Studies of Chromens. Part 2. Synthesis of 7-Methoxy-2,2-dimethylchromen-3-carboxylic acid

Panayiotis Anastasis and Philip E. Brown *
Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

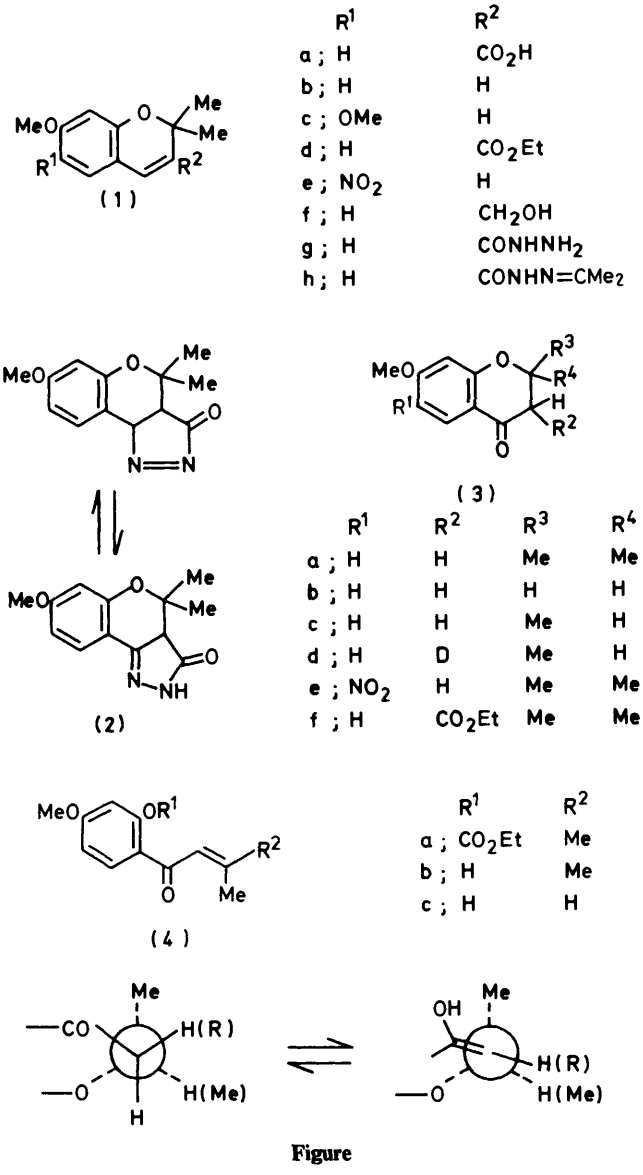
The preparation of the title compound (1a) is described. Effects of C-2 methyl groups on ring opening and alkylation of chroman-4-ones under basic conditions are discussed. The reaction of hydrazine with 3-ethoxycarbonyl-7-methoxy-2,2-dimethylchromen (1d) and 3-ethoxycarbonyl-7-methoxy-2,2-dimethylchroman-4-one (3f) failed to give the pyrazolidinone or pyrazolinone.

As part of a programme aimed at the development of anti-juvenile hormone derivatives which could be released slowly under field conditions [1] we wished to investigate the biological properties of 7-methoxy-2,2-dimethylchromen-3-carboxylic acid (1a). We expected the olefinic bond to be less reactive than those of precocene I (1b) and precocene II (1c) and therefore less susceptible to environmental degradation. For the same reason we did not anticipate (1a) itself being as biologically active as (1b) or (1c) but it was hoped that its stability and solubility (as its sodium salt) in water would make it a more practical biological control agent. We also wished to investigate the pyrazolinones (2) which could possibly liberate (1b) under mild conditions.[2]

