Reaction of Ketenes with *N,N*-Disubstituted 2-Aminomethylenecycloalkanones III. Synthesis of *N,N*-Disubstituted 3,3-Dichloro-4-amino-5,6-polymethylene-3,4-dihydro-α-pyrones.

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Received June 8, 1972

The reaction of dichloroketene with *N,N*-disubstituted 2-aminomethylenecyclopentanones, cyclohexanones, cycloheptanones and cyclooctanones gave the 1,4-cycloadducts, namely *N,N*-disubstituted 3,3-dichloro-4-amino-5,6-polymethylene-3,4-dihydro-α-pyrones. The structures of these products were determined by uv, ir and nmr spectral data, as well as by dehydrochlorination of the adduct, 3,3-dichloro-4-diphenylamino-5,6-tetramethylene-3,4-dihydro-α-pyrone, which led to 3-chloro-4-diphenylamino-5,6-tetramethylene-α-pyrone.

The by-product of the cycloaddition reaction was the *N,N*-disubstituted dichloroacetamide, the formation of which varies according to the substituents on the nitrogen atom.

Among the various ketenes used in cycloadditions, dichloroketene has received little attention until a few years ago.

Cycloadditions of this heterocumulene to olefins led to 1,2-cycloadducts, such as 2,2-dichloro-3,4-polymethylene-cyclobutanones from cyclopentene (1), cyclohexenes (2,3), cyclooctenes (4), and spiro[3.3]heptanes from methylene-cyclobutanes (5).

The 1,2-cycloaddition to 2-butyne gave 2,3-dimethyl-4,4-dichlorocyclo-2-buten-1-one (6); from aldehydes and imines, β-lactones (7) and β-lactams (8) were obtained.

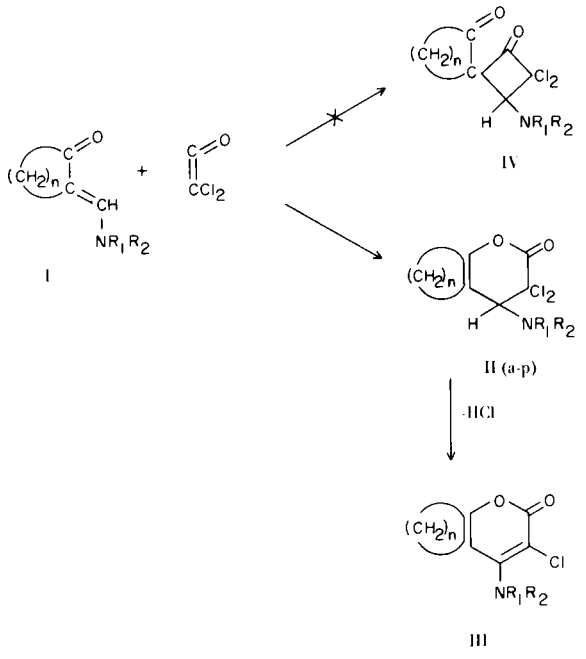
In addition cycloadducts from conjugated homodienes have always been obtained *via* 1,2-cycloaddition (9).

Only a few examples are known of dichloroketene cycloaddition to conjugated heterodienes: *e.g.*, tropone gave a heptafulvene (10), and α,β-unsaturated imines derived from cinnamaldehyde gave δ-lactams which were readily converted into the corresponding α-chloro-2-pyridones (8).

This last reaction is the only example of a 1,4-cycloaddition of dichloroketene found in the literature.

This fact and the higher reactivity of dichloroketene as compared with diphenylketene and ketene in cycloaddition reactions to nucleophilic multiple bonds, prompted us to study the reaction of dichloroketene with *N,N*-disubstituted 2-aminomethylenecycloalkanones (I).

