Directed Lithiation of Some Chroman-4-ols

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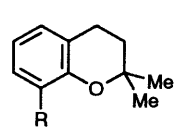
Directed lithiation of chroman-4-ols occurs predominantly at C-5 under kinetic control, but at C-8 at higher temperatures. Dehydration and oxidation of the products provides viable routes to 5-substituted 2*H*-chromenes and chroman-4-ones, respectively. The chroman-4-ones have been converted into novel pyrano[4,3,2-*de*]phthalazines. 2,2,5,7-Tetramethylchroman-4-ol is preferentially lithiated at the 5-methyl group and leads to the pyrano[2,3,4-*de*][1]benzopyran system.

Directed *ortho* lithiation is a firmly established technique in synthetic organic chemistry[1] and has been used to great effect for the formation of polyfunctional aromatic systems,[2] providing complementary methodology to classical aromatic electrophilic substitution.

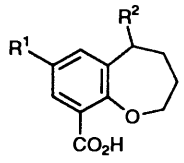
The capacity of an oxygen heteroatom to direct lithiation across a ring junction to the *peri* position has been exploited for the preparation of 8-substituted 2,2-dimethylchromans **1**,[3] and homochroman-9-carboxylic acids **2**.[4] More recently, the relative capabilities of alkoxy and cyclic ether oxygen atoms for directing *ortho* lithiation under kinetically controlled conditions have been studied. In the majority of examples, 8-substituted chromans **3** (n = 2) and 7-substituted dihydrobenzofurans **3** (n = 1) were formed in good overall yield and in greater amounts than the 6- and 5-substituted isomers, inferring that the oxygen heteroatom has a greater ability to direct lithiation than has the alkoxy function.[5]

The ability of benzyl alcohols to undergo *ortho* lithiation is well established[6,7] and in a similar manner, 1,2,3,4-tetrahydro-1-naphthol (1-tetralol) reacts with butyllithium (2 equiv.) in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA; 2 equiv.) in refluxing diethyl ether to afford 8-substituted tetralols **4** in high yield when the dianion is quenched with electrophiles. These tetralols are key intermediates in an elegant synthesis of angular anthracyclinones.[8]

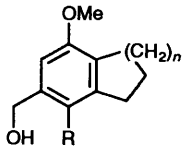
The synthesis of 5-substituted chroman-4-ones is frequently inconvenienced by competitive formation of the 7-isomer. For example, cyclisation of 3-(3-methylphenoxy)propionic acid with polyphosphoric acid gives an approximately equal ratio of 5- and 7-methylchroman-4-ones.[9] The acid-catalysed cyclodehydration of a *meta*-substituted phenol with an acrylic acid usually results in the exclusive formation of the 7-substituted chroman-4-one,[10] though in certain instances both 5- and 7-substituted isomers result, the ratio of which has been shown to be markedly dependent upon the reaction temperature.[11] More often, mixtures of chroman-4-ones and the isomeric 3,4-dihydrocoumarins result from such Lewis acid-catalysed reactions.[12] A regioselective synthesis of 5-hydroxychroman-4-ones has been described, which utilises the $TiCl_4$-promoted acylation of a cyclohexane-1,3-dione with an acryloyl chloride followed by a Fries rearrangement to give 5,6,7,8-tetrahydrochroman-4,5-diones as the key steps. Subsequent dehydrogenation affords the 5-hydroxychroman-4-ones in good yield.[13] Application of the Kabbe route[14] to the synthesis of 5-substituted chroman-4-ones relies upon the availability of suitably substituted 2′-hydroxyacetophenones, entailing additional synthetic work which detracts from the normal convenience of this route. Direct routes to 5-substituted 2*H*-chromenes are also fraught with the possibility of isomer formation. The Claisen rearrangement of aryl prop-2-ynyl ethers derived from *meta*-substituted phenols affords a mixture of the 5- and 7-substituted 2*H*-chromenes, which is not always easy to separate,[15] and in which the 7-isomer is usually dominant.



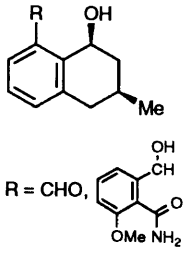
1 R = OH, CO_2H



2 R^1 = Me, R^2 = OMe or Ph



3 n = 1, R = CHO, CH(OH)Ph, CO_2H (as lactone)
n = 2, R = CHO, CH(OH)Ph, CO_2H (as lactone)

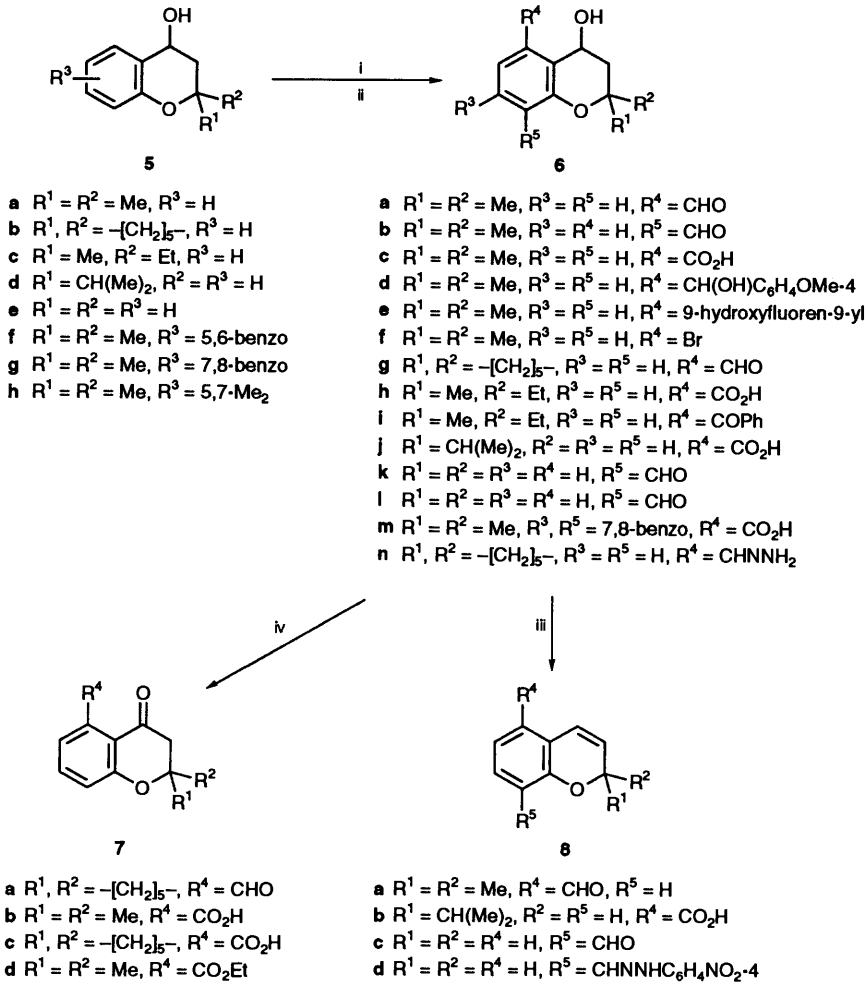


4 R = CHO,

We now report a general, facile and regioselective synthesis of 5-substituted chroman-4-ols **6** *via* directed *ortho* lithiation of a range of chroman-4-ols **5**. The versatility of the chromanols **6** in synthesis is illustrated by their conversion into 5-substituted 2*H*-chromenes, 5-substituted chroman-4-ones, a novel furanobenzopyran, pyrano[2,3,4-*de*][1]benzopyrans and fused pyrano[4,3,2-*de*]phthalazines, a new heterocyclic ring system.

Discussion

The substituted chroman-4-ones used in this work were obtained from a 2′-hydroxyacetophenone and a carbonyl compound using the procedure described by Kabbe.[14] Reduction of the chroman-4-ones with an excess of sodium borohydride in refluxing ethanol gave the chroman-4-ols in excellent yield.[16] The C-2 unsymmetrically substituted chroman-4-ols



Scheme 1 *Reagents and conditions:* i, 2.01 equiv. BuLi, 2.01 equiv. TMEDA, Et_2O, N_2, 0 °C–room temp.; ii, 2.01 equiv. electrophile, N_2, 0 °C–room temp.; iii, TsOH, PhMe, heat; iv, CrO_3, AcOH, 35 °C

were obtained as mixtures of diastereoisomers in all cases and were used as such.

Dilithiation of 2,2-dimethylchroman-4-ol **5a** was accomplished using the BuLi/TMEDA complex (2 equiv.)[17] in diethyl ether (see Scheme 1). The dianion when quenched with *N*-formylpiperidine (2 equiv.) at 0 °C gave a mixture 4-hydroxy-2,2-dimethylchroman-5-carbaldehyde **6a** and 4-hydroxy-2,2-dimethylchroman-8-carbaldehyde **6b** in a ratio of *ca.* 24:1 measured by GC–MS and in an overall yield of 79% after aqueous work-up.

