Extended conjugation in di- and tri-arylmethane dyes. Part 4.[1] Steric and electronic effects in analogues of Malachite Green containing a 2*H*-1-benzopyran unit

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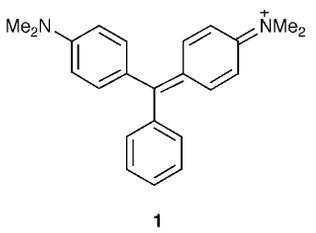
Received (in Cambridge, UK) 6th October 1999, Accepted 23rd November 1999
Published on the Web 14th January 2000

Triarylmethane dyes containing a 2,2-dimethyl-2*H*-1-benzopyran unit have been synthesised. The visible spectral parameters of these novel dyes are akin to those of the 1- and 2-naphthyl analogues of Malachite Green with the effects of a methoxy group superimposed to represent the influence of the oxygen heteroatom. Steric constraints are accommodated by an increased departure from molecular coplanarity along the *y*-axis.

Introduction

The response of the triphenylmethane (TPM) system *e.g.* **1**



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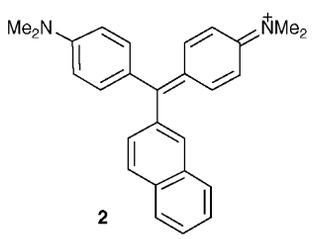

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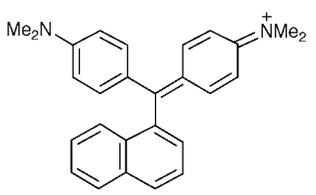

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to the electronic and steric effects of substituents has been thoroughly investigated[2–5] and Dewar[6] and Griffiths[7] have suggested theoretical explanations for the resulting spectral changes. Steric congestion in TPM dyes, associated with the *ortho*-hydrogen atoms, prevents coplanarity of the three aryl rings and the basic structure resembles that of a three-bladed propeller[8] with the rings twisted *ca.* 30° out of the sp^2 plane of the central carbon atom. Nevertheless, TPM dyes provide many examples of carbocations which are efficiently resonance stabilised and which react at measurable rates with even good nucleophiles.[9,10]

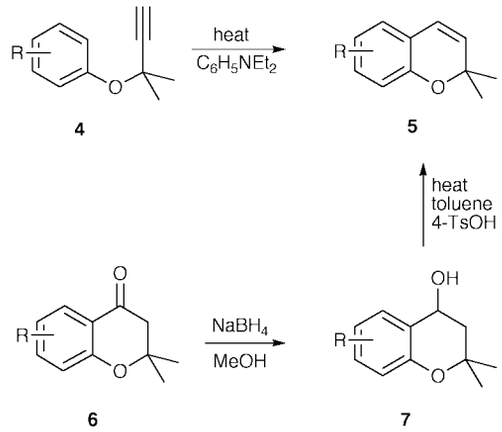
The cationic charge on Malachite Green (MG) **1** is stabilised by conjugation both with substituents in the unsubstituted phenyl ring and with the (dimethylamino)phenyl rings and various attempts have been made to increase the efficiency of this process. Thus, changing the terminal group from dimethylamino in **1** to other dialkylamino[11] and to cyclic amino groups[12] causes red shifts of the main absorption band, largely attributable to increased electron donation by the basic units. Stabilisation by extending the conjugation has also been investigated. Introduction of biphenyl[13] and fluorene[14] moieties in place of the phenyl ring has only a minimal effect on the visible spectra and suggests that conjugation through the extended chromophoric system is ineffective even when twisting about the interannular bond is curtailed as in the fluorene analogue. The 2-naphthyl derivative of Malachite Green **2**[15] exhibits a red shift of the y-band which implies enhanced conjugation attributable to the extension of the chromophore along the *y*-axis, since there is no additional steric hindrance associated with a longitudinally bonded naphthalene unit. However, a comparison between MG and its 1-naphthyl derivative **3** shows red shifts of both the x- and y-bands, but the response in ε_{max} of the two bands is different.[16] The x-band becomes more intense whereas the y-band decreases in intensity, behaviour which is characteristic of enforced rotation about the *y*-axis caused by crowding at the central carbon atom. Steric and electronic factors are in opposition in the transversely conjugated naphthalene dye and the unexpected red shift of the y-band reflects the electronic contribution of the 1-naphthyl group.

As part of our studies in benzopyran chemistry[17] and of steric effects in basic dyes,[18] we now report the synthesis of a series of lithio derivatives of 2,2-dimethyl-2*H*-1-benzopyran, the incorporation of this heterocycle into the Malachite Green dye system and the consequences of its attachment at various sites on the spectral parameters of the dye.

