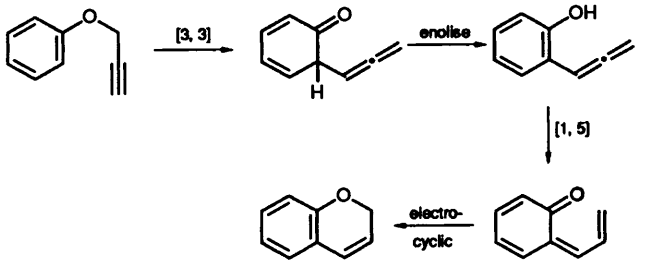
Studies of Chromenes. Part 10.[1] Oxiranes of Nitrochromenes

Philip E. Brown * and Robert A. Lewis
Department of Chemistry, The University, Newcastle upon Tyne NE1 7RU, UK

Syntheses of stable oxiranes of 5- and 7-nitro-, and 5,7-dinitro- 2,2-dimethyl(chromenes and of 7-2*H*-ethoxycarbonylamino)-2,2-dimethyl-5-nitro-2*H*-chromene are described. Thermal cyclisation of the precursor phenyl prop-2-ynyl ethers proceeds in good yield but in the case of the dinitrophenyl ether the products are highly solvent dependent. The compounds are of interest as possible antitumour alkylating agents that are activated by bioreduction to extremely reactive oxiranes.

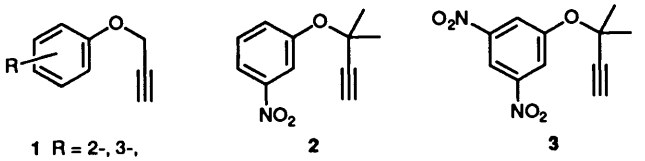
Our interest in bioreductive control of alkylating activity[2] was initially related to the oxiranes of chromenequinones.[1] We sought in these systems an electron-withdrawing effect sufficiently strong to enable the isolation of oxiranes stable enough for their toxicities to tumour cells to be investigated. Reduction to the hydroquinone would result in highly reactive oxiranes which might be adaptable to cancer therapy. Aromatic nitro groups have also shown promise in this respect[3] and we therefore chose to investigate the stabilities and cytotoxicities of oxiranes of 2,2-dimethylnitrochromenes.

Chromenes are most conveniently prepared by thermal cyclisation of aryl prop-2-ynyl ethers[4] through the sequence shown[5] (Scheme 1). The original authors[6] reported that



Scheme 1

nitrophenyl prop-2-ynyl ethers **1** decomposed on heating and gave no chromene although they did note that a 15% yield of chromene was obtained when the alkyne group bore a phenyl substituent. Subsequent work showed that 4-nitrophenyl ethers did indeed cyclise and that the presence of a gem-dimethyl group increased the reaction rates by factors of 200–1400 and allowed good yields (75%) of chromenes to be isolated.[7] More recently several 3-nitrophenyl dimethylprop-2-ynyl ethers, including ether **2**, have been cyclised and from the resultant



1 R = 2-, 3-, or 4-NO_2 **2** **3**

chromenes, oxiranes have been prepared as intermediates in the synthesis of hypertensive agents.[8] The oxiranes were prepared *via* the bromohydrins but we find that direct epoxidation with 3-chloroperbenzoic acid gives good yields. The previous workers[8] reported characterisation of their ethers, chromenes, and oxiranes only by melting (or boiling point) and elemental analysis to which we now add ^1H and ^{13}C NMR, IR and some UV spectroscopic data. We also show that even 3,5-dinitrophenyl dimethylprop-2-ynyl ether **3** cyclises efficiently, though in this case the reaction is highly solvent dependent, and that the dinitrochromene is epoxidised in good yield by the action of 3-chloroperbenzoic acid.

The 'gem-dimethyl effect' has been interpreted as a result of the conformational preferences, **4a** or **4b**, of the ethers.[7,9] When R = H the alkyne group is held preferentially in the conformation **4a** least favourable for cyclisation but the introduction of two methyl groups (R = Me) causes a change to the conformation **4b** required for reaction. We have quantified this effect by molecular mechanics calculations which confirm that when R = H conformation **4a** is favoured by 0.4 kcal mol^{-1} † whilst when R = Me conformation **4b** is more stable by 2.1 kcal mol^{-1}. The relative populations of the **4a** and **4b** conformations (at 150 °C) are thus *ca.* 1.6:1 (R = H) and 1:12 (R = Me) respectively.