In an attempt to achieve complete conversion of the chroman-4-ol **5a** into the dianion, the lithiation mixture was refluxed for 2 h prior to rapid cooling and reaction with *N*-formylpiperidine. Examination of the crude product by GC–MS indicated that only *ca.* 2% of the chroman-4-ol remained, but the ratio of 5-:8-formylated chromanol was now 1.5:1, inferring that 4-hydroxy-2,2-dimethylchroman-5-carbaldehyde is the kinetic product and the 8-carbaldehyde is the thermodynamic product. When the procedure was conducted at *ca.* 0 °C throughout, the formation of the 5-formylated product was favoured (29:1) but 74% of the chroman-4-ol remained unchanged. The gain in regioselectivity is countered by the low conversion into product and is obviously unacceptable. In an attempt to achieve better conversion into **6b**, the reaction mixture was refluxed for 6 h prior to quenching with *N*-formylpiperidine. Examination of the reaction mixture indicated that the ratio of **6a** to **6b** was 1.2:1. Using refluxing hexane as the reaction medium resulted in an isomer ratio of 2.7:1, with a high conversion (88%) in spite of the fact that the alkoxide precipitated out of the refluxing solution. In boiling toluene, a ratio of 1:1.3 was achieved but some 60% of the chroman-4-ol remained unchanged. Despite the inability to achieve total regioselectivity under the various reaction conditions, the marked difference in polarity of the two products **6a** and **6b**, the latter being the more polar, allows a facile separation by flash chromatography making the method a viable route to 5-substituted chroman-4-ols.

The location of the formyl substituent at C-5 is apparent from its effect upon the disposition of the 4-hydroxy group as indicated by the change in the magnitude of the vicinal coupling constants between the C-3 and C-4 protons in the ^1H NMR spectrum. For 2,2-dimethylchroman-4-ol **5a**, $J_{3ax,4}$ 8.9 and $J_{3eq,4}$ 6.1 Hz, it would appear that the coupling involves interaction with a pseudo-axial 4-H, inferring that the hydroxy group occupies a pseudo-equatorial site. Published data for the ^1H NMR spectra of non-planar six-membered rings indicate that axial–axial coupling constants are of the order of 8–13 Hz, with axial–equatorial coupling constants in the range 3–6 Hz. Equatorial–equatorial coupling constants are smaller still.[18] The magnitude of the *vic* coupling constants for the 4-hydroxychroman-5-carbaldehyde **6a** are $J_{3ax,4}$ 6.0 and $J_{3eq,4}$ 4.3 Hz which suggests that the hydroxy group now occupies a pseudo-axial site, whereas those for the 8-formyl isomer **6b** ($J_{3ax,4}$ 9.2 and $J_{3eq,4}$ 6.2 Hz) imply that the hydroxy group occupies a pseudo-equatorial site in common with the chroman-4-ol **5a**. This inference is supported by comparison of space-filling molecular models of 4-hydroxy-2,2-dimethylchroman-

5- and -8-carbaldehydes, which indicate that in the former case the pseudo-axial site is sterically less hindered than the pseudo-equatorial site and is thus preferred by the 4-hydroxy substituent. In the 8-substituted example, a pseudo-equatorial disposition is still feasible for the 4-hydroxy group since there are no pronounced steric *peri* interactions and indeed a similar arrangement is preferred for 2,2-dimethylchroman-4-ol. The aldehyde proton in **6b** resonates at δ 10.3, marginally downfield of that in **6a** (δ 9.97), and is split into a doublet J 0.5 Hz through coupling with 7-H.

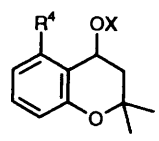
Dehydration of **6a** with toluene-*p*-sulfonic acid (TsOH) in toluene gave the 2*H*-chromene **8a** in good yield. The ^{1}H NMR spectrum of this compound displayed a doublet for each of the alkenyl protons with J 10.2 Hz. The chemical shift of these signals warrants some comment. 3-H resonates at δ 5.81 and 4-H at δ 7.40, both shifted downfield in comparison with the data for 2,2-dimethyl-2*H*-chromene ($\delta_{3\text{-H}}$ 5.62, $\delta_{4\text{-H}}$ 6.32).[19] The considerable downfield shift of 4-H in **8a** of *ca.* 1 ppm must be due to the deshielding effect of the anisotropic carbonyl function at C-5, thus confirming the position of the formyl group. One other feature worthy of note is the long range coupling between 4-H and 8-H, ^5J 0.5 Hz. Such coupling has been reported for 5-substituted 2*H*-chromenes,[20] but is not usually observed for simple 2*H*-chromenes which are unsubstituted in the aromatic ring.[19,21,22]

The dianion derived from the chroman-4-ol **5a** when quenched with CO_2 gave the 5-carboxylic acid **6c**, whilst *p*-anisaldehyde gave the diol **6d**, both in excellent yields. The magnitude of the *vic* coupling constants of these compounds (**6c** $J_{3ax,4}$ 5.7 and $J_{3eq,4}$ 3.3 Hz) and (**6d** $J_{3ax,4}$ 6.4 and $J_{3eq,4}$ 4.5 Hz) are comparable with those of the aldehyde **6a**. The presence of TMEDA in the reaction mixture was essential for successful dilithiation. This feature was illustrated when the reaction of **5a** with CO_2 was repeated without the addition of TMEDA, which resulted in the formation of the carboxylic acid **6c** in reduced yield (41%) and accompanied by a considerable amount of pentanoic acid, which results from reaction of unchanged BuLi with CO_2.

The reaction of fluorenone with the dianion derived from **5a** gave the expected diol **6e**. The ^{1}H NMR spectrum of this compound recorded at 293 K displayed broad signals for all of the proton environments. This phenomenon may be attributed to a combination of the restricted rotation of the 5-(fluoren-9′-yl) moiety about the C(5)–C(9′) bond leading to rotamer formation and the interconversion of the benzopyran ring between two energetically similar conformers. There have been several accounts detailing such dynamic features for the ^{1}H NMR spectra of 9-aryl fluorenes and fluorenols[23] and in some instances enrichment of one rotamer was achieved.[24] Recording the ^{1}H NMR spectrum of **6e** at 348 K resulted in improved resolution of the signals and some coupling of 3-H and 4-H could be observed. Similarly, improved resolution resulted when the ^{1}H NMR spectrum of **6e** was recorded at 253 K.

Dehydration of **6e** using TsOH in refluxing toluene with a short reflux time gave the spiro-fused tetrahydrofuran **11** rather than the 2*H*-chromene. Refluxing the reaction mixture for longer gave a multi-component mixture (TLC). The formation of cyclic ethers from the dehydration of 1-(2-hydroxymethylphenyl)cyclohexan-1-ol, derived from the reaction of cyclohexanone with the dianion obtained from dilithiation of benzyl alcohol, has been documented.[7] The resolution of the signals in the ^{1}H NMR spectrum of **11** is somewhat improved at 293 K compared with that of its precursor **6e**. This improvement is probably a consequence of the fixed configuration of **11** arising from the formation of the ether linkage. The broadening of the signals, especially pronounced for the methyl groups at δ 1.25, may arise from interconversion of the benzopyran ring.

Reaction of the dianion derived from **5a** with chlorotrimethylsilane gave the bistrimethylsilyl compound **9a** in



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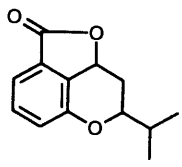
a R^4 = $SiMe_3$, X = $SiMe_3$
b R^4 = SO_2Me, X = S(O)Me



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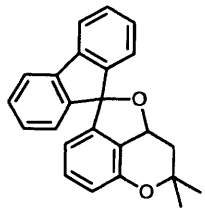

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excellent yield. Similarly, the reaction of the dianion with methyl thiotosylate[25] (MeSTs) gave **9b** as the major product after oxidation with an excess of hydrogen peroxide in acetic acid. It is noteworthy that the 5-methylsulfanyl group was readily oxidised to the methyl sulfone, whereas the sulfenic ester (O–SMe) function was only oxidised to the sulfinic ester and not to the sulfonate. The synthesis of sulfinic esters by oxidation of sulfenic esters is well established and over-oxidation to sulfonates is not usually encountered.[26]

Only limited success attended the reaction of the dianion from **5a** with bromine. After elution of the multi-component reaction product from silica, the five major components were characterised as 2,2-dimethyl-2*H*-chromene, 2,2-dimethylchroman-4-one, 3,3-dibromo-2,2-dimethylchroman-4-one, 5-bromo-2,2-dimethylchroman-4-ol **6f** and unchanged chroman-4-ol **5a**. Using *N*-bromosuccinimide as the electrophile also resulted in the formation of a multi-component mixture. The use of 1,2-dibromoethane as a brominating agent has been documented[27] and reaction of the dianion derived from **5a** with this reagent gave 5-bromo-2,2-dimethylchroman-4-ol **6f** but in a disappointingly low yield (12%) albeit from a relatively clean reaction product.