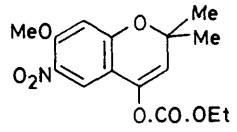
Despite the difficulties frequently encountered in substituting chroman-4-ones at the 3-position,[3] we initially attempted to ethoxycarbonylate the ketone (3a). Kasturi *et al.*[4] had already reported that diethyl carbonate failed to give the β-keto-ester of benzo[*h*]chroman-4-one under basic conditions so we attempted to quench the anion, generated *via* dimsyl sodium, with the more reactive ethyl chloroformate. When this was added the yellow anionic colour was immediately discharged but a high yield of compound (4a), in which the pyran ring had opened, was isolated. Likewise, the use of methylmagnesium carbonate in dimethylformamide [5] afforded only the ring-opened phenol (4b). Since the C-2 unsubstituted chromanone (3b) does not ring open under basic conditions [6] the monomethyl derivative (3c) [7] was investigated. Treatment of this compound with dimsyl sodium, under the same conditions as (3a), did not lead to any ring-opened product (4c). Quenching the anion with deuterium oxide incorporated over 90% deuterium at C-3 (3d), confirming that the anion had indeed been generated.

These results, and the often anomalous behaviour of chroman-4-ones, reflect the differing effects of C-2 substituents on the chromanone carbanion and the phenolate anion. The carbanion is less stabilized than is usual by the adjacent carbonyl group because the latter is conjugated with the heterocyclic oxygen and, more importantly in this case, with the 7-methoxy-group. Moreover, enolisation introduces steric hindrance which becomes particularly significant when C-2 carries two methyl groups (see Figure). Substituents at the 2-position thus tend to stabilize the phenolate anion (*via* the olefinic bond) and further to destabilise the enolate anion. In the extreme case of the related flavanones, the stabilization afforded by a 2-phenyl group makes ring-opened chalcone formation facile. Two methyl groups are apparently required on C-2 to render the phenolate the more stable form, whereas the unsubstituted (3b) and monomethyl (3c) derivatives favour the carbanion and also offer less steric hindrance to 3-substitution.

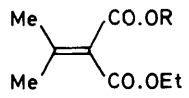
We had already shown that the nitrochromen (1e) possessed insecticidal activity in the brown plant hopper *Nilaparvata lugens* Stal [1] so we attempted ethoxycarbonylation of the nitrochromanone (3e), arguing that although the phenolate anion would be even more stable, the reduced electron release to the carbonyl group would enable the latter to stabilize the carbanion more efficiently. This was found to be so since no ring opening was observed; instead ethoxycarbonylation of the enolate ion occurred giving (5), again suggesting steric hindrance to 3-substitution.



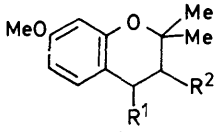
Figure



(5)



(6) a ; R = H
b ; R = Et



(7)

	R^1	R^2
a ;	OH	CO_2Et
b ;	OH	CH_2OH
c ;	H	CO_2Et

Since direct carboxylation of (3a) had not been achieved a new approach to the preparation of (1a) was made in which the ethoxycarbonyl group was incorporated prior to the formation of the chromanone. Attempts to prepare the required monoethyl isopropylidenemalonate (6a) from the readily available isopropylidene isopropylidenemalonate [8] gave only low yields. It proved more convenient to prepare diethyl isopropylidenemalonate (6b) [9] which was then partially hydrolysed to (6a) with 1 equiv. of potassium hydroxide.

The condensation of (6a) with *m*-methoxyphenol in polyphosphoric acid proceeded in moderate yield under conditions mild enough to prevent hydrolysis and decarboxylation. ^{1}H N.m.r. spectroscopy showed the resultant ester (3f) to exist exclusively in the keto-form in agreement with the earlier discussion (see Figure).

When the β-keto-ester (3f) was treated with sodium borohydride, with the intention of dehydrating the chromanol to the chromen (1d), two compounds were obtained. The first was the required chromanol (7a) whilst the second was assigned as the hydroxymethylchromen (1f) by spectroscopy; i.r. spectroscopy showed the absence of any carbonyl groups whilst the ^{1}H n.m.r. spectrum indicated a hydroxymethyl group showing allylic coupling to a single vinylic proton (δ 4.23, 2 H, d, *J* 0.5 Hz).