Discussion

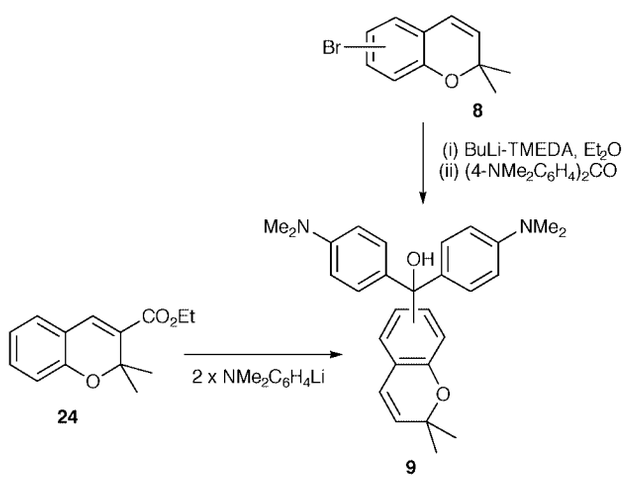
Numerous routes are available for the synthesis of 2*H*-1-benzopyrans **5**,[19] with two methods being particularly valuable because of the availability and cheapness of the starting materials. The electrocyclisation of aryl propargyl ethers **4**,[20] † readily prepared from phenols and alkynols,[21] often gives high yields of benzopyrans (Scheme 1). Whilst involving more steps, the sequence chroman-4-one **6**→chroman-4-ol **7**→2*H*-chromene (2*H*-1-benzopyran) **5**,[22] and commencing from a 2′-hydroxyacetophenone,[23] is equally attractive (Scheme 1). Both routes were used to prepare 6- and 8-bromo-2,2-dimethyl-2*H*-1-benzopyrans, but heating 3-(3-bromophenoxy)-3-methylbut-1-yne in *N*,*N*-diethylaniline gave a mixture of the 5- and 7-bromobenzopyrans which could not be separated; the 7-isomer was only synthesised by dehydration of the corresponding chroman-4-ol. Metallation of the three bromochromenes **8** was accomplished with the butyllithium–TMEDA complex and

† Propargyl = prop-2-ynyl.



Scheme 1

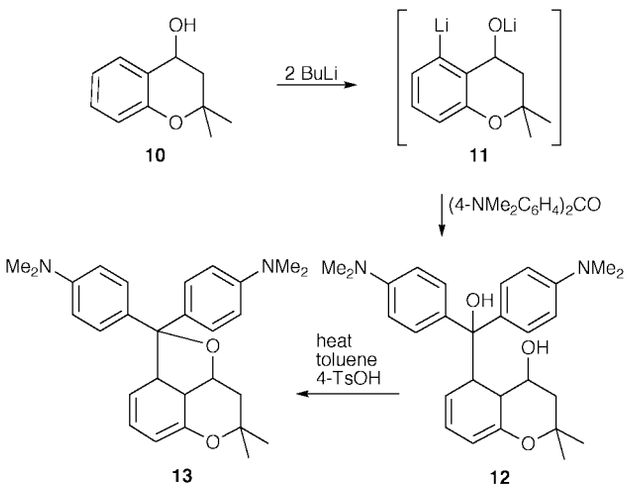
reaction of the resulting lithiochromenes with 4,4′-bis(dimethylamino)benzophenone (Michler's ketone) gave the carbinols **9a**–**c** (Scheme 2).



Scheme 2

Benzyl alcohols are known to undergo directed *ortho*-lithiation when treated with two molar equivalents of the BuLi–TMEDA complex[24] and we have recently generated the 4,5-dilithio intermediate **11** from 2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-ol **10**.[25] The reaction of **11** and Michler's ketone gave a reasonable yield of the diol **12** after hydrolysis. However, when **12** was heated for a short time in toluene in the presence of a catalytic amount of toluene-4-sulfonic acid (4-TsOH) and subsequently basified, the dihydrofuro[2,3,4-*de*]benzopyran **13** was isolated instead of the chromen-5-yl derivative (Scheme 3). Phthalide formation was anticipated in view of earlier findings,[24–26] such dehydration being more facile than loss of water to form the 3,4-double bond. When the dehydration reaction was carried out for a longer period of time, the mixture gradually decomposed without the formation of the benzopyran and a similar lack of success was apparent when $KHSO_4$ was used as the dehydrating agent and under more forcing conditions.

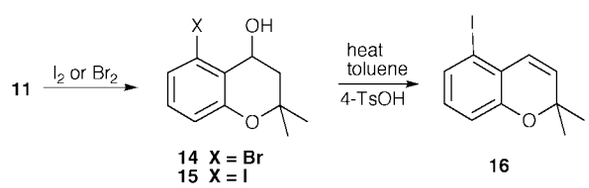
It is interesting to note that solutions of **12** and **13** in glacial acetic acid exhibited an intense deep blue colour, indicating the formation of a TPM cation presumably by cleavage of the phthalide ring in the latter instance, a reaction which is intrinsic to the use of phthalides in pressure sensitive copying paper.[27] However, the dye could not be isolated as the chloride, fluoroborate or perchlorate salt. The increased steric hindrance arising from the *peri* hydroxy group so generated would account for the red shift of the main absorption band giving a blue solution rather than the blue–green colour of MG itself. A blue solution



Scheme 3

was also observed during the dehydration of **12** by 4-TsOH in toluene.

A different approach to the chromen-5-yl derivative of MG was therefore considered. The treatment of an organolithium compound with a halogen gives the halogenated compound and the reaction between the dilithium salt **11** and bromine gave



5-bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-ol **14**. The disappointingly low yield (12%) of product can be attributed to the strong oxidising properties of bromine since the by-products included 2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-one and its 3,3-dibromo derivative.[25]

However, the reaction of **11** with iodine gave 5-iodo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-ol **15** in 46% yield and this was readily converted into the benzopyran **16** in excellent yield by catalytic dehydration with 4-TsOH in hot toluene. The chromen-5-yl isomer of MG carbinol **9d** was obtained by refluxing an excess of the lithium derivative of **16** with Michler's ketone.