4a **4b**

Cyclisation of the 3-nitrophenyl prop-2-ynyl ether **2** proceeded in good yield at 150 °C in xylene (rather than the more usual *N,N*-dimethylaniline at 210–215 °C). Both possible isomers, **5** and **6**, were formed, the 7-nitrochromene

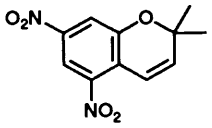
5 R = 5-NO_2
6 R = 7-NO_2
9 R = 5-NH_2
10 R = 5-NAc_2

7 R = 5-NO_2
8 R = 7-NO_2

predominating. Treatment of the nitrochromenes with 3-chloroperbenzoic acid afforded the two isomeric 3,4-oxiranes **7** and **8** as stable crystalline products, the 5-nitrochromene reacting appreciably faster than the 7-isomer. Both oxiranes were toxic to V79 cells but showed no differential cytotoxicity between oxic and apoxic conditions. The 5-aminochromene[10] **9** obtained on reduction reacted rapidly with 3-chloroperbenzoic acid but no oxirane could be isolated; the implied high reactivity of the reduced nitro-oxirane is just that required for bioreductive activation. Acetylation of the amine afforded the *N,N*-diacetyl derivative **10** but even this compound was insufficiently deactivated to allow isolation of an oxirane.

One possible reason for the lack of differential cytotoxicity was the poor solubilities (0.19 and 0.43 mmol dm^{-3}) and

† 1 cal = 4.184 J.



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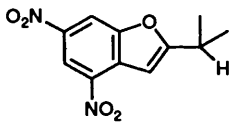

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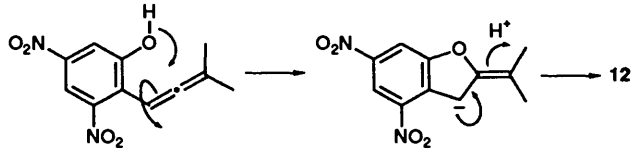
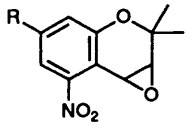
octanol–water partition coefficients (both >99) of the 7- and 5-nitro derivatives respectively. In an attempt to improve these characteristics the 5,7-dinitrochromene was prepared as a precursor of derivatives of aminonitrochromenes in which the amino group was to carry hydrophilic groups. Cyclisation of the dinitrophenyl ether **3** proceeded in good yield in xylene to give the chromene **11** in 79% yield as the sole material isolated. However in dimethyl sulfoxide (at 150 °C) no chromene was detected, the only product being the benzofuran **12**. In dimethyl sulfoxide the intermediate allenic phenol apparently undergoes addition, rather than a 1,5 shift, with the formation of a carbanion stabilised by the strongly electron-withdrawing aromatic ring (Scheme 2). Final protonation of the carbanion takes place at the allylic position allowing formation of a benzofuran. Under the same conditions the 3-nitrophenyl ether **2** gave rise only to the same mixture of chromene isomers as before.

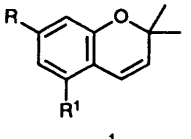


Scheme 2

Product distribution in Claisen-initiated cyclisations are known to be solvent dependent[11] but the complete change from one single product to another in the present case is particularly remarkable. A stable oxirane **13** could be prepared directly from the dinitrochromene but not unsurprisingly its aqueous solubility (0.035 mmol dm^{-3}) made it unsuitable for our purposes though it did show toxicity against V79 cells.



13 R = NO_2
17 R = EtOCONH



14 R = NH_2, R^1 = NO_2
15 R = NO_2, R^1 = NH_2
16 R = EtOCONH, R^1 = NO_2
18 R = H_2NCH_2CONH

Partial reduction of the dinitrochromene with sodium polysulfide gave both of the two possible isomers, **14** and **15**, each of which reacted readily with 3-chloroperbenzoic acid. Though there was some evidence for the presence of oxiranes in the crude products (mass spectrometry) no oxiranes could be isolated. However formation of a carbamate derivative **16** of the major 7-amino isomer with ethyl chloroformate enabled an oxirane **17** to be prepared *via* the bromohydrin. Although the solubility was much improved (9.4 mmol dm^{-3} with an octanol–water partition coefficient of 1.75) this compound again lacked the required differential toxicity. In an attempt to increase aqueous solubility still further the *N*-glycyl derivative **18** was prepared *via* the *tert*-Boc derivative. Attempted epoxidation of the *N*-glycylchromene, either directly with 3-chloroperbenzoic acid or *via* the bromohydrin, led only to complex mixtures from which no oxirane could be obtained.

