Reaction of Ketenes with *N,N*-Disubstituted α-Aminomethyleneketones. XIII. Synthesis of 2*H*-Pyrano[3,2-*d*]-1-benzoxepin Derivatives

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Cycloaddition of dichloroketene to *N,N*-disubstituted (*E*)-4-aminomethylene-3,4-dihydro-1-benzoxepin-5(2*H*)-ones gave *N,N*-disubstituted 4-amino-3,3-dichloro-3,4,5,6-tetrahydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-ones II, which are derivatives of the new heterocyclic system 2*H*-pyrano[3,2-*d*]-1-benzoxepin. Dehydrochlorination with triethylamine of II afforded *N,N*-disubstituted 4-amino-3-chloro-5,6-dihydro-2*H*-pyrano-[3,2-*d*]-1-benzoxepin-2-ones III in good to moderate yields. In the triethylamine treatment of IIh (NR_2 = diphenylamino), 3-chloro-5,6-dihydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-one was isolated in low yield near to IIIh, whereas IIc (NR_2 = diisopropylamino) gave in low yield 4-diisopropylamino-5,6-dihydro-2*H*-pyrano-[3,2-*d*]-1-benzoxepin-2-one.

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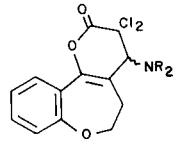
In a previous paper (1) we described the synthesis of a new heterocyclic system, 1,2-oxathiino[5,6-*d*]-1-benzoxepin, by reaction of sulfene with a number of *N,N*-disubstituted (*E*)-4-aminomethylene-3,4-dihydro-1-benzoxepin-5(2*H*)-ones I.

In pursuing our work on heterocyclic systems incorporating potential pharmacologically active molecules, we wish to report now the dipolar 1-4 cycloaddition of

Table I

N,N-Disubstituted 4-amino-3,3-dichloro-3,4,5,6-tetrahydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-ones IIc,f-h (a)



Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIc	Diisopropylamino	86	129 (b)	$C_{19}H_{23}Cl_2NO_3$	59.38 59.34	6.03 6.11	3.64 3.66
IIf	Morpholino	44	139 (b)	$C_{17}H_{17}Cl_2NO_4$	55.15 54.82	4.63 4.40	3.78 3.81
IIg	Methylphenylamino	70	154 (b)	$C_{20}H_{17}Cl_2NO_3$	61.55 61.42	4.39 4.24	3.59 3.54
IIh	Diphenylamino	82	209 (c)	$C_{25}H_{19}Cl_2NO_3$	66.38 66.63	4.23 4.26	3.10 3.29

IR and NMR Spectral Data

	IR, cm^{-1} C=O	C=C	NMR, δ
IIc	1780	1650	1.06 and 1.18 (2 d, J = 4.8, 4 CH_3), 2.60-3.35 (m, CH_2-5 + 2 CHN), 3.85 (s, CH−4), 4.36 (t, J = 5.4, CH_2-6), 6.85-7.30 (m, 3 H aryl), 7.82 (dd, J' = 7.8, J'' ~ 2, CH−11)
IIf	1783	1660	2.6-3.2 (m, 2 CH_2N + CH_2-5), 3.64 (mc, 2 CH_2O + CH−4), 4.32 and 4.35 (2 t, J = 5.4 CH_2-6), 6.95-7.50 (m, 3 H aryl), 7.87 (dd, J' = 7.2, J'' ~ 2, CH−11)
IIg	1784	1662	2.55-2.90 (m, CH_2-5), 2.80 (s, CH_3N), 4.30-4.75 (m, CH_2-6), 5.18 (near s, CH−4), 6.9-7.7 (m, C_6H_5N + 3 H aryl), 7.93 (dd, J' = 7.8, J'' ~2, CH−11)
IIh	1785	1665	2.92 (t, J = 5.4, CH_2-5), 3.95-4.70 (m, CH_2-6), 5.30 (near s, CH−4), 6.70-7.65 (m, 2 C_6H_5N + 4 H aryl)