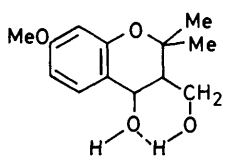
Attempts to isolate the expected intermediate (7b) by chromatography were unsuccessful but the crystalline diol was eventually obtained from the crude reaction mixture by crystallization. Although (7b) was found to be stable in the crystalline form, it readily underwent dehydration in warm organic solvents to afford (1f). The relative ease with which dehydration of (7b) occurs may be due to the C-3 hydroxymethyl group aiding removal of the activated benzylic hydroxyl *via* an intermediate such as (8). The chromanol ester (7a) does not dehydrate under similar conditions.

Reaction of (3f) with less than 1 equiv. of reducing agent afforded both (7a) and (7b) together with starting material. The keto-ester was not reduced either with the less reactive sodium cyanoborohydride, even after 72 h at pH 3.5 at which pH it is most effective, or with the bulky lithium tri-t-butoxyaluminium hydride.

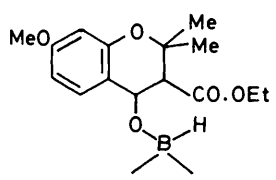
The reduction of the ester group by sodium borohydride is considered to be a result of intramolecular delivery from initially formed species such as (9). The presence of neighbouring groups is usually a feature of those esters which have been observed to undergo reduction with sodium borohydride.[10]

The stereochemistry of (7a) and (7b) was assigned as *cis* on the basis of the ^{1}H n.m.r. coupling constants of 5 Hz (7a) and 4.5 Hz (7b) for 3-H and 4-H.[11] Initial attack at the C-4 carbonyl group by sodium borohydride might be expected to occur from the side opposite to the ester group leading to the *cis*-chromanol.

The required chromen (1d) was eventually obtained in high



(8)



(9)

yield by hydrogenation of the β-keto-ester (3f) to the chroman (7c) followed by dehydrogenation with dichlorodicyanobenzoquinone (DDQ) which was immediate in boiling benzene.[12] Hydrolysis of the ester afforded the required acid (1a).

In an attempt to prepare the pyrazolinone (2) *via* the related pyrazolidinone, the chromen ester (1d) was treated with hydrazine hydrate. The product proved difficult to purify but its ^{1}H n.m.r. spectrum showed the absence of the ethoxycarbonyl group whilst a signal at δ 6.67 indicated that the vinylic 4-H was still present. The crude product was thus assumed to be the carbohydrazide (1g) and this was confirmed by condensation with acetone to afford (1h). The presence of the 7-methoxy-group in conjugation with the α,β-unsaturated ester does not favour 1,4 addition of hydrazine and initial attack takes place at the ester carbonyl making an unfavourable 5-*endo-trig* ring closure necessary.

In principle, reaction of the β-keto-ester (3f) with hydrazine hydrate could provide an alternative route directly to (2). Attempts to cyclise the initially formed hydrazone, which models show to be a reasonably favourable process, by prolonged heating in ethanol or dioxan gave only starting material whilst boiling in glacial acetic acid resulted in the formation of the *N'*-acetyl derivative. This aspect was not further investigated.

The acid (1a) is being tested for biological activity on *N. lugens* and other insects; the results will be reported elsewhere.

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 Hz) with $SiMe_4$ as internal standard. Mass spectra were obtained on a MS9 instrument. Homogeneity of non-crystalline materials was established by thin-layer chromatography in at least three solvent systems of differing polarities.

1-(2-Ethoxycarbonyloxy-4-methoxyphenyl)-3-methylbut-2-en-1-one (4a).—A solution of the chromanone (3a) (0.100 g, 0.49 mmol) in dry tetrahydrofuran (5 ml) was added at −10 °C to a solution of dimsyl sodium (1.10 mol equiv.) diluted with dry tetrahydrofuran (10 ml). After 1 min ethyl chloroformate (0.706 g, 0.65 mmol) was added to the yellow mixture and stirring continued for a further 2 min. Work-up and fractionation of the yellow oil on silica gel (benzene as eluant) afforded (4a) (0.123 g, 91%) as a homogeneous (t.l.c.) *oil*; $\nu_{max.}$ (film) 1 765, 1 660, 1 615, 1 570, and 1 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 208 (ε 9 600), 230 (12 000), and 284 nm (15 000); δ($CDCl_3$) 1.37 (3 H, t), 1.97 and 2.13 (each 3 H and d, *J* 0.5 Hz), 3.82 (3 H, s), 4.30 (2 H, q), 6.47 (1 H, m), 6.57—6.93 (2 H, m), and 7.70 (1 H, d, *J* 8 Hz) (Found: M^+, 278.1125. $C_{15}H_{18}O_5$ requires *M*, 278.1154).