The isolation of the stable oxiranes reported here defines the electronic requirements for a nitro–amino bioreductive switch in terms of preparative chemistry. Further development requires adjustment of more biologically oriented factors such as aqueous solubility, octanol–water partition, and redox potentials.

Experimental

M.p.s (Kofler hot-stage) are uncorrected. IR spectra were recorded on a Nicolet 20 SXB FT instrument and UV spectra determined with a Perkin-Elmer Model 137 instrument. Routine (60 MHz) NMR spectra were obtained on a Perkin-Elmer R24 machine with tetramethylsilane as internal standard; 200 MHz spectra were obtained on a Bruker WP-200 spectrometer. Mass spectra were obtained on either an AEI MS9 or a Kratos MS80 instrument. *J* Values are given in Hz. Elemental analyses were performed with a Carlo Erba Model 1106 CHN machine. Homogeneity of non-crystalline compounds was established by TLC in at least three solvents of differing polarities. Ether refers to diethyl ether and light petroleum to that fraction with b.p. 40–60 °C. Assignment of 8-H and 4-H NMR signals of chromenes was often assisted by their mutual long-range coupling.[12] Superscripts *, # and ′ indicate alternative ^{13}C NMR assignments. Molecular modelling was carried out using 'PCMODEL' from Serena Software, Bloomington, Indiana, USA.

2-Methylbut-3-yn-2-yl 3-Nitrophenyl Ether **2**.—3-Nitrophenol (1.00 g, 7.19 mmol), anhydrous potassium carbonate (1.19 g, 8.62 mmol), potassium iodide (1.91 g, 11.5 mmol), and 3-chloro-3-methylbutyne (1.47 g, 14.4 mmol) in dry acetone (125 cm^3) was boiled under reflux for 24 h. The mixture was filtered and the insoluble salts washed with acetone (2 × 50 cm^3) and the combined filtrates evaporated. The residual oil was taken into ether and washed with aqueous sodium hydroxide (1 mol dm^{-3}; 2 × 20 cm^3), brine (1 × 20 cm^3), and dried ($MgSO_4$). Flash chromatography (10% ethyl acetate–light petroleum as eluent) gave an oil which on Kugelrohr distillation afforded the title ether as a pale yellow oil (b.p. 110 °C/0.1 mmHg, lit.,[8] b.p. 96–106 °C/0.2 mmHg) (1.32 g, 89%), ν_{max}(film)/cm^{-1} 3292 (H–C≡C), 2116 (C≡C), 1531, 1349 and 1139; δ_H($CDCl_3$) 1.64 (6 H, s, gem-Me_2), 2.64 (1 H, s, HC≡), 7.38 (1 H, t, *J* 8.0, 5-H), 7.47 (1 H, ddd, *J* 8.0, 2.2 and 1.4, 6-H), 7.84 (1 H, ddd, *J* 8.0, 2.2 and 1.4, 4-H) and 8.05 (1 H, t, *J* 2.2, 2-H); δ_C($CDCl_3$) 29.5 (gem-Me_2), 73.4 (CMe_2), 75.4 (HC≡), 84.9 (C≡CH), 115.7 (C-2*), 117.5 (C-4*), 127.1 (C-6#), 129.5 (C-5#), 148.8 (C-3) and 156.3 (C-1) (Found: C, 64.5; H, 5.5; N, 6.7%; M^+, 205.0743. Calc. for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.4; N, 6.8%; *M*, 205.0739).

Thermolysis of the Ether **2**.—The above nitroprop-2-ynylic ether **2** (14.8 g, 72 mmol) in *o*-xylene (110 cm^3) was boiled under reflux overnight. The solvent was evaporated and the residue chromatographed on silica (4% ethyl acetate–light petroleum as eluent) to give two fractions. The first was the 5-nitrochromene **5** (8.7 g, 59%) obtained as a pale yellow oil by Kugelrohr distillation (b.p. 105 °C/0.15 mmHg, lit.,[8] b.p. 77–80 °C/0.5 mmHg), ν_{max}(film)/cm^{-1} 1526 and 1341; δ_H($CDCl_3$) 1.41 (6 H, s, gem-Me_2), 5.83 (1 H, d, *J* 10.2, 3-H), 6.87 (1 H, dd, *J* 10.2 and 0.7, 4-H), 6.98 (1 H, ddd, *J* 8.1, 1.3 and 0.7, 8-H), 7.13 (1 H, t, *J* 8.1, 7-H) and 7.45 (1 H, dd, *J* 8.1 and 1.3, 6-H); δ_C($CDCl_3$) 25.5 (gem-Me_2), 76.1 (C-2), 115.9 (C-4a), 116.9 (C-6*), 117.4 (C-8*), 121.8 (C-3), 128.3 (C-7), 134.5 (C-4), 146.1 (C-5) and 154.2 (C-8a) (Found: C, 64.7; H, 5.4; N, 7.0%; M^+, 205.0763. Calc. for $C_{11}H_{11}NO_3$; C, 64.4; H, 5.4; N, 6.8%; *M*, 205.0739).