(a) All compounds were prepared according to the literature (2), reaction time, 20 minutes. (b) From anhydrous diethyl ether. (c) From ethyl acetate.

dichloroketene to enaminones I to give derivatives of a new heterocycle incorporating both 2*H*-pyran and 1-benzoxepin rings, namely 2*H*-pyrano[3,2-*d*]-1-benzoxepin. By our method of cycloadding dichloroketene 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 good yield, *N,N*-disubstituted 4-amino-3,3-dichloro-3,4,5,6-tetrahydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-ones IIc,f-h (Table I), whose structure was confirmed by ir and nmr spectral data.

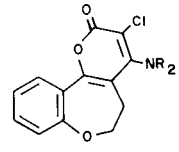
Also enaminones Ia,b,d,e gave the corresponding cycloadducts, but they were too unstable to be purified and characterized, therefore they were used in the next step without further purification. All these adducts were dehydrochlorinated with triethylamine according to (3) to afford *N,N*-disubstituted 4-amino-3-chloro-5,6-dihydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-ones IIIa,b,d-h in good to moderate yield (Table II and III). Near to dehydrochlorinated product IIIh, a second compound could be isolated in low yield, which contained chlorine but not the diphenylamino group. On the basis of uv, ir, nmr and mass spectral data we propose for it the structure of 3-chloro-5,6-dihydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-one (IV). This compound could be formed by reductive cleavage of the C(4)−N bond of the bulky diphenylamino group, where the reducing agent could be triethylamine under prolonged reflux (4).

The diisopropylamino adduct IIc gave no dehydrochlorinated product after 22 hours reflux: near to recovered IIc, a product not containing chlorine but still the diisopropylamino group was isolated in low yield, for which we propose the structure of 4-diisopropylamino-5,6-dihydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-one (V). Also in this case, a reductive cleavage of the C(3)−Cl bond could take place in order to permit an unhindered arrangement of the diisopyropylamino group.

The biological screening, concerning compounds IIIa,b,d-h, included herbicide, insecticide, plant health and *in vitro* antimicrobial activity (1). Compound IIIb showed a total inhibition and IIIa a moderate inhibition of

Table II

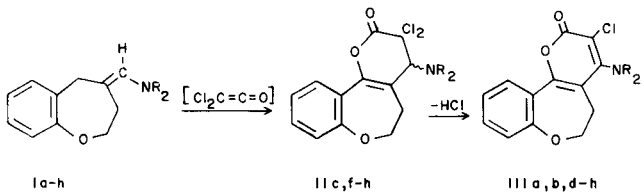
N,N-Disubstituted 4-amino-3-chloro-5,6-dihydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-ones IIIa,b,d-h (a)



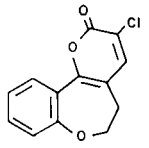
Formula Number	NR_2	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	Dimethylamino	30	130 (b)	$C_{15}H_{14}ClNO_3$	61.76 61.58	4.84 4.99	4.80 4.94
IIIb	Diethylamino	56	101 (b)	$C_{17}H_{18}ClNO_3$	63.85 63.65	5.67 5.66	4.38 4.26
IIId	Pyrrolidino	68	178 (c)	$C_{17}H_{16}ClNO_3$	64.26 64.47	5.08 5.07	4.41 4.31
IIIe	Piperidino	24	174 (c)	$C_{18}H_{18}ClNO_3$	65.16 65.40	5.47 5.48	4.22 4.20
IIIf	Morpholino	91	182 (c)	$C_{17}H_{16}ClNO_4$	61.18 60.91	4.83 4.99	4.20 4.20
IIIg	Methylphenylamino	30	158 (b)	$C_{20}H_{16}ClNO_3$	67.90 67.77	4.56 4.70	3.96 4.05
IIIh	Diphenylamino	36 (d)	194 (b)	$C_{25}H_{18}ClNO_3$	72.20 72.48	4.36 4.53	3.37 3.38

(a) Compounds IIIf,g,h were prepared from IIf,g,h and IIIa,b,d,e from the raw, unstable cycloadducts obtained from the corresponding enaminones II and dichloroketene, by dehydrochlorination with triethylamine according to the literature (3), reflux times, 8-12 hours. (b) From anhydrous diethyl ether. (c) From ethyl acetate. (d) Also 12% of compound IV, see Experimental.