In agreement with our previous findings in the reactions of ketene (11) and diphenylketene (12) with *N,N*-disubstituted 2-aminomethylenecycloalkanones (I), we found that I reacts with dichloroketene, generated *in situ* by dehydrochlorination of dichloroacetyl chloride with triethylamine, to give 1:1 adducts through a 1,4-cycloaddition, namely *N,N*-disubstituted 3,3-dichloro-4-amino-5,6-polymethylene-3,4-dihydro-α-pyrones (II).



These reactions occur in anhydrous benzene at room temperature.

In Tables I and II are reported three new *N,N*-disubstituted 2-aminomethylenecyclopentanones; the 1,4-cycloadducts obtained are listed in Table III.

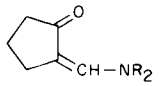
Ir spectra of the reaction mixtures did not show the presence of 1,2-cycloadducts (IV) and such compounds have never been found during the purification stages.

Ir and nmr spectra of the cycloadducts are in good agreement with the proposed structure (II).

The ir spectra given in Table IV show both a strong CO absorption at 1782-1796 cm^{-1}, indicative of a δ-lactone

TABLE I

N,N-Disubstituted 2-Aminomethylenecyclopentanones, Ia-c



Formula Number	NR_2	Yield, %	M.p., °C	Molecular Formula	Analyses % -- Calcd. (Found) C	H	N
Ia	$N(CH(CH_3)_2)_2$	48	83-84 (a)	$C_{12}H_{21}NO$	73.80 (74.07	10.84 10.59	7.17 7.32)
Ib	$N(CH_3)C_6H_5$	56	106-107 (b)	$C_{13}H_{15}NO$	77.58 (77.34	7.51 7.45	6.96 7.22)
Ic	$N(C_6H_5)_2$	63	137-138 (b)	$C_{18}H_{17}NO$	82.10 (81.90	6.51 6.43	5.32 5.35)

(a) From petroleum ether (b.p. 40-70°). (b) From cyclohexane.

TABLE II

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

Formula Number	uv λ max, nm (ε)	ir (cm^{-1}) C=O	C=C	nmr (a)
Ia	328 (27,250)	1683	1572	2.54 near t, =C*H*-N; 6.02 h, J = 6.7, 2 C*H*$(CH_3)_2$; 7.05-7.45 m, CH_2CO; 7.5-8.5 m, 2CH_2; 8.74 d, J = 6.7, 4 CH_3.
Ib	237 (4,460) 341 (24,900)	1698	1580	2.43 near t, =C*H*-N; 2.47-3.05 m, C_6H_5; 6.50 s, CH_3-N; 7.22-7.56 m, CH_2CO; 7.56-8.50 m, 2 CH_2.
Ic	232 (8,410) 285 (7,600) 349 (25,350)	1699	1578	2.28 near t, =C*H*-N; 2.40-3.03 m, 2 C_6H_5; 7.5-7.9 m, CH_2CO; 8.1-8.4 m, 2 CH_2.

(a) The letters s,d,t,h,m,b denote the multiplicities of peaks (singlet, doublet, triplet, heptuplet, multiplet, broad).

bearing two α-chlorine atoms, and a weak endocyclic double bond absorption at about 1700 cm^{-1}.

This latter absorption appears in the same region with the same pattern as in the case of the diphenylketene-cycloadducts (12) and in cyclopentanone derivatives (IIa-c) does not differ appreciably from the other cycloadducts (IId-p). According to the structure IV, cyclopentanones derivatives should absorb at about 1740 cm^{-1}; the lack of this band clearly supports structure II.

The nmr spectra (Table IV) show C-4 protons as near-singlets at 4.7-6.4 τ, according to the amine substitutions.

The broadening of the signal may result from a coupling with the protons of both methylene groups adjacent to the double bond.

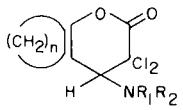
Indeed the methine singlet at 4.98 τ of the adduct IIf (Table III) shows a half-height line width of about 2.7 Hz; this value decreases to 1.7 and 1.5 Hz by irradiation at 7.75 and 8.20 τ (the chemical shift values of both α-methylene groups).

