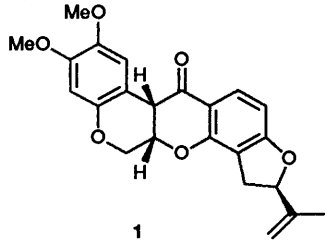
Synthesis of the 5-Thiorotenoid System from Thiochroman-3-one

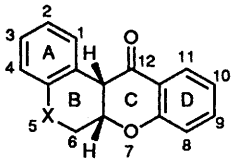
Christopher D. Gabbutt, John D. Hepworth* and B. Mark Heron
Department of Chemistry, University of Central Lancashire, Preston, PR1 2HE, UK

Base-induced cyclisation of the diketones **10** (X = H or F), prepared in a two-step sequence from thiochroman-3-one, affords 6*H*,12*H*-[1]benzothiopyrano[3,4-*b*][1]benzopyran-12-ones **11**. Reduction with diisobutylaluminium hydride affords a separable mixture of the *cis*- and *trans*-5-thiorotenoids. Dieckmann cyclisation of ethyl 2-(ethoxycarbonylmethylthio)phenylethanoate affords a mixture of 4-ethoxycarbonyl- and 2-ethoxycarbonyl-thiochroman-3-ones. Attempts to prepare a thiorotenoid by condensation of these β-keto esters with 4-methoxyphenol resulted in formation of the novel bis[1]benzothiopyrano[3,2-*b*:4',3'-*e*]pyran ring system.

Rotenone **1** and compounds containing the rotenoid core **2** (X = O) are widely distributed in nature[1] and exhibit a diverse range of potent biological properties including insecticidal,[2] piscicidal,[3] antifeedant,[4] antimicrobial and antiviral activity.[5]

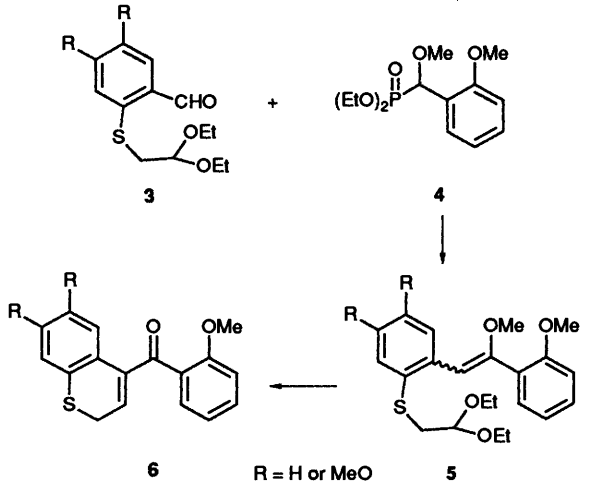


1



2 X = O or S

A variety of synthetic approaches to the rotenoid system have been reported including the use of Hoesch condensations,[6] enamines,[7] thermal condensation of 4-ethoxycarbonylchroman-3-ones with activated phenols,[8] reaction of isoflavones with dimethylsulfoxonium methylide,[9] Claisen rearrangement of prop-2-ynyl ethers,[10] aroylation of 4-phenylsulfonylchromans[11] and intramolecular radical cyclisations.[12] Recently, Crombie *et al.* have reported a synthesis of 5-thiorotenoids **2** (X = S),[13] involving union of the diethyl acetal **3** and the phosphonate **4** by a Wadsworth–Emmons reaction and a subsequent Mukaiyama-type ring closure of **5** to the thiochromene **6** as the key steps (Scheme 1). Demethylation proceeded with concomitant ring closure to the thiorotenoid **2** (X = S). Our interest in benzothiopyrans[14] and the potential of thiochroman-3-ones in synthesis[15] prompt us to report an enamine-based route to 5-thiorotenoids.

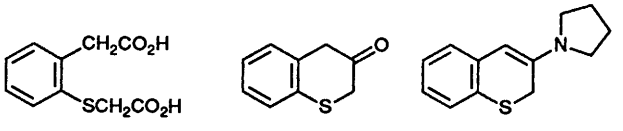


3 + **4** → **5** → **6** (R = H or MeO)

Scheme 1

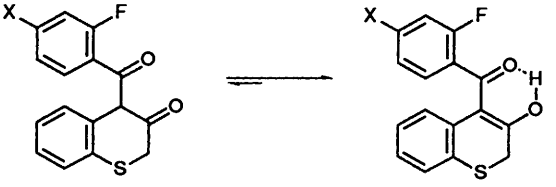
Results and Discussion

Thiochroman-3-one **8** was obtained in an overall yield of 44% from benzo[*b*]thiophene.[14] This significantly improved yield is largely attributable to the direct conversion of the disodium salt of 2-mercaptophenylacetic acid into the diacid **7**, thereby avoiding disulfide formation. Conversion of thiochroman-3-one **8** into the enamine **9** was carried out using the procedure described by Clark and McKinnon.[16]



