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SYNTHESIS AND REACTIONS OF SOME CHLORO-2,2-DIMETHYLCHROMENS

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Abstract—5-, 6-, 7-, and 8-Chloro-2,2-dimethylchromens have been prepared from the corresponding chlorocoumarin and their conversion into the 3,4-dihalogenochroman derivatives is described. The 4-halogen atom is shown to be the more susceptible to hydrolysis by conversion of the resulting halohydrins into chromanones and epoxides. The formation of bis-chromens during the dehalogenation of 3-halogenochromanones is reported.

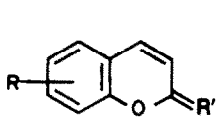
In continuation of our investigations[1] into the influence of substituents on the chemistry of 2,2-dimethylchromen, and in view of the biological significance of some 2,2-dimethylchromens[2] we now report the preparation of 5-, 6-, 7-, and 8-chloro-2,2-dimethylchromens (**2a–d**) and their reactions with halogens. Some chemistry of the derived 3,4-dihalogenochromans is also described.

5-Chloro-[3] and 8-chloro-coumarin (**1**; R = 5- or 8-Cl) were prepared from the appropriate 2-hydroxybenzaldehyde, whilst the 6- and 7- isomers[4] were obtained directly from the corresponding chlorophenol. Reaction of the coumarins with MeMgI[5] and cyclisation of the resulting diol in boiling acetic acid yielded the chloro-2,2-dimethylchromens (**2a–d**). Addition of Br_2 or Cl_2 in chloroform gave the respective 3,4-dibromo- and 3,4-dichloro-2,2-dimethylchroman derivatives (**3a–h**). No evidence of halogen substitution in the aromatic ring was obtained, in contrast to the observations with 2,2-dimethylchromen itself[6] and various methoxy derivatives.[1]

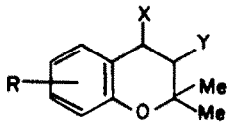
Preparative scale hydrolysis by prolonged boiling with aqueous acetone afforded the 3-halogenochroman-4-ols (**4a–h**). Confirmation of the greater susceptibility of the 4-halogen atom to nucleophilic attack followed from the oxidation of the resulting halohydrins (**4a–h**) to the 3-halogeno-2,2-dimethylchroman-4-ones (**5a–h**). Although previous workers[1,7] have reported the successful dehalogenation of halogenochromanones on treatment with Zn dust and acetic acid, in this work the chromanone (**5j–l**) was either obtained as a minor product or not at all. The major product lacked a CO group and mass spectrometry indicated a molecular formula of $C_{20}H_{20}Cl_2O_2$. Significant peaks in the mass spectrum corresponded to $(M-CH_3)$, $(M-2CH_3)$, and $\frac{1}{2}(M-2CH_3)$. Signals arising from the *gem*-dimethyl group and the aromatic protons appeared in the ^1H NMR spectrum, along with a signal at $\delta 5.62$ assigned to H-3 in the symmetrical structures (**8a–c**) proposed for these products. In the case of the 8-chloro-3-halogeno-2,2-dimethylchroman-4-ones (**5d, h**), only the bis-chromen was isolated and the reaction was not attempted with the 5-chloro compounds. 5-Chloro- and 8-chloro-2,2-dimethylchroman-4-ones (**5i, l**) were obtained by reaction of the corresponding 3-bromochromanones (**5a, d**) with benzoin.[8] The chromanones (**5j–l**) were identical with those obtained by Fries rearrangement of the appropriate chlorophenyl 3-methylbut-2-enoate;[9] the 3-chlorophenyl ester yielded only the 7-chlorochromanone. Reduction of the ketones yielded the chroman-4-ols (**4k, l**).

Prolonged stirring of the halogenochromanols (**4a–h**) with powdered potassium hydroxide in dry ether gave the epoxides (**6a–d**). When the 6-chloro-epoxide was purified by distillation, on some occasions the oily distillate set to a glassy solid. The ^1H NMR spectrum consisted of sharp multiplets superimposed on broad peaks, suggesting that polymerisation of the epoxide had occurred. A close similarity between the sharp signals in this spectrum and the spectrum of crystalline epoxide was apparent.

