Expedient Syntheses of the Rotenoid and Thiorotenoid Systems

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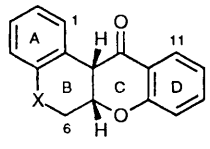
A simple four-step synthesis of a 6,6-disubstituted 6a,12a-dihydro-6*H*,12*H*-[1]benzopyrano[3,4,-*b*]-[1]benzopyran-12-one **6** from a chroman-4-one **3** is described. Application of the synthetic strategy to a thiochroman-4-one leads to the 5-thiorotenoid system.

Rotenoids[1] are tropical plant products found principally in the *Leguminosae* species and possess a variety of important biological attributes including piscicidal,[2] antiviral,[3] insecticidal[4] and antifeedant activities.[5] The structural feature common to this class of compounds is the tetracyclic unit 6a,12a-dihydro-6*H*,12*H*-[1]benzopyrano[3,4-*b*][1]benzopyran-12-one **1** (X = O), with the strongly pharmacologically active compound, rotenone **2**, containing an additional furan ring.



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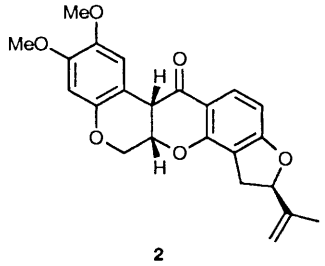
X = O or S



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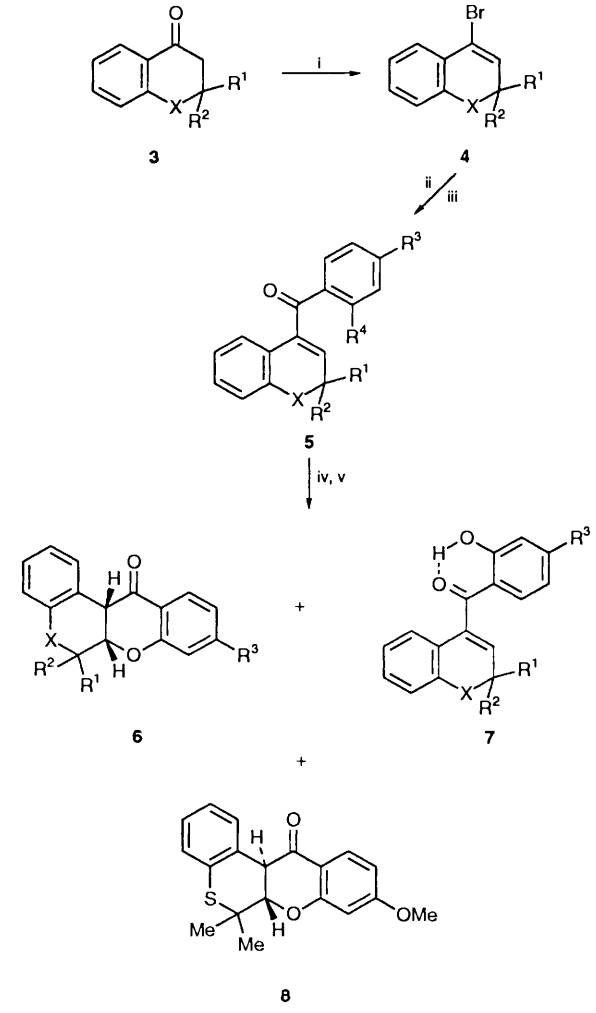
A variety of synthetic approaches to the rotenoid system **1** (X = O) has been reported including the use of Hoesch condensations,[6] acylation of enamines,[7] thermal condensation of 4-ethoxycarbonylchroman-3-ones with phenols,[8] reactions of isoflavones with dimethylsulfoxonium methylide,[9] Claisen rearrangement of prop-2-ynyl ethers,[10] aroylation of 4-phenylsulfonylchromans[11] and intramolecular radical reactions.[12] These strategies involve elaborate multi-step procedures from starting materials which are not readily available or are expensive and often result in low overall yields of the rotenoids.

We now report a facile four-step sequence of a simple 6,6-disubstituted rotenoid **6** (X = O, R^1R^2 = $-[CH_2]_5-$, R^3 = OMe) starting from 2'-hydroxyacetophenone (Scheme 1). The route has much potential for extension to a range of substituted rotenoids from inexpensive starting materials.