Moreover, the cyclobutanone structure (IV) was ruled out since two asymmetric carbon atoms likely would give two diastereoisomers and as a consequence two methine proton signals in nmr spectrum. These bands, however, are also absent in the spectrum of the crude reaction product.

Further proof of the lactonic structure (II) was obtained by chemical means. That is, lactone IIf was dehydro-

TABLE III

N,N-Disubstituted 3,3-Dichloro-4-amino-5,6-polymethylene-3,4-dihydro-α-pyrones (IIa-p)



Formula Number	n	R_1	R_2	Yield, %	M.p., °C	Molecular Formula	Analyses % -- Calcd. (Found) C	H	N
IIa	3	$CH(CH_3)_2$	$CH(CH_3)_2$	54	98-99 (a)	$C_{14}H_{21}Cl_2NO_2$	54.91 (54.75	6.91 6.74	4.57 4.63)
IIb	3	CH_3	C_6H_5	48	105-106 (a)	$C_{15}H_{15}Cl_2NO_2$	57.70 (57.57	4.84 5.03	4.49 4.65)
IIc	3	C_6H_5	C_6H_5	42	169-170 (b)	$C_{20}H_{17}Cl_2NO_2$	64.18 (64.17	4.58 4.54	3.74 3.79)
IId	4	$CH(CH_3)_2$	$CH(CH_3)_2$	61	116-117 (c)	$C_{15}H_{23}Cl_2NO_2$	56.25 (56.25	7.24 7.47	4.37 4.53)
IIe	4	CH_3	C_6H_5	51	122-123 (c)	$C_{16}H_{17}Cl_2NO_2$	58.91 (58.86	5.25 5.38	4.29 4.36)
IIf	4	C_6H_5	C_6H_5	56	183-184 (b)	$C_{21}H_{19}Cl_2NO_2$	64.96 (64.90	4.93 5.02	3.61 3.69)
IIg	5	CH_3	CH_3	59	90-91 (a)	$C_{12}H_{17}Cl_2NO_2$	51.81 (51.78	6.16 5.97	5.04 5.14)
IIh	5	$CH(CH_3)_2$	$CH(CH_3)_2$	50	81-82 (a)	$C_{16}H_{25}Cl_2NO_2$	57.49 (57.63	7.54 7.74	4.19 4.26)
IIi	5	CH_3	C_6H_5	73	93-94 (a)	$C_{17}H_{19}Cl_2NO_2$	60.01 (60.16	5.63 5.61	4.12 4.22)
IIl	5	C_6H_5	C_6H_5	83	169-170 (d)	$C_{22}H_{21}Cl_2NO_2$	65.68 (65.57	5.26 5.12	3.48 3.49)
IIm	6	CH_3	CH_3	46	79-80 (c)	$C_{13}H_{19}Cl_2NO_2$	53.43 (53.50	6.55 6.72	4.79 4.76)
IIn	6	$CH(CH_3)_2$	$CH(CH_3)_2$	43	98-99 (c)	$C_{17}H_{27}Cl_2NO_2$	58.62 (58.76	7.81 7.72	4.02 3.99)
IIo	6	CH_3	C_6H_5	54	119-120 (d)	$C_{18}H_{21}Cl_2NO_2$	61.02 (61.25	5.97 6.14	3.95 4.12)
IIp	6	C_6H_5	C_6H_5	36	208-209 (b)	$C_{23}H_{23}Cl_2NO_2$	66.35 (66.22	5.57 5.50	3.36 3.43)

(a) From petroleum ether (b.p. 40-70°). (b) From anhydrous diethylether-acetone. (c) From petroleum ether, after elution from Florisil®. (d) From anhydrous diethylether.

chlorinated (160°, collidine) to 3-chloro-4-diphenylamino-5,6-tetramethylene-α-pyrone (III, n = 4, $R_1 = R_2 = C_6H_5$), whose structure is consistent with uv, ir and nmr spectral data (see Experimental).

