Reaction of Sulfene and Dichloroketene with *N,N*-Disubstituted α-Aminomethyleneketones. Synthesis of 5*H*-Pyrano[3,4-*e*]-1,2-oxathiin and 2*H*,5*H*-Pyrano[4,3-*b*]pyran Derivatives

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The polar 1,4-cycloaddition of sulfene to *N,N*-disubstituted (*E*)-3-aminomethylene-2,3,5,6-tetrahydro-4*H*-pyran-4-ones II, prepared from 2,3,5,6-tetrahydro-4*H*-pyran-4-one *via* the 3-hydroxymethylene derivative, occurred only in the case of aliphatic *N*-substitution to give, generally in satisfactory yield, 4-dialkylamino-3,4,7,8-tetrahydro-5*H*-pyrano[3,4-*e*]-1,2-oxathiin 2,2-dioxides, which are derivatives of the new heterocyclic system 5*H*-pyrano[3,4-*e*]-1,2-oxathiin. The cycloaddition of dichloroketene to II occurred only in two cases of aromatic *N*-substitution to give 3,3-dichloro-3,4,7,8-tetrahydro-4-(methylphenyl)(diphenyl)amino-2*H*,5*H*-pyrano[4,3-*b*]pyran-2-ones IVi,ℓ. Dehydrochlorination of IV with triethylamine was successful only in the case of IVℓ to give 3-chloro-7,8-dihydro-4-diphenylamino-2*H*,5*H*-pyrano[4,3-*b*]pyran-2-one in low yield.

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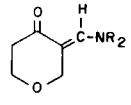
In previous papers [1,2] we described the reactions of sulfene and dichloroketene with *N,N*-disubstituted 3-aminomethylene-2,3,5,6-tetrahydro-4*H*-thiopyran-4-ones to give derivatives of two polycondensed sulfur heterocycles, namely 5*H*-thiopyrano[3,4-*e*]-1,2-oxathiin and 2*H*,5*H*-thiopyrano[4,3-*b*]pyran, respectively. In the case of isosteric *N,N*-disubstituted 3-aminomethylene-4-piperidinones the cycloaddition was operative only with sulfene to give de-

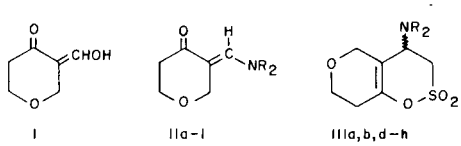
Table I

N,N-Disubstituted (*E*)-3-Aminomethylene-2,3,5,6-tetrahydro-4*H*-pyran-4-ones IIa-ℓ [a]

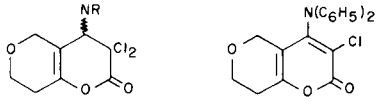


Formula Number	NR_2	Yield %	Mp °C or Bp °C/mm	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa	$N(CH_3)_2$	71	82 [b]	$C_8H_{13}NO_2$	61.91 61.76	8.44 8.15	9.03 9.00
IIb	$N(C_2H_5)_2$	77	49 [b]	$C_{10}H_{17}NO_2$	65.54 65.41	9.35 9.32	7.64 7.62
IIc	$N(CH_3)(CH_2)_2N(CH_3)_2$	59	140-150/0.4	$C_{11}H_{20}N_2O_2$	62.23 61.89	9.50 9.32	13.20 13.33
IId	Pyrrolidino	77	84 [b]	$C_{10}H_{15}NO_2$	66.27 66.57	8.34 8.48	7.73 7.69
IIe	Piperidino	82	79 [b]	$C_{11}H_{17}NO_2$	67.66 67.40	8.78 8.81	7.17 7.10
IIf	Morpholino	74	137 [c]	$C_{10}H_{15}NO_3$	60.90 60.75	7.67 7.62	7.10 7.00
IIg	4-Methylpiperazino	74	82 [b]	$C_{11}H_{18}N_2O_2$	62.83 62.99	8.63 8.60	13.32 13.48
IIh	4-Carbethoxypiperazino	80	95 [b]	$C_{13}H_{20}N_2O_4$	58.19 58.37	7.51 7.48	10.44 10.56
IIi [d]	$N(CH_3)C_6H_5$	68	120-130/0.3	$C_{13}H_{15}NO_2$	71.87 71.59	6.96 7.16	6.45 6.31
II ℓ	$N(C_6H_5)_2$	48	116 [c]	$C_{18}H_{17}NO_2$	77.40 77.32	6.13 6.25	5.01 5.01

