Reaction of Sulfene with Heterocyclic *N,N*-Disubstituted α-Aminomethyleneketones. XI. Synthesis of 1,2-Oxathiino[5,6-*d*]-1-benzoxepin Derivatives

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Received February 19, 1982

The 1,4-cycloaddition of sulfene to *N,N*-disubstituted (*E*)-4-aminomethylene-3,4-dihydro-1-benzoxepin-5(2*H*)-ones gave, generally in excellent yield, *N,N*-disubstituted 4-amino-3,4,5,6-tetrahydro-1,2-oxathiino-[5,6-*d*]-1-benzoxepin 2,2-dioxides, which are derivatives of the new heterocyclic system 1,2-oxathiino[5,6-*d*]-1-benzoxepin. This reaction did not occur only with the *N,N*-diphenylenaminone.

J. Heterocyclic Chem., **19**, 937 (1982).

In pursuing our study of sulfene 1,4-cycloaddition to heterocyclic *N,N*-disubstituted α-aminomethyleneketones in order to synthesize new heterocyclic systems derived from 1,2-oxathiin and incorporating potential pharmacologically active molecules (1), we now wish to report the reaction of *N,N*-disubstituted (*E*)-4-aminomethylene-3,4-dihydro-1-benzoxepin-5(2*H*)-ones III with sulfene to afford derivatives of a new heterocyclic system incorporating the pharmacologically interesting 1-benzoxepin moiety (2), namely 1,2-oxathiino[5,6-*d*]-1-benzoxepin (3).

The starting enaminones IIIa-h (Table I) were prepared in excellent yield from 3,4-dihydro-4-hydroxymethylene-1-benzoxepin-5(2*H*)-one II and secondary amines, following previously described procedures (6,7). They are probably *E* isomers, at least as can be seen from the upfield shifts of the CH_2-2 (~0.15-0.3 δ) and CH_2-3 (~0.35-0.6 δ) protons caused by the phenyl group(s) in compounds

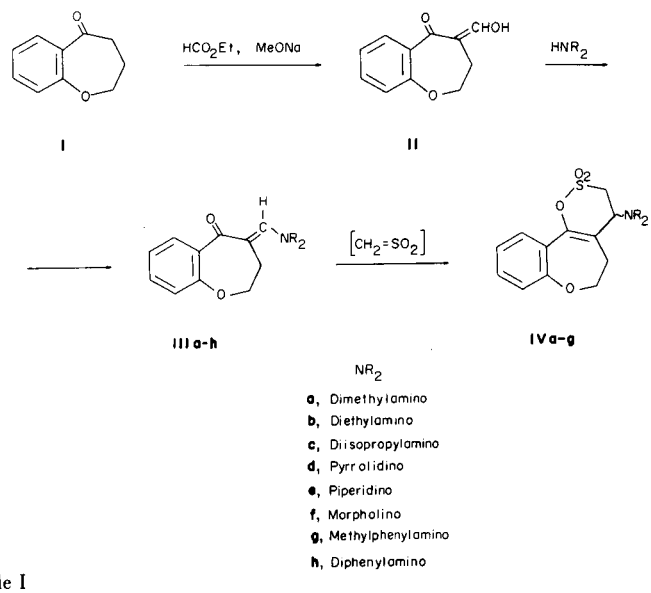
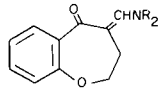


Table I

N,N-Disubstituted (*E*)-4-Aminomethylene-3,4-dihydro-1-benzoxepin-5(2*H*)-ones (a)



Formula Number	NR_2	Yield %	Mp °C (b)	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	Dimethylamino	91	104	$C_{13}H_{15}NO_2$	71.87	6.96	6.45
					71.64	7.07	6.36
IIIb	Diethylamino	77	65	$C_{15}H_{19}NO_2$	73.44	7.81	5.71
					73.71	7.81	5.63
IIIc	Diisopropylamino	83	116	$C_{17}H_{23}NO_2$	74.97	8.39	5.07
					75.20	8.64	5.22
IIId	Pyrrolidino	97	107	$C_{15}H_{17}NO_2$	74.05	7.04	5.76
					73.75	6.85	5.76
IIIe	Piperidino	96	105	$C_{16}H_{19}NO_2$	74.68	7.44	5.44
					74.40	7.62	5.47
IIIf	Morpholino	96	150	$C_{15}H_{17}NO_3$	69.48	6.61	5.40
					69.30	6.50	5.36
IIIg	Methylphenylamino	89	89	$C_{18}H_{17}NO_2$	77.40	6.13	5.01
					77.42	6.26	5.00
IIIh	Diphenylamino	82	134	$C_{23}H_{19}NO_2$	80.92	5.61	4.10
					80.81	5.75	3.99

(a) Enaminones IIa,b,d,e,f and IIc,g,h were prepared according to the literature (6) and (7), respectively. (b) From ethyl acetate.

