Reaction of Sulfene and Dichloroketene with *N,N*-Disubstituted 5-Aminomethylene-1,5,6,7-tetrahydro-2-methyl-1-phenylindol-4-ones. Synthesis of 1,2-Oxathiino[6,5-*e*]indole and of Pyrano[2,3-*e*]indole Derivatives

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The 1,4-cycloaddition of sulfene to *N,N*-disubstituted 5-aminomethylene-1,5,6,7-tetrahydro-2-methyl-1-phenylindol-4-ones afforded *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 only in the case of aliphatic *N*-substitution. The 1,4-cycloaddition of dichloroketene occurred normally only in the case of 1,5,6,7-tetrahydro-2-methyl-1-phenyl-5-piperidinomethyleneindol-4-one to give 3,3-dichloro-3,4,5,6-tetrahydro-8-methyl-7-phenyl-4-piperidino-7*H*-pyrano[2,3-*e*]indol-4-one. Attempted recrystallisation, dehydrochlorination or treatment with palladium on carbon of this adduct, as well as reaction of similar enaminoketones with dichloroketene, gave instead the same product, namely 3-chloro-8-methyl-7-phenyl-7*H*-pyrano[2,3-*e*]indol-4-one, as a result of dehydrochlorination, dehydrogenation and subsequent hydrogenolysis of the C-NR_2 bond in the primary adduct.

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Tricyclic heterocycles incorporating the indole nucleus are very interesting as potential pharmacologically active molecules, and from a synthetic viewpoint, substituted 1,5,6,7-tetrahydroindol-4-ones are starting compounds particularly suitable for fusion of heterocycles to the 4,5-indole positions (1). As part of our continuing study of the polar 1,4-cycloadditions of *N,N*-disubstituted 2-aminomethyleneketones to sulfene (2) and dichloroketene (3), we wish to report the reaction of *N,N*-disubstituted 5-aminomethylene-1,5,6,7-tetrahydro-2-methyl-1-phenylindol-4-ones III with sulfene and dichloroketene to give 1,2-oxathiino[6,5-*e*]indole and pyrano[2,3-*e*]indole derivatives, respectively. The former heterocycle is a new system incorporating the indole nucleus, whereas only few examples of the latter are known (4). We have chosen the easily available 1,5,6,7-tetrahydro-2-methyl-1-phenylindol-4-one (I) (5) as starting ketone in order to obtain 1,5,6,7-tetrahydro-5-hydroxymethylene-2-methyl-1-phenylindol-4-one (II) in good yield by reaction with ethyl formate and sodium methoxide in benzene. The starting enaminoketones IIIa-d (Table I) were prepared from II and secondary amines, following previously described procedures (6,7). They are probably *E* isomers, at least as can be seen from the strong upfield shift of the C-6 and also C-7 methylene protons (0.5-0.6 and 0.15-0.4 ppm, respectively) caused by the phenyl groups in compounds IIIc,d in comparison with IIIa,b (Table II). Reaction of III with methanesulphonyl chloride and triethylamine (sulfene prepared *in situ*) occurred readily only in the case of aliphatic *N*-substitution (IIIa,b) to give *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 (VIa,b), whose structure was confirmed by ir and nmr spectral data (Table III). In the case of aromatic *N*-substitution, *i.e.*, enaminoketones IIIc,d, they were recovered unchanged from the reaction mixture.

The reaction of III with dichloroacetyl chloride and triethylamine (dichloroketene prepared *in situ*) gave the expected result of a simple 1,4-cycloaddition only in the case of IIIb, namely formation of 3,3-dichloro-3,4,5,6-tetrahydro-8-methyl-7-phenyl-4-piperidino-7*H*-pyrano[2,3-*e*]-indol-2-one (IV, NR_2 = piperidino). In all other cases tried (IIIa,c,d) the same crystalline product containing chlorine was isolated (15-31% yield), which was identified as 3-chloro-8-methyl-7-phenyl-7*H*-pyrano[2,3-*e*]indol-2-one (V) by uv, ir, nmr and ms data (see Experimental). On the other hand, compound IV (NR_2 = piperidino) is very unstable, and its attempted recrystallisation from ethyl acetate, dehydrochlorination with triethylamine or refluxing in benzene with 10% palladium on carbon always gave V in a low yield.

