Analogues of Antijuvenile Hormones

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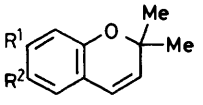
Several analogues of precocenes I and II have been synthesized, including derivatives of 6,7-dihydroxy-2,2-dimethylchromen, 7,8-dihydroxy-2,2-dimethylchromen, 7-hydroxy-2,2-dimethyl-6-nitrochromen, and 6-amino-7-hydroxy-2,2-dimethylchromen. 5,6-Dimethoxy-3,3-dimethylindene was also synthesized. Improved procedures for the dehydration of chroman-4-ols to chromens and for the reduction of chroman-4-ones to chroman-4-ols are reported. Analogues have been tested for activity in the brown planthopper *Nilaparvatus lugens* Stal. None had significant morphogenetic effects, but two possessed insecticidal activity and showed both antagonism and synergism when used in conjunction with permethrin.

SINCE the discovery of the antijuvenile hormones precocene I (1a) and precocene II (1b) in 1976 [1] numerous analogues of these chromens have been synthesized.[2-4] To date only one, 7-ethoxy-6-methoxy-2,2-dimethylchromen (1c), has been reported to have an activity comparable with that of precocene II, the more active of the original natural products.[3]

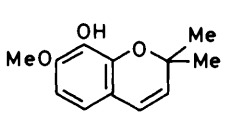


(1)

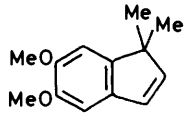
	R^1	R^2		R^1	R^2
a;	OMe	H	f;	OMe	$O[CH_2]_6Me$
b;	OMe	OMe	g;	OMe	OAc
c;	OEt	OMe	h;	OMe	$O{\cdot}CO{\cdot}[CH_2]_{10}Me$
d;	OMe	OH	i;	OMe	NO_2
e;	OMe	NH_2			

The currently accepted mode of action, which involves epoxidation of the highly activated double bond, partly rationalizes this result. Nevertheless, we were encouraged to investigate further chromen derivatives by the varied responses of different target insect species,[2] our particular interest being in the brown planthopper *Nilaparvatus lugens* Stal, a major pest of rice crops. Initially, we looked for antijuvenile activity among simple analogues of the precocenes in which the apparently less critical 6-position was modified, our objectives being twofold. First, we wished to investigate how a change in the lipophilic properties of the molecule affected activity. Second, we had in mind that hydrolyzable lipophilic residues might assist transport of the molecule to the active site within the copora allata of the insect. Such labile linkages might also be of value in the preparation of antijuvenile hormones which could be released slowly under field conditions as a means of insect control. This would require compounds (1d) or (1e), for example, to be active. The chromen (2) was also synthesized with this function in mind. The indene (3) was investigated since it too possesses an activated double bond, but has a different geometry in the non-aromatic ring.

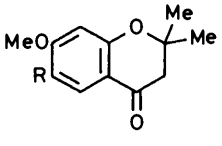
Derivatives of the chromen (1d) were synthesized by the condensation of methoxyhydroquinone with 3,3-dimethylacrylic acid in polyphosphoric acid to give the chromanone (4a). The two alternative structures, 6-hydroxy-8-methoxy-2,2-dimethylchroman-4-one and 6-hydroxy-5-methoxy-2,2-dimethylchroman-4-one, both require the aromatic protons to appear as two doublets in the ^1H n.m.r. spectrum instead of the two singlets observed. Reduction of compound (4a) with an excess of



(2)

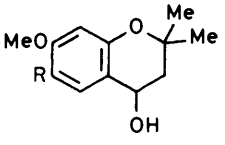


(3)



(4)

a; R = OH
b; R = H
c; R = NO_2



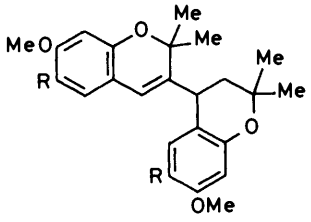
(5)

a; R = OH
b; R = OMe
c; R = H
d; R = NO_2

lithium aluminium hydride in boiling diethyl ether gave only 6-hydroxy-7-methoxy-2,2-dimethylchroman, a well documented reaction when the intermediate chromanol is activated by *para*, but not *meta*, electron-releasing groups.[5,6] Reduction to the chromanol can be achieved by using exactly one equiv. of reducing agent, but we have found it more convenient to use an excess of reagent in tetrahydrofuran as solvent, by which means the chromanol (5a) was obtained in 90% yield. This usefully avoids over-reduction, although it is not suggested that this is a general result since the outcome depends on the relative rates of the initial attack on the carbonyl group and of the subsequent reduction of the alcohol. The first is retarded, the second accelerated by electron release to the reaction centre, so that the balance is highly sensitive to the experimental conditions. Sodium borohydride is also of value in this respect, but reduction with this reagent can be slow.