The C-2 spirocyclohexane- **5b** and 2-ethyl-2-methyl-chroman-4-ols **5c** were readily dilithiated using the standard conditions, the ethereal solution of the dianions being reddish orange, and afforded the 5-substituted analogues **6g**, **6h** and **6i** on reaction with *N*-formylpiperidine, CO_2 and benzonitrile, respectively. 2-Isopropylchroman-4-ol **5d** behaved similarly on reaction with BuLi/TMEDA followed by CO_2 and gave the 5-carboxylic acid **6j**. Subsequent dehydration gave the 2*H*-chromene-5-carboxylic acid **8b** accompanied by a small amount of the tricyclic lactone **10** isolated as a single diastereoisomer. The signals for 3-H and 4-H in the ^{1}H NMR spectrum of the acid **8b** are both shifted downfield [$\delta_{3\text{-H}}$ 5.87, $\delta_{4\text{-H}}$ 7.47 (J 10.4 Hz)] in comparison with those of 2-isopropyl-2*H*-chromene ($\delta_{3\text{-H}}$ 5.55, $\delta_{4\text{-H}}$ 6.32)[22] and compare favourably with those of the chromene-5-carboxylic acid **8a**. The absence of hydroxy stretching bands in the IR spectrum of **10** together with a carbonyl stretch at 1760 cm^{-1} (lactone carbonyl 1750–1780 cm^{-1})[28] and the lack of exchangeable protons in the ^{1}H NMR spectrum confirm the structure of **10**. Examination of the coupling constants obtained from **10** suggests that 8a-H is pseudo-axially disposed ($J_{8a,8ax}$ 11.5 and $J_{8a,8eq}$ 5.4 Hz).

During the dilithiation of the unsubstituted chroman-4-ol **5e** using the described procedure, the initially formed alkoxide precipitated out of the diethyl ether solution. The suspension of the dianion when quenched with *N*-formylpiperidine gave two new hydroxy aldehydes in a ratio of 22:1. The major product

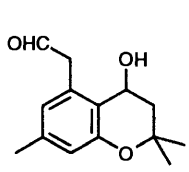
was characterised as 5-formylchroman-4-ol **6k**. A similar reaction but with the mixture being refluxed for 2 h gave the same components (TLC), but now the major component was the 8-formylchroman-4-ol (**6l**) arising from ring heteroatom-directed lithiation. In the ^{1}H NMR spectrum of **6l**, the formyl proton resonates at δ 10.3 and is coupled (J 0.5 Hz) to 7-H, data which compare favourably with those for **6b**. Such long-range coupling was not apparent in either the isomer **6k** or the other 5-formylchroman-4-ols obtained in this work. The signals for the aromatic protons of **6l** are well resolved, giving multiplets at δ 6.95, 7.55 and 7.67, whilst those of **6k** give multiplets at δ 7.17 (7-H) and 7.42 (6-H and 8-H) in a pattern common to the 5-formylchroman-4-ols **6a** and **6g**.

The structure of **6l** was confirmed by dehydration to **8c**. The key feature in the ^{1}H NMR spectrum of **8c** is the chemical shift of 4-H, which appears as a double triplet at δ 6.43 showing coupling with 3-H (J 10.0 Hz) and allylic coupling to 2-H (J 1.8 Hz). This chemical shift compares favourably with that of 4-H in 2*H*-chromene ($\delta_{4\text{-H}}$ 6.30)[22] and is further upfield than that in **8a**, where 4-H resonates at δ 7.40 as a consequence of deshielding by the 5-formyl function.

Attempts to dilithiate the dimethylnaphthopyran **5f** failed even after a prolonged period at room temperature (RT) in ether, the alcohol being recovered after routine work-up. The alkoxide anion formed on addition of BuLi was insoluble in the refluxing ether, which may have prevented further reaction. In marked contrast, the isomeric compound **5g** was readily dilithiated and converted into the carboxylic acid **6m** on reaction with CO_2. It is noteworthy that carbonation of the dianions derived from chroman-4-ols **5a**, **5c**, **5d** and **5g** gave the carboxylic acids **6c**, **6h**, **6j** and **6m**, respectively, as the exclusive products, whereas under similar conditions 7-methoxy-1-tetralol gave a 5-membered *peri*-fused lactone in good yield as a result of intramolecular cyclisation.[29]

Reaction of the chroman-4-ol **5h**, in which the usual site of deprotonation (C-5) is blocked by a methyl group, with BuLi (2 equiv.) and TMEDA in diethyl ether proceeded smoothly to give a bright yellow solution. Subsequent reaction with *N*-formylpiperidine gave a product which exhibited a hydroxy stretch at 3308 cm^{-1}, but no carbonyl stretching band in its IR spectrum. Furthermore, the presence of a single exchangeable proton (*ca.* δ 3.1) was indicated by addition of D_2O. The doubling of the signals in the ^{1}H NMR spectrum of this compound showed the presence of diastereoisomers and in approximately equal amounts. These spectroscopic data exclude the 8-formylated chroman-4-ol, which would result from lithiation directed by the heterocyclic oxygen atom.

The deprotonation of methyl groups adjacent to directing metallation groups (*e.g.* $CONEt_2$, SO_3Et) in preference to the deprotonation of a vacant *ortho* position has been established.[30] Indeed this often inconvenient benzylic deprotonation has been circumvented by the development of an ingenious protection/deprotection strategy.[31] If the 5-methyl group in **5h** is deprotonated and then quenched with *N*-formylpiperidine, the aldehyde **12** would be expected. However, an intramolecular cyclisation ensues resulting in the formation of a diastereoisomeric mixture of the six-membered hemiketal **13**. The structure of **13** was confirmed chemically by both elimination and oxidation. The former was achieved by reaction of **13** with methanesulfonyl chloride in the presence of Et_3N in refluxing CH_2Cl_2 according to the procedure described by Miki *et al.*[32] and gave the pyrano[2,3,4-*de*][1]benzopyran **14** in 89% yield. The structure of this novel pyranobenzopyran was confirmed by ^{1}H NMR spectroscopy. The vinyl ether moiety is indicated by the presence of doublets at δ 5.86 and 6.63 (J 5.8 Hz). An ABX system is present for 3a-H and 4-H. The mass spectrum of this compound was informative giving the molecular ion (M$^+$ 216), together with a base peak at m/z 160, arising from a retro



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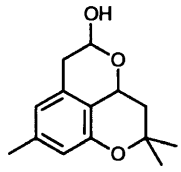

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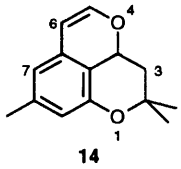

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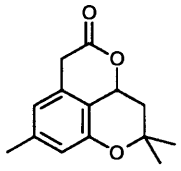

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Diels–Alder elimination of isobutene. This type of fragmentation is common to many chroman-4-ones, although chroman-4-ols usually eliminate water.[33]

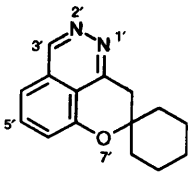
This 1,4-dioxaphenalene system has been found in the leaves of Cassia siamea as barakol, a 4*H*-chromene,[34] and as prenylated* coumarin derivatives in *Bothriocline* species.[35] More recently it has been found that the mild toxin, citrinin, an isochroman, is converted in water at 140 °C into the highly toxic citrinin H1, a benzo-fused pyrano[2,3,4-*de*][1]benzopyran.[36]

Pyridinium chlorochromate (PCC)[37] is a versatile oxidising agent which is particularly effective for the oxidation of lactols to lactones.[38] Addition of PCC (3 equiv.) to a stirred solution of the lactol **13** in CH_2Cl_2 gave the lactone **15** in excellent yield. The ^{1}H NMR spectrum of this compond was particularly simple. The key feature is the presence of a singlet at δ 3.68 accounting for 2 protons and assigned to 6-H, adjacent to the carbonyl function. Further evidence for the presence of the carbonyl function was the lactone carbonyl band at 1726 cm^{-1} in the IR spectrum and a lowfield signal at δ 170.7 in the ^{13}C NMR spectrum. Once again the molecular ion is observed in the mass spectrum (M$^+$ 232) and the base peak at m/z 176 stems from a retro Diels–Alder fragmentation.

The 4-hydroxy function of the carboxylic acid **6c** or the aldehyde **6g** could not be oxidised with PCC despite its successful use for oxidation of the lactol. Limited success attended the use of dimethyl sulfoxide–trifluoroacetic anhydride (Swern conditions)[39] for the selective oxidation of the 4-hydroxy function of the aldehyde **6g** affording a small amount of the 5-formylchroman-4-one **7a**. The use of CrO_3 in acetic acid has been successfully employed for the oxidation of chroman-4-ols to chroman-4-ones[40] and proved successful for the oxidation of the 4-hydroxychroman-5-carboxylic acid **6c** to the chroman-4-one **7b**, which was readily converted into the ethyl ester **7d**. Application of this oxidation procedure to the chroman-4-ol **6g** gave a mixture of the 4-oxochroman-5-carbaldehyde **8a** and the 4-oxochroman-5-carboxylic acid **7c**. A 5-formyl substituent has previously been introduced into the chroman-4-one nucleus by the oxidative cleavage of a 5-styryl function using OsO_4–$NaIO_4$.[41] The structures of the new chroman-4-ones **7a**, **7b**, **7c** and **7d** were readily established by ^{1}H NMR spectroscopy, the key feature in all instances being the presence of a singlet at *ca.* δ 2.8 accounting for the equivalent 3-H protons. Typically, 3-H resonates at *ca.* δ 2.7 in chroman-4-ones.[42]

The usefulness of these new dicarbonyl compounds **7a** and **7d** in heterocyclic synthesis was briefly investigated. Reaction of

* Prenyl = 3,3-dimethylallyl.