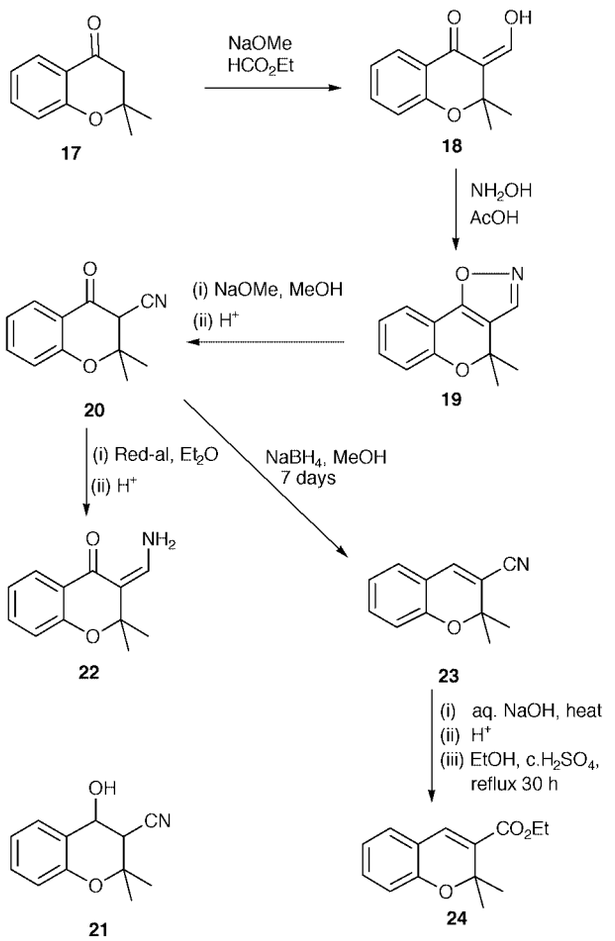
4-Bromo-2,2-dimethyl-2*H*-1-benzopyran was obtained from 2,2-dimethyl-2*H*-1-benzopyran by addition of bromine and subsequent dehydrobromination of the 3,4-dibromochroman.[28] It was also conveniently prepared by reaction of 2,2-dimethylchroman-4-one with PBr_3.[29] Reaction with butyllithium alone or when complexed with TMEDA gave the 4-lithiochromene, quenching of which with Michler's ketone yielded the chromen-4-yl analogue of Malachite Green dye base **9e**.

3-Bromo-2,2-dimethyl-2*H*-chromene, derived from the chromene by reaction with moist *N*-bromosuccinimide and subsequent acid-catalysed dehydration of the resulting *trans*-3-bromochroman-4-ol, undergoes a ring-opening reaction upon treatment with BuLi to yield an allene[30] which precludes its use in the synthesis of the chromen-3-yl MG derivative. An alternative approach to TPM dye bases involves the reaction of an ester with two equivalents of 4-(dimethylamino)phenyllithium and consequently the synthesis of a benzopyran-3-carboxylic ester was investigated.

The treatment of salicylaldehydes with acrolein derivatives under basic conditions results in the formation of 3-substituted-2*H*-chromenes and can be very high yielding,[31] but an extremely low yield (1%) of ethyl 2,2-dimethyl-2*H*-chromenecarboxylate has been reported for the reaction between salicyl-

aldehyde and ethyl 3-methylcrotonate in the presence of potassium carbonate, the main product being 2,2-dimethylchromene.[32] The conditions used were stringent and it is possible that this led to hydrolysis of the ester and subsequent decarboxylation. However, under milder conditions, using DABCO as the base, there was no evidence of a reaction occurring after 24 hours at 90 °C or after a further 24 h at 120 °C. Whilst 3-cyanochromene is formed in good yields from salicylaldehyde and acrylonitrile,[33] the use of 3-methylacrylonitrile results in an appreciable reduction in the yield of the 2-methyl derivative[34] and it is therefore unsurprising that no reaction occurred between salicylaldehyde and 3,3-dimethylacrylonitrile.

2,2-Dimethyl-4-oxochroman-3-carbonitrile **20** was synthesised from 2,2-dimethylchroman-4-one **17** through conversion of the 3-hydroxymethylene derivative **18** into the isoxazole **19** and subsequent ring cleavage (Scheme 4).[35] A 10% excess of



Scheme 4

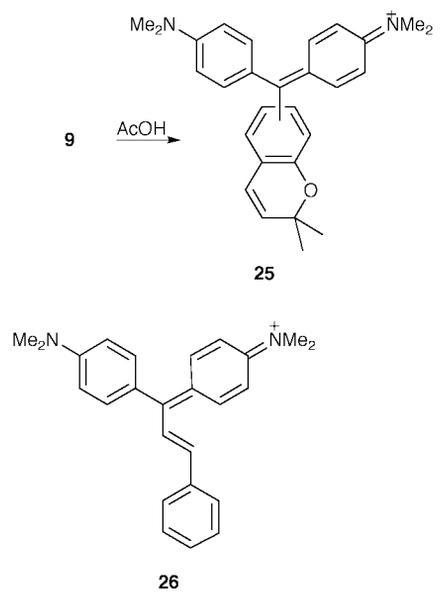
Red-al is known to reduce ketones rapidly[36] and since this reagent is ineffective for the reduction of nitriles, especially those possessing an α-hydrogen atom,[37] it may allow the selective reduction of **20** into the alcohol **21**. Treatment of **20** at room temperature with a 50% excess of Red-al in dry diethyl ether produced a 1 : 1 mixture of **20** and a product. Neither the ratio nor the composition of the reaction mixture was influenced by using a larger excess of the hydride and/or a longer reaction time. Surprisingly, the ^{1}H NMR spectrum showed this product to be 2,2-dimethyl-3-(aminomethylene)chroman-4-one **22** and not the expected hydroxynitrile **21**. The ^{1}H NMR spectrum of **22** is very similar to that of the corresponding thiochroman-4-one derivative which has been made by an unequivocal route.[38] In particular, this spectrum displayed two broad, exchangeable signals at 9.4 and 5.1 ppm which were attributed to the amino group in which one hydrogen atom is intramolecularly hydrogen bonded to the adjacent carbonyl group.