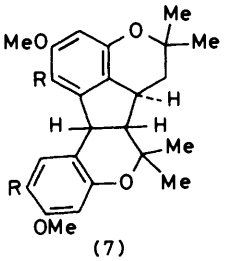
Dehydration of the chromanol to the chromen (1d) was effected in 93% yield by a trace of toluene-*p*-sul-

phonic acid in boiling benzene, despite the report [7] that the chroman-4-ol (5b) gives a quantitative yield of dimer (6a) under these conditions. Repetition of the procedure using 5% of the acid and a longer reaction time led to the formation of a mixture of two compounds. These could not be separated by chromatography, but one component was isolated in the pure state by repeated crystallization, and was assigned the dimeric structure (7a) from spectroscopic data and by analogy with the previously described compound (7b).[8] The non-isolable component was presumed to be the dimer (6b).[9] The clean and rapid



(6)

a; R = OMe
b; R = OH



(7)

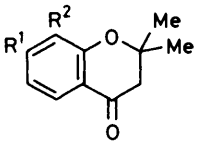
a; R = OH
b; R = OMe

(generally two minutes) dehydration of chroman-4-ols by *traces* of toluene-*p*-sulphonic acid also contrasts with the formation of unidentified polymeric products reported by Schwarz [7] on the attempted dehydration of compound (5c) with this reagent. Under the conditions described herein we have found this to be the method of choice and the use of such reagents as aqueous hydrochloric acid,[1] phosphoryl chloride in pyridine,[10] alumina at 160 °C,[11] heating in dimethyl sulphoxide,[12] and acetic acid–hydrochloric acid [13] has become obsolete.

The hydroxychromen was converted into the required alkyl and acyl derivatives [(1b), (1f), (1g), and (1h)] by reaction of the sodium salt of the phenol (1d) with the appropriate halide.

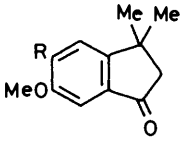
For the 6-amino- and 6-nitro-derivatives (1e) and (1i), 7-methoxy-2,2-dimethylchroman-4-one (4b) [6] was nitrated with cupric nitrate and acetic anhydride to give compound (4c). Reduction with sodium borohydride, followed by dehydration of the chromanol (5d), gave the nitrochromen (1i). Reduction of the nitro-group to form the aminochromen (1e) was effected by sulphurated sodium borohydride.[14]

The analogue (2) was prepared by a method based on the same general chromanone synthesis [15] in which pyrogallol was heated with 3,3-dimethylacrylic acid in polyphosphoric acid. When equimolar amounts of pyrogallol and acid were used a 1 : 1 mixture of compounds (8a) and (8b) was obtained in 28% yield, together with the dimethylacrylic acid dimer. Increasing the quantity of dimethylacrylic acid to four equivalents gave compound (8a) in 40% yield; only 8% of the dihydroxychroman-4-one (8b) was produced. The structure (8a) was assigned on the basis of the large bathochromic shifts of λ 21 and 24 nm in the λ 233 and 315 nm bands, respectively, caused by the addition of fused sodium acetate to the solution, and typical of chroman-4-ones that possess a free 7-hydroxy-group. An authentic sample of 7-hydroxy-2,2-dimethylchroman-4-one [16] showed similar bathochromic shifts (λ 237→257 and 314→337 nm) on the addition of sodium acetate. In contrast, the u.v. spectra of compound (4a) (which must have the free hydroxy-group *meta* to the carbonyl group) and of authentic samples of 7-acetoxy-2,2-dimethylchroman-4-one [16] and 7-methoxy-2,2-dimethylchroman-4-one [6] showed no significant changes on the addition of sodium acetate.



(8)

	R^1	R^2
a;	OH	O·CO·CH=CMe_2
b;	OH	OH
c;	OMe	O·CO·CH=CMe_2



(9)

a; R = OH
b; R = OAc
c; R = OMe

Reduction of the methylated product (8c) with lithium aluminium hydride simultaneously removed the ester group to give 8-hydroxy-7-methoxy-2,2-dimethylchroman-4-ol, which was dehydrated in the usual way to form compound (2). Although the yield of compound (8a) was only moderate and has not been optimized the ready availability of the starting material provides an easy route to derivatives that possess different functionalities on C-7 and C-8 hydroxy-groups.

Since the activated double bond of the precocenes appears to be the active site of the molecule we also investigated the indene (3), in which the heterocyclic oxygen atom is missing, as a possible insecticide. This was made by a route [17,18] similar to that used for the chromens in which *o*-methoxyphenol was heated with 3,3-dimethylacrylic acid in polyphosphoric acid. A single product was obtained in 51% yield and was assigned the structure (9a) because the aromatic protons appeared in the ^{1}H n.m.r. spectrum as two singlets and because of the bathochromic shift of λ 22–23 nm in the u.v. spectrum on the addition of fused sodium acetate. No changes were observed in the u.v. spectrum of compound (9c) on the addition of sodium acetate. The dimethoxyindene (3) was obtained after methylation, *via* the indanol.