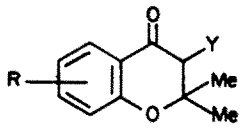
The epoxides reacted with hydrogen chloride to give the 4-chloro-2,2-dimethylchroman-3-ols (**7a–c**) and with LAH to give the chroman-3-ols (**7d–g**). Reaction of the 6-chloro-epoxide with methanol gave the 4-methoxychroman-3-ol (**7i**), but the 7-chloro-isomer was recovered unchanged after prolonged boiling. The stability of this epoxide is in sharp contrast to the reactivity of 3,4-epoxy - 7 - methoxy - 2,2 - dimethylchroman,[1,10] recently suggested as the species responsible for the biological activity of precocene 1.



1: R' = O
2: R' = Me_2



3: X = Y = Br or Cl
4: X = OH; Y = Br, Cl or H
6: XY = O
7: X = Cl, OMe or H; Y = OH



5: Y = Br, Cl or H

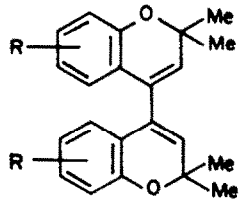


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Table 1. Physical and analytical data from chromens (2), chromans (3, 6), chromanols (4, 7), and chromanones (5)

Compound[a]	R	X	Y	m.p. °C (b.p. °C/mmHg)	Yield (%)	Found (%) (Required) C	H	Cl	Br
2a	5-Cl			(92-3/0.8)	57	67.8	6.0	18.3	
						(67.9	5.7	18.2)	
2b	6-Cl			(98/1.0)	53	67.8	5.8	17.9	
2c	7-Cl			(87-8/3.0)	65	67.7	5.7	18.0	
2d	8-Cl			(73/1.0)	54	67.8	5.7	18.2	
3a	5-Cl	Br	Br	71-2	95	37.1	3.1	9.8	44.9
						(37.2	3.1	10.0	45.1)
3b	6-Cl	Br	Br	69.5-70	92	37.3	2.9	9.9	45.0
3c	7-Cl	Br	Br	65-6	86	37.0	3.1	9.9	45.0
3d	8-Cl	Br	Br	45	91	37.1	3.2	10.0	45.2
3e	5-Cl	Cl	Cl	61-2	74	49.5	4.3	40.1	
						(49.8	4.2	40.1)	
3f	6-Cl	Cl	Cl	58-9	88	50.2	4.3	40.1	
3g	7-Cl	Cl	Cl	65-6	70	49.7	4.1	40.0	
3h	8-Cl	Cl	Cl	25	80	50.1	4.1	39.6	
4a	5-Cl	OH	Br	85	70	45.3	4.0	12.1	27.2
						(45.3	4.1	12.2	27.4)
4b	6-Cl	OH	Br	83-4	91	45.2	4.1	12.2	27.3
4c	7-Cl	OH	Br	132-3[b]	96	45.1	4.3	12.0	27.2
4d	8-Cl	OH	Br	75-75.5	98	45.4	4.3	12.0	27.2
4e	5-Cl	OH	Cl	78-78.5[a]	64	53.2	4.8	29.0	
						(53.4	4.9	28.7)	
4f	6-Cl	OH	Cl	103	88	53.4	4.7	28.8	
4g	7-Cl	OH	Cl	76-7[a]	56	53.5	4.9	28.6	
4h	8-Cl	OH	Cl	69-70	95	53.8	4.9	28.8	
4i	6-Cl	OAc	Br	64.5-65		46.9	4.3	10.6	23.8
						(46.8	4.2	10.6	24.0)
4j	7-Cl	OAc	Br	66-7[a]		47.0	4.1	10.5	24.1
5a	5-Cl		Br	119-20[a]	83	45.4	3.6	12.0	27.4
						(45.6	3.4	12.3	27.6)
5b	6-Cl		Br	78-9	65	45.8	3.4	12.0	27.6
5c	7-Cl		Br	66-7	86	45.4	3.6	12.1	27.6
5d	8-Cl		Br	95-6[a]	88	45.8	3.3	12.2	27.6
5e	5-Cl		Cl	92-3	91	53.7	4.0	28.6	
						(53.9	4.1	28.9)	
5f	6-Cl		Cl	67-8	69	54.0	4.1	28.6	
5g	7-Cl		Cl	90-1[a]	69	54.0	4.1	28.8	
5h	8-Cl		Cl	47-8	75	53.6	4.0	29.0	