These results could be explained by a preliminary dehydrochlorination of the primary adduct IV, followed by a full aromatisation by spontaneous dehydrogenation in the 5,6-positions and hydrogenolysis of the C-N bond in the 4-position.

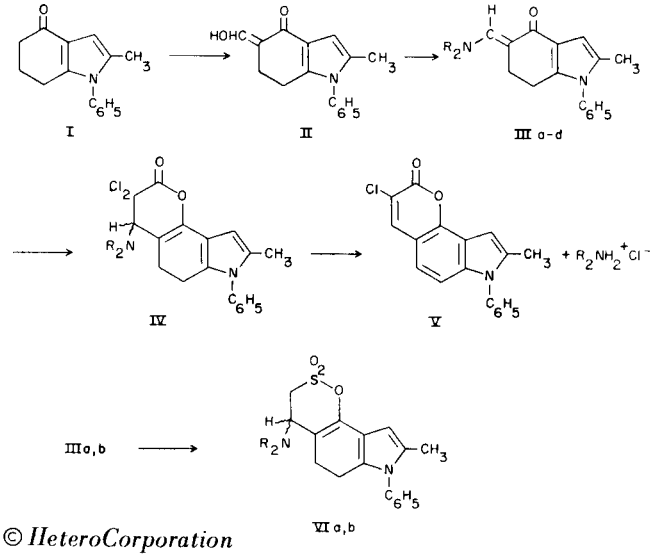

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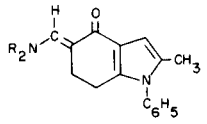
Table I

N,N-Disubstituted 5-Aminomethylene-1,5,6,7-tetrahydro-2-methyl-1-phenylindol-4-ones (IIIa-d)



Compound No.	NR_2	Yield %	M.p. °	Molecular Formula	Anal. C	Calcd./Found H	N
IIIa	$N(CH_3)_2$	96	161 (a)	$C_{18}H_{20}N_2O$	77.11	7.19	9.99
					77.04	7.45	10.04
IIIb	Piperidino	98	156 (a)	$C_{21}H_{24}N_2O$	78.72	7.55	8.74
					78.69	7.63	8.86
IIIc	$N(CH_3)C_6H_5$	81	163 (a)	$C_{23}H_{22}N_2O$	80.67	6.48	8.18
					80.47	6.52	7.95
IIId	$N(C_6H_5)_2$	80	190 (a)	$C_{28}H_{24}N_2O$	83.14	5.98	6.93
					82.86	6.08	6.96

(a) From ethyl acetate.

Table II

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

	Uv λ Max Nm (Log ε)	Ir, Cm^{-1} C=O	C=C	Nmr, δ
IIIa	256 (4.10) 353 (4.04)	1639	1548	2.10 (s, CH_3-2), 2.58 (mc, CH_2-7), 2.92 (mc, CH_2-6), 3.04 and 3.06 (2s, $2NCH_3$), 6.47 (m, CH-3), 7.1-7.8 (m, =CHN + NC_6H_5)
IIIb	255 (4.18) 295.5 (3.85) 360 (4.43)	1634	1545	1.59 (m, $3CH_2$ pip.), 2.05 (s, CH_3-2), 2.57 (mc, CH_2-7), 2.79 (mc, CH_2-6), 3.32 (m, $2NCH_2$), 6.37 (m, CH-3), 7.00-7.55 (m, =CHN + NC_6H_5)
IIIc	260 (4.15) 298 (3.87) 370 (4.36)	1642	1552	2.07 (near s, CH_3-2), 2.44 (s, CH_2-6 + CH_2-7), 3.37 (s, NCH_3), 6.47 (m, CH-3), 6.85-7.55 (m, $2NC_6H_5$), 7.58 (near s, =CHN)
IIId	265 (3.87) 289.5 (3.89) 376 (4.14)	1640	1550	2.07 (s, CH_3-2), 2.19 (mc, CH_2-7), 2.32 (mc, CH_2-6), 6.49 (m, CH-3), 6.9-7.6 (m, $3NC_6H_5$), 7.73 (m, =CHN)