The second fraction was the 7-nitrochromene **6** obtained as bright yellow needles (3.6 g, 24%), m.p. 87 °C (from EtOH) (lit.,[8] m.p. 83–85 °C), ν_{max}(KBr)/cm^{-1} 1521 and 1345; δ_H($CDCl_3$) 1.43 (6 H, s, gem-Me_2), 5.80 (1 H, d, *J* 9.9, 3-H), 6.34 (1 H, d, *J*

9.9, 4-H), 7.04 (1 H, d, *J* 8.3, 5-H), 7.55 (1 H, d, *J* 2.3, 8-H) and 7.66 (1 H, dd, *J* 8.3 and 2.3, 6-H); $\delta_C(CDCl_3)$ 28.1 (gem-Me_2), 77.4 (C-2), 111.6 (C-8), 116.1 (C-6), 121.0 (C-3*), 126.4 (C-5*), 127.2 (C-4a), 134.8 (C-4), 148.2 (C-7) and 153.4 (C-8a) (Found: C, 64.7; H, 5.4; N, 6.8%; M^+, 205.0746. Calc. for $C_{11}H_{11}NO_3$; C, 64.4; H, 5.4; N, 6.8%; *M*, 205.0739).

3,4-*Epoxy*-2,2-*dimethyl*-7-*nitrochroman* **8**.—A mixture of the 7-nitrochromene **6** (0.358 g, 1.75 mmol) and 3-chloroperbenzoic acid (1.20 g, 7.0 mmol) in dichloromethane (15 cm^3) was stirred at room temperature until TLC indicated that all the chromene had reacted (3 d). The mixture was diluted with more dichloromethane (60 cm^3) and washed with dilute aqueous sodium sulfite (2 ×) and sodium hydrogen carbonate (3 ×) and then brine. The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (25% ethyl acetate–light petroleum as eluent) gave the title epoxide as pale yellow prisms (0.307 g, 80%), m.p. 87–88 °C (from ether) (lit.,[8] m.p. 85–86 °C); ν_{max}(KBr)/cm^{-1} 1533 and 1348; λ_{max}(EtOH)/nm 219 (ε 10 000 dm^3 mol^{-1} cm^{-1}) 228sh (9300), 276 (5400) and 331 (1900); $\delta_H(CDCl_3)$ 1.25 (3 H, s), 1.57 (3 H, s), 3.55 (1 H, d, *J* 4.3, 3-H), 3.94 (1 H, dd, *J* 4.3 and 0.5, 4-H), 7.47 (1 H, d, *J* 8.3, 5-H), 7.59 (1 H, d, *J* 2.2, 8-H) and 7.73 (1 H, dd, *J* 8.3 and 2.2, 6-H); $\delta_C(CDCl_3)$ 22.8, 25.5, 49.9 (C-1), 62.8 (C-3), 74.4 (C-2), 113.2 (C-8*), 115.7 (C-6*), 127.1 (C-4a), 130.1 (C-5), 149.3 (C-7[n]) and 153.2 (C-8a[n]) (Found: C, 59.6; H, 4.9; N, 6.1%; M^+, 221.0666. Calc. for $C_{11}H_{11}NO_4$; C, 59.7; H, 5.0; N, 6.3%; *M*, 221.0688).