None of the compounds tested showed significant morphogenetic activity in *N. lugens*, though insecticidal activity was noted with the aminochromen (1e) and the nitrochromen (1i) at high dose levels. Again, precocene II was the most toxic of the compounds tested. Further investigations of the insecticidal properties were carried out with mixtures of these chromens with permethrin, a pyrethroid insecticide. Both antagonism and synergism were observed at different dose levels, but the biological aspects of this work will be described more fully in a separate paper.

EXPERIMENTAL

M.p.s are uncorrected. I.r. spectra of solids (KBr) and liquids (film) were recorded on a Hilger and Watts Infrascan. U.v. spectra were determined with a Perkin-Elmer Model 137 spectrometer. N.m.r. spectra were obtained on a Varian EM 360 spectrometer (60 MHz) with tetramethylsilane as internal standard. Mass spectra were obtained on a MS9 instrument.

6-Hydroxy-7-methoxy-2,2-dimethylchroman-4-one (4a).—Methoxyhydroquinone (8.0 g) and 3,3-dimethylacrylic acid (6.3 g) were stirred in polyphosphoric acid (200 g) for 4 h at 30 °C, then gradually heated to 100 °C and left at that temperature for 1 h. When it had cooled to 50 °C the dark red syrup was poured into ice–water (500 ml), with vigorous stirring. The oily precipitate was extracted with ethyl acetate (3 × 200 ml), washed with sodium hydrogencarbonate and water, and dried ($MgSO_4$). Evaporation afforded a syrup which was purified by silica gel chromatography (C_6H_6–Et_2O as eluant) to yield the *chroman-4-one* (4a) (6.1 g, 48%), m.p. 150—151 °C (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 3 360, 1 660, and 1 615 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 6 300), 242 (10 000), 276 (16 000), and 347 nm (13 000); δ($CDCl_3$) 1.47 (6 H, s), 2.67 (2 H, s), 3.90 (3 H, s), 5.60br (1 H, s), 6.35 (1 H, s), and 7.30 (1 H, s) (addition of deuterium oxide caused the signal at δ 5.60 to disappear) (Found: C, 64.5; H, 6.2%; M^+, 222.0893. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%; *M*, 222.0892).

6-Hydroxy-7-methoxy-2,2-dimethylchroman.—The chromanone (4a) (0.222 g, 1.0 mmol) in dry diethyl ether (20 ml) was treated with lithium aluminium hydride (0.114 g, 3.0 mmol) and the solution was boiled under reflux for 30 min. The mixture was cooled and diethyl ether added, followed by water, and the solution acidified with 1M hydrochloric acid. The organic layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded pure *6-hydroxy-7-methoxy-2,2-dimethylchroman* (0.181 g, 87%), m.p. 116—117 °C (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 3 400br, 1 617, 1 600, and 1 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 209 (ε 11 000), 220 (8 000), 226sh (6 800), 287 (5 500), and 291sh nm (5 400); δ($CDCl_3$) 1.27 (6 H, s), 1.77 (2 H, dd, *J* and *J'* 7 Hz), 2.67 (2 H, dd, *J* and *J'* 7 Hz), 3.78 (3 H, s), 5.10 (1 H, s), and 6.30 and 6.55 (each 1 H and s) (addition of deuterium oxide caused the signal at δ 5.10 to disappear) (Found: C, 69.25; H, 7.5%; M^+, 208.1089. $C_{12}H_{16}O_3$ requires C, 69.25; H, 7.75%; *M*, 208.1099).

(±)-6-Hydroxy-7-methoxy-2,2-dimethylchroman-4-ol (5a).—The chromanone (4a) (3.00 g, 13.5 mmol) was dissolved in dry tetrahydrofuran (THF) (50 ml) and lithium aluminium hydride (0.760 g, 20.0 mmol) added. The solution was stirred for 3 h and then diluted with ethyl acetate (100 ml). The organic layer was shaken with 1M hydrochloric acid, followed by water, and dried ($MgSO_4$). Evaporation afforded the pure *hydroxychromanol* (5a) (2.70 g, 90%), m.p. 142.5—143.5 °C (from $CDCl_3$); $\nu_{max.}$ (KBr) 3 120, 3 420, and 3 480 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 16 000), 225 (7 200), and 298 nm (4 600); δ($CHCl_3$) 1.30 (3 H, s), 1.43 (3 H, s), 1.67—2.37 (3 H, m, OH and CH_2), 3.83 (3 H, s), 4.73 (1 H, dd, *J* 6.5 and *J'* 8 Hz), 5.27 (1 H, s), 6.33 (1 H, s) and 6.93 (1 H, s) [addition of deuterium oxide caused the signal at δ 5.27 to disappear and those at δ 1.67—2.37 to simplify to an ABX system (J_{AX} 8 Hz J'_{AB} 13 Hz) (J_{BX} 6.5 Hz, J'_{BA} 13 Hz)] (Found: M^+, 224.1044. $C_{12}H_{16}O_4$ requires *M*, 224.1049).