Thus this reaction opens another way to the synthesis of substituted α-pyrones; work in this direction is in progress.

Amine substituents were chosen in order to evaluate the influence of both the basic strength of the amine and steric hindrance on the formation of cycloadducts.

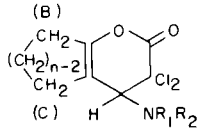
The enamines (I) used were prepared from aliphatic (dimethylamine, morpholine, diisopropylamine), aliphatic-aromatic (*N*-methylaniline) and fully aromatic amines (diphenylamine).

It was observed that, besides the 1,4-cycloadducts and except for the products in which steric hindrance from the diisopropylamino group is present. *N*-acylation of the enamine takes place, followed by the release of the amino group and the formation of the corresponding dichloroacetamide.

The presence of *N,N*-dimethyldichloroacetamide was shown by ir spectra (1670 cm^{-1}) of the raw adducts IIg and IIm, but we could not isolate it in the course of the purification stages.

TABLE IV

Ir and Nmr Spectra of Compounds IIa-p



(A)

Formula Number	Ir (cm^{-1}) C=O	C=C	Nmr (a) H(A)	CH_2(B)	CH_2(C)	$(CH_2)_{n-2}$	R_1	R_2
IIa	1790	1706	6.24s	7.20 – 8.30b,m			7.00b,m 2 $CH(CH_3)_2$ 8.88d, J = 6.4, 2 CH_3 9.00d, J = 6.4, 2 CH_3	
IIb	1794	1713	5.07s	7.10 – 8.20b,m			2.50-3.30m (2 C_6H_5)	7.34s (CH_3)
IIc	1796	1715	4.72s	7.20 – 8.40b,m			2.45-3.33m (2 C_6H_5)	
IId	1785	1700	6.41s	7.74m		8.24m	7.00b,m, 2 $CH(CH_3)_2$ 8.88d, J = 6, 2 CH_3 8.97d, J = 6, 2 CH_3	
IIe	1791	1711	5.29s	7.45 – 8.05b,m		8.23m	2.50-3.30m (2 C_6H_5)	7.34s (CH_3)
IIf	1792	1713	4.98s	7.75m	8.20m	8.31m	2.50-3.30m (2 C_6H_5)	
IIg	1786	1695	6.44s	7.60m	7.80m	8.26m	7.50s (2 CH_3)	
IIh	1783	1690	6.37s	7.62m		8.26m	6.98 near h, J = 6.6, 2 $CH(CH_3)_2$ 8.87d, J = 6.6, 2 CH_3 8.95d, J = 6.6, 2 CH_3	
IIi	1789	1696	5.25s	7.55m	7.85m	8.30m	2.50-3.30m (2 C_6H_5)	7.35s (CH_3)
IIl	1788	1698	4.91s	7.75m	7.92m	8.32m	2.50-3.30m (2 C_6H_5)	
IIm	1784	1699	6.40s	7.65m	7.83m	8.35m	7.48s (2 CH_3)	
IIn	1782	1692	6.29s	7.68m		8.35m	6.50-7.50b,m, 2 $CH(CH_3)$ 8.88d, J = 6, 2 CH_3 8.98d, J = 6, 2 CH_3	
IIo	1787	1700	5.20s	7.59m	7.82m	8.32m	2.50-3.30m (2 C_6H_5)	7.34s (CH_3)
IIp	1786	1703	4.88s	7.80m	8.06m	8.38m	2.50-3.33m (2 C_6H_5)	

(a) See note to Table II.

On the contrary, *N*-dichloroacetylmorpholine was the only product isolated from the reaction with 2-morpholinomethylenecyclohexanone (I, n = 4, NR_1R_2 = morpholino), although ir spectrum of the crude residue show the presence of the 1,4-cycloadduct. *N*-Acylation of such an enamine also took place under anhydrous conditions and in absence of triethylamine.