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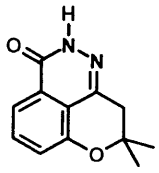

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the former with hydrazine hydrate in ethanol containing a catalytic quantity of glacial acetic acid gave the novel pyrano[4,3,2-*de*]phthalazine **16** in excellent yield. The related compound **17** was similarly obtained from the ester **7d**, although a longer reaction time was required. The ^{1}H NMR spectra of these compounds each displayed a singlet for the 9-H protons at *ca.* δ 3.3. In the former compound, 3'-H resonates at δ 9.38 and the amide proton (2-H) in the latter at δ 11.3. The IR spectrum of **17** recorded in Nujol displayed bands at 1651, 1608 and 3161 cm^{-1} and in CCl_4 at 1641, 1602 and 3150 cm^{-1}, typical for amide C=O and N–H stretching vibrations,[28] and confirms that the compound exists as its amide tautomer. Attempts to obtain the pyranophthalazine **16** directly from the hydroxy aldehyde **6g** using the above conditions failed, the only product isolated being the hydrazone **6n**.

In conclusion, directed *ortho* lithiation of chroman-4-ols provides a facile, reliable route to 5-substituted benzopyran derivatives, which are otherwise difficult to synthesise. Metallation of a 5-methyl function is also preferred to lithiation at the 8-position and gives easy access to the naturally occurring pyrano[2,3,4-*de*][1]benzopyran system.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Distillations were performed using a Kugelrohr apparatus (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. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM 250 instrument for solutions in $CDCl_3$; coupling constants (*J*) are given in Hz. Gas chromatographs were obtained using a Perkin-Elmer PE 8500 instrument equipped with an ion trap detector (Perkin-Elmer ITD) and using a 10.5 m BP1 capillary column. Flash chromatographic separations were performed on Crossfields Sorbsil C60 silica gel (M.P.D. 60 Å, 40–60 μ, activated) according to the published procedure.[43] Chroman-4-one was obtained from Janssen Chimica and was reduced in an identical manner to the other chroman-4-ones.

General Method for the Preparation of 5-Substituted Chroman-4-ols **6** *and* **9**.—Butyllithium (2.5 mol dm^{-3} solution in hexanes; 40.2 mmol) was added to a cold (ice–water cooling bath) stirred solution of the chroman-4-ol **5** (20 mmol) and TMEDA (40.2 mmol) in dry diethyl ether (50 cm^3) after which the cooling bath was removed and the mixture stirred for 4 h. The resulting reddish orange solution (except that derived from the naphthopyran **5g** which was blue and the tetramethyl analogue **5h** which was yellow), was cooled to 0 °C, the electrophile (40.2 mmol) was added and the solution was stirred at room temp. for 2 h prior to dilution with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer extracted with ethyl acetate (4 × 50 cm^3). The combined organic extracts were washed with HCl (*ca.* 0.1 mol dm^{-3}; 2 × 50 cm^3) and water (100 cm^3), dried (Na_2SO_4) and evaporated to afford the crude product which was eluted from silica and then distilled or recrystallised. The following compounds were obtained in this manner.

4-Hydroxy-2,2-dimethylchroman-5-carbaldehyde **6a** (76%) from **5a** and *N*-formylpiperidine as a pale yellow oil after elution from silica with 15% ethyl acetate in hexane and distillation, b.p. 125 °C at 0.3 mbar; ν_{max}(neat)/cm^{-1} 3489br, 1689 and 1594; δ_H 1.38 (3 H, s, 2-Me), 1.43 (3 H, s, 2-Me), 2.08 (1 H, dd, *J* 14.4, 6.0, 3-H$_{ax}$), 2.12 (1 H, dd, *J* 14.4, 4.3, 3-H$_{eq}$), 4.81 (1 H, br m, OH), 5.04 (1 H, m, 4-H$_{eq}$), 7.13 (1 H, m, Ar-H), 7.38–7.41 (2 H, m, Ar-H) and 9.97 (1 H, s, CHO); δ_C 26.0, 28.2, 40.4, 60.5, 74.5, 124.4, 125.1, 129.0, 129.8, 135.4, 154.1 and 195.9 (Found: C, 69.9; H, 6.9. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.9%).

2,2-Dimethyl-5-[1-hydroxy-1-(4-methoxybenzyl)]chroman-4-ol **6d** (69%) from **5a** and *p*-anisaldehyde as off-white microcrystals after elution from silica with 20% ethyl acetate in hexane and recrystallisation from light petroleum (b.p. 30–40 °C)–diethyl ether, m.p. 103.0–105.5 °C; ν_{max}(Nujol)/cm^{-1} 3428br and 1610; δ_H 1.46 (3 H, s, 2-Me), 1.55 (3 H, s, 2-Me), 1.72 (1 H, dd, *J* 11.3, 6.4, 3-H$_{ax}$), 2.04 (2 H, vbr s, OH), 2.39 (1 H, dd, *J* 11.3, 4.5, 3-H$_{eq}$), 3.84 (3 H, s, OMe), 5.17 (1 H, m, 4-H), 6.16 (1 H, d, *J* 1.7, ArC*H*OH), 6.45 (1 H, m, Ar-H), 6.71 (1 H, m, Ar-H), 6.91 (2 H, m, Ar-H) and 7.11–7.23 (3 H, m, Ar-H); δ_C 26.3, 30.3, 40.5, 55.2, 73.1, 78.4, 85.7, 113.0, 113.5, 113.8 (2 × C), 125.9, 129.1 (2 × C), 129.9, 132.4, 145.0, 150.9 and 159.7 (Found: C, 72.5; H, 7.0. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.1%).

5-(9-Hydroxyfluoren-9-yl)-2,2-dimethylchroman-4-ol **6e** (58%) from **5a** and fluorenone as colourless microcrystals after elution from silica with 10% ethyl acetate in hexane and recrystallisation from ethyl acetate–hexane, m.p. 182.5–184.5 °C; ν_{max}(Nujol)/cm^{-1} 3196 and 1597; δ_H(348 K) 1.41 (3 H, s, 2-Me), 1.53 (3 H, s, 2-Me), 1.98–2.11 (2 H, br m, 3-H), 3.07 (1 H, br s, OH), 5.28 (1 H, br s, 4-H), 6.74 (1 H, d, *J* 8.2, 8-H), 6.91 (1 H, br m, 7-H), 7.21–7.46 (7 H, m, Ar-H) and 7.69 (2 H, d, *J* 7.4, Ar-H) (Found: C, 80.5; H, 6.3. $C_{24}H_{22}O_3$ requires C, 80.5; H, 6.2%).

The reaction of the dianion derived from **5a** with bromine gave a dark brown oil which was eluted from silica with 15% ethyl acetate in hexane to give: fraction 1, *2,2-dimethyl-2H-chromene* (31%) as a colourless mobile oil, b.p. 50–55 °C at 0.5 mbar (lit.,[19] b.p. 79–80 °C at 2.5 Torr); fraction 2, *3,3-dibromo-2,2-dimethylchroman-4-one* (17%) as off-white needles from ethyl acetate–light petroleum (b.p. 40–60 °C), m.p. 97.7–99.0 °C (lit.,[44] m.p. 95.0–95.6 °C); ν_{max}(Nujol)/cm^{-1} 1710 and 1608; δ_H 1.75 (6 H, vbr s, 2-Me), 6.98 (1 H, dd, *J* 7.9 and 1.2, 8-H), 7.12 (1 H, m, 6-H), 7.52 (1 H, m, 7-H) and 7.99 (1 H, dd, *J* 8.0, 1.1, 5-H); δ_C 22.2 (2 × C), 74.9, 85.3, 116.1, 118.0, 122.2, 128.8, 136.9, 157.3 and 180.4; fraction 3, *2,2-dimethylchroman-4-one* (15%) as colourless needles from ethyl acetate–hexane, m.p. 87.5–88.5 °C (lit.,[45] m.p. 87.0–88.0 °C); fraction 4, *5-bromo-2,2-dimethylchroman-4-ol* **6f**, (12%) as pale yellow needles from light petroleum (b.p. 40–60 °C), m.p. 63.5–65.0 °C; ν_{max}(Nujol)/cm^{-1} 3448 and 1597; δ_H 1.45 (3 H, s, 2-Me), 1.47 (3 H, s, 2-Me), 2.04 (1 H, dd, *J* 14.6 and 5.4, 3-H), 2.21 (1 H, dd, *J* 14.6 and 2.7, 3-H), 2.87 (1 H, br s, OH), 4.95 (1 H, m, 4-H), 6.82 (1 H, dd, *J* 8.1, 1.3, 8-H) and 7.11–7.19 (2 H, m, 7-H, 6-H) (Found: C, 51.4; H, 5.1; Br, 31.1. $C_{11}H_{13}BrO_2$ requires C, 51.5; H, 5.0; Br, 31.4%); fraction 5, *2,2-dimethylchroman-4-ol* **5a** (9%) identical in all aspects with authentic material.