7 **8** **9**

Acylation of the enamine **9** was achieved by the dropwise addition of 2-fluorobenzoyl chloride in dichloromethane to a cold stirred solution of the enamine under argon. Stirring the solution for 4 h at ambient temperature and hydrolysis with aqueous HCl gave the diketone **10** (X = H) in a disappointingly low yield (31%). Changing the solvent to 1,2-dichloroethane and refluxing the solution for 2 h prior to hydrolysis resulted in an improvement to the yield (42%). The ability of 4-dimethylaminopyridine (DMAP) to promote acylations of alcohols and enolates is well established[17] and a significantly better yield (61%) of **10** (X = F) was recorded for acylation of the enamine **9** with 2,4-difluorobenzoyl chloride to which a catalytic quantity of DMAP had been added.



10 X = H or F

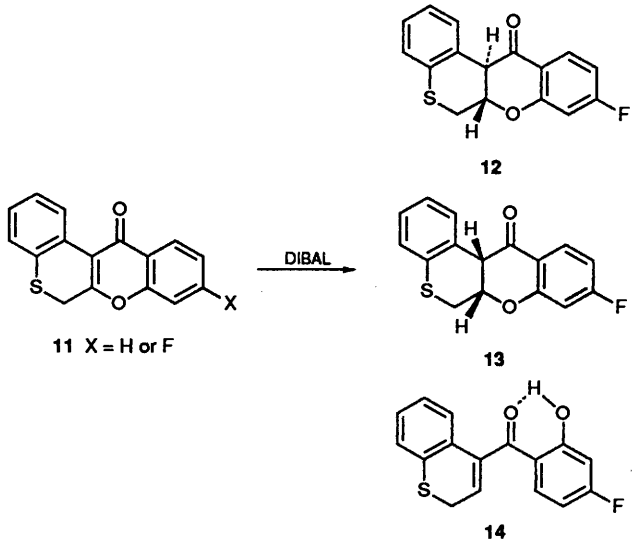
The ^{1}H NMR spectrum of **10** (X = H) revealed a low field exchangeable signal at δ 16.2 which together with the absence of a signal for 4-H and IR absorption bands at *ca.* 1650 cm^{-1}, assigned to a benzylic carbonyl group, and 3300 cm^{-1} indicated complete conversion of the 3-carbonyl group into its enol tautomer. The fluoro derivative **10** (X = F) is similarly completely enolised. The presence of the carbonyl groups is clearly demonstrated by the ^{13}C NMR spectra which display low field signals at *ca.* δ 196 and 177, typical of aliphatic and benzylic carbonyl functions. ^{13}C–^{19}F Coupling was observed for both **10** (X = H) and **10** (X = F) and follows the expected

trend,[18] decreasing with the number of intervening bonds from $^1J_{CF}$ 257 Hz to $^4J_{CF}$ 3.2 Hz.

Heating these enolised diketones above their melting points or refluxing them in toluene containing an excess of K_2CO_3 effected cyclisation to the 6*H*,12*H*-[1]benzothiopyrano[3,4-*b*]-[1]benzopyran-12-ones **11** (X = H, F) in high yield. Intramolecular cyclisation involving nucleophilic displacement of fluoride has previously been reported in a synthesis of chromones.[19]

Molecular models indicate the tetracyclic structures **11** (X = H or F) to be relatively planar overall and the signals for 1-H and 11-H are shifted downfield by the anisotropic carbonyl group giving signals at δ *ca.* 8.6 and 8.3, respectively. The integrity of the α,β-unsaturated carbonyl group is confirmed by the presence of a low field ^{13}C signal at δ *ca.* 175[20] and an IR stretching band at *ca.* 1645 cm^{-1}.

