

Reaction of Sulfene with Heterocyclic *N,N*-Disubstituted
 α -Aminomethyleneketones. IX. Synthesis of 1,2-Oxathiino[6,5-*e*]indole
 Derivatives

Luisa Mosti, Pietro Schenone*, Giulia Menozzi and Sergio Cafaggi

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

Received December 30, 1981

The polar 1,4-cycloaddition of sulfene to *N,N*-disubstituted 5-aminomethylene-1,5,6,7-tetrahydro-1-methylindol-4-ones occurred only in the case of aliphatic *N*-substitution to give, generally in good yield, 4-dialkylamino-3,4,5,6-tetrahydro-7-methyl-7*H*-1,2-oxathiino[6,5-*e*]indole 2,2-dioxides IV. Full aromatization of IVa (4-NR₂ = dimethylamino) with DDQ in refluxing benzene gave in low yield 7-methyl-7*H*-1,2-oxathiino[6,5-*e*]indole 2,2-dioxide, whereas the same reaction of IVe (4-NR₂ = morpholinyl) with excess DDQ afforded in low yield 7-methyl-4-morpholinyl-7*H*-1,2-oxathiino[6,5-*e*]indole 2,2-dioxide.

J. Heterocyclic Chem., **19**, 1031 (1982).

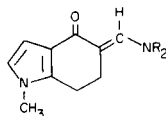
In a previous paper (1) we described a facile synthesis of *N,N*-disubstituted 3,4,5,6-tetrahydro-8-methyl-7-phenyl-7*H*-1,2-oxathiino[6,5-*e*]indol-4-amine 2,2-dioxides by 1,4-cycloaddition of sulfene to *N,N*-disubstituted 5-aminomethylene-1,5,6,7-tetrahydro-2-methyl-1-phenylindol-4-ones.

The need to have more simplified derivatives of the new heterocyclic system 1,2-oxathiino[6,5-*e*]indole in order to perform biological screening, prompted us to prepare a series of 4-dialkylamino-3,4,5,6-tetrahydro-7-methyl-7*H*-1,2-oxathiino[6,5-*e*]indole 2,2-dioxides IV. We started from the easily available, simple indole ketone I, namely 1,5,6,7-tetrahydro-1-methylindol-4-one (2), to obtain 1,5,6,7-tetrahydro-5-hydroxymethylene-1-methylindol-4-one II in excellent yield by reaction with ethyl formate and sodium methoxide following a previously described procedure (1).

The starting enaminones IIIa-f (Table I) were prepared, generally in good yield, from II and secondary amines (3,4). The *N,N*-diphenyl enaminone could not be prepared, starting II and diphenylamine being recovered nearly unchanged after a prolonged reaction time [*cf.* (4)]. Enaminones III are probably *E* isomers, at least as can be seen from the upfield shift of the C-6 and C-7 methylene protons caused by the phenyl group in compound IIIf in comparison with IIId,e (Table II). As in similar cases (1), reaction of III with methanesulphonyl chloride and triethylamine (sulfene prepared *in situ*) occurred in good to moderate yield only in the case of aliphatic *N*-substitution to give 4-dialkylamino-3,4,5,6-tetrahydro-7-methyl-7*H*-1,2-oxathiino[6,5-*e*]indole 2,2-dioxides IVa-e, whose structure was confirmed by ir and nmr spectral data (Table III). In the case of aromatic *N*-substitution, *i.e.* enaminone IIIf, this was recovered unchanged from the reaction mixture.