1-(2-Hydroxy-4-methoxyphenyl)-3-methylbut-2-en-1-one (4b).—The chromanone (3a) (0.100 g, 0.49 mmol) was added to a solution of methylmagnesium carbonate in dimethylformamide[5] (10 ml) and the mixture maintained at 70 °C for 2 h. The cooled solution was then poured into a mixture of

concentrated hydrochloric acid (5 ml) and ice (10 g) layered over with ether (20 ml). The ether layer was separated, the aqueous solution extracted with ether (3 × 20 ml) and the extracts dried over $MgSO_4$. Removal of the ether left an oil which consisted of the known buten-1-one (4b) [13] (0.074 g, 74%) as the only product; $\nu_{max.}$ (film) 3 500—2 300, 1 635—1 615, 1 580, and 1 504 cm^{-1}; $\delta(CDCl_3)$ 1.97 and 2.13 (each 3 H, s), 3.75 (3 H, s), 6.08—6.38 (2 H, m), 6.58br (1 H, s), 7.53 (1 H, d, *J* 10 Hz), and 13.10 (1 H, s) (addition of D_2O caused the signal at δ 13.1 to disappear) (Found: M^+, 206.0960. $C_{12}H_{14}O_3$ requires *M*, 206.0943).

Attempted Reactions of 7-Methoxy-2-methylchroman-4-one (3c) *with Dimsyl Sodium.*—(*a*) A solution of the chromanone (3c) (0.100 g, 0.52 mmol) in dry tetrahydrofuran (5 ml) was added at −10 °C to a solution of dimsyl sodium (1.1 mol equiv.) diluted with dry tetrahydrofuran (10 ml). After 1 min aqueous ether was added and the organic phase was washed well with water and dried. Evaporation of the solvent gave the crystalline starting material (3c) (0.092 g, 92%), m.p. 77—78° ($CHCl_3$-hexane); [7] $\delta(CDCl_3)$ 1.46 (3 H, d, *J* 6 Hz), 2.58 (2 H, d, *J* 7 Hz), 3.80 (3 H, s), 4.56 (1 H, m), 6.38 (1 H, d, *J'* 2 Hz), 6.52 (1 H, dd, *J'* 2 Hz, *J* 9 Hz), and 7.77 (1 H, d, *J* 9 Hz).

(*b*) The above reaction was repeated but after 1 min deuterium oxide (1 ml; 99.8%) was added. Work-up as before afforded the deuteriated chromanone (3d) (0.094 g, 94%), m.p. 76—77 °C ($CHCl_3$–hexane); $\delta(CDCl_3)$ 1.47 (3 H, d, *J* 6 Hz), 2.63br (1.10 H, d, *J* 8 Hz), 3.81 (3 H, s), 4.57 (1 H, m), 6.40 (1 H, d, *J'* 2 Hz), 6.55 (1 H, dd, *J'* 2 Hz, *J* 9 Hz), and 7.80 (1 H, d, *J* 9 Hz).

Variations of the above procedure including changing co-solvents and temperatures and longer reaction times gave only starting material.

