Reaction of Ketenes with *N,N*-Disubstituted α-Aminomethyleneketones. IX. Synthesis of 2*H*,5*H*-Pyrano[3,2-*c*][1]benzopyran Derivatives

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Cycloaddition of dichloroketene to *N,N*-disubstituted 3-aminomethylene-4-chromanones gave in good yield *N,N*-disubstituted 4-amino-3,3-dichloro-3,4-dihydro-5*H*-pyrano[3,2-*c*][1]benzopyran-2-ones only in the case of aromatic *N*-substitution. Dehydrochlorination with triethylamine of these adducts afforded *N,N*-disubstituted 4-amino-3-chloro-5*H*-pyrano[3,2-*c*][1]benzopyran-2-ones in good to moderate yield. The cycloaddition to 3-dimethylaminomethylene-4-chromanone led directly to 3-chloro-4-dimethylamino-5*H*-pyrano[3,2-*c*][1]benzopyran-2-one.

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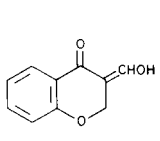
The heterocyclic system of 2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran is found in naturally occurring compounds such as cytromicetin, a fungal metabolite (1), bothrioclinin and similar substances (2), as well as in important synthetic anticoagulant drugs, such as Cyclocumarol (3), and as cyclic form of Warfarin (4). We wish to report now a new synthesis of derivatives III and IV of this system, unsubstituted in 5-position, for which the available synthetic pathways are relatively few (5).



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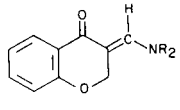
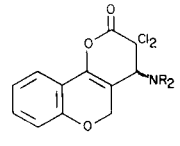
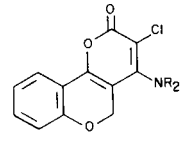


IIa-d



IIIb-d



IVa-d

Starting enaminones for the preparation of such compounds were *N,N*-disubstituted 3-aminomethylene-4-chromanones II (Table I), some of which have been described by one of us in connection with the synthesis of 5*H*-1,2-oxathiino[5,6-*c*][1]benzopyran derivatives (6). The *N,N*-diisopropyl derivative could not be prepared, because in the reaction with I, the relatively strong but scarcely reactive diisopropylamine catalyzed the condensation between two molecules of I giving rise to 2,3-dihydro-3,3′-methylenebischromen-4-one in 94% yield [*cf.* (6,7)]. Enaminones IIc,d are *E* isomers, as can be seen from the strong upward shift (0.8-1 ppm) of C-2 methylene protons caused by the phenyl group(s) in comparison with IIa (see Table I).

Following our method of dichloroketene cycloaddition to *N,N*-disubstituted α-aminomethyleneketones (8), we reacted enaminones IIa-d with dichloroacetyl chloride and triethylamine (dichloroketene prepared *in situ*) and obtained the expected *N,N*-disubstituted 4-amino-3,3-dichloro-3,4-dihydro-5*H*-pyrano[3,2-*c*][1]benzopyran-2-ones (IIIb-d) (Table II). Yields are good only in the case of aromatic *N*-substitution [*cf.* (8)]; in the case of dimethylamino derivative IIa, the corresponding adduct III was formed together with the dehydrochlorinated product IVa, as shown by an ir absorption at 1793 cm^{-1} of the crude product, but could not be isolated: recrystallization of the mixture gave directly IVa in fair yield [see (8)].

Adducts IIIb-d were dehydrochlorinated with triethylamine (10) to give *N,N*-disubstituted 4-amino-3-chloro-5*H*-pyrano[3,2-*c*][1]benzopyran-2-ones (IV) (Table III) in excellent yields only in the case of aromatic *N*-substitution (IVc,d), and in low yield in the case of piperidino derivative (IVb).

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.

3-Hydroxymethylene-4-chromanone (II).

This compound could be obtained as described in (6) in yields as high as 80% by eliminating the extraction of benzene layer with 10% sodium hydroxide. We observed indeed that this treatment caused the formation of 2,3-dihydro-3,3′-methylenebischromen-4-one in yields up to 20% [*cf.* (7)], with a consequent decrease in the yield of II.

Acknowledgement.

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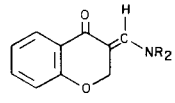
Table I

N,N-Disubstituted 3-Aminomethylene-4-chromanones (IIa-d)



Formula Number	NR_2	Yield %	M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa (d)	$N(CH_3)_2$	78	134 (a)	$C_{12}H_{13}NO_2$	70.91	6.45	6.89
					70.90	6.70	6.93
IIb (b)	Piperidino	74					
IIc (d)	$N(CH_3)C_6H_5$	94	74 (c)	$C_{17}H_{15}NO_2$	76.96	5.70	5.28
					76.78	5.71	5.22
IId (d)	$N(C_6H_5)_2$	78	150 (c)	$C_{22}H_{17}NO_2$	80.71	5.23	4.28
					80.73	5.00	4.11