6-Hydroxy-7-methoxy-2,2-dimethylchromen (1d).—A solution of the hydroxychromanol (5a) (2.00 g, 8.9 mmol) in dry benzene (100 ml) was boiled under reflux with a *trace* of toluene-*p*-sulphonic acid and the water that formed was removed azeotropically for 2 min. The benzene solution was washed with sodium hydrogencarbonate, followed by water. Evaporation of the dried ($MgSO_4$) solvent gave a syrup (1.93 g) which was purified by silica gel chromatography (C_6H_6 as eluant) to give the chromen (1d) as *plates* (1.71 g, 93%), m.p. 88.5—89.5 °C (from CCl_4); $\nu_{max.}$ (KBr) 3 400, 1 617, 1 575, and 1 500 cm^{-1}; $\lambda_{max.}$ 223sh (ε 19 000), 232 (20 000), 277 (2 900), and 327 nm (6 400); δ($CDCl_3$) 1.4 (6 H, s), 3.77 (3 H, s), 5.22 (1 H, s), 5.42 and 6.17 (2 H, ABq, *J* 10 Hz), 6.35 (1 H, s), and 6.53 (1 H, s) (addition of deuterium oxide caused the signal at δ 5.22 to disappear) (Found: C, 70.25; H, 6.9%; M^+, 206.0965. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84%; M^+, 206.0943).

5,6,6a,6b,7,12b-Hexahydro-1,11-dihydroxy-2,10-dimethoxy-5,5,7,7-tetramethylcyclopenta[1,2-c: 5,4,3-d'e']*bischromen* (7a).—The chromanol (5a) (0.500 g), in dry benzene (40 ml), was refluxed with toluene-*p*-sulphonic acid (0.025 g, 0.13 mmol) under azeotropic conditions for 1 h. When cold, the solution was washed with sodium hydrogencarbonate, followed by water, and then dried. Evaporation of the solvent afforded two major components, by n.m.r. spectroscopy. Two recrystallizations from ethyl acetate and one from ethanol afforded the *dimer* (7a) (0.281 g, 31%), m.p. 234—236 °C; $\nu_{max.}$ (KBr) 3 540, 3 570, 1 637, 1 620, 1 510, and 1 490 cm^{-1}; δ($CDCl_3$) 1.27, 1.35, 1.42, and 1.47 (each 3 H and s, 2 × *gem*-Me_2), 1.40—2.43 (3 H, m, non-benzylic H), 2.83—3.40 (1 H, m, PhC*H*CH_2), 3.82 (6 H, s, 2 × OMe), 4.43 (1 H, d, *J* 7 Hz, PhC*H*Ph), 5.15 and 5.45 (each 1 H and s, 2 × OH), and 6.17, 6.32, and 7.32 (each 1 H and s, Ar-H) (addition of deuterium oxide caused the signals at δ 5.15 and 5.45 to disappear) (Found: C, 69.7; H, 6.95%; M^+, 412.1876. $C_{24}H_{28}O_6$ requires C, 69.88; H, 6.84%; *M*, 412.1886).

Reaction of the Hydroxychromen (1d) *with Dimsyl Sodium and Various Halides.*—A solution of the hydroxychromen (1d) (0.200 g, 0.97 mmol) in dry THF (10 ml) was added to a solution of dimsyl sodium (1.00 mmol) in THF, and the mixture was stirred at 30 °C for 3 min. The appropriate halide (1.10 mmol) [see (*a*)—(*d*) below] was then added and the mixture was stirred for a further 10 min. The cold mixture was diluted with ethyl acetate and washed well with water. Silica gel chromatography (benzene as eluant) afforded the corresponding chromen.

(*a*) Addition of methyl iodide to the sodium salt of chromen (1d) afforded the known 6,7-dimethoxy-2,2-dimethylchromen (1b) [1] (0.199 g, 93%) as a light yellow oil; δ($CDCl_3$) 1.37 (6 H, s), 3.77 (6 H, s), 5.38 and 6.18 (each 1 H, ABq, *J* 10 Hz), 6.34 (1 H, s), and 6.43 (1 H, s) (Found: M^+, 220.1077. $C_{13}H_{16}O_3$ requires *M*, 220.1099).

(*b*) Addition of 1-bromoheptane to the sodium salt of chromen (1d) afforded 6-heptyloxy-7-methoxy-2,2-dimethylchromen (1f) (0.263 g, 89%) as a clear *oil;* $\nu_{max.}$ (film) 1 630, 1 612, 1 572, and 1 501 cm^{-1}; $\lambda_{max.}$ (EtOH) 224 (ε 21 800), 230sh (21 000), 278 (3 400), and 324 nm (5 700); δ($CDCl_3$) 0.68—2.37 (13 H, m), 1.37 (6 H, s), 3.78 (3 H, s), 3.90 (2 H, t, *J* 7 Hz), 5.40 and 6.32 (each 1 H, ABq, *J* 10 Hz), 6.33 (1 H, s), and 6.48 (1 H, s) (Found: M^+, 304.2068. $C_{19}H_{28}O_3$ requires *M* 304.2038).