4-Ethoxycarbonyloxy-7-methoxy-2,2-dimethyl-6-nitrochromen (5).—To a solution of lithium di-isopropylamine (0.41 mmol) in dry tetrahydrofuran (2 ml) at −78 °C was added a solution of the chromanone (3e) (0.100 g, 0.40 mmol) in dry tetrahydrofuran (4 ml). The resulting dark brown solution was stirred at −78 °C for 20 min after which ethyl chloroformate (0.048 g, 0.44 mmol) was added. The resultant clear solution was allowed to come to room temperature during 2 h. The solution was diluted with ether (10 ml), washed with dilute hydrochloric acid followed by water, and then dried ($MgSO_4$). Evaporation of the solvent and silica-gel chromatography (benzene–ether as eluant) of the resulting yellow gum afforded the *nitrochromen* (5) (0.119 g, 90%), m.p. 107—108 °C (from benzene–light petroleum); $\nu_{max.}$ (KBr) 1 765, 1 625, 1 570, and 1 520 cm^{-1}; $\lambda_{max.}$ (EtOH) 212sh (ε 13 000), 277 (20 000), 223sh (19 000), 263 (16 000), 296sh (5 700), and 360 nm (5 300); $\delta(CDCl_3)$ 1.40 (3 H, t, *J* 6 Hz), 1.52 (6 H, s), 3.95 (3 H, s), 4.33 (2 H, q, *J* 6 Hz), 5.62 (1 H, s), 6.53 (1 H, s), and 7.92 (1 H, s) (Found: C, 55.7; H, 5.15; N, 4.3%; M^+, 323.1048. $C_{15}H_{17}NO_7$ requires C, 55.76; H, 5.30; N, 4.33%; *M*, 323.1005).

(±)-*3-Ethoxycarbonyl-7-methoxy-2,2-dimethylchroman-4-one* (3f).—3-Methoxyphenol (5.0 g, 40 mmol) and monoethyl isopropylidenemalonate (6a) (10.3 g, 60 mmol) were stirred in polyphosphoric acid (150 g) for 1 h at room temperature then gradually heated to 60 °C during 2 h and finally left for 4 h. Work-up followed by silica-gel chromatography (benzene–light-petroleum as eluant) gave the chromanone (3f) (4.75 g, 43%) as a homogeneous (t.l.c.) *foam*; $\nu_{max.}$ (film) 1 729, 1 674, 1 605, 1 572, and 1 493 cm^{-1}; $\lambda_{max.}$ (EtOH) 214 (ε 17 000), 234 (10 000), 237sh (10 000), 277 (13 000), and 316 nm (6 300); $\delta(CDCl_3)$ 1.27 (3 H, t), 1.48 and 1.53 (each 3 H and s), 3.63 (1 H, s), 3.8 (3 H, s), 4.22 (2 H, q), 6.37 (1 H, d, *J* 2 Hz), 6.37 (1 H, dd, *J* 2 Hz, and 9.0 Hz), and 7.78 (1 H, d, *J* 9 Hz) (Found: M^+, 278.1165. $C_{15}H_{18}O_5$ requires *M*, 278.1154).

Reduction and Attempted Reduction of the Keto Ester (3f).—(a) Sodium borohydride (0.040 g, 1.00 mmol) was added to a solution of the chromanone ester (3f) (0.100 g, 0.36 mmol) in dry ethanol. After 48 h, when all the starting material had reacted (by t.l.c.), ethyl acetate was added and the organic layer washed with saturated ammonium chloride and brine and then dried. The solvents were then removed under reduced pressure at 60 °C. Separation by chromatography on silica gel afforded two major compounds. The first homogeneous (t.l.c.) oily product was (±)-*3-ethoxycarbonyl-7-methoxy-2,2-dimethylchroman-4-ol* (7a) (0.028 g, 28%); $\nu_{max.}$ 3 490, 1 730, 1 620, 1 590, and 1 500 cm^{-1}; $\delta(CDCl_3)$ 1.26 (3 H, t), 1.43 and 1.51 (each s, 3 H), 2.70br (1 H, s), 2.99 (1 H, d, *J* 5 Hz), 3.75 (3 H, s), 4.21 (2 H, q), 4.97br (1 H, s), 6.34 (1 H, d, *J* 2 Hz), 6.52 (1 H, dd, *J* 2 Hz and *J* 9 Hz), and 7.29 (1 H, d, *J* 9 Hz) (addition of D_2O caused the signal at δ 2.70 to disappear and that at 4.97 to collapse to a doublet, *J* 5 Hz) (Found: M^+, 280.1311. $C_{15}H_{20}O_5$ requires *M*, 280.1311).