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 spectrometer; nmr spectra were recorded in deuteriochloroform on a Perkin-Elmer Model R12 instrument (60 MHz; TMS as internal standard; J in Hz). Mass spectra were obtained with a GC/MS Varian Mat 111 spectrometer. Melting points were determined with a Fisher-Johns apparatus.

Compounds IIIb,c,d were prepared according to reference 7, and IIIa according to reference 6.

Compounds VIa,b were prepared according to reference 6, using anhydrous tetrahydrofuran as the solvent.

1,5,6,7-Tetrahydro-2-methyl-1-phenylindol-4-one (I).

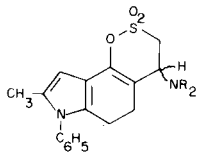
This compound was prepared according to the literature reported procedure (5), m.p. 150° from cyclohexane (lit. 150-152°); uv: λ max nm (log ε) 250 (4.87), 280 sh (4.70); ir (chloroform): ν max 3050, 2990, 2935, 2850, 1643, 1600, 1525, 1502, 1468, 1440, 1415 cm^{-1}; nmr (deuteriochloroform): δ 1.70-2.35 (m, CH_2-6), 2.07 (s, CH_3-2), 2.37-2.75 (m, CH_2-5 + CH_2-7), 6.43 (m, CH-3), 7.1-7.7 (m, NC_6H_5).

1,5,6,7-Tetrahydro-5-hydroxymethylene-2-methyl-1-phenylindol-4-one (II).

To a suspension of freshly prepared sodium methoxide (1.13 g., 21 mmoles) in anhydrous benzene (100 ml.) was added a solution of ethyl formate (1.55 g., 21 mmoles) in the same solvent (20 ml.). The ice-cooled mixture was treated dropwise (stirring), under dry nitrogen, with a solution of I (3.2 g., 14 mmoles) in anhydrous benzene (30 ml.). A precipitate gradually appeared, and after 12 hours at room temperature, it was treated with water (100 ml.). The benzene layer was diluted with diethyl ether and extracted with water, the aqueous extracts were combined, washed with diethyl ether and acidified at 0° with 6*M* hydrogen chloride. The solid which separated was extracted with diethyl ether, the extracts were dried (sodium sulfate) and concentrated (yield 2.48 g., 70%), m.p. 127° from cyclohexane; uv: λ max nm (log ε) 222 sh (4.72), 258 (4.68), 326 (4.59); ir (tetrachloromethane): ν max 1642, 1600, 1520, 1505, 1477, 1445, 1418 cm^{-1}; nmr (deuteriochloroform): δ 2.06 (s, CH_3-2), 2.48 (s, CH_2-6 + CH_2-7), 6.26 (near s, CH-3), 7.0-7.8 (m, =CH-O + NC_6H_5), 11.03

Table III

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 (VIa-b)



Compound No.	NR_2	Yield %	M.p. °	Molecular Formula	Anal. C	Calcd./Found H	N
VIa	$N(CH_3)_2$	45	132 (a)	$C_{19}H_{22}N_2O_3S$	63.66	6.18	7.81
					63.40	6.20	7.50
VIb	Piperidino	80	186 (b)	$C_{22}H_{26}N_2O_3S$	66.30	6.57	7.03
					66.60	6.75	6.91

