Reaction of Sulfene with Heterocyclic *N,N*-Disubstituted α-Aminomethyleneketones. VII. Synthesis of 1,2-Oxathiino-[5,6-*g*]benzothiazole Derivatives

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The polar 1,4-cycloaddition of sulfene to *N,N*-disubstituted 6-aminomethylene-5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)ones gave, generally in good yield, *N,N*-disubstituted 3,4,5,6-tetrahydro-8-phenyl-1,2-oxathiino-[5,6-*g*]benzothiazol-4-amine 2,2-dioxides, which are derivatives of the new heterocyclic system 1,2-oxathiino-[5,6-*g*]benzothiazole. This reaction did not occur only with the *N,N*-diphenylenaminone.

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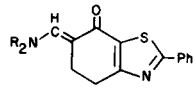
As part of our continuing study of sulfene dipolar 1,4-cycloadditions to *N,N*-disubstituted α-aminomethyleneketones, we became interested in the synthesis of new heterocyclic systems derived from 1,2-oxathiin and incorporating potential pharmacologically active molecules such as indole (1), pyridine and quinoline (2). In this context, we now wish to report the reaction of *N,N*-disubstituted 6-aminomethylene-5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)ones III with sulfene to give derivatives of a new heterocyclic system incorporating the benzothiazole nucleus, namely, 1,2-oxathiino[5,6-*g*]-benzothiazole (3).

We have chosen 5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)-one (I) (4) as the starting ketone with a benzothiazole skeleton in order to obtain 5,6-dihydro-6-hydroxymethylene-2-phenylbenzothiazol-7-(4*H*)one (II) in good yield by reaction with ethyl formate and sodium methoxide in benzene (5). The starting enaminones IIIa-h (Table I) were prepared, generally in good yield, from II and secondary amines, following previously described procedures (7, 8). They are probably *E* isomers, at least as can be determined from the strong upfield shift of the C-5 methylene protons (~0.6-0.9 ppm) caused by the phenyl group(s) in compounds IIIg,h in comparison with IIIa-f (Table II).

Reaction of III with methanesulfonyl chloride and triethylamine (sulfene prepared *in situ*) occurred readily, generally in good to fair yield, only in the case of aliphatic

Table I

N,N-Disubstituted 6-Aminomethylene-5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)ones (IIIa-h) (a)



Compound No.	NR_2	Yield %	M.p. °C (b)	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$N(CH_3)_2$	79	161	$C_{16}H_{16}N_2OS$	67.58	5.67	9.85
					67.32	5.40	9.60
IIIb	$N(C_2H_5)_2$	65	123	$C_{18}H_{20}N_2OS$	69.20	6.45	8.97
					69.13	6.47	8.84
IIIc	$N[CH(CH_3)_2]_2$	33	162	$C_{20}H_{24}N_2OS$	70.55	7.11	8.23
					70.65	7.15	8.14
IIId	pyrrolidino	97	197	$C_{18}H_{18}N_2OS$	69.65	5.85	9.02
					69.70	5.73	8.94
IIIe	piperidino	72	146	$C_{19}H_{20}N_2OS$	70.34	6.21	8.63
					70.05	6.28	8.56
IIIf	morpholino	81	217	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58
					66.50	5.59	8.37
IIIg	$N(CH_3)C_6H_5$	82	153	$C_{21}H_{18}N_2OS$	72.81	5.24	8.09
					72.80	5.10	8.32
IIIh	$N(C_6H_5)_2$	87	195	$C_{26}H_{20}N_2OS$	76.44	4.93	6.86
					76.34	5.09	6.60

(a) Compounds IIIa,b,d,e,f were prepared according to reference 7, and IIIc,g,h were prepared according to reference 8. (b) From ethyl acetate.

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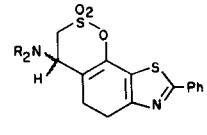
Table II

