Reaction of Ketenes with *N,N*-Disubstituted α-Aminomethyleneketones. XI. Synthesis of 2*H*-Pyrano[3,2-*g*]benzothiazole Derivatives

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Cycloaddition of dichloroketene to *N,N*-disubstituted 6-aminomethylene-5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)ones gave in good yield *N,N*-disubstituted 4-amino-3,3-dichloro-3,4,5,6-tetrahydro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones II, which are derivatives of the new heterocyclic system 2*H*-pyrano[3,2-*g*]benzothiazole.

Dehydrochlorination with triethylamine of II afforded *N,N*-disubstituted 4-amino-3-chloro-5,6-dihydro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones III in good to moderate yield. The dimethylamino adduct was dehydrochlorinated in high yield by refluxing in toluene, whereas the diisopropylamino adduct gave in low yield 6-(2,2-dichloroethylidene)-5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)one with the triethylamine treatment. The dehydrochlorinated product IIId (NR_2 = pyrrolidino) was obtained directly in low yield by cycloaddition of dichloroketene to the corresponding enaminone. Full aromatisation of IIIa,g [NR_2 = $N(CH_3)_2$ and $N(CH_3)C_6H_5$, respectively] to the corresponding *N,N*-disubstituted 4-amino-3-chloro-8-phenyl-2*H*-pyrano-[3,2-*g*]benzothiazol-2-ones was accomplished with DDQ in refluxing benzene.

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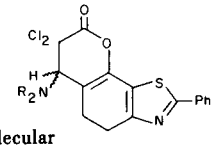
In a previous paper (1) we described the synthesis of a new heterocyclic system, 1,2-oxathiino[5,6-*g*]benzothiazole, by reaction of sulfene with a series of *N,N*-disubstituted 6-aminomethylene-5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)ones I.

In pursuing this work on heterocyclic systems incorporating the benzothiazole moiety, a potential pharmacologically active molecule, we wish to report now the dipolar 1,4-cycloaddition of enaminones I to dichloroketene to give derivatives of a new heterocycle incorporating both 2*H*-pyran and benzothiazole rings, namely 2*H*-pyrano[3,2-*g*]benzothiazole.

Following our method of dichloroketene cycloaddition to *N,N*-disubstituted α-aminomethyleneketones (2), the reaction of I with dichloroacetyl chloride and triethylamine (dichloroketene prepared *in situ*) occurred readily both in the case of aliphatic and aromatic *N*-substitution to give, generally in excellent yield, *N,N*-disubstituted

Table I

N,N-Disubstituted 4-Amino-3,3-dichloro-3,4,5,6-tetrahydro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones IIa-c,e-h (a)



Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa	$N(CH_3)_2$	87	100 dec (b)	$C_{18}H_{16}Cl_2N_2O_2S$	54.69	4.08	7.09
					54.71	4.05	6.97
IIb	$N(C_2H_5)_2$	61	110 (b)	$C_{20}H_{20}Cl_2N_2O_2S$	56.74	4.76	6.62
					56.44	4.79	6.30
IIc	$N[CH(CH_3)_2]_2$	90	149 (c)	$C_{22}H_{24}Cl_2N_2O_2S$	58.54	5.36	6.21
					58.45	5.42	5.97
IIe	piperidino	67	120 (b)	$C_{21}H_{20}Cl_2N_2O_2S$	57.94	4.63	6.43
					57.71	4.60	6.41
IIf	morpholino	84	135 (b)	$C_{20}H_{18}Cl_2N_2O_3S$	54.93	4.15	6.41
					55.03	4.07	6.15
IIg	$N(CH_3)C_6H_5$	90	170 (c)	$C_{23}H_{18}Cl_2N_2O_2S$	60.40	3.97	6.12
					60.70	4.25	6.12
IIh	$N(C_6H_5)_2$	92	152 (c)	$C_{28}H_{20}Cl_2N_2O_2S$	64.74	3.88	5.39
					64.94	3.91	5.22

(a) All compounds were prepared from the corresponding enaminones I (1) and dichloroacetyl chloride plus triethylamine acccording to (2) (reaction time 30 minutes). (b) From anhydrous diethyl ether. (c) From ethyl acetate.

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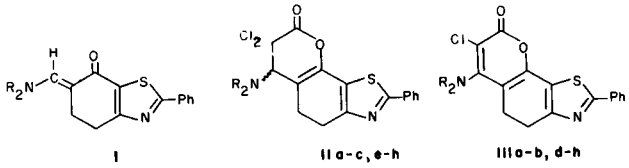
4-amino-3,3-dichloro-3,4,5,6-tetrahydro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones IIa-c,e-h (Table I), whose structure was confirmed by uv, ir and nmr spectral data (Table II). Under these conditions, the pyrrolidino enaminone Id gave directly the dehydrochlorinated product IIId, albeit in low yield.

