Reaction of Sulfene and Dichloroketene with Open-chain *N,N*-Disubstituted α-Aminomethyleneketones. Synthesis of 4-Dialkylamino-3,4-dihydro-5,6-dimethyl-1,2-oxathiin 2,2-Dioxides and of 6,(5)(Di)alkyl-3-chloro-4-methylphenylamino-2*H*-pyran-2-ones

Alberto Bargagna, Pietro Schenone, Francesco Bondavalli and Mario Longobardi*

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

Received June 21, 1979

Cycloaddition of sulfene to *N,N*-disubstituted 4-amino-3-methyl-3-buten-2-ones (III) occurred in fair to good yield only in the case of aliphatic *N*-substitution to give 4-dialkylamino-3,4-dihydro-5,6-dimethyl-1,2-oxathiin 2,2-dioxides, whereas *N,N*-disubstituted 1-amino-1-penten-3-ones (II) did not react at all. Cycloaddition of dichloroketene to II, III and *N,N*-disubstituted 4-amino-3-buten-2-ones occurred only in the case of the methylphenylamino derivative, giving in good to moderate yield 6,(5)(di)alkyl-3,3-dichloro-3,4-dihydro-4-methylphenylamino-2*H*-pyran-2-ones, which were dehydrochlorinated with DBN to 6,(5)(di)alkyl-3-chloro-4-methylphenylamino-2*H*-pyran-2-ones.

J. Heterocyclic Chem., **17**, 33 (1980).

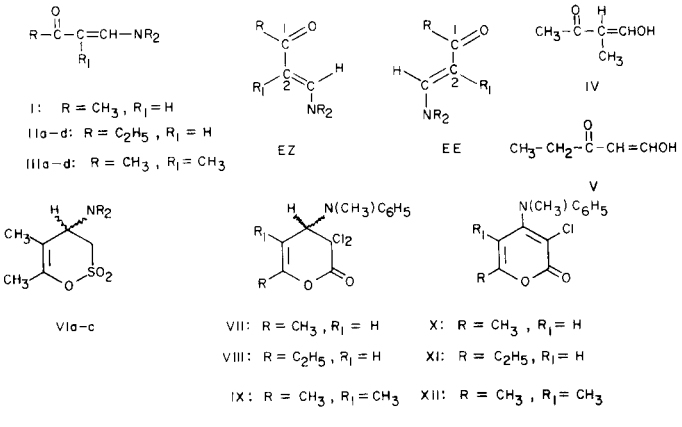
In previous work (1) we had shown that the cycloaddition of sulfene to open-chain α-aminomethyleneketones such as I did not occur. In order to gain more insight into the controlling features of these kinds of reactions, we have extended the cycloaddition of sulfene to other open-chain enaminones such as II, homologs of I as regards the R group, and III, where a double methyl substitution occurred on both carbon atoms bearing the carbonyl and the aminomethylene group.

The main problem concerned first the synthesis of enaminones II, because Diels (2) and later Benary (3) had apparently shown that the sole α-hydroxymethyleneketone obtained by reaction of ethyl formate and sodium with butanone was 4-hydroxy-3-methyl-3-buten-2-one IV, from which only enaminones III could be prepared [*cf.* (4)].

We have reinvestigated the preparation of IV and found that the solid obtained in the reaction was actually IV, confirmed from its nmr spectrum (see Experimental), whereas the liquid by-product formerly discarded was a mixture of IV and the hitherto unknown 1-hydroxy-1-penten-3-one V. The latter could not be obtained pure, but was mostly separated from IV by slow distillation *in vacuo* at room temperature. Although this procedure gave a liquid which still contained about 25% of IV, as determined by nmr, the mixture was nevertheless employed by us to prepare impure enaminones IIa-d (Table I) by reaction with secondary amines following previously described procedures (5,6). The purification of II was achieved by column chromatography on Florisil ® .

The reaction with amines should be carried out immediately, because another feature of V is a facile decomposition provoked by light and room temperature, as was shown by the appearance of a yellowish colour and changes in the nmr spectrum. *N,N*-Disubstituted 4-amino-3-methyl-3-buten-2-ones IIIa-d (Table II) were prepared like enaminones II, starting from the solid, easily available α-hydroxymethyleneketone IV.