The second product, obtained as a homogeneous (t.l.c.) oil, was formulated as (±)-*3-hydroxymethyl-7-methoxy-2,2-dimethylchromen* (1f) (0.20 g, 25%); $\nu_{max.}$ 3 400, 1 615, 1 580, and 1 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 212sh (ε 7 000), 224 (11 200), 282 (6 300), 306 (5 000), and 314 sh nm (4 600); $\delta(CDCl_3)$ 1.47 (6H, s), 1.40—1.80br (1 H, s), 3.80 (3 H, s), 4.23 (2 H, d, *J* 0.5 Hz), 6.30—6.55 (3 H, m), and 6.94 (1 H, d, *J* 9 Hz) (addition of D_2O caused the signal at δ 1.40—1.80 to disappear) (Found: M^+, 220.1100. $C_{13}H_{16}O_3$ requires *M*, 220.1099).

(b) The above reaction was repeated under essentially the same conditions but this time the solvents were removed under reduced pressure at room temperature. Addition of chloroform–light petroleum (b.p. 40—60 °C) to the resultant gum afforded the crystalline (±)-*3-hydroxymethyl-7-methoxy-2,2-dimethylchroman-4-ol* (7b) (0.033 g, 38%), m.p. 143—148 °C (from $CHCl_3$); $\nu_{max.}$ (KBr) 3 320, 1 620, 1 582, and 1 505 cm^{-1}; $\delta(CDCl_3)$ 1.43 (6 H, s), 1.92—2.75 (3 H, m, 3-H + 2OH), 3.77 (3 H, s), 3.98 (2 H, d, *J* 6 Hz), 4.98 (1 H, d, *J* 4.5 Hz), 6.33 (1 H, d, *J* 2 Hz), 6.50 (1 H, dd, *J* 2 Hz, *J'* 8 Hz), and 7.28 (1 H, d, *J* 8 Hz) (addition of D_2O caused the signal at δ 1.92—2.75 to collapse to a multiplet at 2.13 integrating for 1 H and the signals at δ 3.98 and 4.98 sharpened. Irradiation at δ 2.07 caused the doublets at 3.98 and 4.98 to collapse to singlets. Irradiation at δ 3.98 caused the multiplet at 2.13 to collapse to a doublet *J* 4.5 Hz) (Found: C, 65.45; H, 7.65%; M^+, 238.1201. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61%; *M*, 238.1205).

(c) Sodium borohydride (0.01 g, 0.25 mmol) was added to a solution of the chromanone ester (3f) (0.100 g, 3.36 mmol) in dry tetrahydrofuran (2 ml). After 24 h the mixture was diluted with ethyl acetate, washed with dilute hydrochloric acid followed by water, and dried ($MgSO_4$). Evaporation gave a mixture of three components which consisted of starting material (3f), (7a) and the diol (7b) (*ca.* 2 : 1 : 1 by t.l.c. and n.m.r. spectroscopy).

(d) Lithium tri-t-butoxyaluminium hydride (0.092 g, 0.36 mmol) was added to a solution of (3f) (0.100 g, 0.36 mmol) in dry tetrahydrofuran (3 ml). Work-up after 48 h afforded only starting material (0.098 g, 98%).

(e) Sodium cyanoborohydride (0.100 g, 1.6 mmol) was added to a solution of the chromanone (3f) (0.200 g, 0.72 mmol) in methanol (4 ml) and formic acid (0.5 ml) which had been adjusted to pH 3.5 by the addition of concentrated aqueous sodium hydroxide. After 72 h the solution was diluted with chloroform and then washed with dilute hydrochloric acid, water (3 ×), sodium hydrogen carbonate, and finally

water. Evaporation of the dried ($MgSO_4$) solvent gave the pure starting material (3f) (0.184 g, 92%) (t.l.c. and n.m.r. spectroscopy).