Uv, Ir and Nmr Spectral Data of Compounds IIIa-h

Compound No.	Uv λ max nm (log ε)	Ir, cm^{-1} C=O	Ir, cm^{-1} C=C	Nmr, δ
IIIa	239.5 (4.21) 315 (4.10) 404 (4.35)	1630	1542	3.07 (near s, CH_2-4 + CH_2-5), 3.13 (s, $2NCH_3$), 7.48 (mc, 3H ar 2*m* + 1*p*), 7.57 (near s, =CHN), 7.80-8.15 (m, 2H ar *o*)
IIIb	239.5 (4.23) 316 (4.14) 405 (4.37)	1630	1543	1.27 (t, J = 7.2, $2CH_3$), 3.05 (near s, CH_2-4 + CH_2-5), 3.40 (q, J = 7.2, $2NCH_2$), 7.50 (mc, 3H ar 2*m* + 1*p*), 7.65 (near s, =CHN), 7.80-8.15 (m, 2H ar *o*)
IIIc	239.5 (4.12) 313 (4.04) 411 (4.26)	1622	1540	1.30 (d, J = 6.9, $4CH_3$), 3.05 (mc, CH_2-4 + CH_2-5), 3.95 (mc, 2NCH), 7.50 (mc, 3H ar 2*m* + 1*p*), 7.87 (near s, =CHN), 7.90-8.15 (m, 2H ar *o*)
IIId	240 (4.15) 314 (4.07) 409 (4.30)	1633	1545	1.87 (mc, $2CH_2$ pyrr.), 3.06 (mc, CH_2-4 + CH_2-5), 3.60 (mc, $2NCH_2$), 7.46 (mc, 3H ar 2*m* + 1*p*), 7.80 (near s, =CHN), 8.00 (mc, 2H ar *o*)
IIIe	239.5 (4.20) 312 (4.08) 408 (4.35)	1630	1545	1.66 (mc, $3CH_2$ pip.), 3.06 (mc, CH_2-4 + CH_2-5), 3.48 (mc, $2NCH_2$), 7.51 (mc, 3H ar 2*m* + 1*p*), 7.60 (near s, =CHN), 7.8-8.2 (m, 2H ar *o*)
IIIf	240.5 (4.24) 318 (4.11) 402 (4.38)	1628	1542	3.04 (mc, CH_2-4 + CH_2-5), 3.57 (mc, $2NCH_2$), 3.70 (mc, 2 OCH_2), 7.50 (mc, 3H ar 2*m* + 1*p* + =CHN), 7.97 (mc, 2H ar *o*)
IIIg	242.5 (4.04) 317.5 (3.99) 411 (4.27)	1638	1550	2.44 (mc, CH_2-5), 2.92 (mc, CH_2-4), 3.46 (s, NCH_3), 6.9-7.6 (m, NC_6H_5 + 3H ar 2*m* + 1*p*), 7.72 (near s, =CHN), 7.80-8.15 (m, 2H ar *o*)
IIIh	248 (4.31) 300 (4.21) 323 (4.23) 417 (4.50)	1635	1545	2.15 (mc, CH_2-5), 2.88 (mc, CH_2-4), 6.90-7.65 (m, $2NC_6H_5$ + 3H ar 2*m* + 1*p*), 7.8-8.2 (m, 2H ar *o* + =CHN)

Table III

N,N-Disubstituted 3,4,5,6-Tetrahydro-8-phenyl-1,2-oxathiino[5,6-*g*]benzothiazol-4-amine 2,2-Dioxides (IVa-g) (a)



Compound No.	NR_2	Yield %	M.p. °C (b)	Molecular Formula	Analyses % Calcd./Found C	H	N
IVa	$N(CH_3)_2$	67	176	$C_{17}H_{18}N_2O_3S_2$	56.33 56.43	5.01 4.85	7.73 7.51
IVb	$N(C_2H_5)_2$	58	168	$C_{19}H_{22}N_2O_3S_2$	57.44 58.34	5.68 5.83	7.17 6.88
IVc	$N[CH(CH_3)_2]_2$	22	184	$C_{21}H_{26}N_2O_3S_2$	60.26 60.27	6.26 6.30	6.69 6.64
IVd	pyrrolidino	65	162	$C_{19}H_{20}N_2O_3S_2$	58.74 58.64	5.19 5.37	7.21 7.09
IVe	piperidino	64	190	$C_{20}H_{22}N_2O_3S_2$	59.68 59.39	5.51 5.68	6.96 6.80
IVf	morpholino	78	210	$C_{19}H_{20}N_2O_4S_2$	56.42 56.37	4.98 5.10	6.93 6.63
IVg	$N(CH_3)C_6H_5$	10 (c)	152	$C_{22}H_{20}N_2O_3S_2$	62.24 62.57	4.75 4.74	6.60 6.44

(a) Compounds were prepared according to reference 7. (b) From 95% ethanol. (c) Obtained from the crude reaction mixture by chromatography on Florisil ® (petroleum ether (b.p. 40-70°)-benzene 30:70). The starting enaminone was partly recovered by eluting with ether and benzene.

Table IV

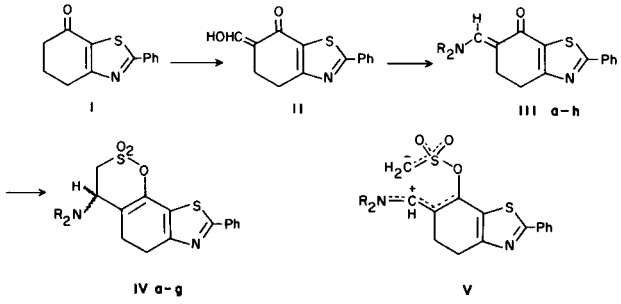
Ir and Nmr Spectral Data of Compounds IVa-g