Chroman-2-spirocyclohexan-4-one **3** (X = O, R^1R^2 = $-[CH_2]_5-$) was obtained in 90% yield from the condensation of 2'-hydroxyacetophenone with cyclohexanone in the presence of pyrrolidine as described by Kabbe.[13] Attempts to obtain the 4-bromo-2*H*-chromene **4** (X = O, R^1R^2 = $-[CH_2]_5-$) by refluxing the chroman-4-one with phosphorus tribromide for 8–12 h[14] gave only an intractable brown tar which could not be purified. However, by reducing the reaction time to only 40 min and eluting the reaction mixture from silica, the 2*H*-chromene was obtained in a single step in 82% yield. This synthesis offers several advantages over the conventional routes to 4-bromo-2*H*-chromenes, which involve the lengthy sequence of reduction of a chroman-4-one and dehydration of the resulting chromanol to give the 2*H*-chromene. Bromination and elimination of HBr from the *trans*-dibromochroman by treatment with alkoxide complete the procedure.[15]



Scheme 1 *Reagents and conditions:* i, PBr_3, heat, 40 min; ii, BuLi, Et_2O, N_2, room temp., 45 min; iii, substituted benzonitrile, room temp., 1 h; iv, BCl_3, CH_2Cl_2, N_2, −10 °C, 1 h; v, NaOAc, EtOH, heat, N_2, 3 h. Note: Only relative stereochemistry of 6a-H and 12a-H shown for **6** and **8**.

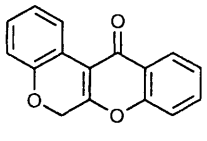
Preliminary experiments established that the optimum conditions for anion formation were reaction of butyllithium with 4-bromo-2,2-dimethyl-2*H*-chromene **4** (X = O, R^1 = R^2 = Me) in diethyl ether at room temperature. Quenching the anion with benzonitrile afforded 4-benzoyl-2,2-dimethyl-2*H*-chromene **5** (X = O, R^1 = R^2 = Me, R^3 = R^4 = H) in good yield, confirming the viability of the key step in the synthetic sequence to the rotenoid system. Indeed 2-methoxy- and 2,4-dimethoxy-benzonitrile gave satisfactory yields of the benzoyl derivatives **5** (X = O, R^1 = R^2 = Me, R^3 = H, R^4 = OMe) and (X = O, R^1R^2 = $-[CH_2]_5-$, R^3 = R^4 = OMe)

respectively. The applications and potential of this particular aspect of chromene chemistry are under active investigation, but it clearly offers a route to synthetically useful 4-substituted 2*H*-chromenes. The influence of the 4-substituent on the chemical shifts of the neighbouring protons merits some comment. Introduction of a 4-bromo substituent shifts 3-H from δ 5.5 in 2,2-dimethyl-2*H*-chromene[16] to δ 6.0 and in the 4-formyl derivative[17] a further downfield shift of *ca.* 0.3 ppm is observed. Space-filling models indicate that the formyl group can not be coplanar with the rest of the molecule but is orthogonally disposed. A 4-benzoyl substituent is similarly orientated but an upfield shift to δ 5.95 is noted for 3-H. Introduction of methoxy groups at the 2- and 2,4-positions of the benzoyl function has no further effect on the chemical shift of 3-H, possibly because a reduction in conjugation of the C=O with the phenyl ring resulting from the severe steric congestion is compensated by the increased electron density arising from the methoxy substituent.

Whilst 5-H resonates at *ca.* δ 7.4 in the 4-bromo-2*H*-chromenes, it is shifted to δ 8.2 in the 4-formyl compound in keeping with its proximity to the anisotropic carbonyl function. An upfield shift of *ca.* 0.3 ppm is observed in the 4-benzoyl derivative, which molecular models suggest may result from the location of 5-H near to the shielding zone of the aromatic ring. Further upfield shifts of *ca.* 0.3 ppm occur in the 2-methoxy- and 2,4-dimethoxy-benzoyl derivatives, presumably associated with the increased electron density of the aroyl moiety.

A solution of **5** (X = O, R^1R^2 = $-[CH_2]_5-$, R^3 = R^4 = OMe) in dichloromethane containing 1.75 equiv. of boron trichloride when stirred at 0 °C for 1 h resulted in the selective demethylation[18] of the methoxy group adjacent to the carbonyl function. Base-promoted intramolecular ring closure of the crude 2′-hydroxy-4′-methoxybenzoyl-2*H*-chromene **7** (X = O, R^1R^2 = $-[CH_2]_5-$, R^3 = OMe, R^4 = OH) was achieved by refluxing it in ethanol saturated with sodium acetate trihydrate for 2 h under N_2 to prevent aerial oxidation of the rotenoid. Elution of the crude reaction product from silica with 10% ethyl acetate in hexane gave the rotenoid **6** (X = O, R^1R^2 = $-[CH_2]_5-$, R^3 = OMe) (69%). This ring closure circumvents the dehydrorotenoid intermediates **9** common to other strategies and which necessitate a delicate and costly reduction–re-oxidation sequence.[6–8]

The ^{1}H NMR spectrum of compound **6** (X = O, R^1R^2 = $-[CH_2]_5-$, R^3 = OMe) displayed the typical 4 Hz coupling[19]



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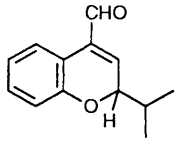

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of the 6a,12a-protons associated with the thermodynamically preferred *cis*-B/C ring fusion, a feature corroborated by the chemical shift of 1-H, δ 7.27.[20] Interestingly, one of the 6-C spiro-cyclohexane ring protons resonates downfield of the main group at δ 2.48, probably because of its proximity to the anisotropic aromatic A-ring, as indicated by space-filling models.

