Reaction of Dichloroketene and Sulfene with *N,N*-Disubstituted 6-Aminomethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones. Synthesis of 6-(2,2-Dichloroethylidene)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one and of 5*H*-Benzo[3,4]cyclohepta[2,1-*b*]pyran and 5*H*-Benzo[3,4]cyclohepta[1,2-*e*]-1,2-oxathiin Derivatives

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The 1,4-cycloaddition of dichloroketene to *N,N*-disubstituted 6-aminomethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones afforded *N,N*-disubstituted 4-amino-3,3-dichloro-3,4,6,7-tetrahydro-5*H*-benzo[3,4]cyclohepta[2,1-*b*]pyran-2-ones only in the case of aromatic or strong hindering aliphatic *N*-substitution. The adducts gave *N,N*-disubstituted 4-amino-3-chloro-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[2,1-*b*]pyran-2-ones by dehydrochlorination with collidine. Upon chromatography on neutral alumina, two products were instead isolated in the case of usual aliphatic *N*-substitution (diethylamine, piperidine), namely 6-(2,2-dichloroethylidene)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one and the dehydrochlorinated 2-pyrone; this latter was the sole product in the case of pyrrolidine substitution. The 1,4-cycloaddition of sulfene occurred readily to give *N,N*-disubstituted 4-amino-3,4,6,7-tetrahydro-5*H*-benzo[3,4]cyclohepta-[1,2-*e*]-1,2-oxathiin 2,2-dioxides in the case of both aliphatic and partially aromatic *N*-substitution.

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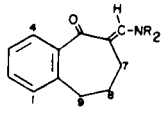
In previous work we have shown the synthetic utility of the 1,4-cycloaddition of dichloroketene and sulfene to *N,N*-disubstituted 2-aminomethyleneketones to give 2-pyrone and 1,2-oxathiin derivatives (1). As a part of a program directed toward the synthesis of heterocyclic structures with presumed CNS activity (2), we extended these 1,4-cycloadditions to a series of *N,N*-disubstituted 6-aminomethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohep-

Table I

N,N-Disubstituted 6-Aminomethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (Ia-g).



Formula Number	NR_2	Yield %	M.p. °C or B.p./mmHg	Molecular Formula	Analyses % Calcd./Found C	H	N
Ia (a)	$N(C_2H_5)_2$	97	140/0.15	$C_{16}H_{21}NO$	78.97 79.19	8.70 8.36	5.76 5.93
Ib (b)	$N[CH(CH_3)_2]_2$	48	144 (c)	$C_{18}H_{25}NO$	79.66 79.46	9.28 9.13	5.16 5.31
Ic (a)		98	102 (c)	$C_{16}H_{19}NO$	79.63 79.36	7.94 7.90	5.80 6.00
Id (a)		95	89 (c)	$C_{17}H_{21}NO$	79.96 79.79	8.29 7.92	5.49 5.62
Ie (a)		84	121 (c)	$C_{16}H_{19}NO_2$	74.68 74.75	7.44 7.22	5.44 5.53
If (b)	$N(CH_3)C_6H_5$	97	96 (c)	$C_{19}H_{19}NO$	82.28 82.15	6.90 6.80	5.05 5.00
Ig (b)	$N(C_6H_5)_2$	92	138 (c)	$C_{24}H_{21}NO$	84.92 84.80	6.24 6.20	4.13 4.39

(a) Prepared according to (4). (b) Prepared according to (5). (c) From ethyl acetate.

Table II

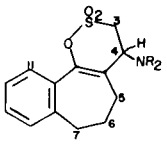
Uv, Ir and Nmr Spectral Data of Compounds Ia-g