Enaminones II and III showed in their ir spectra (Tables I and II) an additional band in the double bond stretching region, which, like I, was attributed to the presence of both isomers *EE* and *EZ* (1); on the other hand, the nmr spectra of enaminones IId and IIId [NR_2 = $N(CH_3)C_6H_5$, Tables I and II] showed that rotamers *EZ* were predominant in this case. As a matter of fact, IIId showed a 0.2 ppm upward shift of the C-2 methyl group protons in comparison with other III, whereas IId showed a 0.3 ppm downward shift of the C-2 proton in comparison with other compounds II. The molecular models showed that a shielding (IIId) or deshielding effect (IId) of the phenyl group on the C-2 methyl group or the C-2 proton, respectively, was possible only in the case of the *EZ* isomer.



0022-152X/80/010033-05$02.25

Table I

N,N-Disubstituted 1-Amino-1-penten-3-ones (IIa-d)

$CH_3-CH_2-\underset{\underset{O}{\|}}{C}-CH=CH-NR_2$

Compound No.	NR_2	Yield %	B.p./mm Hg or M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa	$N(CH_3)_2$	50	85-87/0.1 (a)	$C_7H_{13}NO$	66.11	10.30	11.01
					66.04	10.35	11.22
IIb	$N(C_2H_5)_2$	46	108-110/0.1	$C_9H_{17}NO$	69.63	11.04	9.02
					69.43	11.07	8.73
IIc	Morpholino	51	120-122/0.1	$C_9H_{15}NO_2$	63.88	8.93	8.28
					63.70	8.63	8.22
IId	$N(CH_3)C_6H_5$	43	142-145/0.1	$C_{12}H_{15}NO$	76.16	7.99	7.40
			41 (b)		76.45	8.20	7.43

Uv, Ir and Nmr Spectral Data

	Uv λ max nm (log ε)	Ir, cm^{-1} C=O	(Tetrachloromethane) C=C	Nmr, δ (Tetrachloromethane)
IIa	220 (4.09), 304 (4.42)	1665	1620, 1580	1.02 (t, J = 7.5, CH_3-CH_2), 2.26 (q, J = 7.5, CH_2-CH_3), 2.97 (s, $2NCH_3$), 5.00 (d, J = 12.8, COCH=), 7.50 (d, J = 12.8, =CHN)
IIb	307 (4.46)	1665	1615, 1565	1.01 (t, J = 7.5, CH_3-CH_2), 1.19 (t, J = 7.3, $2CH_3CH_2N$), 2.26 (q, J = 7.5, CH_2-CH_3), 3.26 (q, J = 7.3, $2CH_2N$), 4.97 (d, J = 12.8, COCH=), 7.38 (d, J = 12.8, =CHN)
IIc	304 (4.43)	1663	1620, 1570	1.00 (t, J = 7.5, CH_3-CH_2), 2.25 (q, J = 7.5, CH_2-CH_3), 3.26 (m, $2NCH_2$), 3.66 (m, $2\ OCH_2$), 5.09 (d, J = 13, COCH=), 7.33 (d, J = 13, =CHN)
IId	228 (3.90), 321 (4.50)	1670	1620, 1560	1.05 (t, J = 7.5, CH_3-CH_2), 2.35 (q, J = 7.5, CH_2-CH_3), 3.21 (s, NCH_3), 5.30 (d, J = 13, COCH=), 7.0-7.5 (m, NC_6H_5), 7.80 (d, J = 13, =CHN)

(a) Lit. b.p. 95-96°/4 mm (9), 99.5-101/2.5 mm (10). (b) From anhydrous diethyl ether-petroleum ether.

The results of the cycloaddition of II and III to sulfene (prepared *in situ* from methanesulfonyl chloride and triethylamine) were partly surprising, because the reaction occurred only with enaminones IIIa-c (*i.e.* those bearing an aliphatic *N,N*-disubstitution), giving 4-dialkylamino-3,4-dihydro-5,6-dimethyl-1,2-oxathiin 2,2-dioxides VIa-c (Table III), whereas enaminones IIa-d did not react and were recovered unchanged from the reaction mixture. The unreactivity of IId and IIId seems justified by a decreased electron availability on the nitrogen atom of the enaminone [*cf.* (1)], whereas the failure of IIa-c parallels that reported for enaminones I (1). It seems therefore that in these cases an alkyl substitution on C-2 of the appropriate rotamer is a prerequisite in order to allow the 1,4-cycloaddition. The reaction with dichloroketene (prepared *in situ* from dichloroacetyl chloride and triethylamine) was tried with enaminones I (1), II and III. The cycloaddition was successful only in the case of Id, IId, IIId [NR_2 = $N(CH_3)C_6H_5$], affording in good to moderate yield 6,(5)(di)alkyl-3,3-dichloro-3,4-dihydro-4-methylphenylamino-2*H*-pyran-2-ones VII, VIII and IX (Table IV), whereas in the case of aliphatic *N,N*-disubstitution of the enaminones I, II and III we were unable to isolate any reaction product, even if the initial formation of the cycloadduct could be inferred from the ir absorptions (about 1780 cm^{-1}) of the reaction mixture.