A second fraction, eluted from the silica by increasing the polarity of the eluent to 20% ethyl acetate in hexane, was characterised as compound **7** (X = O, R^1R^2 = $-[CH_2]_5-$, R^3 = OMe, R^4 = OH) (10%) and is a consequence of incomplete cyclisation of the demethylated dimethoxybenzoylchromene **5** (X = O, R^1R^2 = $-[CH_2]_5-$, R^3 = R^4 = OMe). The spectral data indicate an intramolecularly hydrogen bonded hydroxy group (δ OH = 12.6) which would mitigate against a facile ring closure to the rotenoid.

Since rotenone itself and other naturally occurring rotenoids are unsubstituted at the 6-position, it was of interest to apply our synthetic protocol to bromo-2*H*-chromenes unsubstituted or monosubstituted at 2-C, despite the fact that such compounds are difficult to prepare. This would also indicate whether substitution at the 2-position of the starting bromo-2*H*-chromene plays a significant role in the reaction sequence by ensuring that lithiation is directed to the 4-position.

Refluxing chroman-4-one **3** (X = O, R^1 = R^2 = H) in PBr_3 gave an intractable brown gum which did not yield any of the desired 4-bromo-2*H*-chromene **4** (X = O, R^1 = R^2 = H). The use of less severe reaction conditions for the formation of bromoalkenes from 1,3-diketones using PBr_3 in refluxing CH_2Cl_2 has been advocated[21] and heating chroman-4-one in PBr_3 (1.75 h at 90 °C) proved beneficial and a small amount of 4-bromo-2*H*-chromene was obtained after column chromatography. Unfortunately, this parent bromo-2*H*-chromene was unstable, rapidly darkening on removal of the eluent and attention was therefore turned to a mono-substituted analogue.

2-Isopropylchroman-4-one **3** (X = O, R^1 = H, R^2 = Pr^i) was readily obtained from the reaction between 2′-hydroxyacetophenone and isobutyraldehyde. Using the above milder reaction conditions, 4-bromo-2-isopropylchroman-4-one **4** (X = O, R^1 = H, R^2 = Pr^i) was obtained in moderate yield. This compound was relatively stable, only darkening when exposed to air at room temperature over several days. Unfortunately, attempts to obtain the dimethoxybenzoyl derivative **5** (X = O, R^1 = H, R^2 = Pr^i, R^3 = R^4 = OMe) by the established route failed, recovered 2,4-dimethoxybenzonitrile being accompanied by 2-isopropyl-2*H*-chromene, which results from protonation of the anion during aqueous work-up. However, the anion derived from **4** (X = O, R^1 = H, R^2 = Pr^i) and butyllithium was successfully trapped with dimethylformamide forming the aldehyde **10** in moderate yield together with a small amount of the 2*H*-chromene, indicating that Li–halogen exchange is preferred to abstraction of the proton adjacent to the oxygen heteroatom.

In order to make further use of this succinct carbanion strategy and to assess its wider applicability, we turned our attention to the synthesis of a sulfur analogue of the rotenoids **1** (X = S). Only two syntheses of the 5-thiorotenoid unit have been described. One employs a Wadsworth–Emmons reaction[22] and the other relies upon acylation of an enamine[23] as their respective key steps in multistep procedures.

2,2-Dimethylthiochroman-4-one **3** (X = S, R^1 = R^2 = Me), obtained in 74% yield on heating thiophenol and 3,3-dimethylacrylic acid in methanesulfonic acid,[24] was converted in a single step into the 4-bromo-2*H*-thiochrom-3-ene **4** (X = S, R^1 = R^2 = Me) on refluxing in phosphorus tribromide for 40 min. An advantage of this route to bromo-2*H*-thiochromenes, additional to those described above for bromo-2*H*-chromenes, is that the need for dibromothiochromans, which are prone to undergo ring contraction to the benzo[*b*]thiophene system,[25] is obviated.