Table (continued)

Compound*	R	X	Y	m.p. °C (b.p. °C/mmHg)	Yield (%)	Found (%) (Required) C	H	Cl	Br
5i	5-Cl		H	107-8[c]	61	62.5	5.2	16.8	
						(62.7	5.2	16.9)	
5j	6-Cl		H	89-90	26	63.0	5.2	16.6	
5k	7-Cl		H	70-1[a,d]	23	62.6	5.2	16.8	
5l	8-Cl		H	102-3[b,e]	51	62.5	5.0	16.9	
6a	5-Cl	-O-		(128/5.0)	72	62.7	5.2	16.7	
						(62.7	5.2	16.9)	
6b	6-Cl	-O-		61-2	92	62.8	5.2	16.7	
6c	7-Cl	-O-		72[a]	68	62.8	5.2	17.3	
6d	8-Cl	-O-		19-20	67	62.6	5.3	16.9	
7a	6-Cl	Cl	OH	94-94.5	55	53.8	4.7	28.3	
						(53.5	4.9	28.7)	
7b	7-Cl	Cl	OH	63-4[a]	74	53.5	5.1	28.4	
7c	8-Cl	Cl	OH	95.5-96[a]	92	53.5	5.2	28.4	
7d	5-Cl	H	OH	70-71[a]	89	62.0	6.2	16.7	
						(62.1	6.1	16.7)	
7e	6-Cl	H	OH	108-108.5[a]	85	62.2	6.3	16.7	
7f	7-Cl	H	OH	76-76.5[a]	80	62.4	6.2	16.6	
7g	8-Cl	H	OH	97-97.5[a]	80	62.0	5.9	16.8	
7h	6-Cl	H	OAc	73		61.4	6.0		
						(61.3	5.9)		

* All solids crystallised from light petroleum (b.p. 40-60°) except:

[a] from light petroleum (b.p. 60-80°)

[b] from light petroleum (b.p. 80-100°)

[c] DNPH, m.p. 241-2° from acetic acid (Found: C,52.3; H,3.9; Cl,9.3; N,14.3. $C_{17}H_{15}ClN_4O_5$ requires C,52.2; H,3.8; Cl,9.1; N,14.3%).

[d] DNPH, m.p. 213-4° from acetic acid (C, 52.0; H, 3.9; Cl, 9.0; N, 14.2%)

[e] DNPH, m.p. 245-6° from acetic acid (C, 52.3; H, 3.8; Cl, 9.2; N, 14.6%).

EXPERIMENTAL

^{1}H NMR spectra were obtained with a Varian HA 100 spectrometer for solns in $CDCl_3$, and mass spectra with an AEI MS50 spectrometer, at the Physicochemical Measurements Unit, Harwell.

(i) *Preparation of chloro-2,2-dimethylchromens* (2). The chlorocoumarin (9.0 g) was added as a slurry in ether during *ca* 1 hr to a soln of MeMgI [from Mg (3.0 g) and iodomethane (17.9 g)] in ether. After boiling for 4 hr, the complex was decomposed with a 22% ammonium chloride soln, the product was isolated with ether and boiled in AcOH (40 ml) for 1 hr. Isolation with ether and subsequent distillation gave the chloro-2,2-dimethylchromen (Table 1).

(ii) *Preparation of 3,4-dihalogeno-chloro-2,2-dimethylchromans* (3a–h). A soln of Br_2 or Cl_2 in $CHCl_3$ was added dropwise to a soln containing an equimolar amount of the chloro-2,2-dimethylchromen in $CHCl_3$ at 10°. Removal of solvent below 40° and crystallisation of the residue gave the 3,4-dihalogeno-chloro-2,2-dimethylchroman (Table 1).