Several procedures have been reported for the conversion of dehydrorotenones into rotenones. Commonly, borohydride reduction affords the saturated alcohol, which is carefully re-oxidised in a subsequent operation.[1,21] More recently, diisobutylaluminium hydride (DIBAL) has been shown to effect the exclusive reduction of the C=C double bond to afford the unnatural *trans*-B/C fused isomers, which are readily epimerised to the naturally occurring *cis*-B/C fused isomers on treatment with acid.[22]



Treatment of a cold solution of **11** (X = F) in anhydrous THF under argon with 2.5 equiv. of DIBAL resulted in the rapid formation of three new components as indicated by TLC examination of the reaction mixture. Aqueous work-up according to the described procedure[22] and elution from silica gave both the (±)*trans*- and (±)*cis*-B/C fused ring isomers **12** and **13** respectively, together with a small quantity of a viscous orange oil which was spectroscopically characterised as the thiochromene **14** resulting from a retro-Michael reaction. The most striking spectroscopic feature of the ^1H NMR of this compound was the presence of a low field doublet at δ 12.4 assigned to the hydrogen bonded hydroxy proton split by the aromatic fluorine substituent, $^5J_{HF}$ 1.5 Hz. It is noteworthy that the chemoselective reduction of 2-methylisoflavones to the corresponding isoflavanones with DIBAL is not stereospecific and gives a mixture of the *cis*- and *trans*-isomers[23] as observed here. However, Crombie *et al.* noted the formation of the *trans*-B/C ring isomer during the reduction of several 6a,12a-dehydrorotenoids.[22]

The *cis*- and *trans*-isomers **12** and **13** are distinguishable by ^1H NMR spectroscopy. The spectrum of the *trans*-B/C ring isomer displays a doublet at δ 4.15 assigned to 12a-H, with a coupling constant of 12.3 Hz, reflecting a *trans* orientation of the 6a- and 12a-protons. Furthermore, 1-H appears at δ 7.65, deshielded by the 12-carbonyl function in a flattened *trans*-B/C structure, which is characteristic of the *trans*-rotenones.[22] Indeed it has been suggested that the chemical shift of 1-H may be used as a simple diagnostic tool for distinguishing between *cis*- and *trans*-rotenones.[24]

For the *cis*-B/C ring isomer **13**, 1-H is shifted upfield, resonating at δ 7.08 presumably as a result of the 'bent ridge tile' structure associated with the naturally occurring rotenones.[25] The conformation of the *cis*-B/C isomer is further corroborated by the magnitude of the coupling constant between the 6a- and 12a-protons which is considerably smaller (4 Hz) than that of the *trans*-B/C isomer.[12] These isomers can be further distinguished by the chemical shift of C-6a at δ 79.5 for the *trans*-B/C isomer, 5.5 ppm downfield of the corresponding signal of the *cis*-isomer. The presence of the sulfur heteroatom exerts a marked upfield shift on C-6 which resonates in the range δ 28–31 rather than the typical range of δ 65.5–66.5 noted for the oxygen analogues.[26]

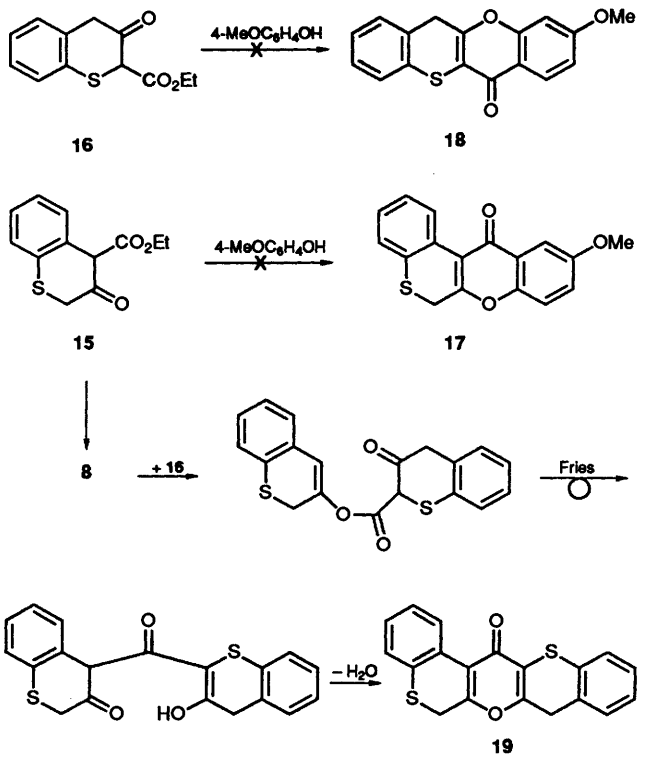
The *trans*-B/C thiorotenoid **12** is not as labile as the related oxygen analogue which readily epimerises to the thermodynamically more stable *cis*-B/C fused isomer *via* acid-promoted enolisation of the 12-carbonyl function. No *cis*-B/C isomer could be detected in the ^1H NMR spectrum of a 3-day-old solution of the *trans*-B/C isomer in $CDCl_3$. This solution was then treated with an acidic perfluorinated ion exchange membrane (Nafion®) and allowed to stand for 3 weeks. The ^1H NMR spectrum of the filtered solution did not display any signals which could be attributed to the *cis*-B/C ring isomer.