The adducts IIb,e-h were dehydrochlorinated with triethylamine according to (3) to give *N,N*-disubstituted 4-amino-3-chloro-5,6-dihydro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones IIIb,e-h (Tables III and IV) in good to moderate yield.

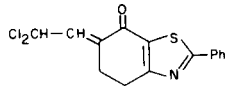
The dimethylamino adduct IIa decomposed by treatment with triethylamine even at room temperature, giving intractable mixtures; therefore, it was dehydrochlorinated by simply refluxing in toluene. Under these neutral conditions the dehydrochlorinated product IIIa was obtained in 83% yield.



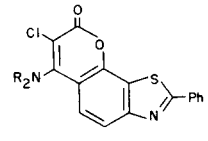
I

IIa-c, e-h

IIIa-b, d-h



IV



Va, g

NR$_2$

a dimethylamino
b diethylamino
c diisopropylamino
d pyrrolidino

NR$_2$

e piperidino
f morpholino
g methylphenylamino
h diphenylamino

The diisopropylamino adduct IIc gave no dehydrochlorinated product after 6 hours reflux: near to recovered IIc and enaminone Ic (1), 6-(2,2-dichloroethylidene)-5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)one IV was obtained in low yield.

We had already observed the formation of compounds similar to IV in the reaction of dichloroketene with other enaminones (4,5). In the present case, because IIc cannot eliminate hydrogen chloride with the base owing to steric hindrance (2,3), heating caused merely its dissociation, as it was proven by the isolation of enaminone Ic. This compound and dichloroketene could then react in a different way following the reaction path already described (4) to give IV.

Full aromatisation of compounds III was attempted only in the case of IIIa and IIIg. With DDQ in refluxing benzene they gave in moderate yield *N,N*-disubstituted 4-amino-3-chloro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones Va,g (Table V).

Attempts to effect the dehydrogenation with palladium on charcoal (6) were not successful, giving complex mixtures of products, partly due to catalytic hydrogenolysis of the C-N and C-Cl bonds.

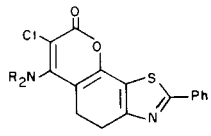
Table II

UV, IR and NMR Spectral Data of Compounds IIa-c,e-h

	UV	IR, cm^{-1}		
	λ max nm (log ε)	C=O	C=C	NMR δ
IIa	224 sh (4.00) 255 (3.92) 339.5 (4.39)	1790	1662	2.57 (s, 2NCH$_3$), 2.7-3.4 (m, CH$_2$-5 + CH$_2$-6), 3.83 (near s, CH-4), 7.30-7.65 (m, 2H ar-*m* + 1H ar-*p*), 7.87-8.10 (m, 2H ar-*o*).
IIb	255 (3.76) 339 (4.17)	1787	1665	1.07 (t, J = 7.2, 2CH$_3$), 2.50-3.45 (m, 2NCH$_2$ + CH$_2$-5 + CH$_2$-6), 3.94 (near s, CH-4), 7.27-7.63 (m, 2H ar-*m* + 1H ar-*p*), 7.75-8.13 (m, 2H ar-*o*).
IIc	230.5 (4.01) 344 sh (4.24) 355 (4.25)	1785	1648	1.10 and 1.15 (2d, J = 6.6, 4CH$_3$), 2.65-3.40 (m, 2NCH + CH$_2$-5 + CH$_2$-6), 3.90 (near s, CH-4), 7.53 (mc, 2H ar-*m* + 1H ar-*p*), 7.88 (mc, 2H ar-*o*).
IIe	255 (3.91) 340.5 (4.31)	1788	1660	1.57 (m, 3CH$_2$ pip.), 2.90 (mc, 2NCH$_2$ + CH$_2$-5 + CH$_2$-6), 3.80 (near s, CH-4), 7.55 (mc, 2H ar-*m* + 1H ar-*p*), 7.90 (mc, 2H ar-*o*).
IIf	255 (3.85) 342 (4.37)	1790	1662	2.5-3.4 (m, 2NCH$_2$ + CH$_2$-5 + CH$_2$-6), 3.68 (m, 2 OCH$_2$), 3.85-4.15 (m, CH-4), 7.48 (mc, 2H ar-*m* + 1H ar-*p*), 7.88 (mc, 2H ar-*o*).
IIg	243 (4.25) 343 (4.37)	1790	1665	2.67 (mc, CH$_2$-5), 2.78 (s, NCH$_3$), 3.02 (mc, CH$_2$-6), 5.01 (near s, CH-4), 6.75-7.10 (m, 3H ar), 7.15-7.60 (m, 5H ar), 7.88 (mc, 2H ar-*o*).
IIh	237.5 (3.52) 290 sh (3.31) 341.5 (3.49)	1792	1663	3.00 (mc, CH$_2$-5 + CH$_2$-6), 5.30 (near s, CH-4), 6.7-7.5 (m, 2NC$_6$H$_5$ + 2H ar-*m* + 1H ar-*p*), 7.72 (mc, 2H ar-*o*).