(iii) *Preparation of chloro-3-halogeno-2,2-dimethylchroman-4-ols* (4a–h). A soln of the 3,4-dihalogeno-chloro-2,2-dimethylchroman in 70% aqueous acetone was boiled under reflux for 24 hr. Dilution with water followed by isolation of the product with ether and subsequent crystallisation gave the 3-halogeno-chroman-4-ol (Table 1).

(iv) *Preparation of chloro-3-halogeno-2,2-dimethylchroman-4-ones* (5a–h). Chloro-3-halogeno-2,2-dimethylchroman-4-ol (1.0 g) and CrO_3 soln (3 ml) [from CrO_3 (9.5 g), water (6.5 ml), and AcOH (53 ml)] were kept at 55–60° for 3 hr. After dilution with water, the product was isolated with ether, eluted from alumina with benzene and the resulting solid was recrystallised to give the 3-halogenochroman-4-one (Table 1).

(v) *Preparation of chloro-2,2-dimethylchroman-4-ones* (5j–l). A mixture of the chlorophenyl 3-methylbut-2-enoate (8.0 g), prepared from the chlorophenol and 3-methylbut-2-enoyl chloride,[11] and $AlCl_3$ (19 g) was heated at 100° for 3 hr. Decomposition with dil HCl and isolation of the product with ether was followed by elution from alumina with benzene and recrystallisation to yield the chloro-2,2-dimethylchroman-4-one (Table 1).

(vi) *Preparation of chloro-3,4-epoxy-2,2-dimethylchromans* (6a–d). A mixture of the chloro-3,3-bromo-2,2-dimethylchroman-4-ol and an excess of powdered KOH was stirred for 3 days. Filtration, removal of the solvent, and crystallisation afforded the epoxide (Table 1).

(vii) *Preparation of 4,x-dichloro-2,2-dimethylchroman-3-ols* (7a–c). Dry HCl was bubbled through an ethereal soln of chloro-3,4-epoxy-2,2-dimethylchroman for 2 hr. Evaporation of the solvent and crystallisation gave the 4,x-dichloro-2,2-dimethylchroman-3-ol (Table 1).

(viii) *Preparation of chloro-2,2-dimethylchroman-3-ols* (7d–g). The chloro-epoxide was boiled with LAH in ether for 6 hr. The usual work-up gave the chloro-2,2-dimethylchroman-3-ol (Table 1).

5-Chlorocoumarin (1; R = 5-Cl). A vigorously stirred, cold soln

of 2-chloro-6-hydroxytoluene[12] (13 g) in Ac_2O (120 ml), conc H_2SO_4 (45 g) and AcOH (120 ml) was treated with a slurry of CrO_3 (35 g) in the same solvent mixture. After 30 min, the mixture was poured into ice, steam distilled, and the yellow solid which separated from the distillate was crystallised from light petroleum (b.p. 60–80°) to yield 2-chloro-6-hydroxybenzaldehyde (11%), m.p. 53°.

The aldehyde (2 g), freshly fused NaOAc (3 g), and Ac_2O (6 ml) were heated at 180–190° for 18 hr. The solid which separated when the mixture was poured into water was crystallised from EtOH to yield 5-chlorocoumarin (81%), m.p. 91°.[3]

8-Chlorocoumarin (1; R = 8-Cl). 3-Chloro-2-hydroxybenzaldehyde[13] reacted as described above to give *8-chlorocoumarin* (54%), b.p. 150° at 0.6 mmHg, m.p. 146–147° from EtOH. (Found: C, 59.6; H, 2.5; Cl, 19.9. $C_9H_5ClO_2$ requires: C, 59.8; H, 2.7; Cl, 19.7%).