The availability of the diacid **7** together with the established synthesis of dehydrorotenones by the thermal condensation of 4-ethoxycarbonylchromenes with activated phenols[8] prompted an investigation into an alternative synthesis of the dehydrothiorotenoid system **11** (X = H) by this route. Esterification of the diacid **7** and subsequent Dieckmann cyclisation of the diester using sodium in refluxing toluene according to the literature procedure[27] gave a 4:1 mixture of 4-ethoxycarbonyl-**15** and 2-ethoxycarbonyl-thiochroman-3-ones **16**, which could not be separated by column chromatography. This assignment and ratio is based upon comparison of the signals at δ 3.56 and 3.77 in the ^1H NMR spectrum of the mixture. The former signal is assigned to the S–CH_2 function of the 4-ethoxycarbonyl isomer by analogy with the corresponding protons in thiochroman-3-one (S–CH_2, δ 3.34) and 4-(2-fluorobenzoyl)-thiochroman-3-one (S–CH_2, δ 3.42). The latter signal is assigned to the benzylic methylene protons of the 2-ethoxycarbonyl isomer.

The keto esters **15** and **16** were heated with 4-methoxyphenol at 160 °C under reduced pressure (12–13 mmHg) for 7 h (Scheme 2). However none of the dehydrothiorotenoid **17** or the isomer **18** was formed. Chromatography provided 4-methoxyphenol, some thiochroman-3-one and a new compound identified as the pentacyclic system **19**.

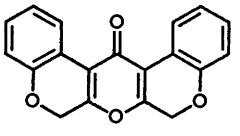
The ^1H NMR spectrum of **19** displayed signals at δ 3.73 and 4.01 each accounting for two protons and a double doublet at δ 8.56. The remaining signals fell within the range δ 7.19–7.41. The IR spectrum indicated the presence of an α,β-unsaturated carbonyl group (ν_{CO} 1641 cm^{-1}) which is confirmed by the presence of a signal at δ 172.0 in the ^{13}C NMR spectrum.

The formation of **19** is thought to occur by a facile 4-de-ethoxycarbonylation of **15** to afford thiochroman-3-one. Trans-esterification of the 2-ethoxycarbonylthiochroman-3-one with enolised thiochroman-3-one followed by a Fries rearrangement and dehydrative ring closure results in **19** (Scheme 2). Similar facile de-ethoxycarbonylation has been previously reported for



Scheme 2

some tetralone and chromanone analogues.[28,29] Furthermore, the bis[1]benzopyranopyranone **20** has been obtained by heating chroman-3-one with its 4-ethoxycarbonyl derivative.[29]



20

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. Fourier Transform IR 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. Flash chromatographic separations were performed on Crossfields Sorbsil C60 silica gel (M.P.D. 60 Å, 40–60μ, activated) according to the published procedure.[30] The preparation of the diacid **7**, thiochroman-3-one and 3-pyrrolidinothiochromene have been described.[14,16]

4-(2-*Fluorobenzoyl*)*thiochroman*-3-*one* **10** (X = H).—A solution of 2-fluorobenzoyl chloride (6.9 mmol) in 1,2-dichloroethane (20 cm^3) was added dropwise over 10 min to a stirred solution of 3-pyrrolidino-2*H*-thiochromene[16] in 1,2-dichloroethane (20 cm^3) under argon at 0 °C. The resulting solution was refluxed for 2 h prior to the cautious addition of dil. HCl (5%; 15 cm^3) whereupon the resulting biphasic system was refluxed for a further 30 min. The cooled solution was poured into water (100 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were washed with saturated $NaHCO_3$ solution (2 × 50 cm^3) and water (100 cm^3). Removal of the dried (Na_2SO_4) solvent gave a brown semi-solid which was eluted from silica with ethyl acetate and hexane (1:3) to afford initially thiochroman-3-one (15%) followed by the *title compound* (42%), m.p. 132.0–133.5 °C, as pale yellow needles from hexane and ethyl acetate, ν_{max}(Nujol)/cm^{-1} 1654 (CO) and 3300 (OH); δ_H 3.42 (2 H, s, 2-H), 6.63–6.68 (2 H, m, Ar-H), 6.91–7.16 (3 H, m, Ar-H), 7.35–7.42 (3 H, m, Ar-H) and 16.15 (1 H, s, OH); δ_C† 36.0 (C-2), 112–133 (12 × C), 159.2 (C-2′, d, $^1J_{CF}$ 251.4), 177.0 (C=O) and 196.2 (C-3) (Found: C, 67.1; H, 3.9; S, 11.3. $C_{16}H_{11}FO_2S$ requires C, 67.1; H, 3.9; S, 11.2%).