Compound No.	Ir, cm^{-1} C=C	Ir, cm^{-1} O=S=O		Nmr, δ
IVa	1638	1380	1178	2.36 (s, $2NCH_3$), 2.88 and 3.03 (2m, CH_2-5 + CH_2-6), 3.15-3.60 (m, CH_2-3), 3.90-4.25 (m, CH-4), 7.25-7.55 (m, 3H ar 2*m* + 1*p*), 7.75-8.05 (m, 2H ar *o*)
IVb	1635	1382	1179	1.10 (t, J = 6.9, $2CH_3$), 2.36 and 2.47 (2 superimp. q, J = 6.6, $2NCH_2$), 2.85 and 2.98 (2m, CH_2-5 + CH_2-6), 3.1-3.6 (m, CH_2-3), 3.95-4.35 (m, CH-4), 7.2-7.6 (m, 3H ar 2*m* + 1*p*), 7.7-8.1 (m, 2H ar *o*)
IVc	1635	1373	1190 1180	1.13 (near d, J = 6.6, $4CH_3$), 2.5-3.7 (m, 2NCH + CH_2-3 + CH_2-5 + CH_2-6), 4.00-4.45 (m, CH-4), 7.20-7.55 (m, 3H ar 2*m* + 1*p*), 7.75-8.05 (m, 2H ar *o*)
IVd	1635	1380	1183	1.80 (mc, $2CH_2$ pyrr.), 2.45-3.40 (m, $2NCH_2$ + CH_2-5 + CH_2-6), 3.45-3.95 (m, CH_2-3), 4.15-4.55 (m, CH-4), 7.45 (mc, 3H ar 2*m* + 1*p*), 7.7-8.1 (m, 2H ar *o*)
IVe	1637	1382	1187	1.55 (mc, $3CH_2$ pip.), 2.55 (mc, $2NCH_2$), 2.88 and 3.01 (2m, CH_2-5 + CH_2-6), 3.3-4.3 (m, CH_2-3 + CH-4), 7.45 (mc, 3H ar 2*m* + 1*p*), 7.65-8.10 (m, 2H ar *o*)
IVf	1638	1387	1192	(a)
IVg	1640	1382	1182	2.4-3.1 (m, CH_2-5 + CH_2-6), 2.90 (s, NCH_3), 3.15-3.70 (m, CH_2-3), 4.90-5.35 (m, CH-4), 6.7-7.6 (m, 8H ar), 7.7-8.1 (m, 2H ar *o*)

(a) The product was insufficiently soluble in the common solvents employed for nmr measurement.

N,N-disubstitution (IIIa-f) to give *N,N*-dialkyl-3,4,5,6-tetrahydro-8-phenyl-1,2-oxathiino[5,6-*g*]benzothiazol-4-amine 2,2-dioxides (IVa-f) (Table III), the structures of which were confirmed by ir and nmr spectral data (Table IV). Enaminone IIIg (*N*-methyl, *N*-phenyl) gave IVg in very low yield, whereas IIIh (*N,N*-diphenyl) did not react at all and was recovered unchanged from the reaction mixture. These facts could be due to a diminished electron availability on the nitrogen atom of the enaminone, which destabilizes the supposed polar intermediate V [*cf.* (9)].

Compounds IVa,b were tested regarding anti-ADH diuresis in the rat (10); none were found to be active.



EXPERIMENTAL

Uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. Ir spectra were taken in chloroform on a Perkin-Elmer Model 257 spectrophotometer, and nmr spectra were recorded in deuteriochloroform on a Perkin-Elmer Model R12 instrument (60 MHz; TMS as internal standard; J in Hz). Melting points were determined with a Fisher-Johns apparatus.

5,6-Dihydro-6-hydroxymethylene-2-phenylbenzothiazol-7-(4*H*)one (II).

This compound was prepared from I (4), ethyl formate and sodium methoxide in benzene following a previously described procedure (5), yield 93%, mp 125° from *n*-hexane; uv: λ max nm (logε) 233 (4.17), 346.5 (4.43); ir (tetrachloromethane): ν max 1632, 1578 cm^{-1}; nmr (tetrachloromethane): δ 2.65 (mc, CH_2-4), 3.04 (mc, CH_2-5), 7.44 (mc, =CH-O + 3H ar 2*m* + 1*p*), 7.92 (mc, 2H ar *o*), 11.95 (broad m, OH; disappears with deuterium oxide).

Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.06; H, 4.45; N, 5.14.

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(5) The procedure was the same described for the preparation of 1,5,6,7-tetrahydro-5-hydroxymethylene-2-methyl-1-phenylindol-4-one (1); see also reference 6 for the synthesis of 5,6-dihydro-6-hydroxymethylene-2-methylbenzothiazol-7-(4*H*)one.

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(10) The biological determinations were made by Smith, Kline and French Laboratories, Philadelphia, PA.