The results obtained with dichloroketene are thus in partial agreement with those reported by us in the case of other open-chain α-aminomethyleneketones (7).

Refluxing VII, VIH and IX in benzene with DBN (12) afforded in good yield the dehydrochlorinated products, namely 6,(5)(di)alkyl-3-chloro-4-methylphenylamino-2*H*-pyran-2-ones X, XI and XII, respectively (Table V).

The structures of compounds VII-XII were supported by ir and nmr spectral data (see Tables IV and V).

In conclusion, the 1,4-cycloaddition of dichloroketene to I, II and III seems to depend only on the *N*-substitution of the enaminone, irrespective of the substituents on C-2 of the *EZ* rotamer.

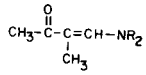
EXPERIMENTAL

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 spectrometer, and nmr spectra were recorded on a Perkin-Elmer Model R12 instrument (60 MHz; TMS as internal standard; J in Hz).

Enaminones IIa-c, IIIa-c were prepared from V plus IV mixture, and IV, respectively, according to (5), and IId, IIId according to (6). The purity of compounds II was checked by tlc (silica gel plates; spray reagent 0.1

Table II

N,N-Disubstituted 4-Amino-3-methyl-3-buten-2-ones (IIIa-d)



Compound No.	NR_2	Yield %	B.p./mm Hg or M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$N(CH_3)_2$	47	39 (a)(b)	$C_7H_{13}NO$	66.11	10.30	11.01
					66.20	10.05	11.30
IIIb	$N(C_2H_5)_2$	56	95-98/0.1 (c)	$C_9H_{17}NO$	69.63	11.04	9.02
					69.51	11.21	8.90
IIIc	Morpholino	70	113-115/0.1	$C_9H_{15}NO_2$	63.88	8.93	8.28
			56 (a)		63.60	8.84	7.99
IIId	$N(CH_3)C_6H_5$	56	125-127/0.1	$C_{12}H_{15}NO$	76.16	7.99	7.40
			32 (a)		75.87	8.23	7.27

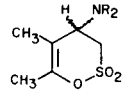
Uv, Ir and Nmr Spectral Data

	Uv λ max nm (log ε)	Ir, cm^{-1} (Tetrachloromethane) C=O	C=C	Nmr, δ (Tetrachloromethane)
IIIa	306 (4.42)	1685	1605, 1510	1.86 (s, CH_3-C=), 2.07 (s, CH_3-CO), 3.10 (s, $2NCH_3$), 7.10 (near s, =CHN)
IIIb	306 (4.42)	1660	1590, 1510	1.21 (t, J = 7.3, $2CH_3CH_2N$), 1.85 (s, CH_3-C=), 2.10 (s, CH_3-CO), 3.38 (q, J = 7.3, 2 NCH_2), 7.16 (near s, =CHN)
IIIc	304 (4.47)	1665	1610, 1560	1.80 (s, CH_3-C=), 2.10 (s, CH_3-CO), 3.44 (m, $2NCH_2$), 3.68 (m, 2 OCH_2), 7.11 (near s, =CHN)
IIId	228 (3.72) 324 (4.39)	1650	1615, 1540	1.66 (s, CH_3-C=), 2.20 (s, CH_3-CO), 3.39 (s, NCH_3), 6.90-7.35 (m, NC_6H_5), 7.05 (near s, =CHN)

(a) From anhydrous diethyl ether-petroleum ether. (b) Lit. (8) b.p. 135-139/23 mm, m.p. 55°. (c) Lit. (8) b.p. 140/14 mm.

