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Synthesis and Reactivity of Some Thiochroman-3,4-diones.

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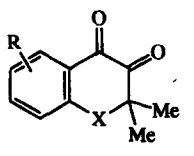
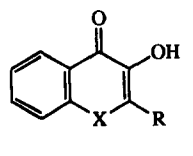
Abstract: Thiochroman-3,4-diones, which result from the reaction of thiochroman-4-ones with isoamyl nitrite, form fused heterocycles on reaction with 1,2-diamines and with *p*-anisaldehyde and ammonium acetate. Cyclopenta-[*c*][1]benzothiopyran-2-one, formed on reaction with dibenzyl ketone, yields a dibenzo[*bd*]thiopyran after cycloaddition of DMAD. With methyl magnesium iodide, a mixture of thiochroman- 3- and 4-ols is formed which was separated only after the selective dehydration of the 4-ol. The resulting 4-methylene derivative was isolated as the hetero Diels-Alder spiro-linked adduct.

Introduction

Despite the well established value of 1,2-diketones in synthesis, the synthesis and chemistry of chroman- and thiochroman-3,4-diones (1a,b) has evoked relatively little interest. This feature is partly a consequence of the quite variable success attending the application of standard oxidative procedures to chroman-4-ones.[1] 3-Hydroxyflavan-4-ones (2a) have been obtained by the dye-sensitized photo-oxidation of chalcones,[2] by the direct oxidation of flavan-4-ones using periodic acid in methanol[3] and by reaction with amyl nitrite.[4] Similarly, oxidation of 2-methylchroman-4-one with isoamyl nitrite affords the 3-hydroxychromone tautomer (2b).[5] Several flavanones have been converted to 3-acetoxyflavones by oxidation with lead (IV) acetate.[6] The synthesis of 2,2-dimethylchroman-3,4-diones (1a) has been achieved by oxidation of chroman-4-ones with isoamyl nitrite[7,8] and by oxidation of a chroman-3-one unit with selenium dioxide.[9] The synthetic potential of these chroman-3,4-diones is illustrated by their conversion to [1]benzopyrano[3,4-*b*]pyrazines,[7] [1]benzopyrano[3,4-*b*]quinoxalines,[10,11] azaquinoxalines[8] and [1]benzo-pyrano[3,4-*e*][1,2,4]triazines.[12]

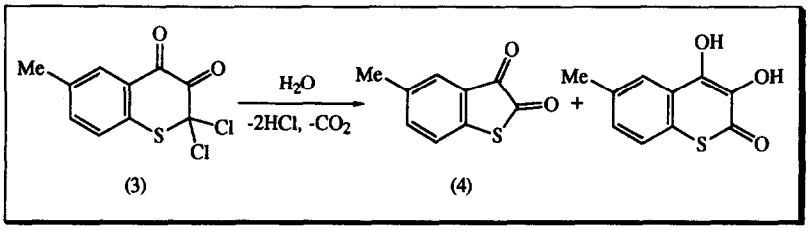


(1a) X = O; R = H
(1b) X = S; R = H
(1c) X = S; R = 6-Me
(1d) X = S; R = 5,6-Benzo



(2a) X = O; R = Ph
(2b) X = O; R = Me
(2c) X = S; R = Me

In marked contrast to the oxygen analogue (1a), the thiochroman-3,4-dione system is virtually unknown. The 2-methyl analogue, obtained by hydrolysis of 3-(4-dimethylaminophenylimino)-2-methylthiochroman-4-one, exists as the 3-hydroxythiochromone tautomer (2c).[13] 2,2-Dichlorothiochroman-3,4-dione, (3) obtained by chlorination of 3-hydroxy-6-methylthiochromone with sulfuryl chloride, is hydrolysed principally to the benzo[*b*]thiophene-2,3-dione (4) by elimination of the C-2 function as carbon dioxide.[14]

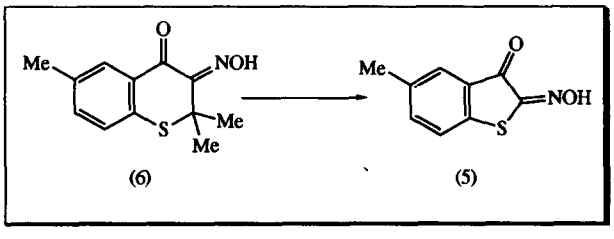


Previous attempts to obtain these diones by hydrolysis of 3-chloro-3-sulfenamidothiochroman-4-ones, readily available from the reaction of excess thionyl chloride with the thiochroman-4-one and subsequent reaction of the 3-chloro-3-chlorosulfenyl intermediates with a secondary amine, failed, giving instead 3-chlorothiochroman-4-ones and on further reaction the benzo[*b*]thiophenes.[15] We now report our studies on the synthesis and chemistry of some 2,2-dimethylthiochroman-3,4-diones.

Discussion

Treatment of an alcoholic solution of 2,2-dimethylthiochroman-4-one with an excess of isoamyl nitrite and concentrated hydrochloric acid gave the thiochroman-3,4-dione (1b) in excellent yield as bright orange crystals. The 2,2,6-trimethyl analogue (1c) and the 5,6-benzologue (1d) were similarly obtained from the respective thiochroman-4-ones. 2-Methyl-3-hydroxythiochromone (2c) was obtained by a similar procedure from both 2-methylthiochroman-4-one and the isomeric thiochroman-3-one.