In the reduction of **20** with $NaBH_4$ in methanol, the 2*H*-chromene **23** was the only product isolated. Under optimum conditions, 7 days refluxing with 20 molar equivalents of $NaBH_4$ in methanol, the yield of chromene was 25% and 50% of the starting material **20** was recovered. No trace of the chroman-4-ol **21** could be detected when the reaction was monitored by GC-MS, even though 2-cyanotetral-1-ones can be reduced to the alcohol in this way[39] and both of these oxonitriles exist almost exclusively in the keto form.[40]

The mechanistic course of the borohydride reduction of ketones is still unclear and has been found to vary according to the conditions.[41] The high resistance of the carbonyl group to reduction in this instance may result from a combination of the electronic influences of the nitrile group and the heterocyclic oxygen atom since both 2-cyanotetral-1-one and 2,2-dimethylchroman-4-one are easily reduced by sodium borohydride. These factors may also be partly responsible for the absence of the chromanol **21** from the reaction mixture. It is possible that the 3-hydrogen atom of **21** is sufficiently acidic to be abstracted by the basic species generated in the reaction;[41] base-catalysed dehydrations of chromanols are not uncommon.[25]

The cyanochromene **23** was hydrolysed, the resulting acid was esterified and the ester **24** converted into the dye base **9f** by reaction with 4-(dimethylamino)phenyllithium (Scheme 2). Steric hindrance around the ester function may be the cause of the poor yields obtained in the two latter stages.

TPM dye bases **9a**–**f** are converted into the dyes **25a**–**f** on



treatment with acids. It has been shown[42] that optimum conversion to the cation is achieved in 98% acetic acid; use of mineral acids leads to di- and tri-protonated species which are usually yellow rather than the green, blue or violet colour of the mono-cations. The spectral parameters for the six chromenyl analogues of Malachite Green and several relevant derivatives are given in Table 1.

The benzopyranyl unit in the 6- and 7-chromenyl derivatives of MG **25a**,**b** is longitudinally conjugated and is therefore expected to function in a similar manner to the 2-naphthyl group, the steric effects associated with the pyran ring being negligible. The heteroatom is anticipated to cause similar spectral changes to those found in the 3- and 4-methoxy derivatives of MG.[3] In fact, an almost perfect match is apparent in the data for the x-band (Table 1), implying that the electronic influence of the pyran ring can be correlated to that of a methoxy group. The blue shift of 14 nm of the main absorption band of the 6-chromenyl dye relative to that of MG itself is consistent with

Table 1 Visible absorption data for some analogues of Malachite Green in 98% acetic acid

Malachite Green analogue	λ_{max} (x)/nm	ε_{max} (x)/10^4 l mol^{-1} cm^{-1}	λ_{max} (y)/nm	ε_{max} (y)/10^4 l mol^{-1} cm^{-1}
Malachite Green (**1**)	621	10.4	427.5	2.0
6-Chromenyl (**25a**)	607	10.2	484	3.1
4-Methoxy	608	10.6	465	3.4
7-Chromenyl (**25b**)	623	9.4	478	2.1
3-Methoxy	622.5	10.7	435	1.8
8-Chromenyl (**25c**)	622	11.0	418	1.3
2-Methoxy	625	11.5	442	1.3
4-Chromenyl (**25d**)	631	11.4	397	0.7
5-Chromenyl (**25e**)	626.5	12.2	429	1.6
3-Chromenyl (**25f**)	627	7.3	478	1.3
2-Naphthyl (**2**)	626.5	10.5	458	3.2
1-Naphthyl (**3**)	630	12.0	460	1.1
Styryl (**26**)	656	5.7	488	3.55

interaction between the electron donating heteroatom and the carbocationic site. Conversely, the small red shift (2 nm) of the x-band of the 7-chromenyl derivative shows that the effect of a *meta*-situated heteroatom is weakly electron withdrawing. In both dyes, the response of the y-band is a significant red shift and an increase in ε_{max} which is associated with an increased electron density along the *y*-axis. The 2-naphthyl derivative of MG exhibits increases in λ_{max} and ε_{max} of both bands similar to those of the 7-chromenyl dye and of the y-band of the 6-isomer.[15]

The 4- and 8-chromenyl dyes **25d**,**c** are analogous to the transversely conjugated 1-naphthyl derivative of MG[16] in which both steric and electronic factors are important and the spectral parameters of these systems are quite similar. The x-bands show a shift to longer wavelength and an increase in intensity, together with blue shifts and reduction in intensity of the y-bands. These spectral changes are consistent with enforced rotation of the chromenyl moiety out of the plane of the molecule to relieve steric strain. Such twisting is expected on theoretical grounds since the bond joining the chromenyl unit to the central carbon atom is essentially single in character, whilst those to the (dimethylamino)phenyl rings possess some double character and hence require more energy for rotation.[7] Thus, increased departure from molecular coplanarity is predicted along the *y*-axis. It appears that steric hindrance is more significant in the 4-chromenyl dye **25d** since the spectral changes are greater than for the 8-isomer **25c**. This feature could be attributable to the *gem*-dimethyl group which may lie closer to the central carbon atom in the former dye as a consequence of the conformation of the pyran ring.[43] It is also noteworthy that the x-bands of the chromen-8-yl derivative and 2-methoxyMG[3] are quite similar with respect both to wavelength and to intensity of absorption, though the responses of the y-band are somewhat different.