Compound No.	Uv	Ir, cm^{-1} (a)		Nmr, δ (a)						
	λ max nm (log ε)	C=O	C=C	CH_2-8	CH_2-7	CH_2-9	H(1-3)	H-4	=CHN	NR_2
Ia	251 (3.98) 352.5 (4.33)	1652	1548	1.84q J = 6.5	2.25t J = 6.5	2.72t J = 6.5	7.22m	7.52m	7.57s	1.22 (t, J = 7, $2CH_3$) 3.30 (q, J = 7, $2NCH_2$)
Ib	251 (4.00) 356 (4.38)	1645	1530	1.84q J = 6.5	2.27t J = 6.5	2.73t J = 6.5	7.22m	7.53m	7.78s	1.27 (d, J = 6.6, $4CH_3$) 3.87 (h, J = 6.6, 2NCH)
Ic	252.5 (3.92) 356 (4.29)	1650	1540	1.90m	2.29t J = 6.5	2.73t J = 6.5	7.24m	7.53m	7.69s	1.90 (m, $2CH_2$) 3.53 (m, $2NCH_2$)
Id	252.5 (3.95) 355.5 (4.31)	1648	1532	1.64m	2.28t J = 6.5	2.73t J = 6.5	7.22m	7.54m	7.47s	1.64 (m, $3CH_2$) 3.38 (m, $2NCH_2$)
Ie	252 (3.95) 352 (4.29)	1658	1548	1.82n.q J = 6	2.29n.t J = 6.2	2.74t J = 6.5	7.27m	7.57m	7.46s	3.47 (m, $2NCH_2$) 3.58 (m, $2OCH_2$)
If	257 (3.98) 359 (4.27)	1654	1540	1.83n.q J = 6.5	2.28n.t J = 6	2.78n.t J = 6.5	7.20m	7.60m	7.91s	3.48 (s, NCH_3) 7.20 (m, NC_6H_5)
Ig	260 (4.11) 285 sh (3.92) 370 (4.30)	1655	1540	1.39n.q J = 6.5	1.83n.t J = 6.5	2.69n.t J = 6.5	7.30m	7.30m	8.01s	7.30 (m, $2NC_6H_5$)

(a) In tetrachloromethane.

Table III

N,N-Disubstituted 4-Amino-3,4,6,7-tetrahydro-5*H*-benzo[3,4]cyclohepta[1,2-*e*]-1,2-oxathiin 2,2-Dioxides (IIa-d).



Formula Number	NR_2	Yield %	M.p. °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa	$N(C_2H_5)_2$	71	150 (a)	$C_{17}H_{23}NO_3S$	63.52 63.48	7.21 6.95	4.36 4.49
IIb		94	143 (a)	$C_{17}H_{21}NO_3S$	63.92 63.94	6.63 6.56	4.38 4.22
IIc		85	194 (a)	$C_{18}H_{23}NO_3S$	64.84 64.69	6.95 6.94	4.20 4.18
IId	$N(CH_3)C_6H_5$	44	185 (a)	$C_{20}H_{21}NO_3S$	67.58 67.78	5.95 6.20	3.94 3.79

(a) From anhydrous ethanol. All compounds were prepared according to (4), using anhydrous tetrahydrofuran as solvent.

ten-5-ones (I).

The starting compounds Ia-g (Table I) were prepared from secondary amines and 6-hydroxymethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (3) by previously described procedures (4,5). They are probably *E* isomers, at least as can be argued from the strong upfield shift of the C-7 and C-8 methylene protons (~ 0.45 ppm) caused by the phenyl group in compound If (*cf.* (1) and Table II].

Reaction of aliphatic or partially aromatic *N*-substituted I (Ia,c,d,f) with methanesulphonyl chloride and triethylamine (sulfene prepared *in situ*) occurred readily to give *N,N*-disubstituted 4-amino-3,4,6,7-tetrahydro-5*H*-benzo-[3,4]cyclohepta[1,2-*e*]-1,2-oxathiin 2,2-dioxides (IIa-d)

Table IV

Uv and Ir Spectral Data of Compounds IIa-d

	Uv λ max nm (log ε)	Ir, cm^{-1} (Potassium bromide) C=C	O=S=O	
IIa	253 (4.05)	1654	1357	1170
IIb	253 (4.04)	1661	1370	1182
IIc	253.5 (4.07)	1648	1375	1183
			1365	
IId	251.5 (4.43)	1654	1365	1181

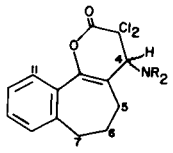
Nmr Spectral Data, δ (deuteriochloroform)

	CH_2-3	CH-4	CH_2-5 / CH_2-6	CH_2-7	4 Har.	NR_2
IIa	3.50 m	4.13 dd	1.9-3.0 m	1.9-3.0 m	7.28 m	1.13 (t, J = 7, $2CH_3$)
	J_{AB} = 9.4	J_{AB} = 9.4				1.9-3.0 (m, $2NCH_2$)
IIb (a)	3.43 m	4.14 dd	2.13 m	2.70 m	7.20 m	1.81 (m, $2CH_2$)
	J_{AB} = 8.8	J_{AB} = 8.8				2.70 (m, $2NCH_2$)
IIc	3.48 m	3.93 dd	2.15 m	2.58 m	7.29 m	1.56 (m, $3CH_2$)
	J_{AB} = 8.8	J_{AB} = 8.8				2.58 (m, $2NCH_2$)
IId	3.57 n.d	5.18 n.t	2.10 m	2.72 m	7.32 m	2.95 (s, NCH_3)
	J_{AB} = 8.6	J_{AB} = 8.6				6.92,7.32 (2m, NC_6H_5)

