Reaction of Sulfenes with Heterocyclic *N,N*-Disubstituted α-Aminomethyleneketones. XII. Synthesis of [1]Benzothiepino[4,5-*e*][1,2]oxathiin Derivatives

Giulia Menozzi, Alberto Bargagna, Luisa Mosti and Pietro Schenone*

Istituto di Scienze Farmaceutiche dell'Università, Viale Benedetto XV-3
16132 Genova, Italy

Received July 22, 1985

The 1,4-cycloaddition of sulfene to *N,N*-disubstituted (*E*)-4-aminomethylene-3,4-dihydro[1]benzothiepin-5(2*H*)-ones I occurred only in the case of aliphatic *N,N*-disubstitution to give in good yield 4-dialkylamino-3,4,5,6-tetrahydro[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-dioxides, which are derivatives of the new heterocyclic system [1]benzothiepino[4,5-*e*][1,2]oxathiin. Also the reaction of I with chlorosulfene occurred only in the case of aliphatic *N,N*-disubstitution to afford chiefly *trans*-4-dialkylamino-3-chloro-3,4,5,6-tetrahydro-[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-dioxides III in satisfactory yield. Adducts III were dehydrochlorinated with DBN to 4-dialkylamino-5,6-dihydro[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-dioxides in good yield.

J. Heterocyclic Chem., **23**, 455 (1986).

In a previous paper [1] we described the synthesis of a new heterocyclic system derived from 1,2-oxathiin and incorporating the 1-benzoxepin moiety, namely [1,2]oxathiino[5,6-*d*][1]benzoxepin.

In pursuing our work on the polar 1,4-cycloaddition of sulfenes to heterocyclic *N,N*-disubstituted α-aminomethyleneketones, we now wish to report the reaction of *N,N*-disubstituted (*E*)-4-aminomethylene-3,4-dihydro[1]benzothiepin-5(2*H*)-ones I with sulfene and chlorosulfene to afford derivatives of a new heterocyclic system containing the 1,2-oxathiin ring fused with the 1-benzothiepin moiety, the thioisoster of 1-benzoxepin, namely [1]benzothiepino-[4,5-*e*][1,2]oxathiin.

The reaction of enaminones Ia-g [3] with methanesulfonyl chloride and triethylamine (sulfene prepared *in situ*) occurred only in the case of aliphatic *N,N*-disubstitution to

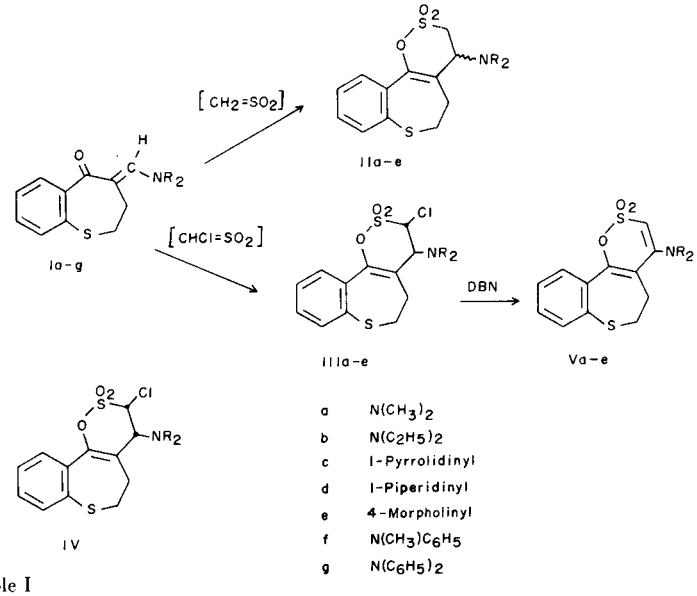
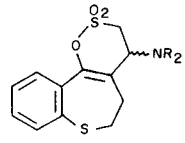


Table I

N,N-Disubstituted 4-Amino-3,4,5,6-tetrahydro[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-Dioxides IIa-e



Formula Number	NR_2	Yield %	Mp °C [a]	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa	$N(CH_3)_2$	81	162	$C_{14}H_{17}NO_3S_2$	54.00	5.50	4.50
					54.25	5.49	4.61
IIb	$N(C_2H_5)_2$	62	137	$C_{16}H_{21}NO_3S_2$	56.61	6.23	4.13
					56.87	6.18	4.38
IIc	1-Pyrrolidinyl	68	151	$C_{16}H_{19}NO_3S_2$	56.95	5.67	4.15
					56.99	5.66	4.29
IId	1-Piperidinyl	74	198	$C_{17}H_{21}NO_3S_2$	58.09	6.02	3.98
					57.96	6.04	4.07
IIe	4-Morpholinyl	69	203	$C_{16}H_{19}NO_4S_2$	54.37	5.42	3.96
					54.41	5.40	4.10

[a] From 95% ethanol.