(*c*) Addition of acetyl chloride to the sodium salt of chromen (1d) afforded *6-acetoxy-7-methoxy-2,2-dimethylchromen* (1 g) (0.221 g, 92%); $\nu_{max.}$ (film) 1 780 cm^{-1}; δ($CDCl_3$) 1.42 (6 H, s), 2.28 (3 H, s), 3.77 (3 H, s), 5.47 and 6.20 (each 1 H,

ABq, *J* 10 Hz), 6.43 (1 H, s), and 6.65 (1 H, s) (Found: M^+, 248.1055. $C_{14}H_{16}O_4$ requires *M* 248.1049).

(*d*) Addition of undecanoyl chloride to the sodium salt of chromen (1d) afforded 7-methoxy-2,2-dimethyl-6-undecanoyloxychromen (1h) (0.331 g, 88%) as a light yellow *oil;* $\nu_{max.}$ (film) 1 760, 1 623, 1 580, and 1 516 cm^{-1}; $\delta(CDCl_3)$ 0.50—2.20 (21 H, m), 1.38 (6 H, s), 2.55 (2 H, t, *J* 7 Hz), 3.73 (3 H, s), 5.42 and 6.17 (each 1 H, ABq, *J* 10 Hz), 6.38 (1 H, s), and 6.60 (1 H, s)(Found: M^+, 388.2622. $C_{24}H_{36}O_4$ requires *M*, 338.2613).

7-*Methoxy*-2,2-*dimethyl*-6-*nitrochroman*-4-*one* (4c).—A solution of the chromanone (4b) (4.0 g, 19.4 mmol) in acetic anhydride (13 ml) was added to a solution of cupric nitrate (6.0 g, 24.8 mmol) in acetic anhydride (10 ml). The mixture was heated at 60—65 °C for 1.5 h and then stirred at room temperature for 1 h. The solution was poured into ice–water (200 ml) and the yellow solid filtered off and washed with water (2 × 50 ml). Recrystallization (CH_2Cl_2) gave the nitrochromanone (4c) (4.0 g, 81%) as pale yellow *plates*, m.p. 143—145 °C, $\nu_{max.}$ (KBr) 1 687, 1 600, 1 556, and 1 505 cm^{-1}; $\lambda_{max.}$ (EtOH) 215sh (ε 12 300), 221 (13 700), 258 (23 100), and 318 nm (5 100); $\delta(CDCl_3)$ 1.47 (6 H, s), 2.77 (2 H, s), 3.97 (3 H, s), 6.50 (1 H, s), and 8.47 (1 H, s) (Found: C, 57.55; H, 5.25; N, 5.6%; M^+, 251. $C_{12}H_{13}NO_5$ requires C, 57.37; H, 5.22; N, 5.58%; *M*, 251).

(±)-7-*Methoxy*-2,2-*dimethyl*-6-*nitrochroman*-4-*ol* (5d).—The chromanone (4c) (4.00 g, 16 mmol) was dissolved in dry, freshly distilled THF (75 ml) and sodium borohydride (0.380 g, 10 mmol) was added. The mixture was stirred for 24 h at room temperature and then diluted with ethyl acetate (50 ml) and washed with 1M hydrochloric acid and water. Evaporation of the dried ($MgSO_4$) solvents gave a syrup (3.9 g) which was purified by silica gel chromatography (C_6H_6–Et_2O as eluant). The column yielded the light yellow, crystalline *nitrochromanol* (5d) (3.6 g, 89%), m.p. 118—120 °C (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 3 400, 3 480, 1 625, 1 565, and 1 505 cm^{-1}; $\lambda_{max.}$ (EtOH) 209 (ε 14 000), 220 (12 000), 247 (6 400), 295 (4 600), and 334 nm (5 600); $\delta(CDCl_3)$ 1.33 (3 H, s), 1.47 (3 H, s), 1.57—2.43 (2 H, m), 2.80br (1 H, s), 3.85 (3 H, s), 4.80 (1 H, t), 6.37 (1 H, s), and 8.13 (1 H, s) (addition of deuterium oxide caused the signal at δ 2.8 to disappear and the signal at δ 1.57—2.43 to simplify) (Found: C, 56.7; H, 5.95; N, 5.45%; M^+, 253. $C_{12}H_{15}NO_5$ requires C, 56.91; H, 5.97; N, 5.53%; *M*, 253).