The purely electronic effects of the chromen-5-yl analogue of MG **25e** are quite similar to those of the chromen-7-yl isomer **25b**. The increased values of λ_{max} (x) and ε_{max} (x) of the former species, together with the blue shift and reduced intensity of its y-band (Table 1), therefore indicate an increase in steric crowding and are illustrative of the *peri* effect.

Electronically, the benzofuran ring has been shown to be closer to 2-hydroxystyrene than to naphthalene,[44] so that the chromen-3-yl compound **25f** could be expected to show the characteristics of a vinylogue. This is clearly not the case, since the visible spectrum of the chromen-3-yl analogue is more similar to that of the 2-naphthyl derivative of MG **2** than to that of the vinylogue of MG **26** (Table 1). This observation suggests that the effects of a vinyl unit may be, to a large extent, a result of its flexibility, an advantage that the rigid chromenyl ring does not possess. It is also possible that the bulk of the *gem*-dimethyl groups has an adverse effect on the conjugation of the chromenyl ring with the rest of the chromophore. Significant crowding about the central carbon atom is suggested by the much reduced ε_{max} (x) and the low ε_{max} (y) values.

In conclusion, the spectral changes arising from the introduction of a 2,2-dimethyl-2*H*-1-benzopyranyl unit into the Malachite Green dye system can be understood by reference to the effects on the dye noted for a methoxy group and a naphthyl unit. Differences may be attributed to the steric influence of the *gem*-dimethyl moiety.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Distillations were performed using a Kugelrohr (Buchi GKR-50 Glass Tube Oven) and all boiling points quoted relate to the oven temperature at which distillation commenced. FTIR spectra were recorded in Nujol on a Mattson Polaris spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM 250 instrument for solutions in $CDCl_3$; *J* values are given in Hz. Flash chromatographic separations were performed on Crossfields Sorbsil C60 silica gel (M.P.D. 60 Å, 40–60 μ, activated) according to the published procedure.[45]

Preparation of bromo-2,2-dimethyl-2*H*-1-benzopyrans

Method A.—A finely ground mixture of the bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-ol (0.01 mol) and potassium hydrogen sulfate (7 mmol) was heated at 100–125 °C at *ca.* 10 mmHg in a Kugelrohr until distillation ceased. The distillate was redistilled to give the benzopyran.

Method B.—A solution of the 3-(bromophenoxy)-3-methylbut-1-yne (0.02 mol) in *N,N*-diethylaniline (60 cm^3) was boiled under reflux for 8 h. The cooled reaction mixture was poured into an excess of dilute sulfuric acid and extracted with ether. The extracts were washed with further sulfuric acid, water and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was distilled to give the benzopyran.

The following compounds were obtained using these methods.

6-Bromo-2,2-dimethyl-2*H*-1-benzopyran. As a colourless oil, A—89%, B—86%, bp 120 °C at 8 mmHg; δ_H 1.49 (6H, s, Me_2), 5.58 (1H, d, *J* 9.8, 3-H), 6.21 (1H, d, *J* 9.8, 4-H), 6.61 (1H, d, *J* 7.8, 8-H), 7.04–7.25 (2H, m, 5-H, 7-H) (Found: C, 55.6; H, 4.8; Br, 33.6. $C_{11}H_{11}BrO$ requires C, 55.3; H, 4.6; Br, 33.4%).

7-Bromo-2,2-dimethyl-2*H*-1-benzopyran. As a colourless oil, A—91%, B gave a *ca.* 7:3 mixture of the 5- and 7-bromobenzopyrans, bp 94 °C at 2 mmHg; δ_H 1.41 (6H, s, Me_2), 5.62 (1H, d, *J* 9.8, 3-H), 6.27 (1H, d, *J* 9.8, 4-H), 6.96–7.42 (3H, m, 5-H, 6-H, 8-H) (Found: C, 55.8; H, 4.7; Br, 33.5. $C_{11}H_{11}BrO$ requires C, 55.3; H, 4.6; Br, 33.4%).

8-Bromo-2,2-dimethyl-2*H*-1-benzopyran. As a colourless oil, A—86%, B—81%, bp 130 °C at 8 mmHg; δ_H 1.46 (6H, s, Me_2), 5.62 (1H, d, *J* 9.8, 3-H), 6.28 (1H, d, *J* 9.8, 4-H), 6.50–6.96 (2H, m, 6-H, 7-H), 7.30 (1H, dd, *J* 2.4, 7.8, 5-H) (Found: C, 55.3; H, 4.8; Br, 33.5. $C_{11}H_{11}BrO$ requires C, 55.3; H, 4.6; Br, 33.4%).