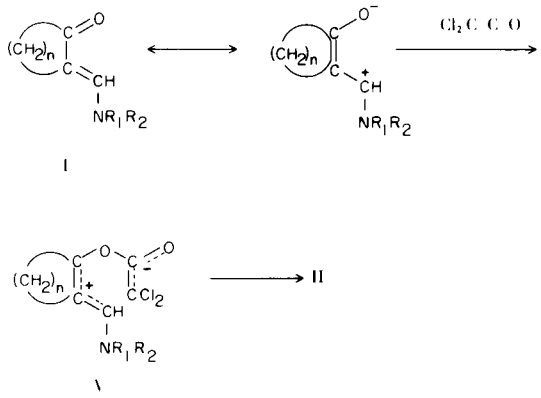
It cannot be stated whether this competitive reaction arises from the acyl halide or from the dichloroketene generated *in situ* by enamine basic strength.

N-Methyldichloroacetanilide was present only in traces in the reaction mixture of *N*-methyl-*N*-phenylenamines whereas the enamines derived from diphenylamine did not produce the corresponding dichloroacetamide. These facts agree well with the decreased nucleophilicity of the enamine nitrogen atom.

Finally, with regard to the steric hindrance of the nitrogen atom substituents toward the 1,4-cycloaddition, it may be stated that this effect is lower than that found in the diphenylketene cycloaddition to the same heterodiene (12). Actually cyclization also occurred well with 2-diisopropylaminomethylenecycloalkanones; the corresponding adducts (IIa,d,h,n) are stable and did not show the retro Diels-Alder reaction already observed by us in the analogous cycloadducts of diphenylketene.

Among the adducts having the same polymethylene cycle, 3,3-dichloro-4-diphenylamino-5,6-polymethylene-3,4-dihydro-α-pyrones (IIc, IIf, III, and IIp) are the most stable and were the most easily crystallizable products. They also have the highest m.p.

With regard to the reaction mechanism, it is well known that the two chlorine atoms increase the electrophilic character of the reagent (9), and it is possible that the reaction proceeds, as in the case of diphenylketene, through a dipolar intermediate (V), stabilized by the two chlorine atoms:



EXPERIMENTAL

Ir spectra were measured with a Perkin-Elmer Model 257 spectrophotometer in carbon tetrachloride solution; uv spectra were taken with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer in ethanol solution.

Nmr spectra were recorded on a Perkin-Elmer Model R-12 (60 Mc/s) instrument in deuteriochloroform solution.

Chemical shifts are reported as τ (ppm) relative to tetramethylsilane as an internal standard; J in Hz.

The melting points were determined on a Mettler FP1 apparatus.

N,N-Disubstituted 2-aminomethylenecyclopentanones (Table I) were prepared by a previously described procedure (12).

General Procedure for *N,N*-Disubstituted 3,3-Dichloro-4-amino-5,6-polymethylene-3,4-dihydro-α-pyrones.

A solution of dichloroacetylchloride (1.3 g., 8.8 mmoles) in anhydrous benzene (30 ml.) was added dropwise (stirring) at room temperature, under dry nitrogen, to a solution of *N,N*-disubstituted 2-aminomethylenecycloalkanone (6 mmoles) and triethylamine (0.9 g., 9 mmoles) in anhydrous benzene (35 ml.). After the addition was complete the reaction mixture was stirred for 15 minutes and filtered.

The filtrate was evaporated and the residue was recrystallized from a suitable solvent (charcoal) or chromatographed on a Florisil® column (60-100 mesh, 3 g.), using petroleum ether (b.p. 40-70°) as eluent (compare Table II).

Reaction of Dichloroketene with 2-Morpholinomethylenecyclohexanone (I, NR_1R_2 = morpholino).

2-Morpholinomethylenecyclohexanone was treated with dichloroacetylchloride and triethylamine following the general procedure described above.