An additional product was isolated from the reaction of isoamyl nitrite with 2,2,6-trimethylthiochroman-4-one. This relatively polar compound was identified as the benzo[*b*]thiophene (5),[16] presumably formed by the ring contraction of the intermediate 3-hydroxyimino-2,2,6-trimethylthiochroman-4-one (6) which proceeds by way of a thiiranium cation and expulsion of acetone or acetone oxime. Ring contraction of thiochromans with a suitably disposed 3-substituent is well documented.[15,17]

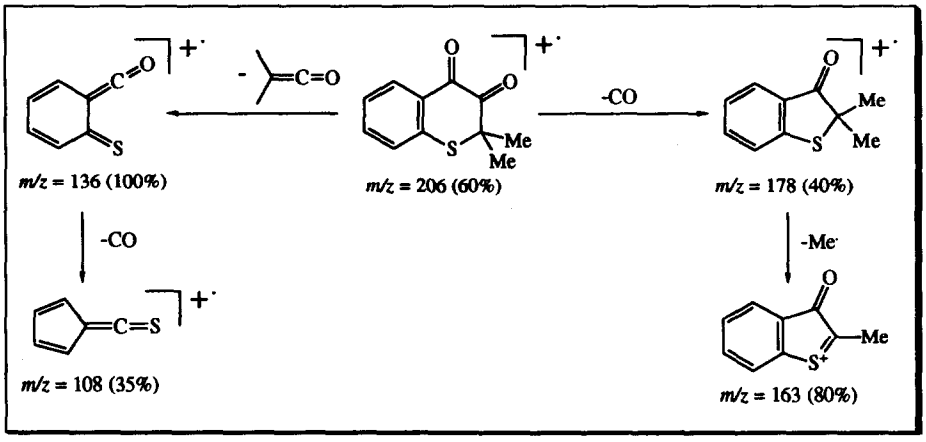


The most notable feature in the ^1H NMR spectra of the diketones (1b,c,d) is the absence of a signal at ~δ 2.8 associated with the C-3 methylene protons of the starting thiochroman-4-ones.[18] The geminal methyl

groups are equivalent and absorb at approximately δ 1.6, shifted marginally downfield compared with the those of the thiochroman-4-ones as a result of their proximity to the anisotropic 3-carbonyl function.

The ^{13}C NMR spectra of these compounds are much more informative and display low field signals at ~δ 183 and δ 194, which are assigned to C-4 and C-3, respectively. The carbons of the geminal methyl group are equivalent and absorb in the range δ 22-23, whilst C-2, adjacent to the sulfur heteroatom, resonates at ~δ 54, shifted downfield compared with C-2 of 2,2-dimethylthiochroman-4-one (δ 44).[19] The aromatic carbons fall within the range δ 125-143.

A low resolution electron impact mass spectrum and the proposed fragmentation pathways are illustrated below. The fragmentation pattern is common to all of the thiochroman-3,4-diones prepared in this work. An M-15 fragment is not observed, a feature which is characteristic of both 2,2-dimethylchroman- and 2,2-dimethyl-thiochroman -4-ones.[20]



The infrared spectra of these compounds display two distinct absorption bands at approximately 1720 and 1675 cm^{-1} assigned to the 3- and 4-carbonyl functions respectively, as in the case of the oxygen analogues.[8]

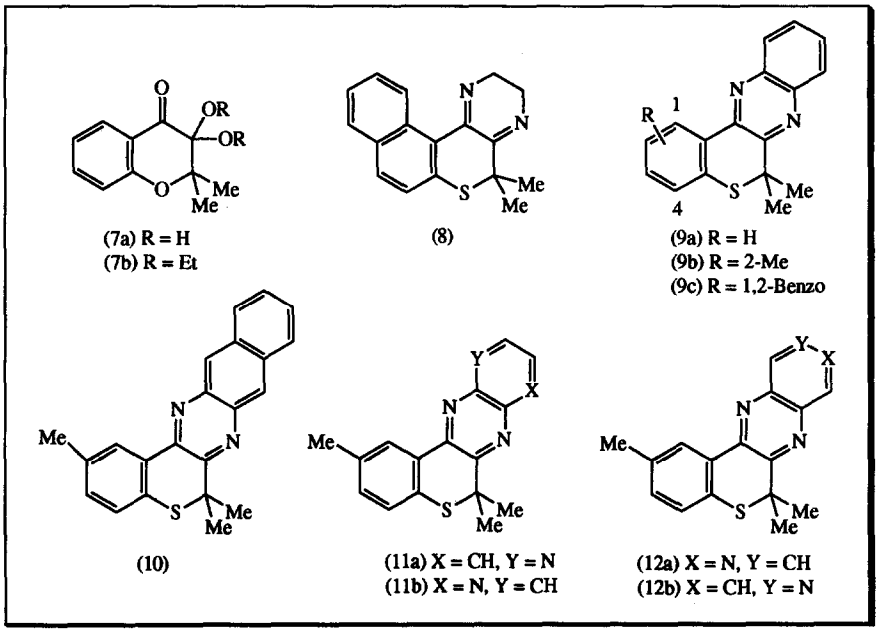
An investigation into alternative syntheses of the thiochroman-3,4-diones was also undertaken. Selenium dioxide is a versatile oxidising reagent[21] which readily oxidises methylene ketones to the dicarbonyl compounds. Refluxing a solution of 2-methylthiochroman-3-one and SeO_2 in aqueous dioxane afforded the 3-hydroxy-thiochromone (2b), but little success attended the corresponding reaction with 2,2-dimethyl-thiochroman-4-one and only a 2 % yield of the diketone (1b) was obtained. Some improvement in the yield of (1b) (10 %) was recorded when a catalytic amount of trifluoroacetic acid was added to the reaction mixture followed by the portionwise addition of further SeO_2 to the refluxing solution.

The low yield of the diketone (1b) from this route is attributed to the reluctance of the carbonyl group in thiochroman-4-ones to enolise, a well established feature of thiochroman-3-ones,[22] since the mechanism of this oxidative route relies upon appreciable enolisation of the substrate as a key step.[23]

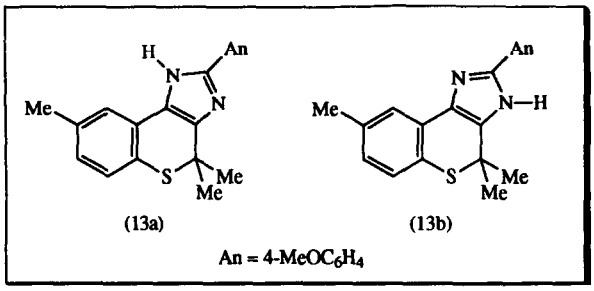
In marked contrast to the oxygen analogues (1a), the diones obtained in this work were not prone to the facile and reversible covalent hydrate (7a) and hemiketal formation (7b)[8] even when subjected to prolonged reflux in water, dilute acid or methanol. This feature may be due to subtle interplay between internal strain of the respective heterocyclic rings and the electronic characteristics of what are effectively vinylogous ester and

thioester functions. The facile formation of covalent hydrates from cyclic 1,2-diketones is common and their formation has been explained by assuming that hydration is accompanied by some reduction in the strain associated with the cyclic system.[24]