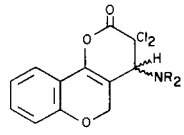
Uv, Ir and Nmr Spectral Data

	Uv λ max nm (log ε)	Ir, cm^{-1} C=O	C=C	Nmr, δ
IIa (d)	214.5 (4.20) 233.5 (4.13) 255 sh (4.02) 317 (3.99) 364 (4.26)	1665	1550	3.09 (s, $2NCH_3$), 5.26 (near s, CH_2-2), 6.75-7.50 (m, CH-6 + CH-7 + CH-8), 7.56 (near s, =CHN), 7.95 (dd, J′ = 6.5, J″ = 2.5, CH-5)
IIc (d)	216 sh (4.15) 233 sh (4.03) 262 (3.97) 322.5 (3.90) 376.5 (4.23)	1652	1545	3.49 (s, NCH_3), 4.50 (s, CH_2-2), 6.75-7.55 (m, CH-6 + CH-7 + CH-8 + NC_6H_5), 7.76 (near s, =CHN), 7.99 (dd, J′ = 7, J″ = 2, CH-5)
IId (d)	218 sh (4.15) 241.5 (3.97) 265 (4.07) 330 sh (3.77) 386.5 (4.21)	1658	1548	4.26 (near s, CH_2-2), 6.70-7.65 (m, 13 Har.), 7.96 (near s, =CHN), 8.02 (dd, J′ = 7.2, J″ = 2.4, CH-5)

(a) From ethyl acetate. (b) Already described in (6). (c) From anhydrous diethyl ether. (d) Enaminones IIc,d were prepared according to (9), and IIa according to (6).

Table II

N,N-Disubstituted 4-Amino-3,3-dichloro-3,4-dihydro-5*H*-pyrano[3,2-*c*][1]benzopyran-2-ones (IIIb-d) (c)



Formula Number	NR_2	Yield %	M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIb	Piperidino	23	124 (a)	$C_{17}H_{17}Cl_2NO_3$	57.64	4.83	3.95
					57.71	4.91	3.92
IIIc	$N(CH_3)C_6H_5$	79	155 (a)	$C_{19}H_{15}Cl_2NO_3$	60.65	4.02	3.72
					60.38	4.19	3.49
IIId	$N(C_6H_5)_2$	90	175 (b)	$C_{24}H_{17}Cl_2NO_3$	65.76	3.91	3.19
					65.51	4.20	2.95

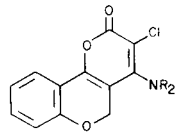
Uv, Ir and Nmr Spectral Data

	Uv λ max nm (log ε)	Ir, cm^{-1} C=O	Ir, cm^{-1} C=C	Nmr, δ
IIIb	215 (4.17) 260 (4.02) 345 (3.60)	1783	1678	1.48 (m, $3CH_2$ pip.) 2.75 (m, $2NCH_2$ pip.), 3.73 (s, CH-4), 4.93 (s, CH_2-5), 6.75-7.35 (m, CH-7 + CH-8 + CH-9), 7.46 (dd, J′ = 7.2, J″ = 2, CH-10)
IIIc	217 (4.20) 246.5 (4.17) 279 sh (3.77) 326 sh (3.41)	1783	1695	2.76 (s, NCH_3), 4.82 (m, CH_2-5 + CH-4), 6.70-7.40 (m, CH-7 + CH-8 + CH-9 + NC_6H_5), 7.50 (dd, J′ = 6.6, J″ = 2, CH-10)
IIId	2.37 (4.34) 278 (4.08) 320 sh (3.69)	1792	1700	5.03 (near s, CH_2-5), 5.22 (m, CH-4), 6.70-7.50 (m, 14 Har.)

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

Table III

N,N-Disubstituted 4-Amino-3-chloro-5*H*-pyrano[3,2-*c*][1]benzopyran-2-ones (IVa-d)



Formula Number	NR_2	Yield %	M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IVa	$N(CH_3)_2$	51	180 (a)	$C_{14}H_{12}ClNO_3$	60.55	4.35	5.04
					60.30	4.10	5.10
IVb (b)	Piperidino	31	182 (a)	$C_{17}H_{16}ClNO_3$	64.46	5.09	4.42
					64.40	5.00	4.32
IVc (b)	$N(CH_3)C_6H_5$	91	160 (a)	$C_{19}H_{14}ClNO_3$	67.16	4.15	4.12
					67.02	4.30	3.88
IVd (b)	$N(C_6H_5)_2$	81	232 (a)	$C_{24}H_{16}ClNO_3$	71.73	4.01	3.48
					71.65	4.04	3.41

Uv, Ir and Nmr Spectral Data

	Uv λ max nm (log ε)	Ir, cm^{-1} C=O	Ir, cm^{-1} C=C	Nmr, δ
IVa	245 (3.91) 269.5 (4.09) 304.5 (3.83) 350 (4.07)	1700	1635	3.05 (s, $2NCH_3$), 5.08 (s, CH_2-5), 6.8-7.5 (m, CH-7 + CH-8 + CH-9), 7.69 (dd, J′ = 8, J″ = 2, CH-10)
IVb (b)	240 (3.83) 271 (3.95) 307 (3.75) 352 (4.01)	1700	1633	1.70 (m, $3CH_2$ pip.), 3.25 (m, $2NCH_2$ pip.), 5.04 (s, CH_2-5), 6.75-7.50 (m, CH-7 + CH-8 + CH-9), 7.69 (dd, J′ = 7.2, J″ = 2, CH-10)
IVc (b)	2.41 (4.17) 279 (3.91) 318 sh (3.75) 374 (4.31)	1722	1632	3.45 (s, NCH_3), 4.49 (s, CH_2-5), 6.75-7.60 (m, CH-7 + CH-8 + CH-9 + NC_6H_5), 7.74 (dd, J′ = 7.2, J″ = 2, CH-10)
IVd (b)	247 sh (4.13) 277 (4.26) 378 (4.30)	1712	1633	4.45 (near s, CH_2-5), 6.60-7.55 (m, CH-7 + CH-8 + CH-9 + $2NC_6H_5$), 7.76 (dd, J′ = 7.2, J″ = 2, CH-10)

(a) From ethyl acetate. (b) Compounds IVb,c,d were prepared from IIIb,c,d, respectively, by dehydrochlorination with triethylamine according to (10).

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