7-*Methoxy*-2,2-*dimethyl*-6-*nitrochromen* (1i).—The chromanol (5c) (2.5 g, 9.9 mmol) was boiled in dry benzene (50 ml) with a trace of toluene-*p*-sulphonic acid under azeotropic conditions. After 30 min, the usual work-up afforded a syrup which was purified by silica gel chromatography (benzene as eluant) to give the crystalline *nitrochromen* (1i) (2.2 g, 93%), m.p. 90—93 °C (from benzene–chloroform); $\nu_{max.}$ (KBr) 1 625, 1 560br, and 1 510br cm^{-1}; $\lambda_{max.}$ (EtOH) 215sh (ε 14 000), 227 (21 000), 233 (19 000), 269 (17 000), 297 (6 000), and 368 nm (6 000); $\delta(CDCl_3)$ 1.47 (6 H, s), 3.93 (3 H, s), 5.63 and 6.32 (2 H, ABq, *J* 9.5 Hz), 6.47 (1 H, s), and 7.73 (1 H, s) [Found: C, 61.45; H, 5.6; N, 5.7%; M^+, 235, (*M* — Me) 220. $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.95%; *M*, 235].

6-*Amino*-7-*methoxy*-2,2-*dimethylchromen* (1e).—Solid sodium borohydride (80.1 mg, 2.13 mmol) and sulphur (0.204 g) were diluted with anhydrous THF (5 ml) under a nitrogen atmosphere. The boiling mixture was allowed to cool (*ca.* 1 h) and a solution of the nitrochromen (1i) (0.500 g, 2.13 mmol) in THF (5 ml) was added. The solution was stirred at 70°C for 1 h and then aqueous sodium hydroxide (5%, 10 ml) was added, followed by diethyl ether (50 ml) The organic phase was washed with water and dried ($MgSO_4$) and, on evaporation, gave a syrup which was fractionated on silica gel (C_6H_6–Et_2O as eluant) to afford the unchanged nitrochromen (1i) (12%) (t.l.c. and n.m.r. spectroscopy) and the aminochromen (1e) (0.31 g, 71%) as a light yellow *syrup*; $\nu_{max.}$ (film) 3 370, 3 450, 1 625, 1 600, 1 583 and 1 505 cm^{-1}; $\lambda_{max.}$ (EtOH) 215 sh (ε 15 000), 235 (21 000), 270sh (3 900), and 327 nm (4 500); $\delta(CDCl_3)$ 1.37 (6 H, s), 3.25br (2 H, s), 3.77 (3 H, s), 5.43 and 6.22 (2 H,ABq, *J* 9 Hz), and 6.37br (2 H, s) (addition of deuterium oxide caused the signal at δ 3.25 to disappear) (Found: M^+, 205.1137. $C_{12}H_{15}NO_2$ requires *M*, 205.1103).

Reaction of Pyrogallol with 3,3-*Dimethylacrylic Acid in Polyphosphoric Acid.*—(a) *With one equiv. of* 3,3-*dimethylacrylic acid.* Finely powdered pyrogallol (0.500 g, 4.5 mmol) and 3,3-dimethylacrylic acid (0.455 g, 4.5 mmol) were stirred in polyphosphoric acid (40 g) at 40 °C for 5 h, then gradually heated to 80 °C over 4 h. Work-up afforded a yellow syrup which was fractionated on silica gel (benzene–diethyl ether as eluant) to give three components. The first material eluted was an acrylic acid dimer (n.m.r. and mass spectroscopy) while the second material eluted was considered to be 8-(3,3-*dimethylacryloyloxy*)-7-*hydroxy*-2,2-*dimethylchroman*-4-*one* (8a) (0.185 g, 14%), m.p. 176—178 °C (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 3 190, 1 736, 1 660, 1 602, 1 578, and 1 509 cm^{-1}; $\lambda_{max.}$ (EtOH) 218 (ε 25 000), 233 (19 000), 280 (12 000), and 315sh nm (5 700); $\lambda_{max.}$ (EtOH–NaOAc) 218 (ε 25 500), 254 (8 800), 276sh (3 900), and 339 nm (20 000); $\delta(CDCl_3)$ 1.40 (6 H, s), 2.02br and 2.23br (each 3 H, s), 2.70 (2 H, s), 4.67 (3 H, s), 5.97br (1 H, s), 6.57 (1 H, d, *J* 9 Hz), 6.83br (1 H, s), and 7.63 (1 H, d, 9 Hz) (addition of D_2O caused the signal at δ 6.83 to disappear) (Found: C, 65.8; H, 6.2%; M^+, 290.1147. $C_{16}H_{18}O_5$ requires C, 66.19; H, 6.25%; *M*, 290.1154).

The third constituent was 7,8-*dihydroxy*-2,2-*dimethylchroman*-4-*one* (8b) (0.132 g, 14%), m.p. 138—141 °C ($CHCl_3$–light petroleum) (lit.,[19] m.p. 141–143 °C); $\nu_{max.}$ (KBr) 3 160—3 580br and 1 666 cm^{-1}; $\delta(CDCl_3)$ 1.47 (6 H, s), 2.70 (2 H, s), 5.83br (2 H, s), 6.60 and 7.43 (each 1 H, d, *J* 9 Hz) (addition of D_2O caused the signal at δ 5.83 to disappear) (Found: M^+, 208.0752. $C_{11}H_{12}O_4$ requires *M*, 208.0735).