Table III

N,N-Disubstituted 4-Amino-3-chloro-5,6-dihydro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones IIIa-b,d-h (a)



Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$N(CH_3)_2$	83	244 (b)	$C_{18}H_{15}ClN_2O_2S$	60.25	4.21	7.81
					60.17	4.19	7.55
IIIb	$N(C_2H_5)_2$	75	205 (c)	$C_{20}H_{19}ClN_2O_2S$	62.09	4.95	7.24
					62.40	5.12	7.16
IIId	pyrrolidino	26	235 (b)	$C_{20}H_{17}ClN_2O_2S$	62.41	4.45	7.28
					62.45	4.53	7.01
IIIe	piperidino	52	228 (c)	$C_{21}H_{19}ClN_2O_2S$	63.23	4.80	7.02
					63.00	4.48	6.95
IIIf	morpholino	37	265 (d)	$C_{20}H_{17}ClN_2O_3S$	59.92	4.27	6.99
					60.06	4.27	7.18
IIIg	$N(CH_3)C_6H_5$	78	223 (c)	$C_{23}H_{17}ClN_2O_2S$	65.63	4.07	6.66
					65.90	4.38	6.64
IIIh	$N(C_6H_5)_2$	75	249 (c)	$C_{28}H_{19}ClN_2O_2S$	69.63	3.97	5.80
					69.33	4.13	5.81

(a) Compound IIIa was obtained by refluxing IIa (2 g, 5 mmoles) in toluene (50 ml) for 4 hours, followed by filtration of the precipitate and concentration of the mother liquor. Total yield, 1.5 g; compounds IIIb,e,f,g,h were obtained from the corresponding II by dehydrochlorination with triethylamine in benzene at 110° for 10 hours according to (3); compound IIId was obtained directly in the reaction of enaminone Id with dichloroacetyl chloride and triethylamine. (b) From 95% ethanol. (c) From ethyl acetate. (d) From dimethyl sulfoxide.

Table IV

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

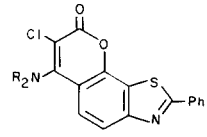
	UV λ max nm (log ε)	IR, cm^{-1} C=O	C=C	NMR δ
IIIa	228.5 (4.00) 276 (3.84) 302 sh (3.77) 392 (4.27)	1695	1512	(a)
IIIb	230 (3.93) 280 (3.75) 302 (3.70) 395 (4.29)	1700	1510	1.15 (t, J = 7.2, $2CH_3$), 3.02 (near t, J ∿ 5, CH_2-5 + CH_2-6), 3.37 (q, J = 7.2, 2 NCH_2), 7.50 (mc, 2H ar-*m* + 1H ar-*p*), 7.87 (mc, 2H ar-*o*).
IIId	228 (3.59) 276 (3.50) 304 sh (3.42) 390 (3.90)	1692	1515	1.99 (m, $2CH_2$ pyrr.), 3.05 (near t, J ∿ 4.5, CH_2-5 + CH_2-6), 3.64 (m, 2 NCH_2), 7.52 (mc, 2H ar-*m* + 1H ar-*p*), 7.88 (mc, 2H ar-*o*).
IIIe	230 (3.87) 278 (3.76) 303 sh (3.67) 393 (4.14)	1700	1515	1.71 (m, $3CH_2$ pip.), 3.02 (near t, J ∿ 5, CH_2-5 + CH_2-6), 3.33 (m, 2 NCH_2), 7.52 (mc, 2H ar-*m* + 1H ar-*p*), 7.88 (mc, 2H ar-*o*).
IIIf	229.5 (3.81) 277 (3.66) 303 sh (3.61) 397 (4.09)	1698	1510	(a)
IIIg	239.5 (3.84) 299 (3.61) 407 (4.10)	1718	1510	2.30-2.75 (m, CH_2-5), 2.8-3.2 (m, CH_2-6), 3.38 (s, NCH_3), 6.6-7.6 (m, NC_6H_5 + 2H ar-*m* + 1H ar-*p*), 7.82 (mc, 2H ar-*o*).

