, filtered and the solution was evaporated under reduced pressure. The residue was worked up as described below.

IIIa + IVa.

The oily residue was dissolved by gentle warming in the minimum amount of diethyl ether-acetone 5:1 to give by cooling a precipitate, which was chromatographed on silica gel to afford IIIa with petroleum ether-diethyl ether 10:1 and IVa with diethyl ether-acetone 5:2 as eluants.

IIIb,e + IVb,e.

The oily residue was purified by chromatography on Florisil (diethyl ether-acetone 5:1); by chromatography on silica gel, IIIb,e (petroleum ether-diethyl ether 10:1) and IVb,e (diethyl ether-acetone 5:2) were isolated.

IIId,ℓ and IIIg + IVg.

The oily residue was purified by chromatography on silica gel (diethyl ether-acetone 5:1) to give IIId,ℓ and IIIg + IVg. The latter mixture was further chromatographed on silica gel to give IVg (diethyl ether) and IIIg (acetone-chloroform 2:1).

IVi.

This adduct was obtained pure from the oily residue by chromatography on silica gel (petroleum ether).

IIIf.

The solid residue was treated with benzene (25 ml) at room temperature, the residue was dissolved in acetone and chromatographed on silica gel (acetone) to give pure IIIf. We were unable to isolate IVf and a third component present in the mixture by chromatography on silica gel of the benzene solution.

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REFERENCES AND NOTES

[1] A. Bargagna, F. Evangelisti and P. Schenone, *J. Heterocyclic Chem.*, **18**, 111 (1981), and references cited therein.

[2] F. Evangelisti, P. Schenone and A. Bargagna, *ibid.*, **16**, 217 (1979), and references cited therein.

[3] G. Menozzi, L. Mosti, P. Schenone and S. Cafaggi, *ibid.*, **19**, 937 (1982).

[4] A. Bargagna, P. Schenone, F. Bondavalli and M. Longobardi, *ibid.*, **17**, 33 (1980).

[5] "Nuclear Magnetic Resonance for Organic Chemists", D. W. Mathieson, ed, Academic Press, New York, 1967, p 182.

[6] P. Schenone, L. Mosti, G. Bignardi and A. Tasca, *Ann. Chim. (Rome)*, **64**, 603 (1974).

[7] J. Dabrowski and K. Kamienska-Trela, *Spectrochim. Acta*, **22**, 211 (1966).

[8] A. Gandini, P. Schenone and G. Bignardi, *Monatsh. Chem.*, **98**, 1518 (1967).

[9] G. Bignardi, P. Schenone and F. Evangelisti, *Ann. Chim. (Rome)*, **61**, 326 (1971).