The key step, formation of the dimethoxybenzoyl-2*H*-thiochromene **5** (X = S, R^1 = R^2 = Me, R^3 = R^4 = OMe), was readily accomplished, suggesting a useful procedure for the formation of a variety of 4-substituted 2*H*-thiochromenes. Selective demethylation and subsequent intramolecular ring closure of the crude product **7** (X = S, R^1 = R^2 = Me, R^3 = OMe, R^4 = OH) proceeded smoothly under N_2 in ethanol saturated with sodium acetate. Elution of the crude reaction product from silica gave a mixture (52%) of the *cis*- and *trans*-B/C fused 5-thiorotenoids **6** (X = S, R^1 = R^2 = Me, R^3 = OMe) and **8** (*cis*:*trans* isomer ratio ~99:1 by ^{1}H NMR spectroscopy), together with some uncyclised material **7** (X =

S, $R^1 = R^2 = Me$, $R^3 = OMe$, $R^4 = OH$). The ^1H NMR spectrum of the *cis*-isomer **6** (X = S, $R^1 = R^2 = Me$, $R^3 = OMe$) displayed 3.4 Hz coupling of the 6a,12a protons which together with the chemical shift of 1-H of δ 7.34, confirms the *cis*-B/C ring fusion.[23] Further coupling of 12a-H is apparent, which 2D ^1H-^1H COSY experiments established involved 1-H and that $J_{1,12a}$ was 0.7 Hz. We believe that this is the first example of benzylic coupling of this nature which has been observed in the thiorotenoid system, though coupling of a similar magnitude between 1-H and 12a-H has been observed for rotenone **2**.[26] This ^4J coupling was also apparent in the *trans*-B/C isomer of **8** ($J_{1,12a} = 0.8$ Hz). In the *trans*- isomer, 1-H resonates at δ 7.56, shifted downfield in comparison with that of the *cis*-B/C isomer (δ 7.34), as it is now approximately co-planar with the 12-C carbonyl function as depicted by space-filling models. Such a downfield shift is in accord with studies on rotenolones and isorotenolones in which 1-H resonates at ~δ 7.6–8.0 ($CDCl_3$) for the *trans*- series,[20] and also with the chemical shift of 1-H in (+/−) *trans*-isorotenone δ 7.64 ([$^2H_6$]-acetone) relative to δ 6.71 ([$^2H_6$]acetone) for 1-H of the (+/−) *cis*-isorotenone.[27] Downfield shifts are also noted for 12a-H and 6a-H in the ^1H NMR spectrum of the *trans*-B/C isomer which now resonate at δ 4.04 and δ 4.73 respectively (*cf.* δ 3.90 and δ 4.50 for 12a-H and 6a-H in the *cis*-B/C isomer) with $J_{6a,12a} = 12.5$ Hz which is consistent with a *trans*-B/C ring fusion.[23,27] The stereochemistry of the product is a consequence of the diastereoselective prototropy following cyclisation which clearly favours the *cis*-B/C fused product. In this connection it is noted that *cis*-B/C ring fusion is thermodynamically favoured for the naturally occurring rotenoids.[28]

In conclusion, syntheses of the rotenoid and thiorotenoid systems have been accomplished in 34 and 17% overall yields, respectively, from readily available starting materials in 4 steps by applying carbanion methodology.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Distillations were performed using a Kugelrohr (Buchi GKR-50 Glass Tube Oven) and all boiling points quoted relate to the oven temperature at which the distillation commenced; pressures are quoted in units of mbar (1 bar = 10^5 Pa). Fourier transform infrared spectra were recorded on a Mattson Polaris spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM 250 instrument for solutions in $CDCl_3$, *J* values are given in Hz. 2D ^1H-^1H COSY experiments were recorded on a Bruker AMX 500 MHz instrument for solutions in $CDCl_3$. Flash chromatographic separations were performed on Crossfields Sorbsil C60 silica gel (M.P.D. 60 Å, 40–60 μ, activated) according to the literature procedure.[29]

Preparation of 4-*Bromo*-2H-*chromenes and -thiochromenes.*—A solution of the chroman-4-one or thiochroman-4-one (25 mmol) in phosphorus tribromide (125 mmol) was refluxed for 40 min and then cooled in ice and cautiously poured onto crushed ice (300 g). The aqueous solution was extracted with ethyl acetate (5 × 50 cm^3) and the combined extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4) and evaporated to afford a pale yellow oil. This oil was eluted from silica with 5% ethyl acetate in hexane to afford the crude product, which was then distilled.

4-*Bromo*-2H-*chromene*-2-*spirocyclohexane*[14] **4** (X = O, R^1-$R^2 = -[CH_2]_5-$). This compound was obtained as a colourless oil (82%), b.p. 115 °C (0.6 mbar); δ_H 1.49–1.99 (10 H, m, $[CH_2]_5$), 6.05 (1 H, s, 3-H), 6.83 (1 H, d, *J* 8.1, 8-H), 6.92 (1 H, m, 6-H), 7.19 (1 H, m, 7-H) and 7.41 (1 H, dd, *J* 8.1 and 1.3, 5-H); δ_C 21.3 (2 × C), 25.1, 35.6 (2 × C), 79.1, 116.4, 117.3, 121.0, 121.5, 126.8, 130.3, 131.6 and 152.9.

