Reaction of Ketenes with *N,N*-Disubstituted α-Aminomethyleneketones. XVI. Synthesis of *N,N*-Disubstituted 4-Amino-5,6-tetramethylene-3-phenyl-2-pyranones

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1,4-Cycloaddition of phenylchloroketene (prepared *in situ* from α-chlorophenylacetyl chloride and triethylamine) to a number of *N,N*-disubstituted (*E*)-2-aminomethylenecyclohexanones gave the corresponding adducts, namely *N,N*-disubstituted 4-amino-3-chloro-3,4,5,6,7,8-hexahydro-2*H*-1-benzopyran-2-ones III in the case of aliphatic *N,N*-disubstitution or aromatic *N*-monosubstitution. Purification of III was possible only in the case of IIIh (NR_2 = NMePh), therefore they were dehydrochlorinated *in situ* with DBN to give the title compounds in moderate overall yields.

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Some years ago we described the first examples of polar 1-4 cycloaddition of dichloroketene to *N,N*-disubstituted α-aminomethylenecyclanones to give adducts which were converted to 2-pyranones by dehydrochlorination with tertiary amines [1,2].

This reaction was later extended to a number of open-chain [3] and heterocyclic [4] α-aminomethyleneketones to afford polysubstituted 2-pyranones and heterocyclic systems incorporating the 2-pyranone moiety, respectively.

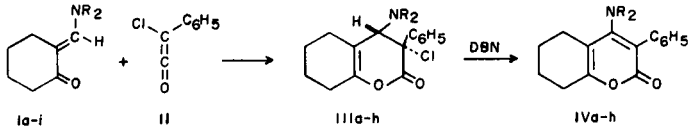
We were interested to see whether the replacement of one or two chlorine atoms of dichloroketene could allow this cycloaddition. It was found that, when both chlorine atoms were substituted with electronegative groups such as thioalkyl [5] and phenyl [6] groups, the reaction still took place, whereas the cycloaddition did not occur when a sole electronegative substituent was present in the ketene moiety, as for example with haloketenes and methylchloroketene [7].

We wish to report now the results obtained with the cycloaddition of *N,N*-disubstituted (*E*)-2-aminomethylenecyclohexanones I, namely the same enaminones employed among others in the case of dichloroketene [1], to a disubstituted ketene bearing two different electronegative substituents, namely phenylchloroketene II.

The choice of II was determined by the further, possible dehydrochlorination step of the adducts to *N,N*-disubstituted 4-amino-3-phenyl-2-pyranones, and was substantiated by the recent report on the reaction of phenylchloroketene with β-methoxy α,β-unsaturated ketones, containing a conjugated carbonyl system similar to α-aminomethyleneketones, to give (4 + 2) cycloaddition products which underwent conversion to 2-pyranones on treatment with zinc and acetic acid [8].

The reaction of phenylchloroketene II (prepared *in situ* from α-chlorophenylacetyl chloride and triethylamine) with a series of *N,N*-disubstituted (*E*)-2-aminomethylenecyclohexanones Ia-i occurred both in the case of aliphatic *N,N*-disubstitution and aromatic *N*-monosubstitution (Ii did not react) to give cycloadducts IIIa-h. We found that III were in general unstable and difficult to obtain pure; only in the case of IIIh isolation and purification in low yield were possible by silica gel chromatography. Therefore, the crude cycloadducts were dehydrochlorinated directly in benzene solution with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) to afford *N,N*-disubstituted 4-amino-5,6,7,8-tetrahydro-3-phenyl-2*H*-1-benzopyran-2-ones (or 4-amino-5,6,7,8-tetramethylene-3-phenyl-2-pyranones) IVa-h (Table I) in moderate overall yields.

The structure of 2-pyranones IV was proven by their uv, ir and nmr spectral data (Table II). The moderate overall yield of IV (23-36%) was undoubtely due to the impossibility to isolate pure cycloadducts III and to submit these to the dehydrochlorination step. When this was possible (IIIh), the relative dehydrochlorinated product IVh was obtained in 90% yield.