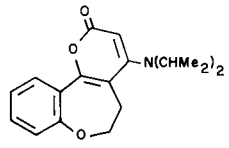
Staphylococcus aureus; all the others were found to be inactive.



Ia-h IIc,f-h IIIa,b,d-h



IV



V

NR_2

a, Dimethylamino
b, Diethylamino
c, Diisopropylamino
d, Pyrrolidino
e, Piperidino
f, Morpholino
g, Methylphenylamino
h, Diphenylamino

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer and the ir spectra were taken in chloroform with 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) and the mass spectra on a GC/MS Varian Mat 111 spectrometer. Melting points were determined with a Fisher-Johns apparatus. Enaminones I have been already described (1).

3-Chloro-5,6-dihydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-one (IV).

The residue obtained in the dehydrochlorination of IIh was treated with a little anhydrous diethyl ether, whereby a mixture of IIIh and IV separated. By repeated recrystallizations from 95% ethanol, pure IIIh was obtained in 36% yield (see Table II). Compound IV was obtained by concentrating the mother liquors; yield, 12%, mp 138° from 95% ethanol; uv: λ max nm (log ε) 215.5 (4.20), 247 (3.78), 356 (4.07); ir (chloroform): ν max 1733, 1628, 1530 cm^{-1}; nmr (deuteriochloroform): δ 2.91 (t, J = 5.1, CH_2-5), 4.33 (t, J = 5.1, CH_2-6), 6.8-7.6 (m, 4 H aryl), 8.07 (dd, J' = 7.8, J'' = 2.4, CH−11); ms: m/e 251 (5%), 250 (32), 249 (14), 248 (100), 223 (4), 222 (28), 221 (12), 220 (72), 213 (4), 207 (15), 205 (38), 185 (24), 169 (11), 157 (50), 129 (14), 128 (24), 127 (28), 120 (17).

Anal. Calcd. for $C_{13}H_9ClO_3$: C, 62.79; H, 3.65; Cl, 14.26. Found: C, 62.81; H, 3.78; Cl, 14.13.