4-*Bromo*-2,2-*dimethyl*-2H-*chromene* **4** (X = O, $R^1 = R^2 =$ Me). This compound was obtained as a colourless oil (67%), b.p. 90 °C (0.5 mbar); δ_H 1.47 (6 H, s, 2-Me), 6.02 (1 H, s, 3-H), 6.81 (1 H, d, *J* 8.2, 8-H), 6.94 (1 H, m, 6-H), 7.17 (1 H, m, 7-H) and 7.43 (1 H, dd, *J* 8.2 and 1.3, 5-H); δ_C 27.6 (2 × C), 78.3, 116.4, 117.0, 120.6, 121.0, 126.8, 130.5, 131.8 and 153.0 (Found: C, 55.3; H, 4.4; Br, 33.2. $C_{11}H_{11}BrO$ requires C, 55.3; H, 4.6; Br, 33.4%).

4-*Bromo*-2H-*chromene* **4** (X = O, $R^1 = R^2 = H$). This compound was obtained after 1.75 h at 90 °C as a pale yellow oil after elution from silica (37%), which rapidly darkened on storage at room temperature, and was not distilled; δ_H 4.81 (2 H, d, *J* 4.0, 2-H), 6.16 (1 H, t, *J* 4.0, 3-H), 6.16 (1 H, dd, *J* 8.1 and 1.2, 8-H), 6.98 (1 H, m, 6-H), 7.20 (1 H, m, 7-H) and 7.42 (1 H, dd, *J* 8.1 and 1.3, 5-H); δ_C 66.7, 115.8, 118.1, 121.6, 121.9, 123.5, 127.0, 130.6 and 154.4. Satisfactory elemental analysis could not be otained for this compound.

4-*Bromo*-2-*isopropyl*-2H-*chromene* **4** (X = O, $R^1 = Pr^i$, $R^2 = H$). This compound was obtained after 2 h at 90 °C as a colourless oil (49%) which gradually darkened on exposure to air at room temperature, b.p. 100 °C (0.5 mbar); δ_H 1.05 (3 H, d, *J* 6.9, 2-$CHMe_2$), 1.08 (3 H, d, *J* 6.9, 2-$CHMe_2$), 2.07 (1 H, m, 2-C*H*Me_2), 4.65 (1 H, dd, *J* 6.9 and 3.8, 2-H), 6.12 (1 H, d, *J* 3.8, 3-H), 6.83 (1 H, dd, *J* 8.1 and 1.3, 8-H), 6.94 (1 H, m, Ar-H), 7.19 (1 H, m, Ar-H) and 7.44 (1 H, dd, *J* 8.0 and 1.4, 5-H); δ_C 17.7, 17.8, 33.2, 81.7, 115.7, 118.3, 121.1, 121.4, 125.9, 126.9, 130.6 and 154.2. Satisfactory elemental analysis could not be obtained for this compound.

4-*Bromo*-2,2-*dimethyl*-2H-*thiochromene* **4** (X = S, $R^1 = R^2 =$ Me). This compound was obtained as a pale yellow oil (71%), b.p. 120 °C (0.6 mbar); δ_H 1.43 (6 H, s, 2-Me), 6.28 (1 H, s, 3-H), 7.20 (3 H, m, 6-H, 7-H and 8-H) and 7.43 (1 H, dd, *J* 8.2 and 1.3, 5-H); δ_C 29.0 (2 × C), 43.1, 121.2, 125.6, 127.4, 128.8, 128.9, 130.7, 132.9 and 136.3 (Found: C, 51.6; H, 4.2; Br, 31.1; S, 12.7. $C_{11}H_{11}BrS$ requires C, 51.8; H, 4.3; Br, 31.3; S, 12.6%).

Preparation of 4-*Aroyl*-2H-*chromenes and -thiochromenes.*—To a stirred solution of the 4-bromo-2*H*-chromene or 4-bromo-2*H*-thiochromene (15 mmol) in anhydrous diethyl ether (40 cm^3) at room temperature and under N_2, butyllithium (2.5 mol dm^{-3} in hexanes; 15 mmol) was added *via* a syringe in a single portion. The resulting orange solution was stirred at room temp for 45 min, after which the benzonitrile (15.5 mmol) was added in a single portion. This gave a pale yellow solution which was stirred at room temp. for 1 h and then poured into water (200 cm^3) and extracted with ethyl acetate (4 × 50 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4) and evaporated to give a yellow semi-solid which was eluted from silica with 10% ethyl acetate in hexane to give the title compounds. In addition, a small amount of the debrominated 2*H*-chromene was invariably isolated.