Table III

4-Dialkylamino-3,4-dihydro-5,6-dimethyl-1,2-oxathiin 2,2-Dioxides (VIa-c) (b)



Compound No.	NR_2	Yield %	M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
VIa	$N(CH_3)_2$	49	93 (a)	$C_8H_{15}NO_3S$	46.81	7.37	6.82
					47.11	7.64	6.69
VIb	$N(C_2H_5)_2$	54	82 (a)	$C_{10}H_{19}NO_3S$	51.48	8.21	6.00
					51.79	8.26	6.26
VIc	Morpholino	33	107 (a)	$C_{10}H_{17}NO_4S$	48.57	6.93	5.66
					48.50	7.04	5.99

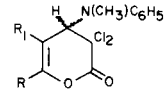
Uv, Ir and Nmr Spectral Data

	Ir, cm^{-1} (Chloroform) C=C	O=S=O		Nmr, δ (Deuteriochloroform)
VIa	1686	1373	1180	1.75 (m, CH_3-5), 2.00 (m, CH_3-6), 2.27 (s, 2 NCH_3), 3.2-3.5 (m, CH_2-3), 3.60-3.95 (m, CH-4)
VIb	1685	1370	1175	1.08 (t, J = 7.3, $2CH_3$-CH_2N), 1.74 (m, CH_3-5), 1.98 (m, CH_3-6), 2.46 (2 superimp. q, J = 7.3, 2 CH_2N), 3.30 (m, CH_2-3), 3.70-4.15 (m, CH-4)
VIc	1685	1370	1185	1.75 (m, CH_3-5), 1.95 (m, CH_3-6), 2.50 (m, $2NCH_2$), 3.23-3.47 (m, CH_2-3), 3.70 (m, 2 OCH_2), 3.70-4.10 (m, CH-4)

(a) From anhydrous diethyl ether. (b) All compounds were prepared according to (5), using anhydrous benzene as the solvent. The crude products were purified by chromatography on Florisil ® (petroleum ether-diethyl ether 2:1).

Table IV

6,(5)(Di)alkyl-3,3-dichloro-3,4-dihydro-4-methylphenylamino-2*H*-pyran-2-ones (VII-IX) (b)



Compound No.	R	R_1	Yield %	M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
VII	CH_3	H	53	102 (a)	$C_{13}H_{13}Cl_2NO_2$	54.57	4.58	4.89
						54.61	4.59	5.16
VIII	C_2H_5	H	77	80 (a)	$C_{14}H_{15}Cl_2NO_2$	56.02	5.04	4.67
						56.30	4.99	4.46
IX	CH_3	CH_3	56	110 (a)	$C_{14}H_{15}Cl_2NO_2$	56.02	5.04	4.67
						56.34	5.10	4.69

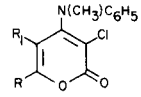
Ir and Nmr Spectral Data

	Ir, cm^{-1} (Tetrachloromethane) C=O	C=C	Nmr, δ (Tetrachloromethane)
VII	1795	1703	2.06 (s, CH_3-6), 2.67 (s, NCH_3), 4.84 and 5.05 (2d, J = 6, CH-5 + CH-4), 6.6-7.3 (m, NC_6H_5)
VIII	1785	1690	1.20 (t, J = 7.3, CH_3CH_2), 2.34 (q, J = 7.3, CH_2CH_3), 2.67 (s, NCH_3), 4.88 and 5.08 (2d, J = 6, CH-5 + CH-4), 6.66-7.37 (m, NC_6H_5)
IX	1788	1705	1.78 (s, CH_3-5), 2.03 (s, CH_3-6), 2.63 (s, NCH_3), 4.64 (near s, CH-4), 6.73-7.30 (m, NC_6H_5)

(a) From anhydrous diethyl ether. (b) All compounds were prepared according to (11).

Table V

6,(5)(Di)alkyl-3-chloro-4-methylphenylamino-2*H*-pyran-2-ones (X-XII) (b)



Compound No.	R	R_1	Yield %	M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
X	CH_3	H	72	97 (a)	$C_{13}H_{12}ClNO_2$	62.53	4.84	5.61
						62.48	5.07	5.67
XI	C_2H_5	H	52	78 (a)	$C_{14}H_{14}ClNO_2$	63.75	5.37	5.31
						63.62	5.30	5.07
XII	CH_3	CH_3	75	115 (a)	$C_{14}H_{14}ClNO_2$	63.75	5.37	5.31
						63.98	5.66	5.09

Ir and Nmr Spectral Data

	Ir, cm^{-1} (Chloroform) C=O	C=C		Nmr, δ (Deuteriochloroform)
X	1690	1655	1520	2.15 (s, CH_3-6), 3.56 (s, NCH_3), 5.75 (near s, CH-5), 7.03-7.50 (m, NC_6H_5)
XI	1690	1641	1515	1.17 (t, J = 7.3, CH_3-CH_2), 2.46 (q, J = 7.3, CH_2-CH_3), 3.54 (s, NCH_3), 5.79 (near s, CH-5), 7.0-7.5 (m, NC_6H_5)
XII	1712	1632	1520	1.70 (near s, CH_3-5), 2.28 (near s, CH_3-6), 3.28 (s, NCH_3), 6.6-7.4 (m, NC_6H_5)

(a) From anhydrous diethyl ether-acetone. (b) All compounds were prepared by dehydrochlorination with DBN of VII-IX, according to (12).