(b) *With four equiv. of* 3,3-*dimethylacrylic acid.* Finely powdered pyrogallol (2.25 g, 20 mmol) and 3,3-dimethylacrylic acid (8.20 g, 80 mmol) were stirred in polyphosphoric acid (100 g) at 40 °C for 2 h, then gradually heated to 80 °C for 2 h. Work-up afforded a yellow syrup which, on chromatography, gave the chroman-4-ones (8a) (2.31 g, 40%) and (8b) (0.25 g, 8%).

8-(3,3-*Dimethylacryloyloxy*)-7-*methoxy*-2,2-*dimethylchroman*-4-*one* (8c).—The chromanone (8a) (1.00 g, 3.5 mmol), methyl iodide (1.13 g, 8.0 mmol), and anhydrous potassium carbonate (1.10 g, 8.0 mmol) were boiled under reflux for 8 h in acetone (25 ml). When the mixture was cold a white precipitate formed which was filtered off and washed with ethyl acetate (2 × 20 ml). Evaporation of the filtrate afforded a yellow gum which was crystallized from chloroform–light petroleum to afford the *chroman*-4-*one* (8c) (0.915 g, 86%), m.p. 114—115 °C (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 1 720 and 1 670 cm^{-1}; $\lambda_{max.}$ (EtOH) 218 (ε 27 000), 234 (22 000), 278 (15 000), and 310sh nm (4 900); $\delta(CDCl_3)$ 1.45 (6 H, s), 2.02 and 2.25 (each 3 H, d, *J* 1 Hz), 2.70 (2 H, s), 3.88 (3 H, s), 6.02 (1 H, m), 6.63 (1 H, d, *J* 9 Hz), and 7.77

(1 H, d, *J* 9 Hz) (Found: C, 66.7; H, 6.9%; M^+, 304.1324. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62%; *M*, 304.1311).

(±)-8-*Hydroxy*-7-*methoxy*-2,2-*dimethylchroman*-4-*ol*.—The chromanone (8c) (0.800 g, 2.6 mmol), in dry THF (40 ml), was stirred with lithium aluminium hydride (0.380 g, 10.0 mmol). After 24 h the solution was diluted with diethyl ether (20 ml) and ethyl acetate (40 ml), and washed with dilute hydrochloric acid followed by water. Evaporation of the dried ($MgSO_4$) solvents gave the crystalline (±)-8-*hydroxy*-7-*methoxy*-2,2-*dimethylchroman*-4-*ol* (0.483 g, 82%) as the only product, m.p. 148.5—149.5 °C (from $CHCl_3$); $\nu_{max.}$ (KBr) 3 500sh, 3 190, 1 616, and 1 512 cm^{-1}; $\lambda_{max.}$ (EtOH) 215 (ε 21 000), 230sh (6 500), and 275 nm (700); δ($CDCl_3$) 1.33 and 1.48 (each 3 H and s), 1.60—2.40 (3 H, m, *OH* + *CH*$_2$), 3.87 (3 H, s), 4.82 (1 H, dd, *J* 6.5, *J'* 8 Hz), 5.48br (1 H, s), 6.50 (1 H, d, *J* 9 Hz), and 6.93 (1 H, d, *J* 9 Hz) [addition of deuterium oxide caused the signal at δ 5.48 to disappear and those at δ 1.6—2.4 to simplify to an ABX system (J_{AX} 8, J'_{AB} 13 Hz) (J_{BX} 6.5, J'_{BA} 13 Hz)] (Found: C, 64.45; H, 7.3%; M^+, 244.1055. $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19%; *M*, 224.1049).

8-*Hydroxy*-7-*methoxy*-2,2-*dimethylchromen* (2).—The above chromanol (0.400 g, 1.8 mmol) was boiled under reflux in benzene (50 ml) with a catalytic quantity of toluene-*p*-sulphonic acid for 2 min. When cold, the organic layer was washed with sodium hydrogencarbonate solution, followed by water, and then dried ($MgSO_4$). Evaporation of the solvent afforded pure *chromen* (2) (0.349 g, 94%), m.p. 72.5—73.5 °C (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 3 575, 3 460, 1 625, 1 515, and 1 500 cm^{-1}; δ($CDCl_3$) 1.45 (6 H, s), 3.85 (3 H, s), 5.37 (1 H, s), 5.47 and 6.25 (each 1 H, ABq, *J* 10 Hz), and 6.42 (2 H, d, *J* 1 Hz) (addition of D_2O caused the signal at δ 5.37 to disappear) (Found: C, 70.0; H, 6.74%; M^+, 206.0961. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84%; *M*, 206.0943).