IIIh	226.5 sh (3.62) 274.5 (3.63) 311 sh (3.41) 410 (3.85)	1712	1513	2.25-2.70 (m, CH_2-5), 2.75-3.15 (m, CH_2-6), 6.9-7.6 (m, 2 NC_6H_5 + 2H ar-*m* + 1H ar-*p*), 7.83 (mc, 2H ar-*o*).

(a) The product was insufficiently soluble in the common solvents employed for nmr measurement.

Table V

N,N-Disubstituted 4-Amino-3-chloro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones Va-g



Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
Va	$N(CH_3)_2$	20	260 (a)	$C_{18}H_{13}ClN_2O_2S$	60.59 60.46	3.67 3.66	7.85 7.60
Vg	$N(CH_3)C_6H_5$	51	225 (b)	$C_{23}H_{15}ClN_2O_2S$	65.95 65.90	3.61 3.80	6.69 6.63

UV, IR and NMR Spectral Data

	UV λ max nm (log ε)	IR, cm^{-1} C=O	C=C	NMR δ
Va	224 (4.37) 270 (4.19) 321 (4.44)	1710	1537 (c)	(d)
Vg	230 (4.38) 270 (4.30) 338.5 (4.36) 354 sh (4.30)	1730	1528	3.50 (s, NCH_3), 6.70-7.85 (m, CH-5 + CH-6 + NC_6H_5 + 2 H ar-*m* + 1 H ar-*p*), 7.95-8.25 (m, 2 H ar-*o*).

(a) From ethyl acetate-chloroform. (b) From ethyl acetate. (c) In potassium bromide. (d) The product was insufficiently soluble in the common solvents employed for nmr measurement.

EXPERIMENTAL

Uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. Ir spectra were taken in chloroform on a Perkin-Elmer Model 257 spectrophotometer; nmr spectra were recorded in deuteriochloroform on a Perkin-Elmer Model R12 instrument (60 MHz, TMS as internal standard, J in Hz). Melting points were determined with a Fisher-Johns apparatus.

Enaminones I have been already described (1).

6-(2,2-Dichloroethylidene)-5,6-dihydro-2-phenylbenzothiazol-7-(4*H*)one (IV).

A solution of IIc (4.7 g, 0.0104 moles) in anhydrous triethylamine (50 ml) and benzene (20 ml) was refluxed with stirring for 6 hours. After cooling, the reaction mixture was filtered and the solution concentrated *in vacuo*. Starting IIc (0.7 g, 15%) was recovered by adding anhydrous ether to the residue. The solid obtained by evaporation of the ether solution was chromatographed on a Florisil® column (60-100 mesh, 40 g) to give IV (0.8 g, 24%) with 1:1 benzene-petroleum ether (bp 40-60°), and enaminone Ic (0.6 g, 17%) (1) with benzene and ether.

Compound IV had a mp of 162-163° from anhydrous ethanol; uv: λ max nm (log ε) 240 (3.92), 251 (3.91), 337.5 (4.39); ir (chloroform): ν max 1667, 1620 cm^{-1}; nmr (deuteriochloroform): δ 2.80-3.45 (m, CH_2-4 + CH_2-5), 6.57 (d, J = 9.6, $CHCl_2$), 6.95 and 7.11 (2 t, J′ = 9.6, J″ = 1.8, =CH), 7.55 (mc, 2 H ar *m* + 1 H ar *p*), 8.01 (mc, 2 H ar *o*) [*cf.* (4,5)].

Anal. Calcd. for $C_{15}H_{11}Cl_2NOS$: C, 55.56; H, 3.42; N, 4.32; Cl, 21.87. Found: C, 55.44; H, 3.57; N, 4.51; Cl, 21.81.

General Procedure for *N,N*-Disubstituted 4-Amino-3-chloro-8-phenyl-2*H*-pyrano[3,2-*g*]benzothiazol-2-ones (Va,g).

A warm solution of DDQ (1.14 g, 5 mmoles) in anhydrous benzene (50 ml) was added dropwise under dry nitrogen to a refluxing and stirred solution of IIIa or IIIg (5 mmoles) in anhydrous benzene (200 ml). After the addition was complete, the reaction mixture was further refluxed (25 and 18 hours for IIIa and IIIg, respectively) and filtered. The filtrate was washed 3 times with 10% sodium hydroxide and water, dried (sodium sulfate), and evaporated under reduced pressure. The residue was chromatographed on silica gel (200 g) to give, with petroleum ether-chloroform 1:1 up to 1:2, compounds Va or Vg (Table V).

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