Table I

N,N-Disubstituted 5-Aminomethylene-1,5,6,7-tetrahydro-1-methylindol-4-ones (IIIa-f) (a)



Formula Number	NR ₂	Yield %	Mp, °C	Molecular Formula	Analyses %		
					C	H	N
IIIa	N(CH ₃) ₂	96	135 (b)	C ₁₂ H ₁₆ N ₂ O	70.56	7.90	13.72
					70.45	8.09	13.51
IIIb	N(C ₂ H ₅) ₂	92	120 (b)	C ₁₄ H ₂₀ N ₂ O	72.38	8.68	12.06
					72.41	8.80	12.15
IIIc	pyrrolidino	97	161 (b)	C ₁₄ H ₁₈ N ₂ O	73.01	7.88	12.17
					72.79	7.91	11.98
IIIId	piperidino	66	87 (b)	C ₁₅ H ₂₀ N ₂ O	73.73	8.25	11.47
					73.66	8.44	11.21
IIIe	morpholino	90	136 (b)	C ₁₄ H ₁₈ N ₂ O ₂	68.27	7.37	11.37
					67.95	7.38	11.18
IIIIf	N(CH ₃)C ₆ H ₅	51	154 (c)	C ₁₇ H ₁₈ N ₂ O	76.66	6.81	10.52
					76.42	7.04	10.72

(a) Enaminones IIIa-e were prepared according to reference 3, and IIIIf according to reference 4. (b) From ethyl acetate. (c) From chloroform.

Full aromatization of adducts IV was tried with DDQ [cf. (5)] only in the case of IVa and IVe. Prolonged reflux in benzene of equimolar amounts of IVa and DDQ caused elimination of the dimethylamino group and aromatization, giving in low yield 7-methyl-7*H*-1,2-oxathiino[6,5-*e*]indole 2,2-dioxide V, namely the least substituted derivative known of the parent heterocycle 1,2-oxathiino[6,5-*e*]indole. With IVe, a more prolonged reflux time and excess DDQ gave in low yield the full aromatized compound VI without loss of the 4-morpholinyl group. These results are in contrast with those obtained by us in the case of furo[2,3-*h*]-1,2-benzoxathiin system, where a full aromatization could not be reached by DDQ oxidation (6). On the other hand, they agree with the strong trend of another heterocycle containing the indole moiety towards a full aromatization (1).

We have also tried the reaction of IIIa,f with dichloroacetyl chloride and triethylamine (dichloroketene prepared *in situ*), but unlike similar enaminones (1) the results were disappointing, since only intractable tars were obtained.

The biological screening, concerning compounds IV b-e, included herbicide, insecticide, plant health and *in vitro* antimicrobial activity (7). None of the compounds was found to be active.