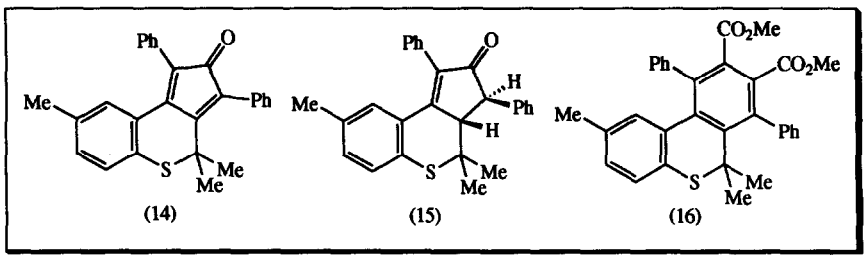
The thiochroman-3,4-diones readily condensed with 1,2-diaminoethane, 1,2-diaminobenzene and 2,3-diaminonaphthalene to afford the 5*H*-naphtho[2,1-*b*]thiopyrano[1,2-*b*]pyrazine (8), [1]benzothiopyrano-[3,4-*b*]quinoxaline (9a,b) and the benzologue (9c), and [1]benzothiopyrano[3,4-*b*]benzo[*g*]quinoxaline (10). Condensation with 2,3-diaminopyridine and 3,4-diaminopyridine gave isomeric mixtures of the azaquinoxalines (11a,b) and (12a,b) respectively. The major isomer in each case (11a and 12a) is thought to arise from attack by the more nucleophilic 3-amino group on the more electrophilic 3-carbonyl function. The spectroscopic properties of these novel heterocyclic systems are comparable with those of the related oxygen analogues.[8,10,11] Notably, the 3-hydroxythiochromone (2c) failed to condense with 1,2-diaminobenzene even after prolonged reaction times.



Reaction of (1c) with *p*-anisaldehyde and an excess of ammonium acetate in refluxing ethanol, the Bredereck synthesis,[25] gave the novel [1]benzothiopyrano[3,4-*d*]imidazole system. The ^{1}H NMR spectrum of this compound displayed a broad signal at δ 7.3 for the NH proton. The equivalent C-2 methyl groups resonate at δ 1.7 and the methoxy group at δ 3.8. It is not possible to assign the precise structure of this imidazole as the 1*H*- (13a) or 3*H*- (13b) tautomer from these spectroscopic data. We infer from the simplicity of the 1H NMR spectrum that (13a) and (13b) are undergoing rapid prototopic interconversion, a process which is well documented for *N*-unsubstituted imidazoles.[26]

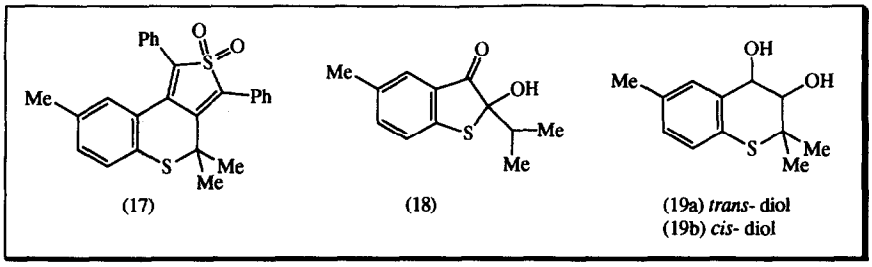


The base catalysed condensation of (1c) with dibenzyl ketone gave the intensly coloured (λ_{max} = 495 nm, ε = 8.4 x 10^3 mol $dm^{-3}cm^{-1}$) cyclopentadienone (14) together with a small amount of the dihydro-compound. The latter, initially obtained with some ethyl acetate of recrystallisation and which could only be removed by sublimation, has been assigned the structure (15). Assignment of the *trans* stereochemistry follows from the magnitude of $J_{3,3a}$ (2.5 Hz) which is comparable with those of other dihydrocyclopentadienones. A larger vicinal coupling (~ 7.5 Hz) is normally observed for the *cis* isomers.[27] Although the pathways leading to (15) are at present unclear, this process does appear to have a literature precedent; the condensation of 9,10-phenanthraquinone with dibenzyl ketone is particularly fickle, affording mixtures of phencyclone and 1,3-dihydrophencyclone.[28]



The structure of the cyclopentadienone (14) was further corroborated by its facile cycloaddition with dimethyl acetylenedicarboxylate (DMAD) to afford the dibenzo[*bd*]thiopyran (16). The ^{1}H NMR spectrum of this cycloadduct displayed a relatively broad signal at δ 1.24 which is assigned to the geminal dimethyl group. That the apparent loss of resolution of this signal is a consequence of a dynamic conformational inversion of the thiopyran ring was confirmed by variable temperature ^{1}H NMR experiments. Thus recording the spectrum at 45 °C caused the broad signal to intensify to a sharp singlet, whilst at -40 °C the broad signal was resolved into sharp signals at δ 1.08 and δ 1.39. The calculated coalescence temperature (T_c = 285 K) and free energy of the process ($\Delta G^{\#}$ = 69.6 KJmol^{-1} at 285K) are comparable with literature values for related dynamic processes.[29]

Attempts to prepare the thieno[3,4-*c*][1]benzothiopyran 2,2-dioxide (17) by base catalysed condensation of dibenzylsulfone with the dione (1c) failed. The only new product isolated from the multicomponent mixture was characterised as the 2,3-dihydrobenzo[*b*]thiophen-3-one (18) from its infrared spectrum (ν_{CO} = 1719, ν_{OH} = 3454 cm^{-1}) and its ^{1}H NMR spectrum which displayed doublets at δ 0.94 and δ 1.01 for the methyl groups and a multiplet at δ 2.18 for the methine proton for the diastereotopic isopropyl function. Rationalisation of the formation of this product remains uncertain.