N iodine-10% sulfuric acid 2:1; eluant acetone-chloroform-triethylamine 50:50:2). Enaminones II were purified by chromatography on Florisil ® (1 g./30 g. Florisil ®), using petroleum ether (b.p. 40-60°) as eluant.

4-Hydroxy-3-methyl-3-buten-2-one IV and 1-Hydroxy-1-penten-3-one V.

The mixture of sodium salts of IV and V was prepared from butanone, ethyl formate and sodium according to Benary (3). The sodium salts (30 g., 0.245 moles) were dissolved in water (100 ml). and the solution was acidified at 0° with 6*M* hydrogen chloride. The liquid which separated was extracted with diethyl ether, the extracts were dried (sodium sulfate) and concentrated to give a liquid; yield, 7.5-8.0 g. (30-32%). The liquid was placed in a sublimation apparatus equipped with a trap cooled with dry ice to give, at room temperature and 0.1 mm Hg. a sublimate of IV [3.2-3.5 g. (42-43%), m.p. 73°, lit. (2,3) m.p. 73°] and a liquid in the trap (2.3-2.5 g., 29-31%). The latter consisted of V and IV in a ratio of about 75/25, as revealed from the nmr spectrum. Attempts to fully separate IV and V by distillation *in vacuo* or column chromatography on Florisil ® failed, because V decomposed quickly not only by such treatments, but also by keeping at room temperature and by the presence of light.

4-Hydroxy-3-methyl-3-buten-2-one (IV).

This compound had ir (tetrachloromethane): ν max, 3380, 1710, 1630, 1580, 1190 cm^{-1}; nmr (tetrachloromethane): δ 1.80 (s, =C-CH_3), 2.10 (s, CO-CH_3), 7.62-7.86 (m, =CH), 14.35-14.75 (m, OH; disappears with deuterium oxide).

1-Hydroxy-1-penten-3-one (V).

This compound had nmr (tetrachloromethane): δ 1.12 (t, J = 6.9, CH_3-CH_2), 2.41 (q, J = 6.9, CH_2-CH_3), 5.54 (d, J = 4.3, COCH=), 7.86 (d, J = 4.3, =CH-O-), 10.00 (mc, OH; disappears with deuterium oxide). These data were obtained by extrapolating the signals due to IV.

Acknowledgement.

The authors wish to thank Dr. Maria Canepa for the microanalyses and Dr. E. Sottofattori and Mr. F. Fasce for the uv, ir and nmr spectra.

REFERENCES AND NOTES

(1) F. Evangelisti, P. Schenone and A. Bargagna, *J. Heterocyclic Chem.*, **16**, 217 (1979).

(2) O. Diels and K. Ilberg, *Ber.*, **49**, 158 (1916).

(3) E. Benary, H. Meyer and K. Charisius, *ibid.*, **59**, 108 and 600 (1926).

(4) V. W. Weselowsky and A. M. Moiseenkov, *Synthesis*, 58 (1974).

(5) P. Schenone, G. Bignardi and S. Morasso, *J. Heterocyclic Chem.*, **9**, 1341 (1972).

(6) G. Bignardi, P. Schenone and F. Evangelisti, *Ann. Chim. (Rome)*, **61**, 326 (1971).

(7) A. Bargagna, F. Evangelisti and P. Schenone, *J. Heterocyclic Chem.*, **16**, 93 (1979).

(8) E. Benary, *Ber.*, **63**, 1573 (1930).

(9) N. K. Kochetkov, M. G. Ivanova and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 676 (1956); *Chem. Abstr.*, **51**, 1830b (1957).

(10) Z. Arnold and J. Zemlicka, *Collect. Czech. Chem. Commun.*, **24**, 2385 (1959); *Chem. Abstr.*, **54**, 1275b (1960).

(11) G. Bignardi, F. Evangelisti, P. Schenone and A. Bargagna, *J. Heterocyclic Chem.*, **9**, 1071 (1972).

(12) L. Mosti, G. Bignardi, F. Evangelisti and P. Schenone, *J. Heterocyclic Chem.*, **13**, 1201 (1976).