4-(2,4-*Difluorobenzoyl*)*thiochroman*-3-*one* **10** (X = F) (61%), m.p. 134.5–136.5 °C, as pale orange needles from hexane and ethyl acetate, was obtained using a similar procedure except that DMAP (0.2 g) was added to the solution of 2,4-difluorobenzoyl chloride prior to addition to the cold solution of the enamine, ν_{max}(Nujol)/cm^{-1} 1649 (CO) and 3300 (OH); δ_H 3.42 (2 H, s, 2-H), 6.64–6.70 (2 H, m, Ar-H), 6.82–6.89 (2 H, m, Ar-H), 7.00–7.04 (1 H, m, Ar-H), 7.38–7.43 (2 H, m, Ar-H) and 16.07 (1 H, s, OH); δ_C 35.9 (C-2), 104.8 (C-3′, t, $^2J_{CF}$ 25.4), 112.0 (C-5′, dd, $^2J_{CF}$ 19.6, $^4J_{CF}$ 3.2), 120.6 (C-1′, dd, $^2J_{CF}$ 16.4, $^4J_{CF}$ 3.6), 126.0–128.8 (7 × C), 132.5 (C-6′, d, $^3J_{CF}$ 11.5), 159.9 (C-2′, dd, $^1J_{CF}$ 257, $^3J_{CF}$ 12.2), 164.5 (C-4′, dd, $^1J_{CF}$ 254, $^3J_{CF}$ 12.3), 176.0 (C=O) and 196.1 (C-3) (Found: C, 62.8; H, 3.2; S, 10.7. $C_{16}H_{10}F_2O_2S$ requires C, 63.1; H, 3.3; S, 10.5%).

6H,12H-[1]*Benzothiopyrano*[3,4-b][1]*benzopyran*-12-*one* **11** (X = H).—A solution of 4-(2-fluorobenzoyl)thiochroman-3-one (2 mmol) in toluene (30 cm^3) containing K_2CO_3 (4 mmol) was refluxed for 90 min. The cooled solution was diluted with water (100 cm^3) and extracted with ethyl acetate (3 × 50 cm^3). Evaporation of the dried (Na_2SO_4) extracts gave the *benzothiopyranobenzopyran* **11** (X = H) (97%), m.p. 117.0–118.5 °C, as pale brown needles from hexane and ethyl acetate, ν_{max} (Nujol)/cm^{-1} 1650 (CO); δ_H 3.79 (2 H, s, 6-H), 7.20–7.34 (2 H, m, Ar-H), 7.39–7.46 (3 H, m, Ar-H), 7.62–7.70 (1 H, m, Ar-H), 8.29 (1 H, dd, *J* 7.9 and 1.5, 11-H) and 8.57 (1 H, dd, *J* 7.9 and 1.4, 1-H); δ_C 29.1 (C-6), 116–133 (12 × C), 154.7 (C-7a), 160.8 (C-6a) and 175.0 (C-12) (Found: C, 72.3; H, 3.7; S, 12.1. $C_{16}H_{10}O_2S$ requires C, 72.2; H, 3.8; S, 12.0%).

9-*Fluoro*-6H,12H-[1]*benzothiopyrano*[3,4-b][1]*benzothiopyran*-12-*one* **11** (X = F) was similarly obtained (93%), m.p. 166.5–167.5 °C, ν_{max}(Nujol)/cm^{-1} 1641 (CO); δ_H 3.78 (2 H, s, 6-H), 7.11–7.33 (4 H, m, Ar-H), 7.39–7.43 (1 H, m, Ar-H), 8.30–8.34 (1 H, m, 11-H) and 8.53 (1 H, dd, *J* 8.0 and 1.4, 1-H); δ_C 29.1 (C-6), 104.3 (C*-8, d, $^2J_{CF}$ 25.7), 114.1 (C*-10, d, $^2J_{CF}$ 23.1), 116–130 (8 × C), 129.1 (C-11, d, $^3J_{CF}$ 10.6), 155.6 (C-7a, d, $^3J_{CF}$ 15.1), 160.9 (C-6a), 165.5 (C-9, d, $^1J_{CF}$ 255) and 174.2 (C-12) (Found: C, 67.8; H, 3.2; S, 11.5. $C_{16}H_9FO_2S$ requires C, 67.6; H, 3.2; 11.3%).