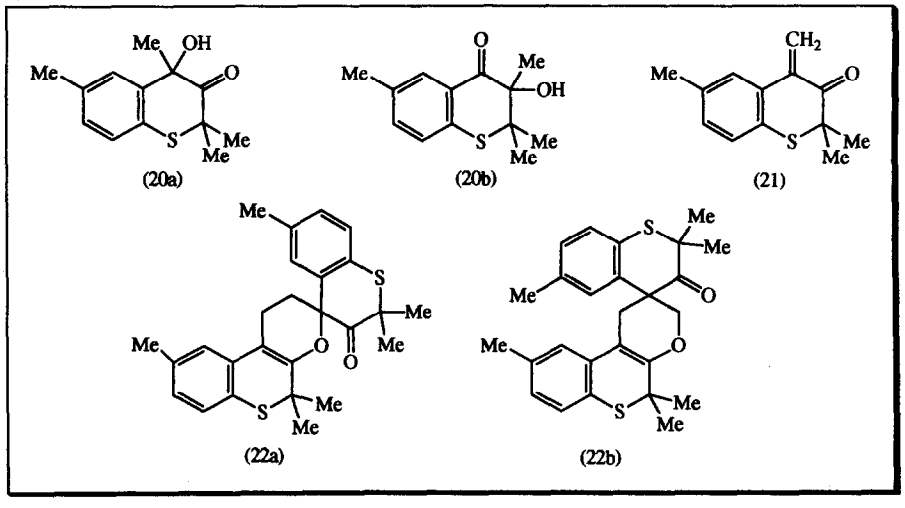


(17) (18) (19a) *trans*- diol (19b) *cis*- diol

Reduction of the thiochroman-3,4-dione (1c) was accomplished using sodium borohydride in refluxing ethanol. Investigation of the product by ^1H NMR spectroscopy indicated that both the *trans*- and *cis*-thiochroman-3,4-diol (19a,b) were formed, based on analysis of the coupling constants derived from the two AX patterns (δ 3.82 and δ 4.49; J = 8.9 Hz, transoid and δ 3.61 and δ 4.62; J = 3.9 Hz, cisoid).[30] These isomeric thiochroman-3,4-diols could not be separated by flash chromatography.

Re-oxidation of the thiochroman-3,4-diol (19) to the original diketone (1c) was readily accomplished in good yield on treatment with a four-fold excess of pyridinium chlorochromate[31] (PCC) in cold dichloromethane.

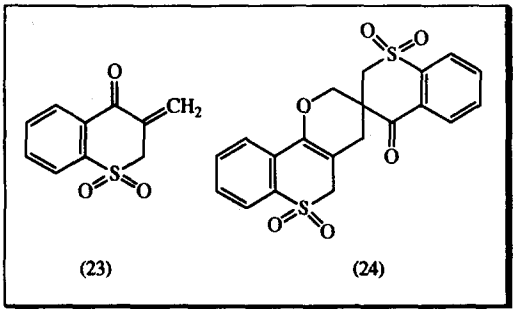
Reaction of the thiochroman-3,4-dione (1c) with one equivalent of methyl magnesium iodide gave a mixture of the keto-alcohols (20a) and (20b) which could not be separated. Thiochroman-4-ols are known to undergo a facile dehydration in refluxing benzene or toluene containing a catalytic amount of 4-toluenesulfonic acid (4-TsOH).[32] The ease of this dehydration is explained by the stability of the intermediate benzylic carbocation assisted by conjugation with the sulfur heteroatom. The corresponding thiochroman-3-ol is expected to be more difficult to dehydrate and a separation of (20a) and (20b) was envisaged based on the selective dehydration of (20a).



(20a) (20b) (21) (22a) (22b)

Refluxing the mixture (20a,b) in benzene containing 4-TsOH gave unchanged 3-hydroxythiochroman-4-one (20b) (ν_{CO} = 1679, ν_{OH} = 3467 cm^{-1}) together with a new high melting solid after elution from silica. The

^{1}H NMR spectrum of this dehydration product was complex and could not be correlated with the anticipated dehydration product (21). However, assuming that (21) is formed initially, then a hetero Diels-Alder cycloaddition between two molecules can be expected leading to the spiro-linked adduct (22a) or its isomer (22b). Indeed, the facile dimerisation of 3-methylenethiochroman-4-one 1,1-dioxide (23), obtained by direct methylenylation of the thiochroman-4-one 1,1-dioxide with paraformaldehyde and *N*-methylanilinium trifluoroacetate, has been reported to give the 3-acyl dimer (24).[33]



(23) (24)

The complexity of the ^{1}H NMR signals for the pyran ring protons of (22a or b) suggests two adjacent methylene groups as in (22a) rather than two isolated methylene functions (22b). Furthermore, if the 3-acyl isomer (22b) had been formed an AB system would have been expected at ~δ 4 for the OCH_2 group as such a feature is present in the ^{1}H NMR spectrum of (24).[33] Unequivocal proof for the formation of the 2-acyl isomer (22a) was provided by a DEPT ^{13}C NMR experiment, which indicated that the carbon atom adjacent to the oxygen heteroatom (δ 84.1) was quaternary, a feature which can only arise from structure (22a). Similar exclusive formation of the 2-acyl isomer has been observed in [4+2]-cycloadditions involving α,β-unsaturated ketones, leading to 2-acyl-3,4-dihydro-2*H*-pyrans[34] and quinone methides based on the quinoline,[35] benzothiopyran,[36] flavan,[37] benzothiepin[38] and benzoxepin[39] systems.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded on a Mattson-Polaris Fourier Transform spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM250 instrument for solutions in $CDCl_3$; coupling constants are given in Hz. Flash chromatographic separations were performed on Crossfields Sorbsil C60 silica gel (M.P.D. 60Å, 40-60μ, activated) according to the published procedure.[40] Thiochroman-4-ones were obtained by literature procedures.[18]

Preparation of 2,2,6-Trimethylthiochroman-3,4-dione

Concentrated hydrochloric acid (10.5 cm^3) was added dropwise over 1.5 h to a cold stirred solution of 2,2,6-trimethylthiochroman-4-one (17.5 mmol) and isoamyl nitrite (50 mmol) in ethanol (25 cm^3) and methanol (20 cm^3) during which time the solution gradually became bright yellow. On completion of the addition, the reaction mixture was allowed to warm to room temperature (~1 h) and was then heated to 80 °C for 45 min. The cooled solution was then poured into water (1000 cm^3) and extracted with diethyl ether (4 x 75 cm^3). The

combined ether extracts were washed with brine (50 cm^3), dried (Na_2SO_4) and evaporated to afford a bright orange oil. The isoamyl alcohol was removed by bulb-to-bulb distillation and the remaining crude product was purified by elution from silica gel with 5% ethyl acetate in hexane to afford three fractions:

Fraction 1. Unreacted **2,2,6-trimethylthiochroman-4-one** (6%).