[a] Enaminones IIa-h were prepared according to general procedure a) and IIi,ℓ according to general procedure b) described in the literature [5]. [b] From anhydrous diethyl ether. [c] From ethyl acetate. [d] Mixture of (*E*) and (*Z*) isomers, see Table II.



I IIa-l IIIa,b,d-h



IVi, l V l

NR_2

a $N(CH_3)_2$
b $N(C_2H_5)_2$
c $N(CH_3)(CH_2)_2N(CH_3)_2$
d Pyrrolidino
e Piperidino
f Morpholino
g 4-Methylpiperazino
h 4-Carbethoxypiperazino
i $N(CH_3)C_6H_5$
l $N(C_6H_5)_2$

rivatives of 1,2-oxathiino[5,6-*c*]pyridine [3].

As a continuation of our work in this field, we wish to report now the polar 1,4-cycloadditions of sulfene and dichloroketene to a number of *N,N*-disubstituted 3-aminomethylene-2,3,5,6-tetrahydro-4*H*-pyran-4-ones II to afford derivatives of the new heterocyclic system 5*H*-pyrano-[3,4-*e*]-1,2-oxathiin and of 2*H*,5*H*-pyrano[4,3-*b*]pyran, respectively.

Reaction of 2,3,5,6-tetrahydro-4*H*-pyran-4-one with ethyl formate and sodium according to a literature procedure [4] gave in moderate yield the 3-hydroxymethylene derivative I. The starting enaminones IIa-ℓ (Table I) were prepared, generally in good yield, from I and secondary amines, according to a previously described procedure [5]. They are probably *E* isomers, as can be seen from the upfield shifts of the C-2 protons (0.7-1.0 ppm) caused by the phenyl group(s) in compounds IIi,ℓ in comparison with IIa-h (Table II).

The reaction of II with methanesulfonyl chloride and triethylamine (sulfene prepared *in situ*) occurred as usual-

Table II

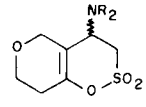
UV, IR an NMR Spectral Data of Compounds IIa-ℓ