(±)-3-*Ethoxycarbonyl*-7-*methoxy*-2,2-*dimethylchroman* (7c).—The chromanone (3f) (2.00 g, 7.2 mmol) dissolved in ethanol (50 ml) was reduced with hydrogen at atmospheric pressure in the presence of palladium on carbon (0.150 g) during 5—6 h. Filtration through Hi-flow and evaporation of the organic solution gave a syrup which was purified on silica gel (benzene–light petroleum as eluant) to afford the homogeneous (t.l.c.) *chroman* (7c) (1.77 g, 93%); $\nu_{max.}$ (film) 1 725, 1 617, 1 583, and 1 503 cm^{-1}; $\lambda_{max.}$ (EtOH) 211 (ε 19 000), 223sh (9 700), 283 (4 000), and 289 nm (3 600); δ($CDCl_3$) 1.28 (6 H, t and s, one *gem*-Me and ester Me), 1.47 (3 H, s, other *gem* Me), 2.88br (3 H, s, CH_2 and C*H*-CO_2Et), 3.73 (3 H, s), 4.17 (2 H, q), 6.28—6.58 (2 H, m), and 6.95 (1 H, d, *J* 8 Hz) (Found: M^+, 264.1357. $C_{15}H_{20}O_4$ requires *M*, 264.1362).

3-*Ethoxycarbonyl*-7-*methoxy*-2,2-*dimethylchromen* (1d).—The above chroman (7c) (1.00 g, 3.97 mmol) and DDQ (1.00 g) in dry benzene (20 ml) were boiled under reflux for 8 h. Filtration of the dark solution and evaporation gave a syrup which was chromatographed on silica gel (benzene–light petroleum) to afford the homogeneous (t.l.c.) *chromen* (1d) (0.685, 69%); $\nu_{max.}$ 1 695, 1 612, 1 558, and 1 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 208 (ε 11 000), 223 (13 000), 249 (16 000), 253sh (16 000), 297sh (8 000), 306 (9 000), and 345 nm (12 600); δ(CCl_4) 1.32 (3 H, t), 1.58 (6 H, s), 3.77 (3 H, s), 4.17 (2 H, q), 6.17—6.93 (3 H, m), and 7.20 (1 H, s) (Found: M^+, 262.1195. $C_{15}H_{18}O_4$ requires *M*, 262.1205).

7-*Methoxy*-2,2-*dimethylchromen*-3-*carboxylic Acid* (1a).—A solution of the ester (1d) (0.400 g, 1.53 mmol) in 50% aqueous ethanol (10 ml) was boiled under reflux with 10% sodium hydroxide solution (10 ml) for 3 h. Work-up afforded the acid (1a) (0.297 g, 83%), m.p. above 183 °C (decomp) ($CHCl_3$); $\nu_{max.}$ (KBr) 3 450br, 1 697, 1 620, 1 585, and 1 506 cm^{-1}; $\lambda_{max.}$ (EtOH) 210sh (ε 12 000), 222 (16 000), 247 (17 000), 298sh (8 700), 310 (9 400), and 337 nm (11 000); δ($CDCl_3$) 1.63 (6 H, s), 3.80 (3 H, s), 6.30—6.58 (2 H, m), 7.03 (1 H, d, *J* 8 Hz), 7.50 (1 H, s, C*H* = C), and 9.27br (1 H, s) (addition of deuterium oxide caused the signal at δ 9.27 to disappear) (Found: C, 66.55; H, 6.05%; M^+, 234.0899. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.02%; *M*, 234.0892).

Reaction of the Chromen Ester (1d) *with Hydrazine Hydrate, followed by Acetone*.—Hydrazine hydrate (5 ml) was added to the chromen ester (1d) (0.200 g, 0.76 mmol) and the mixture boiled under reflux for 8 h. The cooled solution was diluted with water (20 ml) and extracted with ethyl acetate (3 × 25 ml). Evaporation of the dried ($MgSO_4$) solvent afforded a solid (0.154 g) which still showed the presence of a vinylic proton (n.m.r. spectroscopy) but could not be purified further. The crude solid was dissolved in acetone (5 ml) and the solution boiled for 30 min. Evaporation of the solvent afforded a solid which was recrystallized from acetone to afford N′-*isopropylidene*-7-*methoxy*-2,2-*dimethylchromen*-3-*carbohydrazide* (1h) (0.116 g, 53%), m.p. 184—186 °C; $\nu_{max.}$ (KBr) 3 570, 3 510, 3 430, 1 660, 1 640, 1 613, 1 570, and 1 507 cm^{-1}; δ($CDCl_3$) 1.63 (6 H, s), 193 and 2.12 (each 3 H, s), 3.77 (3 H, s), 6.33—6.53 (2 H, m), 6.67 (1 H, s), 6.93 (1 H, d, *J* 8 Hz), and 7.70br (1 H, s) (addition of D_2O caused the signal at δ 7.70 to disappear) (Found: C, 66.9; H, 6.85; N, 9.45%; M^+, 288.1467. $C_{16}H_{20}N_2O_3$ requires, C, 66.64; H, 6.99; N, 9.72%; *M*, 288.1474).