Fraction 2. **2,2,6-Trimethylthiochroman-3,4-dione** (1c) (79%) as bright orange crystals from light petroleum (b.p. 40-60 °C) and hexane; m.p. 112.5-113.5 °C; ν_{max}/(Nujol) 1719, 1677 cm^{-1}; δ_H 1.63 (6H, s, 2-Me), 2.35 (3H, s, 6-Me), 7.17 (1H, d, *J* 8.0, 8-H), 7.32 (1H, dd, *J* 8.0, 1.2, 7-H), 7.83 (1H, d, *J* 1.1, 5-H); δ_C 20.6, 22.6 (2 x C), 54.1, 128.0, 130.2, 131.9, 135.7, 136.1, 136.6, 183.0, 193.9. (Found: M^+, 220.0558; C, 65.1; H, 5.4; S, 14.6. $C_{12}H_{12}O_2S$ requires M^+, 220.0558; C, 65.4; H, 5.5; S, 14.6%).

Fraction 3. **2,3-Dihydro-2-hydroxyimino-5-methylbenzo[*b*]thiophene-3(2*H*)-one** (5) (8%) as bright yellow crystals from hexane and ethyl acetate; m.p. 198-202 °C (decomp.) (Lit. m.p. 200-205 °C[16]); ν_{max}/(Nujol) 3230, 1687 cm^{-1}; δ_H 2.40 (3H, s, 5-Me), 7.32 (1H, d, *J* 8.0, 7-H), 7.45 (1H, dd, *J* 8.0, 1.0, 6-H), 7.70 (1H, d, *J* 1.0, 4-H), 9.26 (1H, bs, NOH). (Found: C, 56.0; H, 3.6; N, 7.25; S, 16.7. $C_9H_7NO_2S$ requires C, 55.9; H, 3.7; N, 7.25; S, 16.6%).

The following compounds were prepared by an identical procedure:

1. **2,2-Dimethylthiochroman-3,4-dione** (1b) (81%) as bright orange crystals from light petroleum (b.p. 40-60 °C); m.p. 73.0-74.0 °C; ν_{max}/(Nujol) 1723, 1679 cm^{-1}; δ_H 1.64 (6H, s, 2-Me), 7.29-7.33 (2H, m, 8-H, 6-H), 7.49 (1H, m, 7-H), 8.02 (1H, dd, *J* 8.1, 1.2, 5-H); δ_C 22.9 (2 x C), 54.4, 126.6, 128.2, 130.3, 132.2, 135.1, 139.3, 183.1, 193.8. (Found: C, 63.9; H, 4.9; S, 15.7. $C_{11}H_{10}O_2S$ requires C, 64.0; H, 4.9; S, 15.6%).

2. **1,2-Dihydro-3,3-dimethyl-3*H*-naphtho[2,1-*b*]thiopyran-1,2-dione** (1d) (74%) as bright orange crystals from hexane and ethyl acetate; m.p. 158.0-159.0 °C; ν_{max}/(Nujol) 1720, 1675 cm^{-1}; δ_H 1.69 (6H, s, 2-Me), 7.23 (1H, d, *J* 8.6, 10-H), 7.49 (1H, m, Ar-H), 7.64 (1H, m, Ar-H), 7.79 (1H, d, *J* 8.6, 9-H), 7.87 (1H, d, *J* 8.6, 8-H), 9.28 (1H, d, *J* 8.6, 5-H); δ_C 22.7 (2 x C), 53.7, 125.1, 125.4, 125.6, 126.7, 128.7, 130.4, 131.9, 132.5, 136.0, 143.4, 184.5, 194.1. (Found: C, 70.2; H, 4.7; S, 12.7. $C_{15}H_{12}O_2S$ requires C, 70.3; H, 4.7; S, 12.5%).

3. **3-Hydroxy-2-methylthiochromone** (2c) from 2-methylthiochroman-4-one (51%) and from 2-methylthiochroman-3-one (72%) as of white needles after elution from silica gel with 50% ethyl acetate in hexane and recrystallisation from ethyl acetate and hexane; m.p. 163.0-164.5 °C [lit. m.p. 164-165 °C[13]]; ν_{max}/(Nujol) 1611, 3304 cm^{-1}; δ_H 2.43 (3H, s, 2-Me), 7.51 (4H, m, Ar-H, OH), 8.50 (1H, dd, *J* 8.2, 1.1, 5-H).

Oxidation of 2-Methylthiochroman-3-one with Selenium Dioxide.

Selenium dioxide (6.2 mmol) was added in a single portion to a stirred solution of 2-methylthiochroman-3-one (5.6 mmol) in water (1cm^3) and dioxane (30 cm^3) at 40 °C. After 3 h. at this temperature, the solution was diluted with brine (400 cm^3) and extracted with ethyl acetate (3 x 50 cm^3) and the extracts were washed with sodium hydroxide (2M, 4 x 50 cm^3). The combined alkaline washings were acidified (c. HCl) and extracted with

ethyl acetate (3 x 50 cm^3). Removal of the combined dried (Na_2SO_4) extracts gave a pale brown solid which was recrystallised from ethyl acetate and hexane to afford **3-hydroxy-2-methylthiochromone** (2c) (62%) identical in all aspects with an authentic sample.

General Method for the Condensation of Thiochroman-3,4-diones with 1,2-Diamines.