Ir spectrum of the raw residue showed a strong band at 1778 cm^{-1} (1-4 cycloadduct) and another strong band at 1670 cm^{-1}.

This residue was refluxed with petroluem ether (b.p. 40-70°) and the extract was chromatographed several times on a Florisil® column, using petroleum ether and chloroform as eluents.

The solid obtained (0.15 g., m.p. 63-64° from ethanol) was identified as *N*-dichloroacetylmorpholine by m.p. (14) and mixture m.p.; the ir spectrum (1690, 1668 cm^{-1}) is superimposable with that of known *N*-dichloroacetylmorpholine.

N-Dichloroacetylmorpholine was also obtained without triethylamine by adding dropwise under nitrogen a solution of dichloroacetylchloride (0.44 g., 3 mmoles) in anhydrous benzene (25 ml.) to 2-morpholinomethylenecyclohexanone (0.64 g., 3.3 mmoles) in anhydrous benzene (30 ml.).

The product obtained was purified by chromatography on Florisil®(0.11 g., 18%).

3-Chloro-4-diphenylamino-5,6-tetramethylene-α-pyrone.

A solution of 1 g. of 3,3-dichloro-4-diphenylamino-5,6-tetramethylene-3,4-dihydro-α-pyrone (Table III, IIf) in 10 ml. of collidine was refluxed under dry nitrogen at 155-160° for 14 hours.

After cooling the reaction mixture was poured in 20 ml. of water and acidified with 2*N* hydrochloric acid.

The acid solution was extracted thoroughly with ether, the ether extracts were dried over anhydrous magnesium sulfate, were filtered and evaporated to give yellow crystals (0.4 g., 44%), m.p. 222-223° from acetone; uv λ max nm 248 (ε, 10,870), 281 (ε, 15,930), 322 (ε, 8,140), 376 (ε, 9,150); ir ν max cm^{-1} 1738, 1638, 1520 (compare ref. (13)); nmr τ 2.50-3.20 (m, 10 H, 2 C_6H_5), 7.45 (mc, 2H, -CH_2-C(OCO)=), 7.90-8.60 (m, 6H, 3 CH_2).

Anal. Calcd. for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.16; N, 3.98. Found: C, 71.80; H, 5.32; N, 3.94.

Acknowledgments.

The authors thank Dr. Maria Canepa for the microanalyses and Mr. A. Panaro for the uv, ir and nmr spectra.

REFERENCES

(1) L. Ghosez, R. Montaigne and P. Mollet, *Tetrahedron Letters*, 135 (1966).

(2) A. Hassner, V. R. Fletcher and D. P. G. Hamon, *J. Am. Chem. Soc.*, **93**, 264 (1971).

(3) G. M. L. Cragg, *J. Chem. Soc. C*, 1829 (1970).

(4) R. Montaigne and L. Ghosez, *Angew. Chem. Intern. Ed. Engl.*, 7, 221 (1968).

(5) P. R. Brook and J. G. Griffiths, *Chem. Commun.*, 1344 (1970).

(6) H. Knoche, *Ann. Chem.*, 722, 232 (1969).

(7) D. Borrmann and R. Wegler, *Chem. Ber.*, **102**, 64 (1969).

(8) F. Duran and L. Ghosez, *Tetrahedron Letters*, 245 (1970).

(9) Review: T. Brady, *Synthesis*, 415 (1971). L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde and P. Mollet, *Tetrahedron*, 27, 615 (1971).

(10) J. Ciabattoni and H. W. Anderson, *Tetrahedron Letters*, 3377 (1967).

(11) A. Gandini, P. Schenone and G. Bignardi, *Monatsh. Chem.*, 98, 1518 (1967).

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

(13) A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. 2, Academic Press, N.Y., 1963, 253.

(14) B. J. Heywood, Brit. Patent 712,745 (1954); *Chem. Abstr.*, **50**, 1083e (1956).