4-(2,4-*Dimethoxybenzoyl*)-2H-*chromene*-2-*spirocyclohexane* **5** (X = O, $R^1R^2 = -[CH_2]_5-$, $R^3 = R^4 = OMe$). This compound was obtained from **4** (X = O, $R^1R^2 = -[CH_2]_5-$) and 2,4-dimethoxybenzonitrile, (66%) as colourless needles from hexane and ethyl acetate, m.p. 109.5–110.5 °C, ν_{max}(Nujol)/cm^{-1} 1664; δ_H 1.46–1.99 (10 H, m, $-[CH_2]_5-$), 3.66 (3 H, s, 4'-OMe), 3.86 (3 H, s, 2'-OMe), 5.94 (1 H, s, 3-H), 6.43 (1 H, d, *J* 1.5, 3'-H), 6.54 (1 H, dd, *J* 8.6 and 1.5, 5'-H), 6.80 (1 H, m, 6-H), 6.91 (1 H, dd, *J* 8.0 and 1.0, 8-H), 7.13 (1 H, m, 7-H), 7.35 (1 H, dd, *J* 8.1 and 1.0, 5-H) and 7.63 (1 H, d, *J* 8.4, 6'-H); δ_C 21.2 (2 × C), 25.2, 34.9 (2 × C), 55.4, 55.5, 76.0, 98.7, 109.4, 116.8, 120.4, 120.7, 121.6, 125.4, 129.3, 133.0, 134.8, 135.4, 152.6, 160.5, 164.3 and 194.0 (Found: M^+, 364.1675; C, 76.0; H, 6.7. $C_{23}H_{24}O_4$ requires *M*, 364.1673; C, 75.9; H, 6.7%).

4-(2-*Methoxybenzoyl*)-2,2-*dimethyl*-2H-*chromene* **5** (X = O, $R^1 = R^2 =$ Me, $R^3 = H$, $R^4 = OMe$. This compound was

obtained from **4** (X = O, $R^1 = R^2$ = Me) and 2-methoxybenzonitrile, (62%) as colourless needles from ethyl acetate and hexane, m.p. 70.5–71.5 °C; ν_{max}(Nujol)/cm^{-1} 1654; δ_H 1.46 (6 H, s, 2-Me), 3.73 (3 H, s, 2′-OMe), 5.99 (1 H, s, 3-H), 6.87–7.01 (3 H, m, Ar-H), 7.05 (1 H, m, Ar-H), 7.18 (1 H, m, Ar-H), 7.46–7.56 (2 H, m, Ar-H) and 7.64 (1 H, dd, *J* 8.2 and 1.4, 5-H); δ_C 26.8 (2 × C), 55.5, 75.3, 111.7, 116.9, 119.0, 120.5, 120.9, 125.8, 128.8, 129.6, 130.5, 132.9, 134.1, 138.0, 152.8, 158.1 and 195.3 (Found: C, 77.7; H, 6.2. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.2%).

4-*Benzoyl*-2,2-*dimethyl*-2H-*chromene* **5** (X = O, $R^1 = R^2$ = Me, $R^3 = R^4$ = H). This compound was obtained from **4** (X = O, $R^1 = R^2$ = Me) and benzonitrile, as a viscous yellow oil (77%), b.p. 180–190 °C (0.4 mbar); ν_{max}(Nujol)/cm^{-1} 1663; δ_H 1.53 (6 H, s, 2-Me), 5.95 (1 H, s, 3-H), 6.86–6.92 (2 H, m, Ar-H), 7.18–7.28 (2 H, m, Ar-H), 7.48–7.51 (2 H, m, Ar-H), 7.60 (1 H, m, Ar-H) and 7.91 (1 H, dd, *J* 8.2 and 1.4, 5-H); δ_C 27.2 (2 × C), 75.4, 117.1, 119.1, 121.0, 125.6, 128.5 (2 × C), 129.9, 130.0 (2 × C), 132.8, 133.2, 135.7, 137.2, 152.6 and 195.2 (Found: C, 81.9; H, 5.9. $C_{18}H_{16}O_2$ requires C, 81.8; H, 6.1%).

4-(2,4-*Dimethoxybenzoyl*)-2,2-*dimethyl*-2H-*thiochromene* **5** (X = S, $R^1 = R^2$ = Me, $R^3 = R^4$ = OMe). This compound was obtained from **4** (X = S, $R^1 = R^2$ = Me) and 2,4-dimethoxybenzonitrile, (61%) as colourless needles from hexane and ethyl acetate, m.p. 110.0–111.0 °C; ν_{max}(Nujol)/cm^{-1} 1637; δ_H 1.45 (6 H, s, 2-Me), 3.55 (3 H, s, 4′-OMe), 3.86 (3 H, s, 2′-OMe), 6.14 (1 H, s, 3-H), 6.33 (1 H, d, *J* 1.5, 3′-H), 6.55 (1 H, dd, *J* 8.6 and 1.5, 5′-H), 6.99 (1 H, m, 6-H), 7.17 (2 H, m, 7-H and 8-H), 7.35 (1 H, dd, *J* 8.2 and 1.1, 5-H) and 7.70 (1 H, d, *J* 8.3, 6′-H); δ_C 28.2 (2 × C), 40.5, 55.2, 55.4, 98.5, 105.1, 121.5, 125.0, 126.2, 127.7, 127.8, 130.7, 132.6, 133.2, 137.5, 140.5, 160.6, 164.5 and 195.0 (Found: M^+, 340.1133; C, 70.7; H, 6.0; S, 9.6. $C_{20}H_{20}O_3S$ requires *M*, 340.1133; C, 70.6; H, 5.9; S, 9.4%).