4-Hydroxyspiro[chroman-2,1'-cyclohexane]-5-carbaldehyde **6g** (83%) from **5b** and *N*-formylpiperidine as a pale yellow oil after elution from silica with 10% ethyl acetate in hexane and distillation, b.p. 175 °C at 0.5 mbar; ν_{max}(neat)/cm^{-1} 3492br, 1687 and 1585; δ_H 1.49–1.77 [10 H, m, (CH$_2$)$_5$], 2.05 (1 H, dd, *J* 14.3, 4.6, 3-H$_{ax}$), 2.10 (1 H, dd, *J* 14.3, 4.1, 3-H$_{eq}$), 4.74 (1 H, br m, OH), 5.06 (1 H, m, 4-H$_{eq}$), 7.19 (1 H, m, Ar-H), 7.41–7.43 (2 H, m, Ar-H) and 9.99 (1 H, s, CHO); δ_C 21.7 (2 × C), 25.5, 34.1, 36.2, 39.4, 60.4, 75.5, 125.1, 125.2, 128.9, 130.0, 135.4, 153.9 and 196.0 (Found: C, 73.1; H, 7.4. $C_{15}H_{18}O_3$ requires C, 73.1; H, 7.4%). The *hydrazone* **6n** (87%) as pale yellow cubes from ethyl acetate–hexane, m.p. 110.0–113.0 °C; ν_{max}(Nujol)/cm^{-1} 3387,

3202 and 1579; δ_H 1.36–1.81 (10 H, m, cyclohexane ring), 2.02 (1 H, dd, *J* 14.2, 4.7, 3-H_{ax}), 2.07 (1 H, br s, OH), 2.16 (1 H, dd, *J* 14.2, 4.0, 3-H_{eq}), 4.84 (1 H, m, 4-H), 5.59 (2 H, bs, NH_2), 6.89 (2 H, m, Ar-H), 7.24 (1 H, m, Ar-H) and 7.87 (1 H, s, CH=N); δ_C 21.9 (2 × C), 25.7, 33.7, 37.2, 39.6, 60.4, 74.5, 119.3, 123.0, 123.5, 128.4, 133.9, 145.7 and 153.6 (Found: C, 69.4; H, 7.8; N, 10.6. $C_{15}H_{20}N_2O_2$ requires C, 96.2; H, 7.8; N, 10.8%).

5-Benzoyl-2-ethyl-2-methylchroman-4-ol **6i** (57%) from **5c** and benzonitrile as a mixture of diastereoisomers (ratio *ca* 1:1.5)* as a viscous yellow oil after elution from silica with 10% ethyl acetate in hexane and distillation, b.p. 185–195 °C at 0.1 mbar; ν_{max}(Nujol)/cm^{-1} 3421, 1673 and 1590; δ_H (for diastereoisomeric mixture) 0.97–1.12 (6 H, m, 2-CH_2CH_3), 1.41 (3 H, s, 2-Me), 1.54 (3 H, s, 2-Me), 1.72–1.93 (4 H, m, 2-CH_2CH_3), 1.97–2.28 (4 H, m, 3-H), 4.80–4.86 (2 H, m, 4-H), 6.74 (2 H, m, 8-H), 6.99 (2 H, m, 6-H), 7.12–7.18 (2 H, m, 7-H) and 7.40–7.49 (2 H, br s, OH); δ_C (for diastereoisomeric miture) 7.95, 8.71, 23.4, 26.0, 30.5, 35.6, 37.5, 38.2, 60.7 (2 × C), 76.0, 76.4, multiple signals 120–131, 139.0, 140.9, 153.7, 153.9, 179.6 and 179.7 (Found: C, 76.9; H, 6.8. $C_{19}H_{20}O_3$ requires C, 77.0; H, 6.8%).

2,2-Dimethyl-5-trimethylsilyl-4-trimethylsiloxychroman **9a** (83%) from **5a** and chlorotrimethylsilane as a colourless mobile oil after elution from silica with 5% ethyl acetate in hexane and distillation, b.p. 110 °C at 0.1 mbar; δ_H 0.29 (9 H, s, $SiMe_3$), 0.39 (9 H, s, $SiMe_3$), 1.34 (3 H, s, 2-Me), 1.51 (3 H, s, 2-Me), 1.98–2.10 (2 H, m, 3-H), 5.14 (1 H, m, 4-H), 6.83 (1 H, m, Ar-H) and 7.20–7.25 (2 H, m, Ar-H) (Found: C, 63.5; H, 9.6. $C_{17}H_{30}O_2Si_2$ requires C, 63.3; H, 9.4%).

The crude product obtained from the reaction of the dianion derived from **5a** and methyl thiotosylate (MeSTs) was dissolved in glacial acetic acid (50 cm^3) containing hydrogen peroxide (100 mmol, 30%) and maintained at 80 °C for 1 h. The cooled reaction mixture was poured into water and extracted with ethyl acetate (5 × 50 cm^3). The combined ethyl acetate extracts were washed with water (2 × 50 cm^3), aq. sat. $NaHCO_3$ (5 × 50 cm^3) and water (100 cm^3), dried (Na_2SO_4), and evaporated to afford a dark brown semi-solid which was eluted from silica with 30% ethyl acetate in hexane to afford, *2,2-dimethyl-5-methylsulfonyl-4-methylsulfinyloxychroman* **9b** (43%) as pale brown needles after recrystallisation from hexane–ethyl acetate, m.p. 173.5–175.0 °C; ν_{max}(Nujol)/cm^{-1} 1593, 1304, 1157 and 1126; δ_H 1.11 (3 H, s, 2-Me), 1.63 (3 H, s, 2-Me), 2.39 (1 H, dd, *J* 15.5, 9.6, 3-H_{ax}), 2.83 [3 H, s, OS(O)Me], 2.97 (1 H, dd, *J* 15.5, 1.7, 3-H_{eq}), 3.35 (3 H, s, SO_2Me), 5.99 (1 H, m, 4-H), 7.21 (1 H, d, *J* 8.0, 8-H), 7.50 (1 H, m, 7-H) and 7.75 (1 H, d, *J* 7.9, 6-H); δ_C 28.5, 30.4, 37.5, 38.7, 45.2, 56.6, 76.4, 119.1, 124.8, 125.2, 130.5, 141.1 and 156.9 (Found: M + NH_4^+, 336.0939; C, 49.0; H, 5.7; S, 20.1%. $C_{13}H_{18}O_5S_2$ requires *M* + NH_4^+, 336.0939; C, 49.0; H, 5.7; S, 20.1%).

3,3a,5,6-Tetrahydro-2,2,8-trimethyl-2H-pyrano[2,3,4-de][1]*benzopyran-5-ol* **13** (90%) from **5h** and *N*-formylpiperidine as a mixture of diastereoisomers (ratio *ca.* 1:1)† as colourless needles after elution from silica with 35% ethyl acetate in hexane and recrystallisation from ethyl acetate and hexane, m.p. 106.5–108.0 °C; ν_{max}(Nujol)/cm^{-1} 3308br, 1616 and 1579; δ_H (for diastereoisomeric mixture) 1.34 (3 H, s, 2-Me), 1.35 (3 H, s, 2-Me), 1.47 (3 H, s, 2-Me), 1.48 (3 H, s, 2-Me), 1.83 (2 H, m, 3-H), 2.15 (2 H, m, 3-H), 2.28 (6 H, s, 8-Me), 2.72–3.23 (6 H, m, 6-H, OH), 4.73 (1 H, m, 3a-H), 4.95 (1 H, m, 3a-H), 5.46 (2 H, m, 5-H), 6.52 (2 H, s, Ar-H) and 6.57 (2 H, m, Ar-H) (Found: C, 72.0; H, 7.8. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.8%).

The following mixtures of isomeric 5- and 8-formylchroman-4-ols were obtained using the general method which had been modified by refluxing the reaction mixtures for 2 h.

Elution of the crude product from the reaction of **5a** with *N*-formylpiperidine from silica with 40% ethyl acetate in hexane gave fraction 1, *4-hydroxy-2,2-dimethylchroman-5-carbaldehyde* **6a** (59%), and fraction 2, *4-hydroxy-2,2-dimethylchroman-8-carbaldehyde* **6b** (39%) as a waxy, pale yellow solid, b.p. 195 °C at 0.3 mbar, m.p. 71.5–73.0 °C; ν_{max}(neat)/cm^{-1} 3409br, 1660 and 1587; δ_H 1.35 (3 H, s, 2-Me), 1.49 (3 H, s, 2-Me), 1.91 (1 H, dd, *J* 13.4, 9.2, 3-H_{ax}), 2.21 (1 H, dd, *J* 13.4, 6.2, 3-H_{eq}), 2.98 (1 H, bm, OH), 4.86 (1 H, m, 4-H_{ax}), 6.94 (1 H, m, 6-H), 7.66–7.73 (2 H, m, Ar-H) and 10.3 (1 H, d, *J* 0.5, CHO); δ_C 25.9, 28.9, 42.0, 62.9, 76.9, 119.8, 124.2, 126.0, 127.7, 134.3, 156.1, and 190.1 (Found: M$^+$, 206.0943; C, 70.0; H, 7.0. $C_{12}H_{14}O_3$ requires *M*, 206.0943; C, 69.9; H, 6.9%).