Reduction of 9-*Fluoro*-6H,12H-[1]*benzothiopyrano*[3,4-b]-[1]*benzothiopyran*-12-*one*.—Diisobutylaluminium hydride in toluene (1.5 mol dm^{-3}; 3.6 mmol) was added to **11** (X = F) (1.4 mmol) in anhydrous THF (20 cm^3) at −70 °C and the mixture was stirred for 1 h under argon. After warming to room temperature, methanol (5 cm^3) was added and the solution was stirred for a further 30 min. The resulting pale yellow solution was poured into HCl (1 mol dm^{-3}; 50 cm^3) and rapidly extracted with dichloromethane (4 × 20 cm^3). The combined extracts were washed with an aqueous suspension of calcium carbonate and brine (2 × 50 cm^3) and water (50 cm^3). Evaporation of the dried (Na_2SO_4) solvent gave a pale yellow solid which was

† ^{13}C assignments followed by $^+$ or * are tentative assignments only and may be reversed. C′ indicates benzoyl group carbons.

eluted from silica with ethyl acetate and hexane (1:9) to give (a) (±) trans-6a,12a-*dihydro*-9-*fluoro*-6H,12H-[1]*benzothiopyrano*[3,4-b][1]*benzopyran*-12-*one* **12** (37%), m.p. 132.5–134.5 °C, as colourless needles from hexane, ν_{max}(Nujol)/cm^{-1} 1690 (CO); δ_H 3.19 (1 H, dd, *J* 12.3 and 3.7, 6-H$_a$), 3.41 (1 H, dd, *J* 12.2 and 10.4, 6-H$_b$), 4.15 (1 H, d, *J* 12.3, 12a-H), 4.83–4.94 (1 H, m, 6a-H), 6.72 (1 H, dd, $^3J_{HF}$ 9.6, J_m 2.4, 8-H), 6.76–6.83 (1 H, m, 10-H), 7.16–7.20 (3 H, m, Ar-H), 7.65 (1 H, m, 1-H) and 7.97 (1 H, dd, J_o 8.7, $^4J_{HF}$ 6.5, 11-H); δ_C 30.9 (C-6), 50.8 (C-12a), 79.5 (C-6a), 104.3 (C$^+$-10, d, $^2J_{CF}$ 24.0), 110.1 (C$^+$-8, d, $^2J_{CF}$ 22.8), 118.9 (C-12b), 124.7 (C-4), 127.1 (C-11a), 127.3 (C*-3), 127.5 (C*-2), 130.4 (C-11, d, $^3J_{CF}$ 10.7), 132.1 (C-4a), 132.6 (C-1), 161.7 (C-7a, d, $^3J_{CF}$ 13.3), 167.2 (C-9, d, $^1J_{CF}$ 257) and 188.8 (C-12) (Found: C, 67.0; H, 3.8; F, 6.8; S, 11.4. $C_{16}H_{11}FO_2S$ requires C, 67.1; H, 3.9; F, 6.6; S, 11.2%); (b) (±) cis-6a,12a-*dihydro*-9-*fluoro*-6H,12H-[1]*benzothiopyrano*[3,4-b][1]*benzopyran*-12-*one* **13** (44%), m.p. 128.0–129.5 °C, as colourless needles from hexane, ν_{max}(Nujol)/cm^{-1} 1689 (CO); δ_H 3.27 (1 H, dd, *J* 13.1 and 3.3, 6-H$_a$), 3.39 (1 H, dd, *J* 13.1 and 6.9, 6-H$_b$), 3.96 (1 H, d, *J* 4.0, 12a-H), 5.20–5.26 (1 H, m, 6a-H), 6.63–6.78 (2 H, m, 8-H, 10-H), 7.08 (4 H, m, Ar-H, 1-H) and 7.94 (1 H, dd, J_o 8.7, $^4J_{HF}$ 6.6, 11-H); δ_C 28.3 (C-6), 49.3 (C-12a), 74.0 (C-6a), 104.7 (C$^+$-10, d, $^2J_{CF}$ 24.7), 110.2 (C$^+$-8, d, $^2J_{CF}$ 23.1), 116.3 (C-12b), 124.8 (C-4), 126.1 (C-11a), 126.6 (C*-3), 128.0 (C*-2), 130.1 (C-11, d, $^3J_{CF}$ 11.6), 130.5 (C-4a), 131.5 (C-1), 161.5 (C-7a, d, $^3J_{CF}$ 13.1), 167.6 (C-9, d, $^1J_{CF}$ 257) and 189.5 (C-12) (Found: C, 67.0; H, 3.8; F, 6.6; S, 11.2. $C_{16}H_{11}FO_2S$ requires C, 67.1; H, 3.9; F, 6.6; S, 11.2%) and (c) 4-(4-*fluoro*-2-*hydroxybenzoyl*)-2H-*thiochromene* **14** (8%), as a viscous orange oil, δ_H 3.51 (2 H, d, *J* 6.8, 2-H), 6.22 (1 H, d, *J* 6.9, 3-H), 6.44–6.51 (1 H, m, ArF-H), 6.65–6.70 (1 H, m, ArF-H), 7.03–7.19 (3 H, m, Ar-H), 7.33–7.37 (1 H, m, Ar-H), 7.43–7.50 (1 H, m, Ar-H) and 12.36 (1 H, d, $^5J_{HF}$ 1.5, OH).