Using a procedure identical with that described for the formation of the 4-benzoyl-2*H*-chromenes above, 2-*isopropyl*-2H-*chromene*-4-*carbaldehyde* **10** was obtained from compound **4** (X = O, R^1 = H, R^2 = Pr^i) and dimethylformamide (63%) as a pale yellow oil, b.p. 120 °C (0.6 mbar), ν_{max}(Nujol)/cm^{-1} 1693, δ_H 1.07 (3 H, d, *J* 6.5, 2-CH*Me*$_2$), 1.09 (3 H, d, *J* 6.5, 2-CH*Me*$_2$), 2.14 (1 H, m, 2-C*H*Me$_2$), 4.77 (1 H, dd, *J* 3.9 and 6.4, 2-H), 6.61 (1 H, d, *J* 4.0, 3-H), 6.93 (2 H, m, Ar-H), 7.22 (1 H, m, Ar-H), 8.19 (1 H, dd, *J* 8.3 and 2.0, 5-H) and 9.69 (1 H, s, CHO); δ_C 17.9 (2 × C), 32.7, 79.5, 116.1, 117.7, 121.2, 125.8, 130.4, 133.9, 144.4, 153.5 and 190.8 (Found: C, 77.2; H, 6.9. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%).

Preparation of the 6,6-*Dialkyl*-9-*methoxy*-*rotenoid and* -5-*thiorotenoid*.—A solution of BCl_3 (8.75 mmol, 1 mol dm^{-3} in CH_2Cl_2) was added *via* syringe to a cold stirred solution of the 2,4-dimethoxybenzoyl-2*H*-chromene or 2,4-dimethoxybenzoylthiochromene (5 mmol) in CH_2Cl_2 (40 cm^3). The resulting dark solution was stirred at −10 °C for 1 h, after which the solution was poured into water (200 cm^3) and extracted with CH_2Cl_2 (5 × 50 cm^3). Removal of the solvent from the combined dried (Na_2SO_4) extracts gave a viscous brown oil which was refluxed for 3 h under N_2 in ethanol (30 cm^3) saturated with sodium acetate. The cooled solution was poured into water (300 cm^3) and extracted with ethyl acetate (5 × 50 cm^3). Evaporation of the combined, dried (Na_2SO_4) extracts gave a viscous oil which was chromatographed to afford two fractions in each case.

Elution of the reaction product from **5** (X = O, R^1R^2 = –[CH_2]$_5$–, $R^3 = R^4$ = OMe) from silica with 10% ethyl acetate in hexane gave: fraction (i), *the rotenoid* **6** (X = O, R^1R^2 = –[CH_2]$_5$–, R^3 = OMe) (69%) as colourless needles from hexane and ethyl acetate, m.p. 128.0–129.5 °C; ν_{max}(Nujol)/cm^{-1} 1674; δ_H 1.41–2.00 (9 H, m, –[CH_2]$_5$–), 2.48 (1 H, m, –[CH_2]$_5$–), 3.77 (3 H, s, 9-OMe), 3.89 (1 H, d, *J* 4.0, 12a-H), 4.60 (1 H, d, *J* 4.0, 6a-H), 6.38 (1 H, d, *J* 1.6, 8-H), 6.55 (1 H, dd, *J* 8.8 and 1.6, 10-H), 6.85 (1 H, m, 2-H), 6.95 (1 H, dd, *J* 8.1 and 1.2, 4-H), 7.15 (1 H, m, 3-H), 7.27 (1 H, dd, *J* 8.2 and 1.3, 1-H) and 7.86 (1 H, d, *J* 8.9, 11-H); δ_C 21.0 (2 × C), 25.5, 30.8, 32.8, 43.4, 55.5, 75.3, 100.6, 110.5, 113.2, 113.9, 117.6, 120.7, 127.9, 128.8, 129.1, 152.7, 162.7, 166.4 and 189.4 (Found: MH^+, 351.1596; C, 75.6; H, 6.4. $C_{23}H_{24}O_4$ requires *MH*, 351.1596; C, 75.5; H, 6.4%) and on increasing the polarity of the eluent to 20% ethyl acetate in hexane, fraction (ii) 4-(2-*hydroxy*-4-*methoxybenzoyl*)-2H-*chromene*-2-*spirocyclohexane* **7** (X = O, R^1R^2 = –[CH_2]$_5$–, R^3 = OMe, R^4 = OH) (10%) as a viscous orange oil, b.p. 225–230 °C (0.6 mbar); ν_{max}(Nujol)/cm^{-1} 3220 br, 1691; δ_H 1.36–2.17 (10 H, m, –[CH_2]$_5$–), 3.87 (3 H, 3, 4′-OMe), 5.83 (1 H, s, 3-H), 6.38 (1 H, dd, *J* 8.7 and 1.6, 5′-H), 6.49 (1 H, d, *J* 1.3, 3′-H), 6.84 (1 H, m, 6-H), 6.93 (1 H, dd, *J* 8.1 and 1.2, 8-H), 7.06 (1 H, m, 7-H), 7.20 (1 H, dd, *J* 8.1 and 1.1, 5-H), 7.56 (1 H, d, *J* 8.6, 6′-H) and 12.6 (1 H, s, 2′-OH) (Found: MH^+, 351.1596; C, 75.6; H, 6.3. $C_{23}H_{24}O_4$ requires *M*H, 351.1596; C, 75.5; H, 6.4%).