Table II

IR and NMR Spectral Data of Compounds IIa-e

Compound	IR, cm^{-1} C=C	O=S=O		NMR, δ
IIa	1663	1377	1172	1.85-2.80 (m, CH_2-5), 2.43 [s, $(CH_3)_2N$], 2.95-3.75 (m, CH_2-3 + CH_2-6), 3.80-4.25 (m, CH-4), 7.2-7.8 (m, 4 H ar)
IIb	1660	1375	1168	1.13 (t, J = 7, 2 CH_3), 1.60-3.15 (m, CH_2-5 + 2 CH_2N), 3.15-3.85 (m, CH_2-3 + CH_2-6), 4.0-4.4 (m, CH-4), 7.45 (mc, 4 H ar)
IIc	1663	1373	1176	1.80 (mc, 2 CH_2 pyr), 2.75 (mc, CH_2-5 + 2 CH_2N), 3.1-3.9 (m, CH_2-3 + CH_2-6), 4.05-4.45 (m, CH-4), 7.1-7.8 (m, 4 H ar)
IId	1662	1376	1183	1.55 (mc, 3 CH_2 pip), 2.53 (mc, CH_2-5 + 2 CH_2N), 3.1-3.7 (m, CH_2-3 + CH_2-6), 3.8-4.2 (m, CH-4), 7.45 (mc, 4 H ar)
IIe	1662	1377	1185	1.6-2.9 (m, CH_2-5 + 2 CH_2N), 3.0-4.3 (m, CH_2-3 + CH_2-6 + CH-4 + 2 CH_2O), 7.46 (mc, 4 H ar)

Table IV

IR and NMR Spectral Data of Compounds IIIa-e

Compound	IR, cm^{-1} C=C	O=S=O		NMR, δ
IIIa	1665	1392	1185	2.20 (mc, CH_2-5), 2.69 [s, $(CH_3)_2N$], 3.45 (mc, CH_2-6), 4.02 (d, J = 8.4, CH-4), 5.36 (d, J = 8.4, CH-3), 7.47 (mc, 4 H ar)
IIIb	1665	1392	1184	1.14 (t, J = 6.9, 2 CH_3), 2.20 (mc, CH_2-5), 2.93 (q, J = 6.9, 2 CH_2N), 3.50 (mc, CH_2-6), 4.16 (d, J = 8.4, CH-4), 5.34 (d, J = 8.4, CH-3), 7.43 (mc, 4 H ar)
IIIc	1675 1631	1388	1188	1.86 (mc, 2 CH_2 pyr), 2.33 (mc, CH_2-5), 2.6-3.9 (m, CH_2-6 + 2 CH_2N), 4.33 (d, J = 8.4, CH-4), 5.39 (d, J = 8.4, CH-3), 7.46 (mc, 4 H ar)
IIId	1665	1388	1185	1.50 (mc, 3 CH_2 pip), 1.7-3.7 (m, CH_2-5 + CH_2-6 + 2 CH_2N), 3.90 (d, J = 8.4, CH-4), 5.33 (d, J = 8.4, CH-3), 7.39 (mc, 4 H ar)
IIIe	1643	1392	1186	1.6-3.9 (m, CH_2-5 + CH_2-6 + 2 CH_2N + 2 CH_2O), 4.02 (d, J = 8.4, CH-4), 5.44 (d, J = 8.4, CH-3), 7.47 (mc, 4 H ar)

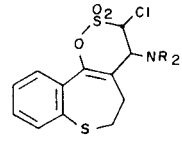
give in good yield 4-dialkylamino-3,4,5,6-tetrahydro[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-dioxides IIa-e (Table I), whose structure was confirmed by ir and nmr spectral data (Table II).

Enaminones If (NR_2 = methylphenylamino) and Ig (NR_2 = diphenylamino) did not react and were recovered unchanged from the reaction mixture, according to a well established trend of this reaction (*cf.* [1]).