Ir and Nmr Spectral Data

	Ir, Cm^{-1} C=C	O=S=O		Nmr, δ
VIa	1653	1373	1178	2.08 (near s, CH_3-2), 2.30 (near s, $2NCH_3$), 2.54 (m, CH_2-10 + CH_2-11), 2.95-4.15 (m, CH_2-7 + CH-8), 6.06 (m, CH-3), 7.0-7.7 (m, NC_6H_5)
VIb	1655	1367 1377	1186	1.50 (m, $3CH_2$ pip.), 2.08 (s, CH_3-2), 2.53 (m, $2NCH_2$ + CH_2-10 + CH_2-11), 3.15-4.20 (m, CH_2-7 + CH-8), 6.04 (m, CH-3), 7.1-7.6 (m, NC_6H_5)

(a) After chromatography on Florisil ® (diethyl ether) followed by recrystallisation from ethyl acetate. (b) From ethyl acetate.

(mc, OH; disappears with deuterium oxide).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.16; H, 6.00; N, 5.71.

3,3-Dichloro-3,4,5,6-tetrahydro-8-methyl-7-phenyl-4-piperidino-7*H*-pyrano[2,3-*e*]indol-2-one (IV, NR_2 = piperidino).

This compound was obtained starting from IIIb (3.2 g., 10 mmoles), dichloroacetyl chloride (2.21 g., 15 mmoles) and triethylamine (1.52 g., 15 mmoles) in anhydrous benzene, by a previously described procedure (8). The crude product (3.79 g., 88%) was purified by several washings with anhydrous diethyl ether (final yield 2.76 g., 64%), m.p. 125°; uv: λ max nm (log ε) 221 (4.13), 276 (3.88), 324 (3.76); ir (chloroform): ν max 1780, 1675 cm^{-1}; nmr (deuteriochloroform): δ 1.45 (m, $3CH_2$ pip.), 2.08 (s, CH_3-2), 2.56 (mc, $2NCH_2$ + CH_2-10 + CH_2-11), 3.66 (near s, CH-8), 6.10 (near s, CH-3), 7.1-7.7 (m, NC_6H_5).

Anal. Calcd. for $C_{23}H_{24}Cl_2N_2O_2$: C, 64.04; H, 5.61; N, 6.49. Found: C, 64.36; H, 5.37; N, 6.18.

3-Chloro-8-methyl-7-phenyl-7*H*-pyrano[2,3-*e*]indol-2-one (V).

When the above reaction was carried out with IIIa,c,d, the only product isolated by chromatography on Florisil ® (diethyl ether) was V (15% from IIIa, 31% from IIIc and 31% from IIId, plus 30% recovered IIId). Compound V was also obtained from IV by attempted recrystallisation from ethyl acetate (13%), by dehydrochlorination with triethylamine (9) (39%) or by refluxing for 2 hours a mixture of IV (1 g.) and 10% palladium on carbon (0.4 g.) in anhydrous benzene (50 ml.) (yield 0.16 g., 23%), m.p. 242° from ethyl acetate; uv: λ max nm (log ε) 2.73 (5.36), 340 (4.78); ir (chloroform): ν max 3010, 1713, 1624, 1595, 1556, 1500, 1455 cm^{-1}; nmr (deuteriochloroform): δ 2.34 (d, J ~ 1.5, CH_3-8), 6.75 (near s, CH-9), 7.01 (near s, CH-5 + CH-6), 7.1-7.8 (m, NC_6H_5), 7.87 (s, CH-4); ms: (m/e) 312 (7%), 311 (33), 310 (22), 309 (M^+, 100), 308 (7), 283 (6), 282 (5), 281 (17), 280 (7), 274 (5), 252 (7), 246 (7), 219 (6), 218 (33), 217 (8), 216 (7), 154 (5), 126 (7), 109 (5), 77 (9), 57 (5), 51 (7), 44 (9).

Anal. Calcd. for $C_{18}H_{12}ClNO_2$: C, 69.79; H, 3.90; Cl, 11.44; N, 4.52. Found: C, 69.62; H, 3.92; Cl, 11.58; N, 4.50.

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