(a) In tetrachloromethane

Table V

N,N-Disubstituted 4-Amino-3,3-dichloro-3,4,6,7-tetrahydro-5*H*-benzo[3,4]cyclohepta[2,1-*b*]pyran-2-ones (Va-c)



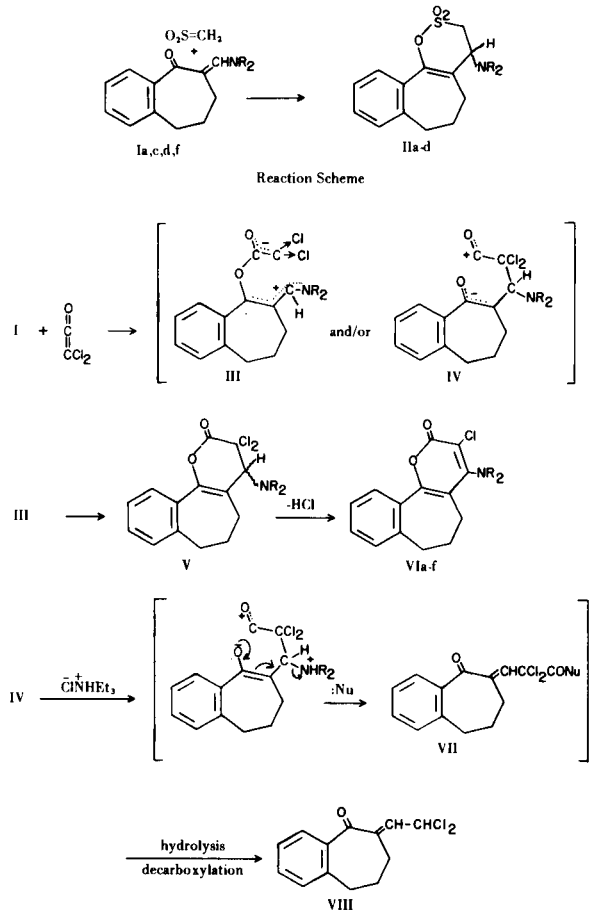
Formula Number	NR_2	Yield %	M.p. °C	Molecular Formula	Analyses % Calcd./Found C	H	N
Va	$N[CH(CH_3)_2]_2$	95	105 (a)	$C_{20}H_{25}Cl_2NO_2$	62.83	6.59	3.66
					62.85	6.40	3.72
Vb	$N(CH_3)C_6H_5$	62	133 (a)	$C_{21}H_{19}Cl_2NO_2$	64.96	4.93	3.61
					65.21	5.27	3.79
Vc	$N(C_6H_5)_2$	78	203 (b)	$C_{26}H_{21}Cl_2NO_2$	69.34	4.70	3.11
					69.42	4.35	3.31

(a) From anhydrous diethyl ether. (b) From ethyl acetate. All compounds were prepared according to (6).

(Table III), whose structure was confirmed by uv, ir and nmr spectral data (Table IV). In the nmr spectra, the C-3 methylene and C-4 methine protons give rise to a typical pattern due to an AB_2 system [*cf.* (4)]. The reaction of I with dichloroacetyl chloride and triethylamine (dichloroketene prepared *in situ*) gave the expected results only in the case of aromatic or strong hindering aliphatic *N*-substitution, namely formation of *N,N*-disubstituted 4-amino-3,3-dichloro-3,4,6,7-tetrahydro-5*H*-benzo[3,4]cyclohepta[2,1-*b*]pyran-2-ones (Va-c) (Tables V and VI) as a result of 1,4-cycloaddition.

Refluxing Va-c with collidine (6) afforded the dehydrochlorinated products, *N,N*-disubstituted 4-amino-3-chloro-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[2,1-*b*]pyran-2-ones (VIa-c) (Tables VII and VIII).