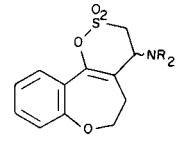
Table II

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

	UV λ max nm (log ε)	IR, cm^{-1} C=O	IR, cm^{-1} C=C	NMR, δ
IIIa	214 (4.08) 250.5 (3.89) 351 (4.24)	1652	1545	2.74 (near t, J = 6, CH_2-3), 3.12 (s, 2 CH_3N), 4.26 (t, J = 6, CH_2-2), 6.90-7.55 (m, 3 H aryl), 7.73 (dd, J′ = 7.2, J″ = 2.4, CH-6), 7.74 (near s, = CHN)
IIIb	214 (4.01) 250.5 (3.80) 351 (4.18)	1646	1535	1.24 (t, J = 7.2, 2 CH_3), 2.67 (t, J = 6, CH_2-3), 3.36 (q, J = 7.2, 2 CH_2N), 4.27 (t, J = 6, CH_2-2), 6.9-7.9 (m, 4 H aryl), 7.82 (mc, =CHN)
IIIc	211 (4.10) 250.5 (3.90) 355.5 (4.31)	1640	1523	1.25 (d, J = 6.6, 4 CH_3), 2.67 (t, J = 6, CH_2-3), 3.86 (h, J = 6.6, 2 CHN), 4.24 (t, J = 6, CH_2-2), 6.90-7.55 (m, 3 H aryl), 7.77 (dd, J′ = 7.2, J″ = 2.4, CH-6), 8.01 (near s, =CHN)
IIId	212.5 (3.95) 252.5 (3.77) 355.5 (4.24)	1645	1530	1.91 (mc, 2 CH_2 pyrr), 2.70 (t, J = 6, CH_2-3), 3.54 (mc, 2 CH_2N), 4.23 (t, J = 6, CH_2-2), 6.9-7.6 (m, 3 H aryl), 7.75 (dd, J′ = 7.2, J″ = 2.4, CH-6), 7.97 (near s, =CHN)
IIIe	213.5 (4.03) 251.5 (3.85) 355 (4.27)	1643	1530	1.64 (mc, 3 CH_2 pip), 2.68 (t, J = 5.4, CH_2-3), 3.42 (mc, 2 CH_2N), 4.23 (t, J = 6, CH_2-2), 6.9-7.6 (m, 3 H aryl), 7.83 (near s, =CHN), 7.85 (dd, J′ = 7.2, J″ = 2.4, CH-6)
IIIf	213 (4.08) 253 (3.84) 351.5 (4.17)	1651	1537	2.72 (t, J = 6, CH_2-3), 3.49 (mc, 2 CH_2N), 3.78 (mc, 2 CH_2O), 4.26 (t, J = 6, CH_2-2), 6.90-7.65 (m, 3 H aryl), 7.65 (near s, =CHN), 7.80 (dd, J′ = 7.2, J″ = 2.4, CH-6)
IIIg	216.5 (4.08) 256 (3.97) 359 (4.21)	1649	1533	2.34 (t, J = 6, CH_2-3), 3.50 (s, CH_3N), 4.09 (t, J = 6, CH_2-2), 6.9-7.6 (m, C_6H_5N + 3 H aryl), 7.80 (dd, J′ = 7.2, J″ = 2.4, CH-6), 7.94 (near s, =CHN)
IIIh	259.5 (4.05) 373 (4.28)	1652	1539	2.08 (t, J = 6, CH_2-3), 3.92 (t, J = 6, CH_2-2), 6.85-7.65 (m, 2 C_6H_5N + 3 H aryl), 7.86 (dd, J′ = 7.2, J″ = 2.4, CH-6), 8.10 (near s, =CHN)

Table III

N,N-Disubstituted 4-Amino-3,4,5,6-tetrahydro-1,2-oxathiino[5,6-*d*]-1-benzoxepin 2,2-Dioxides IVa-g (a)



Formula Number	NR_2	Yield %	Mp °C (b)	Molecular Formula	Analyses % Calcd./Found C	H	N
IVa	Dimethylamino	82	120	$C_{14}H_{17}NO_4S$	56.93	5.80	4.74
					56.88	5.94	4.61
IVb	Diethylamino	75	102	$C_{16}H_{21}NO_4S$	59.42	6.55	4.33
					59.66	6.62	4.19
IVc	Diisopropylamino	79	122	$C_{18}H_{25}NO_4S$	61.51	7.17	3.99
					61.79	7.35	4.05
IVd	Pyrrolidino	76	124	$C_{16}H_{19}NO_4S$	59.79	5.96	4.36
					59.88	5.91	4.23
IVe	Piperidino	78	199	$C_{17}H_{21}NO_4S$	60.87	6.31	4.18
					60.63	6.42	4.19
IVf	Morpholino	78	167	$C_{16}H_{19}NO_5S$	56.96	5.68	4.15
					57.10	5.89	4.03
IVg	Methylphenylamino	21	144	$C_{19}H_{19}NO_4S$	63.85	5.36	3.92
					63.93	5.52	4.06

(a) All compounds were prepared according to the literature (6), using anhydrous THF as the solvent. (b) From 95% ethanol.