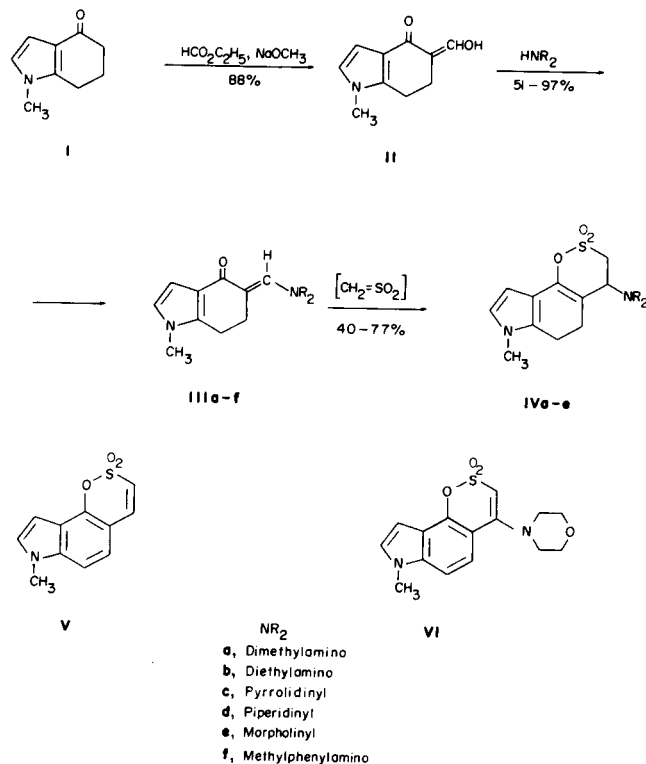


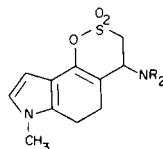
Table II

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

	UV λ max nm (log ϵ)	IR, cm^{-1} (chloroform)		NMR, δ (deuteriochloroform)
		C=O	C=C	
IIIa	237 (4.06) 258 sh (3.89) 285 (3.79) 355 (4.43)	1633	1560	2.5-3.2 (m, $\text{CH}_2\text{-6} + \text{CH}_2\text{-7}$), 3.03 (s, $2\text{CH}_3\text{N}$), 3.51 (s, $\text{CH}_3\text{N-1}$), 6.53 (mc, $\text{CH-2} + \text{CH-3}$), 7.43 (near s, =CHN)
IIIb	216 (4.36) 237 (4.38) 284 sh (4.15) 356 (4.56)	1635	1565	1.22 (t, $J = 7.2$, 2CH_3), 2.50-3.05 (m, $\text{CH}_2\text{-6} + \text{CH}_2\text{-7}$) 3.33 (q, $J = 7.2$, $2\text{CH}_2\text{N}$), 3.54 (s, CH_3N), 6.47 (d, $J = 3$, CH-3), 6.53 (d, $J = 3$, CH-2), 7.50 (near s, =CHN)
IIIc	216 (3.95) 240 (3.96) 285 (3.72) 360 (4.28)	1632	1563	1.88 (mc, 2CH_2 pyr), 2.50-3.25 (m, $\text{CH}_2\text{-6} + \text{CH}_2\text{-7}$) 3.54 (s, CH_3N), 3.33-3.73 (m, $2\text{CH}_2\text{N}$), 6.50 (d, $J = 3$, CH-3), 6.55 (d, $J = 3$, CH-2), 7.64 (near s, =CHN)
IIId	238 (3.92) 260 sh (3.74) 286 (3.67) 358 (4.29)	1630	1563	1.58 (mc, 3CH_2 pip), 2.68 (mc, $\text{CH}_2\text{-6} + \text{CH}_2\text{-7}$), 3.23 (mc, $2\text{CH}_2\text{N}$), 3.45 (s, CH_3N), 6.26 (d, $J = 3$, CH-3), 6.37 (d, $J = 3$, CH-2), 7.10 (near s, =CHN) (a)
IIIe	217 (3.96) 235 (3.94) 261 sh (3.76) 290 (3.76) 353 (4.31)	1640	1568	2.80 (mc, $\text{CH}_2\text{-6} + \text{CH}_2\text{-7}$), 3.45 (mc, $2\text{CH}_2\text{N}$), 3.54 (s, CH_3N), 3.74 (mc, $2\text{CH}_2\text{O}$), 6.47 (near s, $\text{CH-2} + \text{CH-3}$), 7.25 (near s, =CHN)
IIIf	228 sh (4.09) 257 (4.06) 293 (3.88) 364 (4.36)	1640	1565	2.55 (mc, $\text{CH}_2\text{-6} + \text{CH}_2\text{-7}$), 3.36 (s, CH_3N), 3.49 (s, $\text{CH}_3\text{N-1}$), 6.56 (d, $J = 3$, CH-3), 6.63 (d, $J = 3$, CH-2), 6.85-7.55 (m, C_6H_5), 7.61 (near s, =CHN)

(a) In tetrachloromethane.