The reaction between compounds I and dichloroketene took a different course in the case of usual aliphatic *N,N*-disubstitution (*i.e.*, by employing enaminoketones Ia,c,d),



upon chromatography on neutral alumina. For instance, the dense liquid obtained in anhydrous conditions from Ia showed no modification of ir spectrum (1778, 1710, 1675, 1612 cm^{-1}) by chromatography on Florisil®. However, by chromatography on neutral alumina, a crystalline product containing chlorine but not nitrogen was isolated (59% yield), which was identified as 6-(2,2-dichloroethylidene)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (VIII) on the following basis. The uv and ir spectra were in agreement with the absorption of an α,β-unsaturated carbonyl compound; the nmr spectrum showed a typical AB system for two protons, and moreover the patterns of the trimethylene and four aromatic protons. The mass spectrum showed the molecular ion at m/e 258,256,254. The major fragmentation involved loss of chlorine to give an ion at m/e 219, followed by elimination of ethene to give the base peak at m/e 191 and of carbon monoxide to give an ion at m/e 163. The ion at m/e 131 derived from the molecular ion by loss of $\cdot CH_2CH{=}CHCHCl_2$ fragment. Compound VIII was also isolated from the reaction with Id, whereas it was absent in the case of the pyrrolidine enamine Ic. A second product (the sole compound in the case of Ic) was isolated in a low yield by alumina chromatography, namely the dehydrochlorinated 2-pyrone VId-f (Tables VII and VIII). We have interpreted the formation of VIII as a contribution of the less stable dipolar adduct IV [*cf.* (7)], which could give VII by reaction with triethylamine hydrochloride and some nucleophile (Cl^-, HNR_2) present in the solution; hydrolysis

Table VI

Uv and Ir Spectral Data of Compounds Va-c

	Uv λ max nm (log ε)	Ir, cm^{-1} (tetrachloromethane) C=O	C=C
Va	230 (3.99), 264 (3.88)	1782	1660
Vb	248 (4.30), 265 sh (4.17)	1788	1672
Vc	242 (4.30), 264 sh (4.17)	1772 (a)	1678

(a) in potassium bromide.

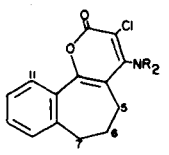
Nmr Spectral Data, δ (tetrachloromethane)

	CH-4	CH_2-5, CH_2-6	CH_2-7	H(8-10)	H-11	NR_2
Va	3.87	2.18	2.74	7.25	7.43	1.15 (2 superimposed d, J = 6.5, $4CH_3$)
	near s	m	m	m	m	3.15 (near h, J = 6.5, 2CHN)
Vb	5.01	2.10	2.75	7.33	7.65	2.79 (s, NCH_3)
	near s	m	m	m	m	7.00,7.33 (2m, NC_6H_5)
Vc (b)	5.41	2.17	2.66	7.15	7.15	7.15 (m, $2NC_6H_5$)
	near s	m	m	m	m	

(b) in deuteriochloroform.

Table VII

N,N-Disubstituted 4-Amino-3-chloro-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[2,1-*b*]pyran-2-ones (VIa-f)



Formula Number	NR_2	Yield %	M.p. °C	Molecular Formula	Analyses % Calcd./Found C	H	N
VIa	$N[CH(CH_3)_2]_2$	37	84 (a)	$C_{20}H_{24}ClNO_2$	69.45 69.73	6.99 6.67	4.05 4.17
VIb	$N(CH_3)C_6H_5$	82	192 (b)	$C_{21}H_{18}ClNO_2$	71.69 71.46	5.16 5.20	3.98 3.96
VIc	$N(C_6H_5)_2$	75	254 (b)	$C_{26}H_{20}ClNO_2$	75.45 75.68	4.87 5.10	3.38 3.52
VId	$N(C_2H_5)_2$	17(59) (c)	145 (b)	$C_{18}H_{20}ClNO_2$	68.03 68.14	6.34 6.06	4.41 4.37
VIe		55(0) (c)	158 (b)	$C_{18}H_{18}ClNO_2$	68.46 68.52	5.75 5.84	4.44 4.48
VIf		6(42) (c)	193 (d)	$C_{19}H_{20}ClNO_2$	69.19 69.22	6.11 5.90	4.25 4.36

(a) After chromatography on Florisil® with petroleum ether. (b) From ethyl acetate. (c) The value between brackets indicates the yield of VIII. (d) From anhydrous diethyl ether. Compounds VIa, VIb, VIc were obtained from Va, Vb, Vc, respectively, by refluxing in collidine (6); all the others, as described in the Experimental.