5-*Hydroxy*-6-*methoxy*-3,3-*dimethylindan*-1-*one* (9a).—*o*-Methoxyphenol (5.0 g, 40 mmol) and 3,3-dimethylacrylic acid (5.0 g, 50 mmol) were stirred in polyphosphoric acid (120 g) for 1 h at 40 °C, then gradually heated to 110 °C for 2 h. Work-up and purification afforded a white crystalline solid (4.2 g, 51%), considered to be the indan-1-one (9a), m.p. 128—129 °C (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 3 340br, 1 680, 1 615, 1 588, and 1 503 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 15 000), 233 (16 000), 273 (11 000), 315 (11 000), and 347sh nm (1 000); $\lambda_{max.}$ (EtOH–NaOAc) 215 (ε 16 000), 235sh (2 800), 255 (8 300), 277sh (5 500), and 338 nm (19 700); δ($CDCl_3$) 1.32 (6 H, s), 2.58 (2 H, s), 3.92 (3 H, s), 6.70br (1 H, s), and 6.93 and 7.13 (each 1 H, and s) (addition of D_2O caused the signal at δ 6.70 to disappear) (Found: C, 69.85; H, 6.85%; M^+, 206.0963. $C_{12}H_{14}O_3$ requires C, 69.92; H, 6.85%; *M*, 206.0943).

The *acetate* (9b) gave the following n.m.r. and i.r. data; δ($CDCl_3$) 1.36 (6 H, s), 2.28 (3 H, s), 2.56 (2 H, s), 3.83 (3 H, s), and 7.11 and 7.19 (each 1 H, s); $\nu_{max.}$ (KBr) 1 765, 1 704, 1 615, 1 586, and 1 490 cm^{-1}.

5,6-*Dimethoxy*-3,3-*dimethylindan*-1-*one* (9c).—The hydroxyindanone (9a) (2.0 g, 9.7 mmol) was boiled under reflux in acetone (40 ml) in the presence of anhydrous potassium carbonate (4.2 g, 30 mmol) and methyl iodide (5.0 g, 35 mmol). Work-up after 5 h afforded the title compound (9c) (1.8 g, 85%), m.p. 72—73 °C (lit.,[17] m.p. 70–71 °C) (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 1 680, 1 605, 1 590, and 1 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 211 (ε 14 000), 231 (18 000), 269 (11 000), and 313 nm (9 800); δ($CDCl_3$) 1.37 (6 H, s), 2.53 (2 H, s), 3.87 and 3.97 (each 3 H, each s), and 6.83 and 7.10 (each 1 H, each s) (Found: C, 70.95; H, 7.3%; M^+, 220.1101. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%; *M*, 220.1099).

(±)-5,6-*Dimethoxy*-3,3-*dimethylindan*-1-*ol*.—To the indanone (9c) (1.50 g, 6.8 mmol) in dry THF (50 ml) was added solid lithium aluminium hydride (0.760 g, 20 mol) and the solution was stirred at room temperature for 12 h. Work-up and silica gel chromatography (benzene–diethyl ether as eluant) afforded (±)-5,6-dimethoxy-3,3-dimethylindan-1-ol (1.30 g, 86%) as a chromatographically homogeneous *gum*, $\nu_{max.}$ (film) 3 340—3 500, 1 610, and 1 503 cm^{-1}; $\lambda_{max.}$ (EtOH) 209 (ε 14 000), 231 (6 660), 284 (4 000), 289 (4 000), and 293sh nm (3 000); δ($CDCl_3$) 1.18 and 1.33 (each 3 H, each s), 1.57—2.60 (3 H, m, CH_2 and OH), 3.85 (6 H, s), 5.17 (1 H, dd, *J* 6, *J'* 7 Hz), and 6.65 and 6.88 (each 1 H, each s) [addition of deuterium oxide caused the signal at δ 1.57—2.60 to simplify to an ABX system (J_{AX} 6, J'_{AB} 13 Hz) (J_{BX} 7, J'_{BA} 13 Hz) and those at δ 5.17 to sharpen] (Found: M^+, 222.1261. $C_{13}H_{18}O_3$ requires *M*, 222.1256).

5,6-*Dimethoxy*-3,3-*dimethylindene* (3).—The above indanol (1.0 g, 4.5 mmol) in dry benzene (50 ml) was boiled under azeotropic conditions with a trace of toluene-*p*-sulphonic acid for 1 min. The benzene was washed with aqueous sodium hydrogencarbonate followed by water, and then dried ($MgSO_4$). Evaporation of the solvent afforded a gum which, on silica gel chromatography (benzene as eluant), afforded the crystalline *indene* (3) (0.864 g, 94%), m.p. 72—74 °C (from $CHCl_3$–light petroleum); $\nu_{max.}$ (KBr) 1 605, 1 595, 1 533, and 1 490 cm^{-1}; $\lambda_{max.}$ (EtOH) 224 (ε 22 000), 276 (6 200), 294sh (4 900), 300 (5 300), 305sh (4 600), and 311sh nm (4 100); δ($CDCl_3$) 1.27 (6 H, s), 3.92 (6 H, s), 6.27 and 6.57 (each 1 H, ABq, *J* 6 Hz), and 6.88 (2 H, s, Ar-H) (Found: C, 76.3; H, 7.85%; M^+, 204. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%; *M*, 204).

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