Reaction of the Chromanone Ester (3f) *with Hydrazine*.—A solution of the keto-ester (3f) (0.400 g, 1.53 mmol) in dry ethanol (8 ml) was boiled under reflux with a 1 : 1 ethanolic solution of hydrazine hydrate (dried over calcium oxide). After 2 h the solution was concentrated to half its volume and extracted with ethyl acetate (2 × 20 ml). The organic phase was washed well with water (3 × 10 ml) and dried ($MgSO_4$). Evaporation afforded a dark red gum (0.310 g) which contained one major component (t.l.c. and n.m.r. spectroscopy). Silica-gel chromatography (ether as eluant) afforded homogeneous (t.l.c.) (±)-3-*ethoxycarbonyl*-4-*hydrazono*-7-*methoxy*-2,2-*dimethylchroman* (0.152 g, 34%); $\nu_{max.}$ (film) 3 320, 1 730, 1 630, 1 590, 1 560, and 1 515 cm^{-1}; δ($CDCl_3$) 1.20 (3 H, t), 1.37 (6 H, s), 3.77 (4 H, s), 4.17 (2 H, q), 4.93—5.73 (1 H, br s), 6.27—6.60 (2 H, m), 6.93 (1 H, d, *J* 8 Hz), and 11.03 (1 H, s) (addition of D_2O caused the signals at δ 4.93—5.73 and 11.03 to disappear) (Found: M^+, 292.1419. $C_{15}H_{20}N_2O_4$ requires *M*, 292.1423).

Attempted Cyclisation of the Hydrazone.—(a) The above hydrazone (0.050 g, 0.17 mmol) in ethanol (3 ml) was boiled under reflux for 48 h. Evaporation of the solvent afforded the starting material (0.050 g, 100%) (t.l.c. and n.m.r. spectroscopy).

(b) Experiment (a) was repeated with dioxan as solvent. Work-up after 48 h afforded the starting material (t.l.c. and n.m.r. spectroscopy).

(c) The above hydrazone (0.100 g, 0.34 mmol) was boiled under reflux in glacial acetic acid (5 ml). After 20 h when all the starting material had reacted (t.l.c.), the solution was diluted with ether and washed with water followed by sodium hydrogen carbonate solution. The dried ($MgSO_4$) organic layer was evaporated to leave the solid (±)-4-(N′-*acetylhydrazono*)-3-*ethoxycarbonyl*-7-*methoxy*-2,2-*dimethylchroman* (0.094 g, 83%), m.p. 160—162 °C (chloroform–light petroleum); $\nu_{max.}$ (KBr) 3 480, 3 180, 1 740, 1 670, 1 625, 1 600, 1 570, and 1 517 cm^{-1}; $\lambda_{max.}$ (EtOH) 210 (ε 15 000), 239 (12 400), 287 (15 000), 291sh (16 500), and 323 nm (23 000); δ($CDCl_3$) 1.23 (3 H, t), 1.60 and 1.77 (each 3 H, s), 2.33 (3 H, s), 3.82 (3 H, s), 4.00 (1 H, s), 4.18 (2 H, q), 6.30—6.62 (2 H, m), 7.00 (1 H, d, *J* 8 Hz), and 10.23 (1 H, s) (addition of D_2O caused the signal at δ 10.23 to disappear) (Found: C, 60.95; H, 6.55; N, 8.35%; M^+, 334.1534. $C_{17}H_{22}N_2O_5$ requires C, 61.15; H, 6.58; N, 8.40%; *M*, 334.1529).

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