A mixture of the thiochroman-3,4-dione (2.5 mmol), the 1,2-diamine (2.5 mmol) and glacial acetic acid (1 cm^3) in ethanol (20 cm^3) was refluxed for 1 h. The reaction mixture was cooled (ice/MeOH) and the precipitated crude product was collected and washed with a little ice cold ethanol. Recrystallisation gave the pure product.

1. **6,6-Dimethyl-6*H*-[1]benzothiopyrano[3,4-*b*]quinoxaline** (9a) (89%) from (1b) and 1,2-diaminobenzene as pale yellow needles from hexane; m.p. 141.0-142.0 °C; δ_H 1.80 (6H, s, 6-Me), 7.35-7.42 (3H, m, Ar-H), 7.68-7.76 (2H, m, Ar-H), 8.07 (1H, m, Ar-H), 8.13 (1H, m, Ar-H), 8.58 (1H, d, *J* 8.4, 1-H). (Found: C, 73.3; H, 5.1; N, 10.0; S, 11.4. $C_{17}H_{14}N_2S$ requires C, 73.3; H, 5.1; N, 10.1; S, 11.5%).

2. **2,6,6-Trimethyl-6*H*-[1]benzothiopyrano[3,4-*b*]quinoxaline** (9b) (98%) from (1c) and 1,2-diaminobenzene as bright yellow needles from ethanol; m.p. 152.0-153.0 °C; δ_H 1.79 (6H, s, 6-Me), 2.49 (3H, s, 2-Me), 7.22 (1H, dd, *J* 8.2, 1.4, 3-H), 7.29 (1H, d, *J* 8.1, 4-H), 7.72 (2H, m, Ar-H), 8.06 (1H, m, Ar-H), 8.14 (1H, m, Ar-H), 8.38 (1H, d, *J* 1.3, 1-H). (Found: C, 73.9; H, 5.5; N, 9.6; S, 11.0. $C_{18}H_{16}N_2S$ requires C, 73.9; H, 5.5; N, 9.6; S, 11.0%).

3. **8,8-Dimethyl-8*H*-naphtho[2,1-*b*]thiopyrano[1,2-*b*]quinoxaline** (9c) (87%) from (1d) and 1,2-diaminobenzene as bright yellow needles from ethanol; m.p. 127.5-129.0 °C; δ_H 1.85 (6H, s, 8-Me), 7.53 (2H, m, Ar-H), 7.63 (1H, m, Ar-H), 7.77 (2H, m, Ar-H), 7.84 (2H, m, Ar-H), 8.18 (1H, m, Ar-H), 9.15 (1H, d, *J* 8.3, 1-H). (Found: C, 76.8; H, 5.1; N, 8.4; S, 10.0. $C_{21}H_{16}N_2S$ requires C,76.8; H, 4.9; N, 8.5; S, 9.8%).

4. **2,6,6-Trimethyl-6*H*-[1]benzothiopyrano[3,4-*b*]benzo[*g*]quinoxaline** (10) (83%) from (1c) and 2,3-diaminonaphthalene as bright yellow needles from hexane and ethyl acetate; m.p. 154.5-155.5 °C; δ_H 1.84 (6H, s, 6-Me), 2.49 (3H, s, 2-Me), 7.25 (2H, m, Ar-H), 7.55 (2H, m, Ar-H), 8.10 (2H, m, Ar-H), 8.45 (1H, d, *J* 1.3, 1-H), 8.64 (1H, s, Ar-H), 8.73 (1H, s, Ar-H). (Found: C, 77.2; H, 5.2; N, 8.3; S, 9.5. $C_{22}H_{18}N_2S$ requires C, 77.2; H, 5.3; N, 8.2; S, 9.4%).

5. **2,6,6-Trimethyl-6*H*-[1]benzothiopyrano[3,4-*e*]pyrido[2,3-*b*]pyrazine** (11a) and **2,6,6-Trimethyl-6*H*-[1]benzothiopyrano[4,3-*e*]pyrido[2,3-*b*]pyrazine** (11b) in a ratio of ~ 8:1 respectively from (1c) and 2,3-diaminopyridine; δ_H† 1.84 (6H, s, 6-Me), 2.47 (3H, s, 2-Me), 7.24 (2H, m, Ar-H), 7.69 (1H, m, Ar-H), 8.36 (1H, d, *J* 1.3, 1-H), 8.49 (1H, m, Ar-H), 9.11 (1H, m, 9-H). (Found:‡ C, 69.6; H, 5.2; N, 14.5; S, 11.1. $C_{17}H_{15}N_3S$ requires C, 69.6; H, 5.2; N, 14.3; S, 10.9%).

6. **2,6,6-Trimethyl-6*H*-[1]benzothiopyrano[4,3-*e*]pyrido[3,4-*b*]pyrazine** (12a) and **2,6,6-Trimethyl-6*H*-[1]benzothiopyrano[3,4-*e*]pyrido[3,4-*b*]pyrazine** (12b) in a ratio of (6:1)

respectively from (1c) and 3,4-diaminopyridine; δ_H† 1.78 (6H, s, 6-Me), 2.47 (3H, s, 2-Me), 7.27 (2H, m, Ar-H), 7.89 (1H, d, *J* 8.3, 4-H), 8.39 (1H, d, *J* 1.2, 1-H), 8.78 (1H, m, Ar-H), 9.56 (1H, s, 8-H). (Found:‡ C, 69.8; H, 5.2; N, 14.5; S, 10.8. $C_{17}H_{15}N_3S$ requires C, 69.6; H, 5.2; N, 14.3; S, 10.9%).

Notes for 5 and 6: † ^1H NMR data given for major isomer only. ‡ Elemental analyses were performed on the isomeric mixtures.

7. **2,3-Dihydro-5,5-dimethyl-5*H*-naphtho[2,1-*b*]thiopyrano[1,2-*b*]pyrazine** (8) (89%) from (1d) and 1,2-diaminoethane as a viscous pale green oil; b.p. 220 - 225 °C at 1 x 10^{-2} mmHg; after aqueous work-up and isolation with dichloromethane; δ_H 1.57 (6H, s, 5-Me), 3.63 (2H, m, CH_2), 3.82 (2H, m, CH_2), 7.34 (1H, d, *J* 8.4, 7-H), 7.44 (1H, m, Ar-H), 7.49 (1H, m, Ar-H), 7.70 (2H, m, Ar-H), 8.86 (1H, d, *J* 8.5, 12-H). (Found: C, 72.5; H, 5.8; N, 10.0; S, 11.6. $C_{17}H_{16}N_2S$ requires C, 72.8; H, 5.8; N, 10.0; S, 11.4%).