Compound	UV, λ max nm (log ε)	IR, cm^{-1} C=O	IR, cm^{-1} C=C	NMR, δ
IIa	327.5 (4.32)	1646	1535	2.47 (t, J = 6, CH_2-5), 3.08 [s, $(CH_3)_2N$], 3.97 (t, J = 6, CH_2-6), 4.85 (near s, CH_2-2), 7.48 (mc, =CHN)
IIb	327.5 (4.34)	1639	1528	1.23 (t, J = 7.2, 2 CH_3), 2.47 (t, J = 6, CH_2-5), 3.29 (q, J = 7.2, 2 CH_2N), 3.97 (t, J = 6, CH_2-6), 4.73 (d, J = 1.2, CH_2-2), 7.63 (mc, =CHN)
IIc	326 (4.10)	1645	1540	2.25 [s, $(CH_3)_2N$], 2.3-2.7 (m, CH_2N + CH_2-5), 3.08 (s, CH_3N), 2.9-3.5 (m, CH_2N), 3.93 (t, J = 6.5, CH_2-6), 4.80 (near s, CH_2-2), 7.54 (near s, =CHN)
IId	333 (4.34)	1642	1520	1.90 (mc, 2 CH_2 pyr), 2.43 (t, J = 6, CH_2-5), 3.51 (mc, 2 CH_2N), 3.92 (t, J = 6, CH_2-6), 4.79 (near s, CH_2-2), 7.70 (near s, =CHN)
IIe	328.5 (4.42)	1638	1525	1.75 (mc, 3 CH_2 pip), 2.55 (t, J ≃ 6, CH_2-5), 3.44 (mc, 2 CH_2N), 4.03 (t, J = 6, CH_2-6), 4.78 (near s, CH_2-2), 7.63 (near s, =CHN)
IIf	326 (4.34)	1647	1535	2.48 (t, J = 6, CH_2-5), 3.40 (mc, 2 CH_2N), 3.72 (mc, 2 CH_2O), 3.95 (t, J = 6, CH_2-6), 4.70 (mc, CH_2-2), 7.53 (mc, =CHN)
IIg	325.5 (4.36)	1650	1537	2.30 (s, CH_3N), 2.45 (2 superimposed t, J = 6, 2 CH_2N + CH_2-5), 3.42 (near t, J = 6, 2 CH_2N), 3.92 (t, J = 6, CH_2-6) 4.68 (near s, CH_2-2), 7.48 (near s, =CHN)
IIh	325 (4.33)	1652	1545	1.28 (t, J = 7, CH_3), 2.48 (t, J = 6, CH_2-5), 3.44 and 3.49 (2 mc, 4 CH_2N), 3.94 (t, J = 6, CH_2-6), 4.18 (q, J = 7, CH_2O), 4.69 (near s, CH_2-2), 7.49 (near s, =CHN)
IIi	249 (4.32) 336 (4.00)	1658	1530	2.50 (mc, CH_2-5), 2.95 and 3.43 (2 s, CH_3N), 4.09 (near s, CH_2-2), 3.89 and 4.44 (2 t, J′ = 6, J″ = 7, CH_2-6), 6.84 and 7.23 (2 mc, C_6H_5), 7.70 (mc, =CHN) [a]
II ℓ	232 (4.00) 281 (3.96) 350 (4.39)	1657	1525	2.54 (t, J = 6, CH_2-5), 3.79 (near s, CH_2-2), 3.89 (t, J = 6, CH_2-6), 6.8-7.7 (m, 2 C_6H_5), 7.85 (mc, =CHN)

[a] (*E*)/(*Z*) ratio 1:1. After redistillation and chromatography on Florisil (diethyl ether), this ratio changed to 3:1.

Table III

4-Dialkylamino-3,4,7,8-tetrahydro-5*H*-pyrano[3,4-*e*]-1,2-oxathiin 2,2-Dioxides IIIa,b,d-h [a]



Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$N(CH_3)_2$	58	82 [b]	$C_9H_{15}NO_4S$	46.34	6.48	6.00
					46.56	6.57	5.96
IIIb	$N(C_2H_5)_2$	52	81 [b]	$C_{11}H_{19}NO_4S$	50.56	7.33	5.36
					50.47	7.31	5.25
IIId	Pyrrolidino	73	81 [b]	$C_{11}H_{17}NO_4S$	50.95	6.61	5.40
					51.15	6.67	5.34
IIIe	Piperidino	80	135 [b]	$C_{12}H_{19}NO_4S$	52.73	7.01	5.12
					52.95	7.22	5.15
IIIf	Morpholino	77	154 [b]	$C_{11}H_{17}NO_5S$	47.99	6.22	5.09
					47.73	6.26	5.04
IIIg	4-Methylpiperazino	49	118 [c]	$C_{12}H_{20}N_2O_4S$	49.98	6.99	9.71
					50.18	6.99	9.70
IIIh	4-Carbethoxypiperazino	67	135 [d]	$C_{14}H_{22}N_2O_6S$	48.54	6.40	8.09
					48.50	6.37	7.96

[a] All compounds were prepared according to the literature [8], using anhydrous tetrahydrofuran as the solvent. Compounds IIIc,g,h were obtained as crude hydrochlorides; therefore they were dissolved in water, the aqueous solution was made alkaline with 4*N* sodium hydroxide and extracted thoroughly with diethyl ether, the ether extracts were dried (magnesium sulfate) and evaporated. Nevertheless, compound IIIc could not be obtained pure by this procedure. [b] From 95% ethanol. [c] From diethyl ether. [d] From ethyl acetate.