According to our recently described cycloaddition of chlorosulfene to *N,N*-disubstituted α-aminomethyleneketones [2], also the reaction of enaminones I with chloromethanesulfonyl chloride and triethylamine (chlorosulfene prepared *in situ*) occurred only in the case of aliphatic *N,N*-disubstitution to yield, apparently as a sole compound, the more stable cycloadduct, namely *trans*-4-dialkylamino-3-chloro-3,4,5,6-tetrahydro[1]benzothiepino-[4,5-*e*][1,2]oxathiin 2,2-dioxides IIIa-e (Table III) in satis-

Table III

N,N-Disubstituted *trans*-4-Amino-3-chloro-3,4,5,6-tetrahydro[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-Dioxides IIIa-e

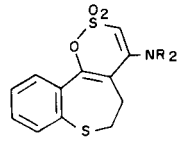


Formula Number	NR_2	Yield %	Mp °C [a]	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$N(CH_3)_2$	88 [b]	158	$C_{14}H_{16}ClNO_3S_2$	48.62	4.66	4.05
					48.66	4.58	4.09
IIIb	$N(C_2H_5)_2$	54	126	$C_{16}H_{20}ClNO_3S_2$	51.39	5.39	3.75
					51.50	5.38	3.69
IIIc	1-Pyrrolidinyl	41	165	$C_{16}H_{18}ClNO_3S_2$	51.67	4.88	3.77
					51.65	4.85	3.60
IIId	1-Piperidinyl	83	162	$C_{17}H_{20}ClNO_3S_2$	52.91	5.22	3.63
					52.65	5.22	3.48
IIIe	4-Morpholinyl	54	169	$C_{16}H_{18}ClNO_4S_2$	49.54	4.68	3.61
					49.60	4.80	3.81

[a] From anhydrous diethyl ether. [b] Calculated on IIIa + IVa mixture.

Table V

N,N-Disubstituted 4-Amino-5,6-dihydro[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-Dioxides Va-e [a]



Formula Number	NR_2	Yield %	Mp °C [b]	Molecular Formula	Analyses % Calcd./Found C	H	N
Va	$N(CH_3)_2$	85 [c]	198	$C_{14}H_{15}NO_3S_2$	54.35	4.89	4.53
					54.20	4.86	4.50
Vb	$N(C_2H_5)_2$	80	138	$C_{16}H_{19}NO_3S_2$	56.95	5.67	4.15
					56.86	5.71	4.12
Vc	1-Pyrrolidinyl	75	209	$C_{16}H_{17}NO_3S_2$	57.29	5.11	4.17
					57.07	5.07	4.02
Vd	1-Piperidinyl	78	205	$C_{17}H_{19}NO_3S_2$	58.43	5.48	4.01
					58.19	5.39	4.12
Ve	4-Morpholinyl	76	186	$C_{16}H_{17}NO_4S_2$	54.68	4.88	3.98
					54.57	4.82	4.04

[a] All compounds were prepared from IIIa-e by dehydrochlorination with DBN according to a previously described procedure [2]: reflux time, 2 hours; purification by silica gel chromatography (diethyl ether). [b] From anhydrous diethyl ether. [c] From IIIa + IVa mixture.