Elution of the reaction product from **5** (X = S, $R^1 = R^2$ = Me, $R^3 = R^4$ = OMe) from silica with 7.5% ethyl acetate in hexane gave: fraction (i), a mixture of the *cis*-**6** (X = S, $R^1 = R^2$ = Me, R^3 = OMe) and trans-5-*thiorotenoids* **8**, (*cis*:*trans* ~99:1 by ^{1}H NMR spectroscopy), (52%) as colourless needles from hexane and ethyl acetate, m.p. 128.0–129.5 °C; ν_{max}(Nujol)/cm^{-1} 1678; *cis*-isomer δ_H 1.49 (3 H, s, 6-Me), 1.61 (3 H, s, 6-Me), 3.80 (3 H, s, 9-OMe), 3.90 (1 H, dd, *J* 3.4 and 0.7, 12a-H), 4.50 (1 H, d, *J* 3.4, 6a-H), 6.43 (1 H, d, *J* 1.5, 8-H), 6.57 (1 H, dd, *J* 8.7 and 1.5, 10-H), 7.00 (1 H, m, 2-H), 7.12 (2 H, m, 3-H and 4-H), 7.34 (1 H, m, 1-H) and 7.86 (1 H, d, *J* 8.7, 11-H); δ_C 26.1, 28.3, 43.6, 46.9, 55.6, 80.2, 100.3, 110.6, 113.2, 124.2, 124.5, 126.9, 127.5, 128.7, 129.2, 132.9, 162.8, 166.3 and 190.3; and *trans*-isomer **8** δ_H 1.53 (3 H, s, 6-Me), 1.59 (3 H, s, 6-Me), 3.88 (3 H, s, 9-OMe), 4.04 (1 H, dd, *J* 12.5 and 0.8, 12a-H), 4.74 (1 H, d, *J* 12.5, 6a-H), 6.55 (1 H, d, *J* 1.5, 8-H), 6.64 (1 H, dd, *J* 8.7 and 1.5, 10-H), 7.12–7.20 (3 H, m, 2-H, 3-H and 4-H), 7.56 (1 H, m, 1-H) and 7.91 (1 H, d, *J* 8.7, 11-H) (Found: M^+, 326.0977; C, 69.9; H, 5.6; S, 10.0. $C_{19}H_{18}O_3S$ requires *M*, 326.0977; C, 69.9; H, 5.6; S, 9.8%) and fraction (ii) 4-(2-*hydroxy*-4-*methoxybenzoyl*)-2,2-*dimethyl*-2H-*thiochromene* **7** (X = S, $R^1 = R^2$ = Me, R^3 = OMe, R^4 = OH) (30%) as a viscous pale yellow oil, b.p. 180 °C (0.5 mbar); ν_{max}(Nujol)/cm^{-1} 3223 and 1631; δ_H 1.52 (6 H, s, 2-Me), 3.84 (3 H, s, 4′-OMe), 5.98 (1 H, s, 3-H). 6.34 (1 H, dd, *J* 8.6 and 1.5, 5′-H), 6.47 (1 H, d, *J* 1.5, 3′-H), 7.09 (1 H, m, 6-H), 7.18 (2 H, m, 7-H and 8-H), 7.35 (2 H, m, 5-H and 6′-H) and 12.6 (1 H, s, OH); δ_C 28.2 (2 × C), 40.5, 55.6, 100.9, 107.7, 113.6, 125.6, 126.5, 128.1, 128.6, 129.7, 132.1, 134.9, 135.8, 136.7, 166.3, 166.6 and 200.5 (Found: C, 70.0; H, 5.5; S, 10.0. $C_{19}H_{18}O_3S$ requires C, 69.9; H, 5.6; S, 9.8%).

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