IIIg,h in comparison with IIIa-f (Table II).

The reaction of III with methanesulfonyl chloride and triethylamine (sulfene prepared *in situ*) occurred in good yield only in the case of aliphatic *N*-substitution to give *N,N*-disubstituted 4-amino-3,4,5,6-tetrahydro-1,2-oxathiino[5,6-*d*]-1-benzoxepin 2,2-dioxides IVa-g (Table III), whose structure was confirmed by ir and nmr spectral data (Table IV).

Enaminone IIIg (NR_2 = methylphenylamino) gave the corresponding adduct IVg in low yield, whereas IIIh (NR_2

Table IV

IR and NMR Spectral Data of Compounds IVa-g

	IR, cm^{-1} C=C		O=S=O	NMR, δ
IVa	1667	1380	1191 1175	2.35 (s, 2 CH_3N), 2.67 (mc, CH_2-5), 3.3-3.6 (m, CH_2-3), 3.8-4.6 (m, CH-4 + CH_2-6), 6.9-7.4 (m, 3 H aryl), 7.55-7.80 (m, CH-11)
IVb	1662	1378	1186 1172	1.10 (t, J = 7.2, 2 CH_3), 2.07-3.13 (m, CH_2-5 + 2 CH_2N), 3.3-3.6 (m, CH_2-3), 3.95-4.55 (m, CH-4 + CH_2-6), 6.95-7.45 (m, 3 H aryl), 7.55-7.85 (m, CH-11)
IVc	1649	1370	1191 1181	1.11 (d, J = 6.6, 4 CH_3), 2.4-2.8 (m, CH_2-5), 3.22 (h, J = 6.6, 2 CHN), 3.45-3.70 (m, CH_2-3), 4.00-4.55 (m, CH-4 + CH_2-6), 6.90-7.35 (m, 3 H aryl), 7.55-7.80 (m, CH-11).
IVd	1662	1378	1182	1.80 (mc, 2 CH_2 pyrr), 2.69 (mc, 2 CH_2N + CH_2-5), 3.40-3.75 (m, CH_2-3), 4.0-4.6 (m, CH-4 + CH_2-6), 6.90-7.45 (m, 3 H aryl), 7.55-7.85 (m, CH-11)
IVe	1662	1376	1182	1.51 (mc, 3 CH_2 pip), 2.0-2.9 (m, 2 CH_2N + CH_2-5), 3.3-3.7 (m, CH_2-3), 3.75-4.70 (m, CH-4 + CH_2-6), 6.85-7.40 (m, 3 H aryl), 7.5-7.8 (m, CH-11)
IVf	1663	1379	1187	2.61 (mc, 2 CH_2N + CH_2-5), 3.35-3.90 (m, CH_2-3 + 2 CH_2O), 3.9-4.7 (m, CH-4 + CH_2-6), 6.95-7.55 (m, 3 H aryl), 7.55-7.85 (m, CH-11)
IVg	1663	1383	1183	2.54 (mc, CH_2-5), 2.85 (s, CH_3N), 3.35-3.70 (m, CH_2-3), 3.95-4.65 (m, CH_2-6), 5.06 (near t, J = 8.4, CH-4), 6.65-7.55 (m, C_6H_5N + 3 H aryl), 7.65-7.90 (m, CH-11)

= diphenylamino) did not react and was recovered unchanged from the reaction mixture, according to a well established trend of this reaction [*cf.* (8)].

The biological screening, concerning compounds IIIa-f, included herbicide, insecticide, plant health and *in vitro* antimicrobial activity (9). Only compounds IIIa,b showed a weak activity in the herbicidal area; all the others were found to be inactive.

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; nmr spectra were recorded in deuteriochloroform on a Perkin-Elmer Model R12 instrument (60 MHz, TMS as the internal standard, J in Hz). Melting points were determined with a Fisher-Johns apparatus.

3,4-Dihydro-4-hydroxymethylene-1-benzoxepin-5(2*H*)-one (II).

This compound was prepared from 3,4-dihydro-1-benzoxepin-5(2*H*)-one I (10) (34 mmoles), ethyl formate (51 mmoles) and sodium methoxide (51 mmoles) in benzene, following a previously described procedure (11), yield, 91%; bp 100-110°/0.4 mm; uv: λ max nm (log ε) 217 (4.27), 250.5 (3.98), 302 (4.04); ir (chloroform): ν max 1635, 1608, 1585, 1558 cm^{-1}; nmr (deuteriochloroform): δ 2.61 (t, J = 5.1, CH_2-3), 4.36 (t, J = 4.8, CH_2-2), 6.95-7.65 (m, 3 H aryl), 7.99 (dd, J′ = 7.2, J″ ~ 2, CH-6), 8.38 (near s, =CH-O), 15.5 (broad s, OH; disappears with deuterium oxide).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.33; H, 5.33.

Acknowledgement.

The authors wish to thank Mr. A. Panaro for the microanalyses and Mr. F. Fasce, C. M. Pacetti and Dr. S. Morasso for the uv, ir and nmr spectra.

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