Table III

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	213.5 (4.15) 233 sh (3.81) 264 (4.08) 335 (4.06)	1700	1620	1525	2.80 (t, J = 5.4, CH_2-5), 3.07 (s, 2 CH_3N), 4.54 (t, J = 5.4, CH_2-6), 7.0-7.5 (m, 3 H aryl), 7.95 (dd, J' = 7.8, J'' ~ 2, CH−11)
IIIb	214 (4.19) 239 sh (3.82) 264.5 (3.94) 340 (4.11)	1700	1618	1520	1.14 (t, J = 7.2, 2 CH_3), 2.82 (t, J = 5.4, CH_2-5), 3.35 (q, J = 7.2, 2 CH_2N), 4.53 (t, J = 5.4, CH_2-6), 6.9-7.5 (m, 3 H aryl), 7.94 (dd, J' = 7.8, J'' ~ 2, CH−11)
IIId	211.5 (4.22) 235 sh (3.88) 267.5 (4.20) 337 (4.09)	1690	1618	1525	1.98 (mc, 2 CH_2 pyrr), 2.75 (t, J = 5.4, CH_2-5), 3.58 (mc, 2 CH_2N), 4.51 (t, J = 5.4, CH_2-6), 6.90-7.55 (m, 3 H aryl), 7.88 (dd, J' = 7.2, J'' = 2.4, CH−11)
IIIe	212 (4.22) 236 sh (3.82) 265.5 (4.07) 336 (4.11)	1700	1620	1525	1.68 (mc, 3 CH_2 pip), 2.81 (t, J = 5.4, CH_2-5), 3.31 (mc, 2 CH_2N), 4.50 (t, J = 5.4, CH_2-6), 6.90-7.55 (m, 3 H aryl), 7.92 (dd, J' = 7.2, J'' = 2.4, CH−11)
IIIf	214.5 (4.18) 235 sh (3.82) 263 (4.00) 338 (4.05)	1705	1618	1520	2.85 (t, J = 5.4, CH_2-5), 3.37 (mc, 2 CH_2N), 3.85 (mc, 2 CH_2O), 4.50 (t, J = 5.4, CH_2-6), 6.9-8.6 (m, 3 H aryl), 7.93 (dd, J' = 7.2, J'' ~ 2, CH−11)
IIIg	215 (4.30) 243 (4.19) 270 sh (3.82) 356 (4.16)	1715	1620	1515	2.56 (t, J = 5.4, CH_2-5), 3.35 (s, CH_3N), 4.21 (t, J = 5.4, CH_2-6), 6.60-7.55 (m, C_6H_5N + 3 H aryl), 8.04 (dd, J' = 7.2, J'' = 2.4, CH−11)
IIIh	213.5 (4.39) 259 sh (4.16) 276 (4.25) 358 (4.16)	1715	1620	1525	2.55 (t, J = 5.4, CH_2-5), 3.95 (t, J = 5.4, CH_2-6), 6.9-7.6 (m, 2 C_6H_5N + 3 H aryl), 8.03 (dd, J' = 7.2, J'' = 2.4, CH−11)

4-Diisopropylamino-5,6-dihydro-2*H*-pyrano[3,2-*d*]-1-benzoxepin-2-one (V).

A solution of IIc (3.84 g, 10 mmoles) in anhydrous triethylamine (100 ml) and benzene (40 ml) was refluxed with stirring for 22 hours. After cooling, the reaction mixture was filtered and the solution was concentrated under reduced pressure to about one third of its volume to give 0.7 g (22%) of V, mp 235° from ethyl acetate; uv: λ max nm (log ε) 211.5 (4.06), 232.5 (3.96), 306 (3.93), 319 (3.91), 390 (4.26); ir (chloroform): ν max 1705, 1645, 1592 cm^{-1}; nmr (deuteriochloroform): δ 1.32 (d, J = 6.6, 4 CH_3), 2.75 (near t, J = 5.4, CH_2-5), 4.34 (near t, J = 5.4, CH_2-6 + 2 CHN), 6.73 (s, CH − 3), 6.95-7.35 (m, 3 H aryl), 7.65-7.85 (m, CH − 11); ms: m/e 314 (30%), 313 (100), 297 (10), 271 (20), 270 (91), 269 (19), 256 (18), 229 (31), 200 (16), 149 (21), 137 (30).

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.73; H, 7.49; N, 4.39.

The filtered solution gave by further concentration a brown, viscous liquid from which 1.2 g (30%) of starting IIc were recovered by treatment with anhydrous diethyl ether.

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REFERENCES AND NOTES

(1) G. Menozzi, L. Mosti, P. Schenone and S. Cafaggi, *J. Heterocyclic Chem.*, **19**, 937 (1982).

(2) G. Bignardi, F. Evangelisti, P. Schenone and A. Bargagna, *ibid.*, **9**, 1071 (1972); A. Bargagna, F. Evangelisti and P. Schenone, *ibid.*, **16**, 93 (1979).

(3) F. Evangelisti, G. Bignardi, A. Bargagna and P. Schenone, *ibid.*, **15**, 511 (1978). Moles and volumes of reagents and solvents were the same employed in the case of V (see Experimental).

(4) Tertiary amines can act as reductive dehalogenating agents as in the case of 3-bromocamphor: A. G. Giumanini and M. M. Musiani, *Z. Naturforsch.*, **32b**, 1314 (1977); *J. Prakt. Chem.*, **322**, 423 (1980).