5-Iodo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-ol 15

n-Butyllithium (29.4 cm^3; 2.5 M in hexane; 67.5 mmol) was added to a cold (0 °C) stirred solution of 2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-ol (6 g; 33.6 mmol) and TMEDA (10.2 cm^3, 67.5 mmol) in dry diethyl ether (90 cm^3), after which the mixture was stirred at room temperature for 4 h. The resulting deep orange solution was cooled to 0 °C and a solution of iodine (10.2 g; 40.3 mmol) in dry diethyl ether (100 cm^3) was added and the slurry was stirred overnight at room temperature and then poured into saturated aqueous ammonium chloride (100 cm^3). The aqueous layer was washed with ethyl acetate (3 × 150 cm^3) and the combined organic extracts were washed with aqueous hydrochloric acid (2 × 50 cm^3, 2 M), water (2 × 150 cm^3) and brine (50 cm^3) before being dried (Na_2SO_4) and evaporated to afford the crude product. This solid was eluted from silica with 20% ethyl acetate in hexane and sublimed (80 °C/0.9 mmHg) to afford colourless crystals of the product (4.7 g; 46%), mp 83–85 °C; δ_H 1.42 (3H, s, 2-Me), 1.44 (3H, s, 2-Me), 1.96 (1H, dd, *J* 14.2, 5.3, 3-H), 2.14 (1H, dd, *J* 14.2, 2.6, 3-H), 2.92 (1H, br s, OH), 4.90 (1H, m, 4-H), 6.78 (1H, dd, *J* 7.9, 1.4, 8-H), 7.16–7.25 (2H, m, 6-H, 7-H) (Found: C, 43.4; H, 4.4. $C_{11}H_{13}IO_2$ requires C, 43.4; H, 4.3%).

5-Iodo-2,2-dimethyl-2*H*-1-benzopyran 16

A solution of 5-iodo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-ol (2.0 g; 6.6 mmol) in toluene (50 cm^3) containing toluene-4-sulfonic acid (*ca.* 0.1 g) was refluxed for 25 min. Dilute sodium hydroxide (20 cm^3, 2 M) was added to the stirred, cooled solution and the two layers were separated. The organic layer was washed with water (200 cm^3) and brine (50 cm^3) and dried (Na_2SO_4). Evaporation of the solvent gave a crude oil, distillation of which gave the product as an orange oil (1.49 g; 79%) bp 90 °C at 0.05 mmHg; δ_H 1.48 (6H, s, Me_2), 5.84 (1H, d, *J* 10.1, 3-H), 6.82 (1H, m, 8-H), 6.94 (1H, d, *J* 10.1, 4-H), 7.16–7.28 (2H, m, 6-H, 7-H) (Found: C, 46.2; H, 3.9. $C_{11}H_{11}IO$ requires C, 46.2; H, 3.9%).

2,2-Dimethyl-4-oxochroman-3-carbonitrile 20

Ethyl formate (3.0 g; 0.04 mol) was added in a single portion to a slurry of sodium methoxide (2.2 g; 0.04 mol) in toluene (20 cm^3) at *ca.* 10 °C. A solution of 2,2-dimethylchroman-4-one[46] (3.1 g; 0.02 mol) in toluene (20 cm^3) was added dropwise to the stirred slurry over *ca.* 15 min. After 24 h, water (100 cm^3) was added and the organic layer was washed with aqueous sodium hydroxide solution (2 × 50 cm^3; 2 M) and water. The aqueous layers were washed with ether and acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 30 cm^3). Evaporation of the dried (Na_2SO_4) solvent and distillation of the solid, brown residue gave 2,2-dimethyl-3-(hydroxymethylene)chroman-4-one **18** (3.1 g; 87%), bp 150 °C at 0.5 mmHg, mp 53–54 °C as pale yellow crystals (lit.[47] gives mp 51–52 °C) ν_{max}(cm^{-1}) 3640 (ν_{O-H}), 1609 ($\nu_{C=O}$); δ_H 1.62 (6H, s, Me_2), 6.91 (1H, m, 8-H), 7.03 (1H, m, 6-H), 7.45 (1-H, m, 7-H), 7.88 (1H, m, 5-H), 7.99 (1H, d, *J* 7.5, C**H**OH), 15.0 (1H, d, *J* 7.5, OH). A mixture of the hydroxymethylene derivative (2.1 g; 0.01 mol), hydroxylamine hydrochloride (1.39 g; 0.02 mol) and ethanol (30 cm^3) was boiled under reflux for 3 h. The residue after removal of the solvent was extracted into chloroform and washed with water and aqueous sodium hydrogen carbonate solution. Removal of the dried (Na_2SO_4) solvent and crystallisation of the brown solid from ethanol gave 4,4-dimethyl-4*H*-1-benzopyrano[3,4-*d*]isoxazole **19** (1.5 g; 73%), mp 51–52 °C as cream needles; ν_{max}(cm^{-1}) 1644 ($\nu_{C=O}$); δ_H 1.65 (6H, s, Me_2), 6.95–7.05 (2H, m, 6-H, 8-H), 7.03 (1H, m, 6-H), 7.31 (1-H, m, 7-H), 7.62 (1H, m, 9-H), 8.12 (1H, s, 3-H). A solution of sodium methoxide [from sodium (2.3 g) and methanol (100 cm^3)] was added dropwise to a stirred suspension of the isoxazole (10.0 g; 0.05 mol) in methanol (200 cm^3). After 3 h, the solvent was removed, water added, the pH adjusted to *ca.* 3 with concentrated hydrochloric acid and the product extracted into chloroform. Removal of the dried (Na_2SO_4) solvent and crystallisation of the bright yellow solid from ethyl acetate–hexane gave cream needles of 2,2-dimethyl-4-oxochroman-3-carbonitrile **20** (7.9 g; 78%), mp 106–107.5 °C; ν_{max}(cm^{-1}) 2249 ($\nu_{C\equiv N}$), 1699 ($\nu_{C=O}$); δ_H 1.55 (3H, s, 2-Me), 1.74 (3H, s, 2-Me), 3.29 (1H, s, 3-H), 6.97–7.11 (2H, m, 6-H, 8-H), 7.57 (1H, m, 7-H), 7.9 (1H, dd, $J_{5,6}$ 7.9, $J_{5,7}$ 1.3, 5-H).