Ethyl 2-(*Ethoxycarbonylmethylthio*)*phenylethanoate*.—A solution of the diacid **7** (33 mmol) in ethanol (150 cm^3) containing concentrated sulfuric acid (1.5 cm^3) was boiled under reflux for 3 h. Removal of the ethanol (100 cm^3) gave a pale brown solution which was poured into water (400 cm^3) and extracted with ethyl acetate (4 × 70 cm^3). The combined extracts were washed with saturated $NaHCO_3$ (5 × 100 cm^3) and water (100 cm^3). Removal of the dried (Na_2SO_4) solvent gave the ester (94%), b.p. 155 °C at 6 × 10^{-2} mmHg, as a colourless oil; δ_H 1.16–1.28 (6 H, m, CH_3), 3.57 (2 H, s, S-CH_2), 3.88 (2 H, s, Ph-CH_2), 4.07–4.20 (4 H, m, CH_2) and 7.21–7.53 (4 H, m, Ar-H).

6,8-*Dihydro*-14H-*bis*[1]*benzothiopyrano*[3,2-b:4′,3′-e]*pyran*-14-*one* **19**.—A solution of the foregoing diester (29 mmol) in dry toluene (100 cm^3) was added dropwise to a stirred refluxing suspension of sodium (36 mmol) in dry toluene (100 cm^3) under argon over 1 h. The resulting orange solution was refluxed for a further 4 h. The cold reaction mixture was cautiously acidified with aqueous acetic acid (10%; 200 cm^3) and extracted with diethyl ether (4 × 75 cm^3). The combined ethereal extracts were washed with saturated $NaHCO_3$ (5 × 70 cm^3) and water (2 × 100 cm^3). Removal of the dried (Na_2SO_4) solvent gave a bright orange oil which was distilled at 140 °C at 6 × 10^{-2} mmHg to yield a mixture of 4-ethoxycarbonylthiochroman-3-one **15** and 2-ethoxycarbonylthiochroman-3-one **16** (4:1) (70%); δ_H 1.05–1.11 (3 H, t, *J* 7.3, 2-CH_2CH_3), 1.34–1.39 (3 H, t, *J* 7.2, 4-CH_2CH_3), 3.56 (2 H, s, SCH_2), 3.77 (2 H, s, $PhCH_2$), 4.09 (2 H, q, *J* 7.3, 2-CH_2CH_3), 4.33 (2 H, q, *J* 7.2, 4-CH_2CH_3), 7.25–7.45 (4 H, m, Ar-H), 12.23 (1 H, s, OH) and 13.63 (1 H, s, OH).

A mixture of 4-methoxyphenol (3.4 mmol) and the ethoxycarbonylthiochroman-3-one isomers (4.2 mmol) was heated at 160 °C at 12–13 mmHg for 7 h. The resulting dark red brown solid was eluted from silica with ethyl acetate in hexane (1:4) to afford (a) thiochroman-3-one **8** (14%) and (b) the *title pentacycle* **19** (26%), m.p. 221.5–223.5 °C, as off-white needles, ν_{max}(Nujol)/cm^{-1} 1641 (CO); δ_H 3.73 (2 H, s, 6-H), 4.01 (2 H, s, 8-H), 7.19–7.41 (7 H, m, Ar-H) and 8.56 (1 H, dd, *J* 8.1 and 1.7, 1-H); δ_C 28.3 (C-6), 34.9 (C-8), 117.4 (C-14a), 122.1 (C-13a), 126.3-131.2 (12 × C), 153.8 (C-7a), 159.3 (C-6a) and 172.0 (C-14) (Found: C, 67.6; H, 3.4; S, 18.9. $C_{19}H_{12}O_2S$ requires C, 67.8; H, 3.6; S, 19.0%).