Table VIII

Uv and Ir Spectral Data of Compounds VIa-f

	Uv λ max nm (log ε)	Ir, cm^{-1} (tetrachloromethane) C=O	C=C	
VIa	235 (4.01), 241 (4.00), 331 (4.08)	1729	1616	1525
VIb	243 (4.31), 270 sh (3.98), 346 (4.27)	1732	1616	1512
VIc	237 sh (4.11), 246 sh (4.14), 258 sh (4.19), 276 (4.29), 349 (4.20)	1726	1614	1510
VId	234 sh (3.89), 240 (3.90), 260.5 (4.08), 330 (4.20)	1720	1614	1505
VIe	234 (3.88), 266.5 (4.27), 318 (4.12)	1688	1615	1510 (a)
VIf	239 (3.89), 263 (4.18), 325 (4.20)	1723	1618	1512

Nmr Spectral Data, δ

	CH_2-5	CH_2-6	CH_2-7	H(8-10)	H-11	NR_2
VIa (b)	2.40 mc	2.40 mc	2.40 mc	7.27 m	7.66 m	1.12 (d, J = 6.6, $4CH_3$) 3.71 (h, J = 6.6, 2NCH)
VIb (c)	1.88 m	1.88 m	2.55 m	7.24 m	7.60 m	3.37 (s, NCH_3) 6.82,7.24 (2m, NC_6H_5)
VIc (c)	1.25 dd J = 7.2	2.28 m	2.28 m	7.24 m	7.78 m	7.24 (m, $2NC_6H_5$)
VId (b)	2.29 m	2.29 m	2.68 m	7.33 m	7.66 m	1.16 (t, J = 7.2, $2CH_3$) 3.39 (q, J = 7.2, $2NCH_2$)
VIe (c)	2.30 m	2.30 m	2.70 m	7.34 m	7.72 m	1.98 (m, $2CH_2$) 3.73 (m, $2NCH_2$)
VIf (c)	2.31 m	2.31 m	2.68 m	7.34 m	7.68 m	1.71 (m, $3CH_2$) 3.40 (m, $2NCH_2$)

(a) In chloroform. (b) In tetrachloromethane. (c) In deuteriochloroform.

and decarboxylation by alumina could afford VIII. The pharmacological screening, concerning compounds IIa,b, VIb,d, included behaviour studies (Irwin test), antipentylenetetrazole, antiamphetamine and antireserpine activity in the mouse, as well as anti-inflammatory activity in the rat (8). None of the compounds was 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 on a Perkin-Elmer Model 257 spectrophotometer; nmr spectra were recorded on a Perkin-Elmer Model R12 instrument. Chemical shifts are reported as δ (ppm) relative to TMS as an internal standard; J in Hz. Mass spectra were obtained with a AEI MS-902 spectrometer. Melting points were determined with a Mettler FP1 apparatus.

6-Hydroxymethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one.

This compound was prepared according to (3), b.p. 120-125° (0.4 mm); uv λ max nm (log ε): 258 (3.72), 301 (3.91); ir (tetrachloromethane) ν max: 1635, 1560 cm^{-1}; nmr (tetrachloromethane): δ 2.06 (m, CH_2-7 + CH_2-8), 2.70 (m, CH_2-9), 7.32 (m, 3Har.), 7.59 (m, H-4), 8.02 (m, =CH-O-), 14.98 (broad m, OH; disappears with deuterium oxide).

Reaction Between Ia,c,d and Dichloroketene.

A solution of dichloroacetyl chloride (2.21 g., 15 mmoles) in anhydrous benzene (40 ml.) was added dropwise (stirring) at room temperature, under dry nitrogen, to a solution of Ia or Ic,d (10 mmoles) and triethylamine (1.52 g., 15 mmoles) in anhydrous benzene (70 ml.). After the addition was complete, the reaction mixture was stirred for 15 minutes and filtered. The filtrate was evaporated under reduced pressure and the residue was chromatographed on neutral alumina grade I (45 g.) to give, with petroleum ether (b.p. 40-70°) as eluant, the compound VIII. Further elution with benzene and with diethyl ether gave the dehydrochlorinated 2-pyrones VId,f.

6-(2,2-Dichloroethylidene)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (VIII).

This compound had m.p. 104-105° from petroleum ether; uv λ max nm (log ε): 253 (4.14); ir (tetrachloromethane) ν max: 1676, 1629 cm^{-1}; nmr (tetrachloromethane): δ 2.00 (near q, J = 6, CH_2-8), 2.43 (near t, J = 6, CH_2-7), 2.82 (near t, J = 6, CH_2-9), 6.51 and 6.87 (2d, J = 9.6, =CH-$CHCl_2$), 7.05-7.60 (m, 3Har), 7.72 (m, H-4); mass spectrum: m/e 258, 256, 254, 219, 191 (base peak), 163, 131, 104, 103, 91, 76, 65.

Anal. Calcd. for $C_{13}H_{12}Cl_2O$: C, 61.20; H, 4.74. Found: C, 61.25; H, 4.87.

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