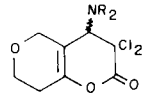
Table IV

IR and NMR Spectral Data of Compounds IIIa,b,d-h

Compound	IR, cm^{-1} C=C	O=S=O		NMR, δ
IIIa	1695	1373	1175	2.15-2.50 (m, CH_2-8), 2.28 [s, $(CH_3)_2N$], 3.15-4.10 (m, CH_2-3 + CH-4 + CH_2-7), 4.15 (mc, CH_2-5)
IIIb	1696	1373	1183	1.08 (t, J = 7.2, 2 CH_3), 2.44 (near q, J = 7.2, 2 CH_2N), 2.65-4.05 (m, CH_2-3 + CH-4 + CH_2-7 + CH_2-8), 4.16 (mc, CH_2-5)
IIId	1707	1380	1186	1.77 (mc, 2 CH_2 pyr), 2.34 (mc, CH_2-8), 2.63 (mc, 2 CH_2N), 3.2-4.1 (m, CH_2-3 + CH-4 + CH_2-7), 4.20 (mc, CH_2-5)
IIIe	1695	1370	1185	1.52 (mc, 3 CH_2 pip), 2.42 (mc, 2 CH_2N + CH_2-8), 3.20-4.05 (m, CH_2-3 + CH-4 + CH_2-7), 4.16 (mc, CH_2-5)
IIIf	1695	1372	1186	2.32 (mc, CH_2-8), 2.51 (mc, 2 CH_2N), 3.25-4.10 (m, 2 CH_2O + CH_2-3 + CH-4 + CH_2-7), 4.17 (mc, CH_2-5)
IIIg	1702	1375	1185	2.28 (s, CH_3N), 2.50 (mc, 4 CH_2N + CH_2-8), 3.48 (mc, CH_2-7), 3.84 (mc, CH_2-3 + CH-4), 4.14 (near s, CH_2-5)
IIIh	1695	1385	1187	1.26 (t, J = 7.2, CH_3), 2.48 (mc, 2 CH_2N + CH_2-8), 3.1-4.1 (m, CH_2-3 + CH-4 + CH_2-7), 3.48 (mc, 2 CH_2N), 4.15 (q, J = 7.2, CH_2O), 4.17 (mc, CH_2-5)

Table V

N,N-Disubstituted 4-Amino-3,3-dichloro-3,4,7,8-tetrahydro-2*H*,5*H*-pyrano[4,3-*b*]pyran-2-ones IVi,ℓ [a]



Formula Number	NR_2	Yield %	Mp °C [b]	Molecular Formula	Analyses % Calcd./Found C	H	N
IVi	$N(CH_3)C_6H_5$	37	165	$C_{15}H_{15}Cl_2NO_3$	54.90 54.67	4.61 4.75	4.27 4.08
IV ℓ	$N(C_6H_5)_2$	92	188	$C_{20}H_{17}Cl_2NO_3$	61.55 61.71	4.39 4.15	3.59 3.50

IR and NMR Spectral Data

	IR, cm^{-1} C=O	C=C	NMR, δ
IVi	1785	1725	2.25-2.70 (m, CH_2-8), 2.73 (s, CH_3N), 3.8-4.3 (m, CH_2-5 + CH_2-7), 4.73 (near s, CH-4), 6.75-7.05 and 7.15-7.50 (2 m, C_6H_5)
IV ℓ	1780	1722	2.08 (mc, CH_2-8), 3.79 (mc, CH_2-7), 4.28 (mc, CH_2-5), 4.98 (near s, CH-4), 6.85-7.55 (m, 2 C_6H_5)

[a] All compounds were prepared according to the literature [9], reaction time, 30 minutes. [b] From ethyl acetate.

ly only in the case of aliphatic *N*-substitution (*cf.* [5]) to give 4-dialkylamino-3,4,7,8-tetrahydro-5*H*-pyrano[3,4-*e*]-1,2-oxathiin 2,2-dioxides IIIa,b,d-h (Table III), generally in good yield. The structure of these adducts was confirmed by ir and nmr spectral data (Table IV).