Elution of the crude product from the reaction of **5e** with *N*-formylpiperidine from silica with 40% ethyl acetate in hexane gave fraction 1, *4-hydroxychroman-5-carbaldehyde* **6j** (26%) as a colourless oil, b.p. 110 °C at 0.4 mbar; ν_{max}(Nujol)/cm^{-1} 3478br, 1684 and 1600; δ_H 2.04–2.22 (2 H, m, 3-H), 4.23–4.35 (3 H, m, 2-H, OH), 5.01 (1 H, m, 4-H), 7.17 (1 H, m, 7-H), 7.41–7.43 (2 H, m, 6-H, 8-H) and 10.0 (1 H, s, CHO) (Found: M$^+$, 178.0630. $C_{10}H_{10}O_3$ requires *M*, 178.0630) and fraction 2, *4-hydroxychroman-8-carbaldehyde* **6l** (67%) as a colourless oil; δ_H 2.02–2.22 (2 H, m, 3-H), 3.00 (1 H, br s, OH), 4.35–4.40 (2 H, m, 2-H), 4.79 (1 H, m, 4-H), 6.95 (1 H, m, 6-H), 7.55 (1 H, dd, *J* 7.8, 1.7, Ar-H), 7.67 (1 H, dd, *J* 7.8, 1.7, Ar-H) and 10.3 (1 H, d, *J* 0.5, CHO). This latter fraction was refluxed in toluene (50 cm^3) containing a catalytic amount of TsOH until TLC examination of the reaction mixture indicated that none of the chromanol remained (*ca.* 25 min). The solution was cooled, diluted with water (200 cm^3) and extracted with ethyl acetate (2 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give *2H-chromene-8-carbaldehyde* **8c** (89%) as a pale brown oil; δ_H 4.97 (2 H, m, 2-H), 5.84 (1 H, dt, *J* 10.0, 3.5, 3-H), 6.43 (1 H, dt, *J* 10.0, 1.8, 4-H), 6.90 (1 H, m, 6-H), 7.14 (1 H, dd, *J* 7.6, 1.5, Ar-H), 7.62 (1 H, dd, *J* 7.7, 1.5, Ar-H) and 10.4 (1 H, s, CHO). A solution of **9c** (1.7 mmol) in ethanol (10 cm^3) containing 4-nitrophenylhydrazine (1.7 mmol) was refluxed for 1 h. The crude product which precipitated from the cooled reaction mixture was collected and recrystallised from ethanol to afford *2H-chromene-8-carbaldehyde 4-nitrophenylhydrazone* **8d** (93%) as brown microcrystals, m.p. 245.5–248.0 °C (decomp.); δ_H 4.90 (2 H, dd, *J* 3.5 and 1.9, 2-H); 5.84 (1 H, dt, *J* 10.0, 3.5, 3-H), 6.45 (1 H, dt, *J* 10.0, 1.9, 4-H), 6.90–7.00 (2 H, m, Ar-H), 7.10–7.14 (2 H, m, Ar-H), 7.82 (1 H, m, Ar-H), 8.04 (1 H, bs, NH) and 8.16–8.21 (3 H, m, Ar-H, CH=N) (Found: C, 65.1; H, 4.4; N, 14.0. $C_{16}H_{13}N_3O_3$ requires C, 65.1; H, 4.4; N, 14.2%).

General Method for the Preparation of 4-Hydroxychroman-5-carboxylic Acids.—An ethereal solution of the dilithiochroman-4-ol prepared as described in the general method above, was added to cold (−10 °C) diethyl ether (100 cm^3) saturated with CO_2. The resulting cloudy solution was stirred and allowed to warm to room temp. over 30 min, during which time a steady stream of CO_2 was passed through it. The mixture was then stirred at room temp. for a further 1 h after which it was diluted with aqueous NaOH (2 mol dm^{-3}; 200 cm^3). The layers were separated, the alkaline layer then being washed with diethyl ether (3 × 50 cm^3), cautiously acidified with conc. HCl and extracted with ethyl acetate (4 × 50 cm^3). The combined extracts were dried (Na_2SO_4) to give, after evaporation the crude carboxylic acid as an off-white solid which was then recrystallised.

4-Hydroxy-2,2-dimethylchroman-5-carboxylic acid **6c** (97%) from **5a** as colourless crystals from ethyl acetate–hexane, m.p. 133.5–137.5 °C; ν_{max}(Nujol)/cm^{-1} 3324br, 2623br and 1680; δ_H 1.45 (3 H, s, 2-Me), 1.50 (3 H, s, 2-Me), 2.07 (1 H, dd, *J* 14.6

* Ratio of diastereoisomers based upon the relative integrals of the signals for 2-Me at δ 1.41 and 1.54.

† Ratio of diastereoisomers based upon the relative integrals of the signals for 3a-H at δ 4.73 and 4.95.

and 5.7, 3-H_{ax}), 2.24 (1 H, dd, *J* 14.6, 3.3, 3-H_{eq}), 5.22 (1 H, m, 4-H_{eq}), 7.10 (1 H, dd, *J* 8.1, 1.6, 8-H), 7.28 (1 H, m, 7-H), 7.71 (1 H, dd, *J* 8.0, 1.7, 6-H) and *ca.* 7.5–9.5 (2 H, vbr s, OH); δ_C 25.8, 29.0, 39.9, 61.2, 74.0, 123.9, 124.3, 125.0, 128.8, 129.4, 154.0 and 172.4 (Found: C, 64.7; H, 6.4. $C_{12}H_{14}O_4$ requires C, 64.8; H, 6.4%).

2-Ethyl-4-hydroxy-2-methylchroman-5-carboxylic acid **6h** (76%) from **5c** as a mixture of diastereoisomers (*ca.* ratio 1:1.2)* as colourless crystals from ethyl acetate–hexane, m.p. 132.5–143.0 °C; ν_{max}(Nujol)/cm^{-1} 3305br, 2614br, 1678 and 1594; δ_H (for diastereoisomeric mixture) 0.95–1.04 (6 H, m, 2-CH_2CH_3), 1.36 (3 H, s, 2-Me), 1.45 (3 H, s, 2-Me), 1.74–1.92 (4 H, m, 2-CH_2CH_3), 2.03–2.25 (4 H, m, 3-H), 5.20–5.24 (2 H, m, 4-H), 7.12 (2 H, m, 8-H), 7.29 (2 H, m, 7-H), 7.68–7.73 (2 H, m, 6-H) and 7.9–9.2 (4 H, br s, OH); δ_C(major isomer) 8.40, 24.9, 30.8, 38.1, 61.2, 76.4, 123.9, 124.4, 125.4, 128.8, 129.2, 154.0 and 172.7; δ_C(minor isomer) 7.88, 23.1, 34.4, 37.5, 61.1, 76.1, 123.9, 124.2, 125.2, 128.8, 129.3, 154.1 and 172.6 (Found: C, 66.1; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%).

4-Hydroxy-2-isopropylchroman-5-carboxylic acid **6j** (92%) from **5d** as a mixture of diastereoisomers (*ca.* ratio 7:1)† as colourless crystals from ethyl acetate–hexane, m.p. 94.0–98.5 °C; ν_{max}(Nujol)/cm^{-1} 3199br, 2661br and 1675; δ_H (major isomer) 1.01–1.11 [6 H, m, $CH(CH_3)_2$], 2.01–2.10 [2 H, m, 3-H, $CH(CH_3)_2$], 2.33 (1 H, m, 3-H), 3.77 (1 H, m, 2-H), 5.34 (1 H, m, 4-H), 7.10 (1 H, dd, *J* 7.8, 1.6, 8-H), 7.24 (1 H, m, 7-H), 7.67 (1 H, dd, *J* 7.9, 1.6, 6-H) and 7.5–9.0 (2 H, br s, OH); δ_C(major isomer) 18.2, 18.3, 31.5, 32.5, 63.2, 79.6, 121.4, 123.2, 124.8, 128.4, 129.1, 155.9 and 172.7; δ_H(minor isomer, only signals given are those which were sufficiently well resolved from those of the major isomer) 1.96 (1 H, m, 3-H), 4.16 (1 H, m, 2-H), 4.97 (1 H, m, 4-H), 7.04 (1 H, m, 8-H), 7.74 (1 H, m, 7-H) and 7.96 (1 H, m, 6-H); δ_C(minor isomer) 17.6, 17.7, 32.1, 33.8, 65.0, 82.8, 118.2, 123.1, 127.3, 128.5, 133.0, 153.6 and 166.4 (Found: C, 66.0; H, 7.0. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%).

3,4-Dihydro-4-hydroxy-2,2-dimethyl-2H-naphtho[1,2-b]*pyran-5-carboxylic acid* **6m** (87%) from **5g** as colourless crystals from ethyl acetate–hexane, m.p. 151.5–156.5 °C; ν_{max}(Nujol)/cm^{-1} 3249br, 2652br and 1668; δ_H 1.59 (3 H, s, 2-Me), 1.62 (3 H, s, 2-Me), 2.17 (1 H, dd, *J* 14.5, 5.6, 3-H_{ax}), 2.35 (1 H, dd, *J* 14.5, 3.1, 3-H_{eq}), 5.34 (1 H, m, 4-H_{eq}), 7.56–7.63 (2 H, m, Ar-H), 7.87 (1 H, dd, *J* 8.0, 1.7, Ar-H), 8.32 (1 H, s, 6-H) and 8.32–8.35 (1 H, m, Ar-H); δ_C 25.9, 29.1, 40.2, 61.2, 74.4, 116.8, 122.6, 125.0, 127.0, 127.5, 127.7, 128.0, 128.5, 132.3, 149.0 and 171.3 (Found: C, 70.5; H, 6.1. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%).