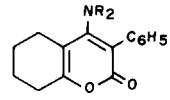
NR_2

a	$N(CH_3)_2$
b	$N(C_2H_5)_2$
c	$N(CH_3)(CH_2)_2N(CH_3)_2$
d	1-Pyrrolidinyl
e	1-Piperidinyl
f	1-Morpholinyl
g	1-(4-Methyl piperazinyl)
h	$N(CH_3)C_6H_5$
i	$N(C_6H_5)_2$

This smooth reaction also suggests that probably both amino and phenyl groups of III are equatorial in order to allow the diaxial proton *anti* to chlorine arrangement, suitable for the E2 elimination (compare [9] for a similar

Table I

N,N-Disubstituted 4-Amino-5,6,7,8-tetrahydro-3-phenyl-2*H*-1-benzopyran-2-ones IVa-h



Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IVa	$N(CH_3)_2$	36	156 [a]	$C_{17}H_{19}NO_2$	75.81	7.11	5.20
					75.74	7.08	5.14
IVb	$N(C_2H_5)_2$	27	115 [b]	$C_{19}H_{23}NO_2$	76.73	7.79	4.71
					76.69	7.93	4.89
IVc	$N(CH_3)(CH_2)_2N(CH_3)_2$	32	95 [b]	$C_{20}H_{26}N_2O_2$	73.59	8.03	8.58
					73.79	7.94	8.61
IVd	1-Pyrrolidinyl	25	122 [b]	$C_{19}H_{21}NO_2$	77.26	7.17	4.74
					77.20	7.16	4.70
IVe	1-Piperidinyl	23	145 [b]	$C_{20}H_{23}NO_2$	77.64	7.49	4.53
					77.58	7.40	4.80
IVf	1-Morpholinyl	27	143 [a]	$C_{19}H_{21}NO_3$	73.29	6.80	5.50
					73.24	6.79	4.78
IVg	1-(4-Methylpiperazinyl)	26	189 [a]	$C_{20}H_{24}N_2O_2$	74.04	7.46	8.63
					74.25	7.50	8.79
IVh	$N(CH_3)C_6H_5$	90 [c]	172 [b]	$C_{22}H_{21}NO_2$	79.73	6.39	4.23
					79.66	6.46	4.47

[a] From diethyl ether. [b] From diethyl ether-acetone 1:2. [c] Obtained by dehydrochlorination with DBN of pure IIIh according to [11].

Table II

UV, IR and NMR Spectral Data of Compounds IVa-h

Compound	UV, λ max nm (log ε)	IR, cm^{-1} C=O	C=C	NMR, δ
IVa	247 (4.01)	1675	1632	1.76 (mc, CH_2-6 + CH_2-7), 2.48 (mc, CH_2-5 + CH_2-8 + $(CH_3)_2N$),
	293.5 (3.94)		1540	7.31 (broad s, C_6H_5)
	325.5 (3.99)			
IVb	251 (3.93)	1673	1632	0.97 (t, J = 7.2, 2 CH_3), 1.76 (mc, CH_2-6 + CH_2-7),
	297.5 (3.95)		1522	2.45 (mc, CH_2-5 + CH_2-8), 2.76 (q, J = 7.2, 2 CH_2N), 7.35 (s, C_6H_5)
	331.5 (3.96)			
IVc	248.5 (3.98)	1673	1630	1.73 (mc, CH_2-6 + CH_2-7), 2.06 (s, $(CH_3)_2N$), 2.1-2.8 (m, CH_2-5 + CH_2-8 +
	298 (3.94)		1527	2 CH_2N), 2.57 (s, CH_3N), 7.29 (s, C_6H_5)
	328 (3.96)			
IVd	233.5 (4.01)	1665	1627	1.5-1.9 (m, CH_2-6 + CH_2-7 + 2 CH_2 pyr), 2.47 (mc, CH_2-5 + CH_2-8),
	247 sh (3.98)		1517	2.92 (mc, 2 CH_2N), 7.29 (s, C_6H_5)
	292 sh (3.84)			
	324 (4.02)			
IVe	226.5 (3.88)	1677	1632	1.44 (mc, 3 CH_2 pip), 1.76 (mc, CH_2-6 + CH_2-7),
	246.5 (3.94)		1528	2.58 (mc, CH_2-5 + CH_2-8 + 2 CH_2N), 7.32 (mc, C_6H_5)
	299 (3.97)			
	325 (3.99)			
IVf	227 (3.93)	1685	1632	1.76 (mc, CH_2-6 + CH_2-7), 2.65 (mc, CH_2-5 + CH_2-8 + 2 CH_2N),
	244 (3.93)		1534	3.55 (mc, 2 CH_2O), 7.32 (mc, C_6H_5)
	298 (4.00)			
	322.5 (4.01)			
IVg	227 (3.94)	1678	1630	1.79 (mc, CH_2-6 + CH_2-7), 2.10-2.85 (m, CH_2-5 + CH_2-8 + 4 CH_2N),
	242 (3.94)		1528	2.22 (s, CH_3N), 7.30 (mc, C_6H_5)
	300 (3.99)			
	323 (3.95)			
IVh	243 (4.17)	1692	1632	1.68 (mc, CH_2-6 + CH_2-7), 1.96 (mc, CH_2-5), 2.71 (mc, CH_3N + CH_2-8),
	307 sh (3.95)		1534	6.80 (mc, C_6H_5), 7.30 (mc, C_6H_5)
	318 (4.00)			
	366 (3.92)			