Less satisfactory was the cycloaddition of dichloroketene (prepared *in situ* from dichloroacetyl chloride and triethylamine) to enaminones II. This reaction occurred only in two cases of aromatic *N*-substitution to give 3,3-dichloro-3,4,7,8-tetrahydro-4-(methylphenyl)(diphenyl)amino-2*H*,5*H*-pyrano[4,3-*b*]pyran-2-ones IVi,ℓ (Table V), of which only IV ℓ could be dehydrochlorinated with triethylamine [6] to afford 3-chloro-7,8-dihydro-4-diphenylamino-2*H*,5*H*-pyrano[4,3-*b*]pyran-2-one V ℓ in low yield.

In a pharmacological screening concerning some compounds III, it was found that IIIe,f showed immunosuppressive activity on IgM antibody secretion in the mouse by i.p. administration in the Jerne Plaque III Assay [7].

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer EPS-3T spectrophotometer. The ir spectra were taken in chloroform on a Perkin-Elmer Model 398 spectrophotometer; the nmr spectra were recorded in deuteriochloroform on a Perkin-Elmer Model R-12 instrument (60 MHz, TMS as internal standard, J in Hz). Melting points were determined with a Fisher-Johns apparatus.

2,3,5,6-Tetrahydro-3-hydroxymethylene-4*H*-pyran-4-one (I).

This compound was prepared from 2,3,5,6-tetrahydro-4*H*-pyran-4-one (10 g, 0.1 moles), ethyl formate (11.1 g, 0.15 moles) and sodium (2.3 g, 0.1 moles) in anhydrous diethyl ether according to a literature procedure [4]. Compound I was obtained from the alkaline solution by acidification with 6 *N* hydrochloric acid at *p*H 5, followed by extraction with diethyl ether-chloroform 2/1; the extraction was repeated twice after acidification at *p*H 3 and 1. This procedure was necessary in order to avoid the formation of a yellow resin, yield, 3.91 g (31%), bp 60-70°/0.3 mm Hg; mp 70° from anhydrous diethyl ether; uv: λ max nm (log ε) 275.5 (3.90); ir (chloroform): ν max 1640, 1585 cm^{-1}; nmr (deuteriochloroform): δ 2.54 (t, J = 6, CH_2-5), 3.94 (t, J = 6, CH_2-6), 4.44 (near s, CH_2-2), 8.33 (near s, =CH-O), 13.55 (broad s, OH; disappears with deuterium oxide).

Anal. Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.37; H, 6.42.

3-Chloro-7,8-dihydro-4-diphenylamino-2*H*,5*H*-pyrano[4,3-*b*]pyran-2-one (V ℓ).

This compound was prepared in 14% yield by dehydrochlorination of IV ℓ with triethylamine according to the literature [6], reflux time 10 hours, mp 259° from ethyl acetate; uv: λ max nm (log ε) 249.5 (4.15), 278 (4.16), 316 (3.92), 367 (3.91); ir (chloroform): ν max 1715, 1645 cm^{-1}; nmr (deuteriochloroform): δ 2.67 (mc, CH_2-8), 3.83 (mc, CH_2-7 + CH_2-5), 6.9-7.6 (m, 2 C_6H_5).

Anal. Calcd. for $C_{20}H_{16}ClNO_3$: C, 67.90; H, 4.56; N, 3.96. Found: C, 68.18; H, 4.68; N, 3.94.

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