Preparation of 2(4-Methoxyphenyl)-4,4,8-trimethyl-4*H*-[1]benzothiopyrano[3,4-*d*]imidazole.

A solution of the dione (1c) (2.25 mmol), *p*-anisaldehyde (2.25 mmol) and ammonium acetate (12.5 mmol) in ethanol (20 cm^3) was refluxed for 4.5 h, during which the initial intense orange colour faded to pale yellow. The cooled solution was poured into water (500 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). Evaporation of the dried (Na_2SO_4) solvent and elution of the resulting gum from silica with 30% ethyl acetate in hexane afforded a yellow solid. Recrystallisation from light petroleum (b.p. 40-60 °C) and diethyl ether gave the **title compound** (13) (67%) as pale yellow needles; m.p. 98.0-100.0 °C; δ_H 1.71 (6H, s, 4-Me), 2.34 (3H, s, 8-Me), 3.84 (3H, s, OMe), 6.93 (3H, m, Ar-H), 7.21 (2H, m, Ar-H), 7.27 (1H, bs, NH), 7.78 (2H, m, Ar-H). (Found: C, 71.3; H, 6.0; N, 8.4; S, 9.6. $C_{20}H_{20}N_2OS$ requires C, 71.4; H, 6.0; N, 8.3; S, 9.5%).

Preparation of 1,3-Diphenyl-4,4,8-trimethyl-2*H*,4*H*-cyclopenta[*c*][1]benzothiopyran-2-one.

A solution of potassium hydoxide (13 mmol) in absolute ethanol (5 cm^3) was added dropwise over 5 min to a stirred refluxing solution of the dione (1c) (5 mmol) and dibenzyl ketone (5 mmol) in absolute ethanol (20 cm^3). On completion of the addition, the solution was refluxed for a further 2 h. The ethanol was removed from the cooled solution and the residue taken up in water (100 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). Removal of the dried (Na_2SO_4) solvent gave a dark brown solid which was eluted from silica with 10% ethyl acetate in hexane to afford two fractions:

Fraction 1. The **title compound** (14) (41%) as deep red microcrystals from light petroleum (b.p. 30-40 °C); m.p. 177.0-178.0 °C; ν_{max}/(Nujol) 1710 cm^{-1}; λ_{max} = 495 nm, $\varepsilon = 8.4 \times 10^3$ mol $dm^{-3}cm^{-1}$; δ_H 1.51 (6H, s, 4-Me), 2.08 (3H, s, 8-Me), 7.02-7.41 (13H, m, Ar-H). (Found: C, 82.3; H, 5.6; S, 7.8. $C_{27}H_{22}OS$ requires C, 82.2; H, 5.6; S, 8.1%).

Fraction 2. ***trans*-3,3a-Dihydro-1,3-diphenyl-4,4,8-trimethyl-2*H*,4*H*-cyclopenta[*c*][1]benzothiopyran-2-one** (15) (15%) as a bright yellow solid after sublimation; 170 °C at 5 x 10^{-2} mmHg; m.p. 193.0-194.5 °C; ν_{max}/(Nujol) 1688 cm^{-1}; δ_H 1.43 (3H, s, 4-Me), 1.48 (3H, s, 4-Me), 1.99 (3H, s, 8-Me), 3.48 (1H, d, *J* 2.5, 3a-H), 3.56 (1H, d, *J* 2.5, 3-H), 7.06 (3H, m, Ar-H), 7.23-7.47 (10H, m, Ar-H). (Found: C, 81.6; H, 6.3; S, 7.9. $C_{27}H_{24}OS$ requires C, 81.8; H, 6.1; S, 8.1%).

Preparation of Dimethyl 7,10-diphenyl-2,6,6-trimethyl-6*H*-dibenzo[*bd*]thiopyran-8,9-dicarboxylate.

A sample of the cyclopentadienone (14) (0.76 mmol) and dimethyl acetylenedicarboxylate (1.5 mmol) in bromobenzene (5 cm^3) was boiled under reflux until TLC indicated that no of the starting material remained (~ 3 h), during this time the intense red solution became pale brown. The bromobenzene was removed by distillation and the residue was eluted from a short silica column with 20% ethyl acetate in hexane to afford the **title compound** (16) (69%) as colourless crystals from hexane; m.p. 207.0-208.0 °C; ν_{max}/(Nujol) 1724 cm^{-1}; δ_H 1.24 (6H, bs, 6-Me), 1.87 (3H, s, 2-Me), 3.39 (3H, s, CO_2Me), 3.44 (3H, s, CO_2Me), 6.58 (1H, d, *J* 1.1, 1-H), 6.85 (1H, dd, *J* 7.9, 1.1, 3-H), 7.19-7.40 (11H, m, Ar-H). (Found: C, 75.6; H, 5.6; S, 6.4. $C_{32}H_{28}O_4S$ requires C, 75.6; H, 5.6; S, 6.3%).

Attempted Preparation of a Thieno[3,4-*c*][1]benzothiopyran 2,2-dioxide.

The dione (1c) (4.5 mmol) was added in a single portion to stirred solution of dibenzyl sulfone (4.5 mmol) in absolute ethanol (20 cm^3) containing sodium ethoxide (9 mmol). The resulting dark brown solution was refluxed for 2 h. The cooled solution was diluted with water (300 cm^3), acidified with hydrochloric acid (2M) and extracted with dichloromethane (3 x 50 cm^3). Evaporation of the dried (Na_2SO_4) solvent gave a brown semi-solid which was eluted from silica with 30% ethyl acetate in hexane to afford **2,3-dihydro-2-hydroxy-2-isopropyl-5-methylbenzo[*b*]thiophen-3(2*H*)-one** (18) (42%) as a viscous yellow oil; b.p. 120-125 °C at 2 x 10^{-2} mmHg; m.p. 76.5-78.0 °C; ν_{max}/(Nujol) 1719, 3454 cm^{-1}; δ_H 0.94 (3H, d, *J* 6.8, CH_3), 1.01 (3H, d, *J* 6.8, CH_3), 2.18 (1H, m, $CH(CH_3)_2$), 2.34 (3H, s, 5-Me), 2.71 (1H, bs, OH), 7.17 (3H, m, Ar-H); δ_C 15.9, 16.2, 21.2, 38.8, 87.3, 122.9, 126.4, 130.5, 130.7, 136.4, 136.5, 208.0. (Found: C, 64.9; H, 6.5; S, 14.2. $C_{12}H_{14}O_2S$ requires C, 64.8; H, 6.4; S, 14.4%).