Table VI

UV, IR and NMR Spectral Data of Compounds Va-e

Compound	UV λ max nm (log ε)	IR, cm^{-1} C=C	O=S=O	NMR, δ
Va	226 (4.13)	1618	1358	2.54 (t, J = 7.8, CH_2-5), 2.92 [s, $(CH_3)_2N$], 3.63 (t, J = 7.8, CH_2-6),
	233 sh (4.08)	1548	1165	5.70 (s, CH-3), 7.63 (mc, 4 H ar)
	251 sh (3.79)			
	277 sh (3.92)			
	296.5 (4.02			
Vb	227 (4.07)	1614	1355	1.19 (t, J = 6.6, 2 CH_3), 2.48 (t, J = 7.2, CH_2-5), 3.22 (q, J = 6.6,
	234 sh (4.03)	1542	1162	2 CH_2N), 3.55 (t, J = 7.2, CH_2-6), 5.78 (s, CH-3), 7.60 (mc, 4 H ar)
	250 sh (3.74)			
	276 sh (3.84)			
	299 (3.98)			
Vc	226 (4.12)	1612	1350	1.91 (mc, 2 CH_2 pyr), 2.44 (t, J = 7.2, CH_2-5), 3.29 (mc, 2 CH_2N),
	235 sh (4.07)	1528	1155	3.53 (t, J = 7.2, CH_2-6), 5.37 (s, CH-3), 7.50 (mc, 4 H ar)
	275 sh (3.95)			
	295 (4.00)			
Vd	227 (4.13)	1618	1355	1.66 (mc, 3 CH_2 pip), 2.52 (t, J = 7.2, CH_2-5), 3.06 (mc, 2 CH_2N),
	233 sh (4.095)	1547	1160	3.54 (t, J = 7.2, CH_2-6), 5.82 (s, CH-3), 7.60 (mc, 4 H ar)
	252 sh (3.78)			
	278 sh (3.91)			
	300 (4.05)			
Ve	226 (4.06)	1617	1363	2.56 (t, J = 7.2, CH_2-5), 3.09 (mc, 2 CH_2N), 3.51 (t, J = 7.2, CH_2-6),
	233 sh (4.01)	1550	1160	3.83 (mc, 2 CH_2O), 5.92 (s, CH-3), 7.50 (mc, 4 H ar)
	254 sh (3.74)			
	278 sh (3.90)			
	300 (4.03)			

factory yield. In the case of enaminone Ia, a mixture of IIIa and *cis* adduct IVa in a ratio of about 3:2 (nmr) was obtained, from which only IIIa could be isolated by silica gel chromatography.

The *trans* conformation of IIIa-e could be deduced from their nmr spectra (Table IV), where the signals of CH-3 and CH-4 appeared as two doublets (J = 8.4 Hz) at δ 5.3-5.4 and 3.9-4.3, respectively (*cf.* [2]).

The adducts IIIa-e were dehydrochlorinated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in refluxing benzene to give in good yield 4-dialkylamino-5,6-dihydro[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-dioxides Va-e (Table V), showing CH-3 as a singlet at δ 5.4-5.9 (Table VI) [2].

As in the preceding case [2], a fully dehydrogenated

1,2-oxathiin 2,2-dioxide ring could thus be introduced with this procedure in the final heterocyclic system.

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-600 instrument (60 MHz, TMS as internal standard, J in Hz). Melting points were determined with a Mettler FP1 apparatus.

General Procedure for *N,N*-Disubstituted 4-Amino,3,4,5,6-tetrahydro-[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-Dioxides II (Table I).

Methanesulfonyl chloride (1.15 g, 10 mmoles) dissolved in anhydrous tetrahydrofuran (30 ml) was added dropwise under nitrogen to a well stirred, ice-cooled solution of enaminone I [3] (10 mmoles) and triehtylamine (1.11 g, 11 mmoles) in the same solvent (100 ml). The mixture was stirred at room temperature for 4 hours, filtered and the solution was evaporated under reduced pressure. The residue was treated with a little anhydrous diethyl ether to give a solid which was purified by recrystallization from 95% ethanol.

General Procedure for *N,N*-Disubstituted *trans*-4-Amino-3-chloro-3,4,5,6-tetrahydro-[1]benzothiepino[4,5-*e*][1,2]oxathiin 2,2-Dioxides III (Table III).

Chloromethanesulfonyl chloride (1.64 g, 11 mmoles) dissolved in anhydrous benzene (20 ml) was slowly added under nitrogen to a well stirred solution of enaminone I [3] (10 mmoles) and triethylamine (10 g, ~0.1 moles) in the same solvent (100 ml) at room temperature. The reaction mixture was refluxed under nitrogen for 20 minutes, cooled and filtered, and the solution was evaporated under reduced pressure. The oily residue was chromatographed on silica gel (diethyl ether) to give pure adducts IIIb-e. The reaction with Ia yielded a mixture of stereoisomers IIIa and IVa in a ratio of about 3:2 (nmr), from which only the more stable *trans* adduct IIIa could be isolated by the silica gel chromatography.

The following significant nmr data of *cis* adduct IVa were obtained from the spectrum of the mixture IIIa + IVa: δ 4.48 (d, J = 4.8, CH-4), 5.50 (d, J = 4.8, CH-3 (*cf.* [2]).

Acknowledgement.

The authors wish to thank Mr. A. Panaro for the microanalyses and Mr. F. Fasce and C. Rossi for the uv, ir and nmr spectra.

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