Dehydration of Substituted Chroman-4-ols.—A solution of the chroman-4-ol (7.5 mmol) in toluene (50 cm^3) containing a catalytic amount of toluene-*p*-sulfonic acid (*ca.* 0.1 g) was refluxed until TLC examination of the reaction mixture indicated that no starting chroman-4-ol remained. The cooled solution was diluted with water (200 cm^3) and ethyl acetate (50 cm^3) and the layers were separated. The organic layer was washed with water (100 cm^3), dried (Na_2SO_4) and evaporated to give an oil which was eluted from silica. The following compounds were obtained by this route.

2,2-Dimethyl-2H-chromene-5-carbaldehyde **8a** (74%) from **6a** after 1.5 h reflux and elution from silica with 10% ethyl acetate in hexane, as a colourless oil after distillation, b.p. 95 °C at 0.7 mbar; ν_{max}(Nujol)/cm^{-1} 1692; δ_H 1.43 (6 H, s, 2-Me), 5.81 (1 H, d, *J* 10.2, 3-H), 7.00 (1 H, m, 8-H), 7.25–7.31 (2 H, m, 7-H, 6-H), 7.40 (1 H, dd, *J* 10.2, 0.5, 4-H) and 10.1 (1 H, s, CHO); δ_C 27.7 (2 × C), 75.7, 118.4, 121.2, 122.2, 126.2, 128.6, 130.9, 133.9, 153.6 and 192.8 (Found: M$^+$, 188.0837; C, 76.5; H, 6.3%. $C_{12}H_{12}O_2$ requires *M*, 188.0837; C, 76.6; H, 6.4%).

8',8a'-Dihydro-7',7'-dimethylspiro{*fluorene-9,2'-7'H-furo*[2,3,4-de][1]*benzopyran*} **11** (76%) from **6e** after 5 min under reflux as off-white crystals from light petroleum (b.p. 60–80 °C)–ethyl acetate, m.p. 115.0–117.0 °C; δ_H 1.25 (6 H, br s, 7'-Me), 1.57 (1 H, m, 8'-H), 2.35 (1 H, br s, 8'-H), 5.10 (1 H, br s, 8a'-H), 6.79 (1 H, d, *J* 7.9, 5'-H), 7.23–7.43 (8 H, m, Ar-H) and 7.71 (2 H, d, *J* 7.5, Ar-H) (Found: C, 84.7; H, 6.0. $C_{24}H_{20}O_2$ requires C, 84.8; H, 5.9%).

After 2.5 h under reflux, the cooled solution from **6j** was diluted with aqueous NaOH (1 mol dm^{-3}; 100 cm^3) and the layers were separated. The toluene layer was extracted with aqueous NaOH (1 mol dm^{-3}; 1 × 30 cm^3), washed with water (2 × 50 cm^3), dried (Na_2SO_4) and evaporated to afford *8,8a-dihydro-7-isopropyl-7H-furo*[2,3,4-de][1]*benzopyran-2-one* **10** (21%) as colourless microcrystals from light petroleum (b.p. 40–60 °C), m.p. 77.0–78.0 °C; ν_{max}(Nujol)/cm^{-1} 1760 and 1602; δ_H 1.04–1.07 [6 H, m, $CH(CH_3)_2$], 1.61 (1 H, m, 8-H_{ax}), 2.10 [1H,m,$CH(CH_3)_2$],2.51(1H,ddd,*J*12.2,5.4and2.1,8-H_{eq}),4.28 (1 H, ddd, *J* 11.9, 4.6 and 2.1, 7-H), 5.44 (1 H, dd, *J* 11.5, 5.4, 8a-H), 7.00 (1 H, dd, *J* 7.8, 1.6, 5-H) and 7.37–7.40 (2 H, m, 3-H, 4-H); δ_C 17.6, 18.2, 30.3, 32.4, 74.0, 81.6, 116.9, 118.5, 126.2, 131.8, 135.2, 152.7 and 169.9 (Found: M$^+$, 218.0943; C, 71.6; H, 6.6. $C_{13}H_{14}O_3$ requires *M*, 218.0943; C, 71.5; H, 6.5%).

The combined aqueous alkaline extracts were cautiously acidified with conc. HCl and extracted with ethyl acetate (4 × 50 cm^3). The combined extracts were washed with water (100 cm^3), dried (Na_2SO_4) and evaporated to afford *2-isopropyl-2H-chromene-5-carboxylic acid* **8b** (68%) as a bright yellow solid, b.p. 160–165 °C at 0.1 mbar; m.p. 74.0–74.5 °C; ν_{max}(Nujol)/cm^{-1} 2645br, 1687 and 1593; δ_H 1.01–1.16 [6 H, m, $CH(CH_3)_2$], 2.03 [1 H, m, $CH(CH_3)_2$], 4.59 (1 H, m, 2-H), 5.87 (1 H, dd, *J* 10.4, 3.5, 3-H), 7.01 (1 H, m, 8-H), 7.18 (1 H, m, 7-H), 7.47 (1 H, dd, *J* 10.4, 0.3, 4-H), 7.61 (1 H, d, *J* 7.7, 6-H) and 11.43 (1 H, br s, OH); δ_C 17.7, 17.8, 33.1, 79.2, 121.0, 122.0, 123.3, 123.9, 125.5, 126.4, 128.1, 154.7 and 172.9 (Found: C, 71.2; H, 6.4. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%).

Oxidation of 4-Hydroxyspiro[*chroman-2,1'-cyclohexane*]*-5-carbaldehyde* **6g**.—(i) A solution of trifluoroacetic anhydride (8.5 mmol) in dry dichloromethane (10 cm^3) was added dropwise over 15 min, to a vigorously stirred solution of anhydrous dimethyl sulfoxide (11.5 mmol) in dry dichloromethane (10 cm^3) at −70 °C, the temperature of the reaction mixture being kept < −60 °C. After 30 min at −70 °C, a solution of the chroman-4-ol **6g** (5.75 mmol) in dry dichloromethane (10 cm^3) was added over 15 min to the mixture, again the temperature of the reaction mixture being kept < −60 °C. The reaction mixture was stirred at −70 °C for 1 h, when a solution of triethylamine (25 mmol) in dry dichloromethane (10 cm^3) was added to it over 5 min; the mixture was then allowed to warm to room temp. over 4 h. It was then washed with water (2 × 50 cm^3) and brine (2 × 50 cm^3), dried (Na_2SO_4) and evaporated to give a viscous oil which was eluted from silica with 10% ethyl acetate in hexane to afford two fractions: fraction 1, *4-oxospiro*[*chroman-2,1'-cyclohexane*]*-5-carbaldehyde* **7a** (21%) as a yellow oil after distillation, b.p. 190 °C at 0.6 mbar; ν_{max}(Nujol)/cm^{-1} 1771, 1690 and 1587; δ_H 1.36–1.74 (8 H, m, cyclohexane ring), 1.99–2.03 (2 H, m, cyclohexane ring), 2.80 (2 H, s, 3-H), 7.21 (1 H, dd, *J* 7.6 and 1.7, 8-H), 7.38 (1 H, dd, *J* 7.7 and 1.8, 6-H), 7.56 (1 H, m, 7-H) and 10.71 (1 H, s, CHO); δ_C 21.4 (2 × C), 25.0, 34.6 (2 × C), 48.8, 80.4, 119.7, 120.3, 123.4, 135.4, 138.2, 160.1, 193.3 and 193.7 (Found: C, 73.7; H, 6.7. $C_{15}H_{16}O_3$ requires C, 73.7; H, 6.6%); and fraction 2, *4-hydroxyspiro*[*chroman-2,1'-cyclohexane*]*-5-carbaldehyde* **6g** (64%).

* Ratio of diastereoisomers based upon the relative integrals of the signals for 2-Me at δ 1.36 and 1.45.

† Ratio of diastereoisomers based upon the relative integrals of the signals for 4-H at δ 5.34 and 4.97.

(ii) 4-Hydroxyspiro[chroman-2,1′-cyclohexane]-5-carbaldehyde **6g** (10 mmol) was maintained at 30–35 °C with chromium trioxide solution [CrO_3 (2.2 g), glacial acetic acid (30 cm^3) and water (5 cm^3)] until TLC examination of the reaction mixture indicated that none of the starting alcohol remained (*ca.* 3 h). The mixture was diluted with water (800 cm^3) and extracted with ethyl acetate (5 × 50 cm^3). The combined extracts were extracted with aqueous NaOH (2 mol dm^{-3}; 3 × 50 cm^3), washed with water (50 cm^3), dried (Na_2SO_4) and evaporated to afford 4-oxospiro[chroman-2,1′-cyclohexane]-5-carbaldehyde **7a** (53%).