situation concerning *trans*-4-amino-3-chloro-3,4,5,6,7,8-hexahydro-1,2-benzoxathiin 2,2-dioxides).

In conclusion, phenylchloroketene appears to be, despite yields limitation, an attractive synthon for the building-up in one step of systems containing the 4-amino-3-phenyl-2-pyranone moiety, and work is in progess to test the generality of the reaction.

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Perkin-Elmer Model 550S 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-100 instrument (60 MHz, TMS as internal standard, J in Hz). Melting points were determined with a Mettler FP1 apparatus.

N-Methyl,*N*-(2-dimethylaminoethyl)-2-aminomethylenecyclohexanone (Ic).

This enaminone was prepared in 75% yield from 2-hydroxymethylenecyclohexanone and *N,N,N'*-trimethylethylenediamine, following the general procedure a) already described [10], bp 140°/0.2 mm; uv: λ max nm (log ε) 332 (4.29); ir (chloroform): ν max 1638, 1525 cm^{-1}; nmr (deuteriochloroform): δ 1.69 (mc, CH_2-4 + CH_2-5), 2.22 (mc, $(CH_3)_2N$ + CH_2N), 2.3-2.9 (m, CH_2-3 + CH_2-6), 3.13 (s, CH_3N), 3.2-3.9 (m, CH_2N), 7.32 (near s, =CHN).

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.67; H, 10.45; N, 13.28.

N,N-Disubstituted 4-Amino-5,6,7,8-tetrahydro-3-phenyl-2*H*-1-benzopyran-2-ones IVa-g.

A solution of α-chlorophenylacetyl chloride (6.2 g, 33 mmoles) in anhydrous benzene (50 ml) was slowly added (2 hours) under nitrogen to a stirred, warm solution (80°) of I (30 mmoles) and triethylamine (10 g, 0.1 mmoles) in the same solvent (100 ml). The reaction mixture was refluxed under nitrogen for 2 hours, cooled and filtered. In the case of Ii, this enaminone was recovered almost quantitatively from the benzene solution.

With the exception of IIIh (see later), evaporation under reduced pressure of the benzene solutions gave unstable liquids which could not be purified; therefore, these solutions were treataed with DBN (5 g, 40 mmoles) and refluxed for 1 hour. The crude liquids obtained following a described procedure [11] were purified by silica gel chromatography, using as eluant diethyl ether in the case of IVa,f,g and diethyl ether-acetone 1:2 in the case of IVb,c,d,e, followed by recrystallization from a suitable solvent (Table I).

3-Chloro-3,4,5,6,7,8-hexahydro-4-methylphenylamino-3-phenyl-2*H*-1-benzopyran-2-one (IIIh).

The filtered benzene solution obtained in the reaction with Ih was evaporated under reduced pressure and the residue was chromatographed on silica gel using diethyl ether-acetone 1:1 as eluant; yield, 20%, mp 141°, from diethyl ether-acetone 1:1; ir (chloroform): ν max 1768, 1710 cm^{-1}; nmr (deuteriochloroform): δ 1.55 (mc, CH_2-6 + CH_2-7), 2.05 (mc, CH_2-5 + CH_2-8), 2.83 (s, CH_3N), 4.89 (s, CH-4), 7.03 (mc, C_6H_5), 7.43 (mc, C_6H_5).

Anal. Calcd. for $C_{22}H_{22}ClNO_2$: C, 71.83; H, 6.03; N, 3.81. Found: C, 71.77; H, 5.95; N, 3.89.

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