Table III

4-Dialkylamino-3,4,5,6-tetrahydro-7-methyl-7H-1,2-oxathiino[6,5-*e*]indole 2,2-Dioxides (IVa-e) (a)

Formula Number	NR ₂	Yield %	Mp, °C (b)	Molecular Formula	Analyses % Calcd./Found		
					C	H	N
IVa	N(CH ₃) ₂	54	128	C ₁₃ H ₁₈ N ₂ O ₃ S	55.30	6.42	9.92
					55.54	6.26	9.69
IVb	N(C ₂ H ₅) ₂	69	120	C ₁₅ H ₂₂ N ₂ O ₃ S	58.02	7.14	9.02
					58.19	7.00	8.99
IVc	pyrrolidino	40	115	C ₁₃ H ₂₀ N ₂ O ₃ S	58.42	6.53	9.08
					58.64	6.63	9.12
IVd	piperidino	53	137	C ₁₆ H ₂₂ N ₂ O ₃ S	59.60	6.88	8.69
					59.65	7.04	8.79
IVe	morpholino	77	149	C ₁₃ H ₂₀ N ₂ O ₄ S	55.54	6.21	8.63
					55.75	6.37	8.72

IR and NMR Spectral Data

	IR, cm ⁻¹ (chloroform)		NMR, δ (deuteriochloroform)	
	C=O	O=S=O		
IVa	1658	1373	1193	2.22 (s, 2 CH ₃ N), 2.58 (mc, CH ₂ -5 + CH ₂ -6), 3.44 (s, CH ₃ N-7), 3.1-4.1 (m, CH ₂ -3 + CH-4), 6.05 (d, J = 3, CH-9), 6.38 (d, J = 3, CH-8)
IVb	1657	1372	1180	1.09 (t, J = 7.2, 2 CH ₃), 2.15-3.00 (m, CH ₂ -5 + CH ₂ -6 + 2 CH ₂ N), 3.54 (s, CH ₃ N), 3.1-4.3 (m, CH ₂ -3 + CH-4), 6.09 (d, J = 3, CH-9), 6.41 (d, J = 3, CH-8)
IVc	1658	1370	1183	1.78 (mc, 2 CH ₂ pyr), 2.70 (mc, CH ₂ -5 + CH ₂ -6 + 2 CH ₂ N), 3.55 (s, CH ₃ N), 3.25-3.85 (m, CH ₂ -3), 4.05-4.45 (m, CH-4), 6.07 (d, J = 3, CH-9), 6.38 (d, J = 3, CH-8)
IVd	1654	1372 1363	1182	1.53 (mc, 3 CH ₂ pip), 2.47 (mc, 2 CH ₂ N), 2.70 (mc, CH ₂ -5 + CH ₂ -6), 3.55 (s, CH ₃ N), 3.25-4.35 (m, CH ₂ -3 + CH-4), 6.11 (d, J = 3, CH-9), 6.44 (d, J = 3, CH-8)
IVe	1655	1377	1187	2.68 (mc, 2 CH ₂ N + CH ₂ -5 + CH ₂ -6), 3.55 (s, CH ₃ N), 3.74 (mc, 2 CH ₂ O), 3.2-4.2 (m, CH ₂ -3 + CH-4), 6.15 (d, J = 2.5, CH-9), 6.47 (d, J = 2.5, CH-8)

(a) All compounds were prepared according to reference 3. (b) All compounds were recrystallized from 95% ethanol.

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. The ir spectra were taken on a Perkin-Elmer Model 398 spectrophotometer and the nmr spectra were recorded on a Perkin-Elmer Model R12 instrument (60 MHz, TMS as internal standard, J in Hz).

1,5,6,7-Tetrahydro-5-hydroxymethylene-1-methylindol-4-one (II).

This compound was prepared from 1,5,6,7-tetrahydro-1-methylindol-4-one I (2) (7.46 g, 50 mmoles), ethyl formate (5.55 g, 75 mmoles) and sodium methoxide (4.05 g, 75 mmoles) in anhydrous benzene following a previously described procedure (1) and keeping the reaction mixture for 72 hours at room temperature, yield, 7.79 g (88%) mp 87° from chloroform; uv: λ max nm (log ε) 216 (4.12), 267 sh (4.01), 319 (4.11); ir (chloroform): ν max 1635, 1578, 1508, 1472 cm⁻¹; nmr (deuteriochloroform): δ 2.65 (mc, CH₂-6 + CH₂-7), 3.55 (s, CH₃N), 6.54 (mc, CH-2 +

CH-3), 7.20 (mc, = CH-O), 14.05 (broad s, OH; disappears with deuterium oxide).