Acknowledgements

We thank the N.A.B. for providing financial support for a research assistantship (to B. M. H.), Dr. M. T. Cox of I.C.I. Pharmaceuticals for his continued interest in this project and Dr. M. Kanjia for NMR spectra.

References

1 L. Crombie, *Fortschr. Chem. Org. Naturst.*, 1963, **21**, 275; A. S. Shawl, N. Mengi, L. N. Misra and Vishwapaul, *Phytochemistry*, 1988, **27**, 3331.
2 I. Yamamoto, *Annual Review of Entomology*, 1970, **15**, 257.
3 K. A. Haque, *Pak. J. Sci. Ind. Res.*, 1971, **14**, 385.
4 J. Nawrot, J. Harmatha, I. Kostova and I.Ognayanov, *Biochem. Syst. Ecol.*, 1989, **17**, 55.
5 A. Takatsuki, N. Nakatana, M. Morimoto, G. Tamura, M. Matsui, K. Arima, I. Yamaguchi and T. Misato, *Appl. Microbiol.*, 1969, **18**, 660.
6 M. Miyano, A. Kobayashi and M. Matsui, *Bull. Agr. Chem. Soc.*, 1960, **24**, 540.
7 M. Miyano, *J. Am. Chem. Soc.*, 1965, **87**, 3958.
8 M. Baran-Marszak, J. Massicot and D. Molho, *Bull. Chem. Soc. Fr.*, 1971, 191.
9 L. Crombie, P. W. Freeman and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1970, 563; L. Crombie, P. W. Freeman and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1277.
10 H. Omakawa and K. Yamashita, *Agr. Biol. Chem.*, 1973, **37**, 195.
11 S. M. F. Lai, J. J. A. Orchinson and D. A. Whiting, *Tetrahedron*, 1989, **45**, 5895.
12 S. A. Ahmed-Junan, P. C. Amos and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1992, 539.
13 L. Crombie, J. L. Josephs, J. Larkin and J. B. Weston, *J. Chem. Soc., Chem. Commun.*, 1991, 972.
14 C. D. Gabbutt, J. D. Hepworth and B. M. Heron, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2603.
15 B. M. Heron, Ph.D. Thesis, Council for National Academic Awards, 1992.
16 P. D. Clark and D. McKinnon, *Can. J. Chem.*, 1982, **60**, 243.
17 E. F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129; T. H. Black, *Org. Prep. Proced. Int.*, 1988, **21**, 181.
18 F. W. Wehrli, A. P. Marchand and S. Wehrli, *Interpretation of Carbon-13 NMR Spectra*, 2nd edn., Wiley, New York, 1988.
19 G. M. Coppola and R. W. Dodsworth, *Synthesis*, 1981, 523.
20 T. N. Huckerby and G. Sunman, *J. Mol. Struct.*, 1979, **56**, 87; H. C. Jha, F. Zilliken and E. Breitmaier, *Can. J. Chem.*, 1980, **58**, 1211.
21 M. Miyano and M. Matsui, *Bull. Agric. Chem. Soc. Jpn.*, 1958, **22**, 128; *Chem. Ber.*, 1958, **91**, 2044.
22 M. J. Begley, L. Crombie, A. Hamid bin A. Hadi and J. L. Josephs, *J. Chem. Soc., Perkin Trans. 1*, 1989, 204.
23 S. Antus, A. Gottsegen and M. Nogradi, *Synthesis*, 1981, 574.
24 L. Crombie and J. W. Lown, *J. Chem. Soc.*, 1962, 775.
25 M. J. Begley, L. Crombie and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1975, 850.
26 R. Nunlist and J. Ralph, *J. Heterocycl. Chem.*, 1988, **25**, 351; L. Crombie, G. W. Kilbee and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1497.
27 R. Verhe and N. Schamp, *Bull. Soc. Chim. Belg.*, 1973, **82**, 283; R. Verhe, N. De Kimpe, L. De Buyck, W. Steurbaut, M. Sadones, R. Willaert, J.-P. Verbeek and N. Schamp, *Bull. Soc. Chim. Belg.*, 1980, **89**, 459.
28 R. Verhe, L. De Buyck, N. De Kimpe and N. Schamp, in *Bio-Organic Heterocycles*, eds. H. C. Van der Plas, M. Simonyi, F. C. Alderweireldt and J. A. Lepoivre, Elsevier, Amsterdam, 1986.
29 N. P. Peet and S. Sunder, *J. Heterocycl. Chem.*, 1981, **18**, 1123.
30 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

Paper 2/04303C
Received 10*th August* 1992
Accepted 26*th August* 1992