Reduction of 2,2,6-Trimethylthiochroman-3,4-dione.

Sodium borohydride (9.5 mmol) was added in a single portion to a stirred solution of the diketone (1c) (4.5 mmol) in ethanol (30 cm^3) and the solution was refluxed for 1 h. The cooled solution was diluted with water (200 cm^3)and extracted with ethyl acetate (4 x 30 cm^3). Removal of the solvent from the combined dried (Na_2SO_4) extracts gave a pale yellow oil which was distilled to afford a mixture of ***trans*- and *cis*-2,2,6-trimethylthiochroman-3,4-diols** (77%); b.p. 160-165 °C at 7x10^{-2} mmHg, which solidified m.p. 76.0-80.0 °C; δ_H *trans*- isomer (19a) 1.33 (6H, s, 2-Me), 2.28 (3H, s, 6-Me), 2.86 (2H, bs, OH), 3.82 (1H, d, *J* 8.9, 3-H), 4.49 (1H, d, *J* 8.9, 4-H), 6.94 (2H, m, Ar-H), 7.35 (1H, d, *J* 1.2, 5-H); δ_H *cis*-isomer (19b) 1.38 (3H, s, 2-Me), 1.39 (3H, s, 2-Me), 2.29 (3H, s, 6-Me), 2.86 (2H, bs, OH), 3.61 (1H, d, *J* 3.9, 3-H), 4.62 (1H, d, *J* 3.9, 4-H), 6.94 (2H, m, Ar-H), 7.52 (1H, d, *J* 1.2, 5-H). (Found: C, 64.3; H, 7.2; S, 14.5. $C_{12}H_{16}O_2S$ requires C, 64.2; H, 7.2; S, 14.3%).

Pyridinium chlorochromate (8.8 mmol) was added in a single portion to a cold stirred solution of a sample of the aforegoing diols (19a,b) (2.2 mmol) in dichloromethane (20 cm^3). The solution instantly became dark brown and

TLC examination revealed that a bright orange component had formed. The cold solution was stirred for a further 40 min prior to elution of the solution through a short path of silica using dichloromethane as eluent. Evaporation of the solvent and recrystallisation of the solid from light petroleum (b.p. 40-60 °C) and hexane gave 2,2,6-trimethylthiochroman-3,4-dione (1c) (78%); m.p. 112.5-113.5 °C identical in all respects to the previously prepared sample.

Reaction of Methyl Magnesium Iodide with 2,2,6-Trimethylthiochroman-3,4-dione.

Methyl magnesium iodide (6.8 mmol, 3.0 M solution in ether) was added dropwise *via* syringe to a cold stirred solution of the dione (1c) (6.8 mmol) in anhydrous ether (30 cm^3) under a nitrogen atmosphere. The resulting solution was maintained at 5 °C for 15 min then allowed to warm to RT over 1 h. The solution was cautiously acidified (aq. 2M HCl) and stirred for a further 15 min prior to extraction with ethyl acetate (3 x 50 cm^3). The combined extracts were washed with brine (50 cm^3), dried (Na_2SO_4) and evaporated to afford a mixture of the hydroxy chromanones (20a) and (20b) after elution from silica with 10% ethyl acetate in hexane.

A solution of this mixture of (20a,b) in benzene (75 cm^3) containing a catalytic amount of 4-toluenesulfonic acid was boiled under reflux, with azeotropic removal of the water. When the reaction was judged to be complete (TLC), the cooled solution was diluted with ethyl acetate (50 cm^3) and washed with water (2 x 100 cm^3). Removal of the dried (Na_2SO_4) solvent gave an oil which was eluted from silica with 10% ethyl acetate in hexane to afford two fractions:

Fraction 1. **4-Methylene-2,2,6-trimethylthiochroman-3-one dimer** (22a) (29%) as colourless crystals from hexane and ethyl acetate; m.p. 192.0-193.5 °C; ν_{max}/(Nujol) 1716 cm^{-1}; δ_H 1.26 (3H, s, 2-Me), 1.40 (3H, s, 2-Me), 1.47 (3H, s, 2-Me), 1.67 (3H, s, 2-Me), 2.07 (1H, m, CH_2), 2.10-2.42 (8H, m, (2 x 6-Me), CH_2), 3.20 (1H, m, CH_2), 6.72 (2H, m, Ar-H), 7.12 (2H, m, Ar-H), 7.28 (1H, d, *J* 1.4, 5-H), 7.39 (1H, d, *J* 1.3, 5-H). (Found: C, 71.7; H, 6.5; S, 15.1. $C_{26}H_{28}O_2S_2$ requires C,71.5; H, 6.5; S, 14.7%).

Fraction 2. **3-Hydroxy-2,2,3,6-tetramethylthiochroman-4-one** (20b) (39%) as an off-white solid; b.p. 110-115 °C at 5 x 10^{-2} mmHg, m.p. 62.0-63.0 °C; ν_{max}/(Nujol) 1679, 3467 cm^{-1}; δ_H 1.36 (3H, s, 2-Me), 1.45 (3H, s, 2-Me), 1.51 (3H, s, 3-Me), 2.32 (3H, s, 6-Me), 4.10 (1H, bs, OH), 7.05 (1H, d, *J* 8.1, 8-H), 7.24 (1H, dd, *J* 8.0, 1.7, 7-H), 7.84 (1H, d, *J* 1.6, 5-H). (Found: C, 66.2; H, 7.1; S, 13.3. $C_{13}H_{16}O_2S$ requires C, 66.1; H, 6.8; S, 13.5%).

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