2,2-Dimethyl-3-(aminomethylene)chroman-4-one 22

Finely powdered 2,2-dimethyl-4-oxochroman-3-carbonitrile (3.0 g; 14.9 mmol) was added at 0 °C to a solution of sodium bis(2-methoxyethoxy)aluminium hydride (70% in toluene, 6 cm^3) in dry diethyl ether (100 cm^3). The yellow solution was stirred at room temperature for 15 min and cooled to 0 °C. Aqueous hydrochloric acid (100 cm^3, 2 M) was then added with care and the mixture was stirred vigorously for 15 min. The two layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were washed with water (2 × 100 cm^3) and brine (50 cm^3) and the solvent was evaporated. Elution from silica gel with 40% ethyl acetate in hexane gave two fractions: fraction 1, starting material (43%); fraction 2, 2,2-dimethyl-3-(aminomethylene)-chroman-4-one (1.25 g; 41%), mp 110–111 °C as pale yellow crystals from light petroleum (bp 40–60 °C); δ_H 1.58 (6H, s, Me_2), 5.10 (1H, br s, NH), 6.87 (1H, dd, *J* 7.8, 2.0, 8-H), 6.95–7.03 (2H, m, 6-H, alkenyl-H), 7.41–7.45 (1H, m, 7-H), 7.96 (1H, dd, *J* 7.9, 2.0, 5-H), 9.40 (1H, br s, NH) (Found: C, 71.1; H, 6.6; N, 6.9; M^+ 203. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.5; N, 6.9%).

2,2-Dimethyl-2*H*-1-benzopyran-3-carbonitrile 23

Sodium borohydride (21 g; 0.56 mol) was added to cold (0 °C) methanol (350 cm^3) whereupon 2,2-dimethyl-4-oxochroman-3-carbonitrile (6.0 g; 29.8 mmol) was added and the mixture was refluxed for 7 days. After cooling, it was poured into aqueous hydrochloric acid (400 cm^3, 2 M) and extracted with ethyl acetate (4 × 150 cm^3). The combined extracts were washed with water (3 × 100 cm^3) and brine (100 cm^3) and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was eluted from silica with 20% ethyl acetate in hexane to give: fraction 1, as an oil **23** which slowly solidified (1.40 g; 25%), bp 115 °C at 0.3 mmHg, mp 30–32 °C (lit.[48] gives bp 147–151 °C at 17 mmHg); ν_{max}(cm^{-1}) 2200 ($\nu_{C\equiv N}$); δ_H 1.60 (6H, s, Me_2), 6.8–7.3 (4H, m, ArH), 7.1 (1H, s, 4-H), M^+ 185; fraction 2, starting material (3 g, 50%).

Ethyl 2,2-dimethyl-2*H*-1-benzopyran-3-carboxylate 24

2,2-Dimethyl-2*H*-1-benzopyran-3-carbonitrile (1.2 g: 6.48 mmol) was boiled in aqueous sodium hydroxide (40 cm^3, 3 M) for 8 h. The mixture was then acidified with aqueous hydrochloric acid (25 cm^3, 6 M) and extracted with ethyl acetate (3 × 100 cm^3). The combined organic layers were washed with water (100 cm^3), dried (Na_2SO_4) and evaporated to give crude 2,2-dimethyl-2*H*-1-benzopyran-3-carboxylic acid (1.2 g; 90%), mp 167–169 °C. This solid was dissolved in ethanol (30 cm^3) containing concentrated sulfuric acid (1 cm^3) and the mixture was refluxed for 30 h. Water (100 cm^3) and ethyl acetate (100 cm^3) were then added to the cooled brown solution and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 80 cm^3) and the combined organic layers were washed with water (100 cm^3), saturated aqueous sodium bicarbonate (2 × 100 cm^3), water (100 cm^3) and brine (50 cm^3) and dried (Na_2SO_4). Removal of the solvent and elution of the

residue from silica with 20% ethyl acetate in hexane gave the product as a colourless oil which solidified on standing (0.35 g: 23%); mp 42–45 °C (lit.[32] gives mp 43–45 °C); δ_H 1.3 (3H, t, *J* 7.0, CH_2CH_3), 1.6 (6H, s, Me_2), 4.2 (2H, q, *J* 7.0, CH_2CH_3), 6.5–7.3 (4H, m, ArH), 7.2 (1H, s, 4-H); M^+ 232.

General method of preparation of the TPM dye bases

A solution of the bromo or iodo 2,2-dimethyl-2*H*-1-benzopyran (0.01 mol) in dry diethyl ether (50 cm^3) was treated dropwise with *n*-butyllithium (2.5 M in hexane; 0.01 mol) or its complex with TMEDA and the resulting mixture was stirred at room temperature for 0.5–1 h. 4,4′-Bis(dimethylamino)benzophenone (8.0 mmol) was added as a slurry in ether (50 cm^3) and the mixture was refluxed for 2–5 h. Water (50 cm^3) was added and the ethereal layer was separated, washed with water (50 cm^3) and brine (20 cm^3) and dried (Na_2SO_4). After removal of the solvent, the residual oil was recrystallised.

The following compounds were prepared using this protocol.