Cautious acidification of the combined aqueous alkaline extracts with conc. HCl and subsequent extraction with ethyl acetate (4 × 50 cm^3) gave on evaporation of the dried (Na_2SO_4), combined extracts, a pale brown solid which crystallised on storage. Recrystallisation of this from ethyl acetate–hexane gave *4-oxospiro[chroman-2,1′-cyclohexane]-5-carboxylic acid* **7c** (33%) as colourless needles, m.p. 127.0–129.5 °C; ν_{max}(Nujol)/cm^{-1} 2700br, 1706 and 1692; δ_H 1.31–1.73 (8 H, m, cyclohexane ring), 1.99–2.06 (2 H, m, cyclohexane ring), 2.82 (2 H, s, 3-H), 7.12 (1 H, dd, *J* 7.8, 1.5, 8-H), 7.34 (1 H, dd, *J* 7.7, 1.6, 6-H) and 11.81 (1 H, bs, OH); δ_C 21.3 (2 × C), 25.0, 34.5 (2 × C), 48.1, 80.2, 117.7, 121.5, 122.4, 132.8, 135.8, 160.3, 171.7 and 193.5 (Found: C, 69.0; H, 6.2. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.2%).

Oxidation of 4-Hydroxy-2,2-dimethylchroman-5-carboxylic Acid **6c**.—Oxidation of **6c** using method (ii) above gave directly *2,2-dimethyl-4-oxochroman-5-carboxylic acid* **7b** (78%) as colourless cubes, m.p. 154.5–157.0 °C from ethyl acetate and hexane; ν_{max}(Nujol)/cm^{-1} 3143br, 1726 and 1659; δ_H 1.49 (6 H, s, 2-Me), 2.85 (2 H, s, 3-H), 7.07 (1 H, d, *J* 7.9, 8-H), 7.31 (1 H, d, *J* 8.0, 6-H) and 7.52 (1 H, m, 7-H); δ_C 26.4 (2 × C), 48.9, 79.4, 117.0, 121.3, 122.0, 132.9, 135.8, 160.6, 172.0 and 193.1 (Found: M^+, 220.0736; C, 65.4; H, 5.8. $C_{12}H_{12}O_4$ requires *M*, 220.0736; C, 65.5; H, 5.5%).

Esterification of **7b** gave *ethyl 2,2-dimethyl-4-oxochroman-5-carboxylate* **7d** (92%) as a colourless oil after distillation, b.p. 150 °C at 0.1 mbar; ν_{max}(neat)/cm^{-1} 1724, 1695 and 1593; δ_H 1.36 (3 H, t, *J* 7.2, OCH_2CH_3), 1.45 (6 H, s, 2-Me), 2.73 (2 H, s, 3-H), 4.39 (2 H, q, *J* 7.2, OCH_2CH_3), 6.89–6.99 (2 H, m, Ar-H) and 7.45 (1 H, m, Ar-H); δ_C 13.9, 26.5 (2 × C), 48.8, 61.7, 79.5, 117.1, 119.4, 119.9, 134.2, 135.3, 159.9, 169.5 and 190.8 (Found: C, 67.4; H, 6.3. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%).

3,3a-Dihydro-2,2,8-trimethyl-2H-pyrano[2,3,4-de][1]benzopyran **14**.—Methanesulfonyl chloride (2.6 mmol) was added *via* syringe to a cold (*ca.* 5 °C) stirred solution of the lactol **13** (2.1 mmol) and triethylamine (5.33 mmol) in dry dichloromethane (25 cm^3). After being stirred for 30 min, the solution was refluxed for 2 h and then cooled, diluted with water (100 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were washed with water (100 cm^3) and aq. HCl (2 mol dm^{-3}; 3 × 50 cm^3), dried (Na_2SO_4) and evaporated to afford the *title compound* **14** (89%) as a colourless oil after distillation, which gradually darkened on storage at room temp., b.p. 140 °C at 0.2 mbar; ν_{max}(neat)/cm^{-1} 1626, 1602 and 1577; δ_H 1.31 (3 H, s, 2-Me), 1.52 (3 H, s, 2-Me), 2.17 (1 H, dd, *J* 13.6, 9.1, 3-H), 2.26–2.34 (4 H, m, 3-H and 8-Me), 5.08 (1 H, m, 3a-H), 5.86 (1 H, d, *J* 5.8, 6-H), 6.42 (1 H, s, Ar-H), 6.55 (1 H, s, Ar-H) and 6.63 (1 H, d, *J* 5.8, 5-H); δ_C 21.3, 24.7, 30.1, 38.3, 68.0, 75.9, 106.4, 108.9, 115.4, 115.5, 130.3, 139.6, 146.0 and 151.2 (Found: M^+, 216.1150. $C_{14}H_{16}O_2$ requires *M*, 216.1150; satisfactory elemental analysis could not be obtained for this compound).

3,3a,5,6-Tetrahydro-2,2,8-trimethyl-2H-pyrano[2,3,4-de][1]-benzopyran-5-one **15**.—Pyridinium chlorochromate (7.8 mmol) was added in a single portion to a cold (*ca.* 5 °C), stirred solution of the lactol **13** (2.6 mmol) in dry dichloromethane (20 cm^3). The solution was stirred for 30 min and then warmed to room temp. and stirred until TLC examination of the reaction mixture indicated that no starting material remained (*ca.* 4 h). The solution was then diluted with water (300 cm^3) and extracted with CH_2Cl_2 (5 × 30 cm^3). The combined extracts were washed with water (50 cm^3), dried (Na_2SO_4) and evaporated to afford the *title compound* **15** (66%) as colourless needles after elution from silica with 30% ethyl acetate in hexane and recrystallisation from ethyl acetate–hexane, m.p. 157.0–157.5 °C; ν_{max}(Nujol)/cm^{-1} 1726, 1620 and 1593; δ_H 1.35 (3 H, s, 2-Me), 1.51 (3 H, s, 2-Me), 2.04 (1 H, dd, *J* 12.7 and 11.2, 3-H), 2.31 (3 H, s, 8-Me), 2.37 (1 H, dd, *J* 12.7 and 6.7, 3-H), 3.68 (2 H, s, 6-H), 5.43 (1 H, dd, *J* 11.2, 6.7, 3a-H) and 6.59 (2 H, s, Ar-H); δ_C 21.4, 24.4, 29.8, 36.8, 38.2, 70.3, 76.1, 113.1, 115.7, 119.0, 131.5, 141.1, 152.2 and 170.7 (Found: M^+, 232.1099; C, 72.5; H, 7.2%. $C_{14}H_{16}O_3$ requires *M*, 232.1099; C, 72.4; H, 7.0%).

Spiro[cyclohexane-1,8′-(9′H)-pyrano[4,3,2-de]phthalazine] **16**.—A solution of 4-oxospiro[chroman-2,1′-cyclohexane]-5-carbaldehyde **7a** (1.3 mmol) and hydrazine hydrate (1.35 mmol) in ethanol (15 cm^3) containing a catalytic quantity of glacial acetic acid was refluxed for 3 h. Removal of the ethanol and addition of diethyl ether to the resulting sticky oil gave a pale yellow solid which was recrystallised from ethyl acetate–hexane to afford the *title phthalazine* **16** (96%) as colourless needles, m.p. 118.5–119.5 °C; ν_{max}(Nujol)/cm^{-1} 1593; δ_H 1.41–1.91 (10 H, m, cyclohexane ring), 3.32 (2 H, s, 9′-H), 7.30 (1 H, d, *J* 6.9, 6′-H), 7.46 (1 H, d, *J* 7.2, 4′-H), 7.78 (1 H, m, 5′-H) and 9.38 (1 H, s, 3′-H); δ_C 21.4 (2 × C), 25.3, 35.1 (2 × C), 39.7, 79.4, 114.6, 116.8, 117.2, 125.8, 134.1, 150.0, 152.1 and 152.9 (Found: M^+, 240.1263; C, 75.2; H, 6.9; N, 11.9%. $C_{15}H_{16}N_2O$ requires *M*, 240.1263; C, 75.0; H, 6.7; N, 11.7%).

8,9-Dihydro-8,8-dimethylpyrano[4,3,2-de]phthalazin-3(2H)-one **17**.—Using the above procedure, ester **7d** gave after 8 h the *title compound* **17** (89%) as colourless microcrystals from ethanol, m.p. 223.0–225.0 °C; ν_{max}(Nujol)/cm^{-1} 3161, 1651, 1608 and 1588; δ_H 1.46 (6 H, s, 8-Me), 2.97 (2 H, s, 9-H), 7.25 (1 H, dd, *J* 7.9 and 0.8, 6-H), 7.67 (1 H, m, 5-H), 7.94 (1 H, dd, *J* 8.0, 0.9, 4-H) and 11.30 (1 H, br s, NH); δ_C 26.5 (2 × C), 39.9, 78.3, 116.1, 117.9, 120.3, 127.5, 133.3, 140.7, 153.2 and 160.8 (Found: C, 66.7; H, 5.4; N, 13.0. $C_{12}H_{12}N_2O_2$ requires C, 66.6; H, 5.6; N, 13.0%).

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