Anal. Calcd. for C₁₀H₁₁NO₂: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.89; H, 6.31; N, 7.97.

7-Methyl-7H-1,2-oxathiino[6,5-*e*]indole 2,2-Dioxide (V).

A warm solution of DDQ (2.27 g, 10 mmoles) in anhydrous benzene (30 ml) was added dropwise under dry nitrogen to a refluxing and stirred solution of IVa (2.82 g, 10 moles) in anhydrous benzene (50 ml). After the addition was complete, the reaction mixture was further refluxed for 10 hours and filtered. The filtrate was washed 2 times with 1M sodium hydroxide and water, dried (sodium sulfate) and evaporated under reduced pressure, yield, 0.63 g (27%), mp 163-164° from 95% ethanol; uv: λ max nm (log ε) 251 sh (4.18), 263 sh (4.32), 268 (4.33), 315 (3.84); ir (potassium bromide): ν max 1625, 1600, 1562, 1490, 1455, 1345, 1165 cm⁻¹; nmr (DMSO-d₆): δ 3.88 (s, CH₃N), 6.55 (d, J = 3, CH-9), 7.13 (d, J = 10.8, CH-4), 7.32 (mc, CH-5 + CH-6), 7.40 (d, J = 3, CH-8), 7.64 (d, J = 10.8, CH-3).

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.16; H, 3.85; N, 5.95. Found: C, 56.26; H, 3.83; N, 5.88.

7-Methyl-4-morpholinyl-7H-1,2-oxathiino[6,5-e]indole 2,2-Dioxide (VI).

This compound was prepared as above, starting from DDQ (5.67 g, 25 mmoles) in anhydrous benzene (150 ml) and IVe (3.24 g, 10 mmoles) in the same solvent (200 ml) with a reflux time of 24 hours, yield 0.55 g (17%), mp 272-273° dec from ethyl acetate; uv: λ max nm (log ϵ) 255 (4.24), 261 (4.24), 283 (3.75), 307 (3.54); ir (potassium bromide): ν max 1618, 1585, 1550, 1510, 1488, 1450, 1347, 1155 cm^{-1} ; nmr (DMSO- d_6): δ 3.14 (mc, 2 CH_2N), 3.50-3.95 (m, 2 CH_2O), 3.89 (s, CH_3N), 6.34 (near s, CH-3) 6.66 (d, J = 2.4, CH-9), 7.51 (d, J = 2.4, CH-8), 7.43 (mc, CH-5 + CH-6).

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.75. Found: C, 56.19; H, 5.02; N, 8.75.

Acknowledgement.

The authors wish to thank Mr. A. Panaro for the microanalyses and

Mr. F. Fasce and C. M. Pacetti for the uv, ir and nmr spectra.

REFERENCES AND NOTES

- (1) L. Mosti, P. Schenone and G. Menozzi, *J. Heterocyclic Chem.*, **16**, 913 (1979).
- (2) J. M. Bobbitt, C. L. Kulkarni, C. P. Dutta, H. Kofod and K. Ng Chiong, *J. Org. Chem.*, **43**, 3541 (1978).
- (3) P. Schenone, G. Bignardi and S. Morasso, *J. Heterocyclic Chem.*, **9**, 1341 (1972).
- (4) G. Bignardi, P. Schenone and F. Evangelisti, *Ann. Chim. (Rome)*, **61**, 326 (1971).
- (5) L. Mosti, P. Schenone and G. Menozzi, *J. Heterocyclic Chem.*, **18**, 1263 (1981).
- (6) L. Mosti, P. Schenone, G. Menozzi, G. Romussi and F. Baccichetti, *ibid.*, submitted for publication.
- (7) The biological tests were made by Diamond Shamrock Corporation, Painesville, Ohio.