Bis[4-(dimethylamino)phenyl](2,2-dimethyl-5-chromenyl)-methanol 9d. Colourless microcrystals after elution from silica with triethylamine–ethyl acetate–hexane (10 : 25 : 65) and recrystallisation from ethyl acetate and hexane, 53% yield, mp 172–174 °C (decomp.) (Found: C, 78.5; H, 7.5; N, 6.4. $C_{28}H_{32}N_2O_2$ requires C, 78.5; H, 7.5; N, 6.5%).

Bis[4-(dimethylamino)phenyl](2,2-dimethyl-6-chromenyl)-methanol 9a. Colourless crystals from ethyl acetate and light petroleum (bp 60–80 °C), 58% yield, mp 147–148 °C (Found: C, 78.7; H, 7.5; N, 6.7. $C_{28}H_{32}N_2O_2$ requires C, 78.5; H, 7.5; N, 6.5%).

Bis[4-(dimethylamino)phenyl](2,2-dimethyl-7-chromenyl)-methanol 9b. Pale green crystals from ethyl acetate and light petroleum (bp 60–80 °C), 17% yield, mp 174–175 °C (Found: C, 78.4; H, 7.5; N, 6.3. $C_{28}H_{32}N_2O_2$ requires C, 78.5; H, 7.5; N, 6.5%).

Bis[4-(dimethylamino)phenyl](2,2-dimethyl-8-chromenyl)-methanol 9c. Colourless crystals from ethyl acetate and light petroleum (bp 60–80 °C), 22% yield, mp 221–223 °C (Found: C, 78.9; H, 7.7; N, 6.4. $C_{28}H_{32}N_2O_2$ requires C, 78.5; H, 7.5; N, 6.5%).

Bis[4-(dimethylamino)phenyl](2,2-dimethyl-4-chromenyl)-methanol 9e. Pale green crystals from ethyl acetate and light petroleum (bp 60–80 °C), 54% yield, mp 194–195 °C (Found: C, 78.3; H, 7.5; N, 6.5. $C_{28}H_{32}N_2O_2$ requires C, 78.5; H, 7.5; N, 6.5%).

Bis[4-(dimethylamino)phenyl](2,2-dimethyl-3-chromenyl)-methanol 9f.

A solution of 4-(dimethylamino)phenyllithium [prepared at 0 °C from 4-bromo-*N,N*-dimethylaniline (0.34 g; 1.70 mmol) and *n*-butyllithium (0.59 cm^3; 2.5 M in hexane; 1.47 mmol) in dry diethyl ether (20 cm^3)] was added dropwise at 0 °C to a solution of ethyl 2,2-dimethyl-2*H*-1-benzopyran-3-carboxylate (0.34 g; 1.46 mmol) in dry diethyl ether (10 cm^3) and the mixture was stirred at room temperature for 24 h. After quenching with water and washing the organic layer with water (30 cm^3) and brine (20 cm^3), the dried (K_2CO_3) solution was evaporated to give a semi-solid. Elution of this residue from silica with triethylamine–ethyl acetate–hexane (10 : 25 : 65) and recrystallisation from hexane and ethyl acetate gave the product (13%), mp > 150 °C (decomp.) as colourless microcrystals (Found: C, 78.6; H, 7.5; N, 6.5. $C_{28}H_{32}N_2O_2$ requires C, 78.5; H, 7.5; N, 6.5%).

Bis[4-(dimethylamino)phenyl](2,2-dimethyl-4-hydroxy-5-chromanyl)methanol 12

n-Butyllithium (29.4 cm^3; 2.5 M in hexane; 67.5 mmol) was added to a cold (0 °C) stirred solution of 2,2-dimethylchroman-4-ol (6.0 g; 33.6 mmol) and TMEDA (10.2 cm^3, 67.5 mmol) in dry diethyl ether (90 cm^3), after which the mixture was stirred at room temperature for 4 h. Finely powdered Michler's ketone (18.1 g; 67.5 mmol) was added in one portion and the mixture was refluxed for 5 h. Water (100 cm^3) was then added to the cooled slurry and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 cm^3) and the combined organic fractions were washed with water (2 × 100 cm^3), brine (50 cm^3) and dried (K_2CO_3) and the solvent removed to afford a green solid. This solid was stirred in dichloromethane (50 cm^3) at 0 °C for 5 min and the colourless insoluble material was filtered off and recrystallised twice from dichloromethane to afford the product (7.87 g; 52%) as colourless microcrystals, mp 159–167 °C.

2,2-Bis[4-(dimethylamino)phenyl]-7,7-dimethyl-8,8a-dihydrofuro[2,3,4-*de*]-1-benzopyran 13

A solution of the above diol (0.31 g; 0.7 mmol) and toluene-4-sulfonic acid (50 mg) in toluene (30 cm^3) was stirred at 90 °C for 15 min. The cooled blue solution was stirred with dilute aqueous sodium hydroxide (100 cm^3, 2 M) until the colour disappeared and the two layers were then separated. The organic layer was washed with water (2 × 30 cm^3), brine (50 cm^3) and dried (K_2CO_3). Removal of the solvent yielded a solid which was recrystallised from ethyl acetate and hexane to afford the product (0.23 g; 70%) as pale green crystals, mp 168 °C (Found: C, 78.6; H, 7.6; N, 6.4. $C_{28}H_{32}N_2O_2$ requires C, 78.5; H, 7.5; N, 6.5%).

Acknowledgement

We thank the University of Central Lancashire for a research studentship (to S. G. R. G.).

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Paper a908044i