Bis-4,4'-(6-chloro-2,2-dimethylchromen) (8; R = 6-Cl). 3-Bromo-6-chloro-2,2-dimethylchroman-4-one (0.3 g) was boiled with AcOH (5 ml) and Zn dust (0.2 g) for 30 min. The mixture was poured into water, extracted with ether and the extracts were washed with $NaHCO_3$ aq, dried, and evaporated. Elution of the residue (0.23 g) from alumina with light petroleum (b.p. 60–80°) gave *bis-4,4'-(6-chloro-2,2-dimethylchromen)* (74%), m.p. 162.5–163.5°, from light petroleum (b.p. 40–60°) (Found: C, 67.9; H, 5.3; Cl, 18.0. $C_{22}H_{20}Cl_2O_2$ requires: C, 68.2; H, 5.2; Cl, 18.3%; M^+ 386.0833. Calc. for $C_{22}H_{20}{}^{35}Cl_2O_2$: 386.0838), δ1.48 (12H, s, 2- and 2'-Me_2), 5.62 (2H, s, 3- and 3'-H), 6.75 (2H, d, $J_{7,8}$ 9.0 Hz, 8- and 8'-H), 6.77 (2H, d, $J_{5,7}$ 2.5 Hz, 5- and 5'-H), 7.05 (2H, dd, $J_{7,8}$ 9.0 Hz, $J_{5,7}$ 2.5 Hz, 7- and 7'-H). Subsequent elution with $CHCl_3$ gave 6-chloro-2,2-dimethylchroman-4-one (18%), m.p. 89–90°, identical with that obtained from the butenoate above.

Similarly obtained were *bis-4,4'-(7-chloro-2,2-dimethylchromen)*, (8; R = 7-Cl) (82%), m.p. 147.5° (Found: C, 68.4; H, 5.3; Cl, 18.5; M^+ 386.0832) and *bis-4,4'-(8-chloro-2,2-dimethylchromen)*, (8; R = 8-Cl) (88%), m.p. 174.5–175° (Found: C, 68.5; H, 5.2; Cl, 18.4; M^+ 386.0833).

8-Chloro-2,2-dimethylchroman-4-one (51). 3-Bromo-8-chloro-2,2-dimethylchroman-4-one (0.2 g) and benzoin (0.15 g) were heated at 120–130° for 2 hr, at which stage tlc indicated the absence of reactants. The early fractions from elution of the product from silica gel with benzene gave benzil, whilst later fractions yielded 8-chloro-2,2-dimethylchroman-4-one (70%), m.p. 102–103°.

5-Chloro-2,2-dimethylchroman-4-one (5i) (61%), m.p. 107–108°, was obtained in a similar manner upon elution from Florisil.

6-Chloro-2,2-dimethylchroman-4-ol (4k; R = 6-Cl; Y = H). A soln of 6-chloro-2,2-dimethylchroman-4-one (0.55 g) in ether (10 ml) was added dropwise to LAH (0.3 g) in ether (10 ml) and the mixture was boiled for 2 hr. The usual work-up afforded *6-chloro-2,2-dimethylchroman-4-ol* (86%), m.p. 118–119°, from light petroleum (b.p. 80–100°) (Found: C, 62.0; H, 6.1; Cl, 16.5. $C_{11}H_{13}ClO_2$ requires: C, 62.1; H, 6.1; Cl, 16.7%).

7-Chloro-2,2-dimethylchroman-4-ol (4l; R = 7-Cl; Y = H). The chromanone (2 g) in MeOH was reduced with $NaBH_4$ (1 g) at reflux during 2 hr to yield the chroman-4-ol (76%), m.p. 85°, from light petroleum (b.p. 60–80°) (Found: C, 62.1; H, 6.1; Cl, 17.0).

6-Chloro-4-methoxy-2,2-dimethylchroman-3-ol. (7i; R = 6-Cl; X = OMe). 6-Chloro-3,4-epoxy-2,2-dimethylchroman (0.2 g) was boiled for 36 hr with MeOH (10 ml). Crystallisation of the oil which remained after evaporation of the MeOH from light petroleum (b.p. 40–60°) gave 6-chloro-4-methoxy-2,2-dimethylchroman-3-ol (60%), m.p. 88–89° (Found: C, 59.4; H, 6.1; Cl, 14.6. $C_{12}H_{15}ClO_3$ requires: C, 59.5; H, 6.2; Cl, 14.7%).

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