3,4-*Epoxy*-2,2-*dimethyl*-5-*nitrochroman* **7**.—A mixture of the 5-nitrochromene **5** (1.0 g, 4.88 mmol) and 3-chloroperbenzoic acid (3.37 g, 19.52 mmol) in dichloromethane (50 cm^3) was stirred at room temperature until TLC indicated that no starting material remained (5 h, *i.e.* notably faster than the 7-nitro isomer). The mixture was washed sequentially with aqueous sodium sulfite (2 ×), saturated sodium hydrogen carbonate (3 ×), and brine and then dried (Na_2SO_4). Removal of the solvent left a yellow oil which was purified by flash chromatography (5% ethyl acetate as eluent) to give the title epoxide (0.904 g, 84%) as colourless *needles*, m.p. 47–48 °C (from ether) (lit.,[8] a glass); ν_{max}(KBr)/cm^{-1} 1529 and 1335; λ_{max}(EtOH)/nm 204 (ε 19 000 dm^3 mol^{-1} cm^{-1}) 224 (11 300), 240 (7150), 269 (3500) and 308 (2150); $\delta_H(CDCl_3)$ 1.24 (3 H, s), 1.52 (3 H, s), 3.51 (1 H, d, *J* 4.5, 3-H), 4.56 (1 H, dd, *J* 4.5 and 0.6, 4-H), 7.00 (1 H, ddd, *J* 8.2, 1.2 and 0.7, 8-H), 7.26 (1 H, d, *J* 8.2, 7-H) and 7.48 (1 H, dd, *J* 8.2 and 1.3, 6-H); $\delta_C(CDCl_3)$ 22.6, 25.3, 45.9 (C-3), 62.1 (C-4), 73.6 (C-2), 115.1 (C-4a), 117.3 (C-6), 123.3 (C-8), 129.5 (C-7), 150.8 (C-5*) and 153.9 (C-8a*) (Found: C, 59.5; H, 5.1; N, 6.1%; M^+, 221.0682. $C_{11}H_{11}NO_4$ requires C, 59.7; H, 5.0; N, 6.3%; *M*, 221.0688).

2,2-*Dimethyl*-2H-*chromen*-5-*amine* **9**.—To a mixture of the 5-nitrochromene **5** (0.892 g, 4.35 mmol) and concentrated hydrochloric acid (20 cm^3) was added granulated tin (1.035 g, 8.7 mmol). The mixture was stirred at 80 °C and when the reaction subsided was allowed to cool. The mixture was made strongly alkaline with aqueous sodium hydroxide (40%) and extracted with ether. The ethereal solution was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (20% ethyl acetate–light petroleum as eluent) gave the title chromen-5-amine as a colourless oil (lit.,[10] m.p. 35–36 °C) (0.693 g, 91%), ν_{max}(film)/cm^{-1} 3467, 3377, 1637 and 1461; $\delta_H(CDCl_3)$ 1.43 (6 H, s, gem-Me_2), 3.61 (2 H, br s), 5.59 (1 H, d, *J* 9.9, 3-H), 6.23 (1 H, dd, *J* 8.0 and 1.0, 6-H), 6.28 (1 H, ddd, *J* 8.0, 1.0 and 0.7, 8-H), 6.32 (1 H, dd, *J* 9.9 and 0.7, 4-H) and 6.91 (1 H, t, *J* 8.0, 7-H); $\delta_C(CDCl_3)$ 27.6, 75.2 (C-2), 107.6 (C-6*), 108.4 (C-4a), 108.6 (C-8*), 116.8 (C-3), 129.2 (C-4[n]), 129.4 (C-7[#]), 142.4 (C-5) and 153.9 (C-8a) (Found: C, 75.1; H, 7.3; N, 7.8%; M^+, 175.1008. Calc. for $C_{11}H_{13}NO$: C, 75.4; H, 7.5; N, 8.0%; *M*, 175.0997).

N,N-*Diacetyl*-2,2-*dimethyl*-2H-*chromen*-5-*amine* **10**.—The chromen-5-amine **9** (0.412 g, 2.35 mmol) was heated in acetic anhydride–acetic acid (5 cm^3, 1:1 v/v) under reflux for 30 min and then poured into ice–water (50 cm^3). The mixture was stirred for 20 min and then extracted with dichloromethane (2 × 15 cm^3). The extract was washed with water, dried (Na_2SO_4) and the solvent evaporated. Flash chromatography of the residue (25% ethyl acetate–light petroleum as eluent) gave the title diacetate (0.420 g, 69%) as colourless *needles*, m.p. 68–69 °C (from ether), ν_{max}(KBr)/cm^{-1} 1718 and 1248; $\delta_H(CDCl_3)$ 1.41 (6 H, s, gem-Me_2), 2.26 (6 H, s, 2 × $COCH_3$), 5.71 (1 H, d, *J* 10.0, 3-H), 6.12 (1 H, dd, *J* 10.0 and 0.7, 4-H), 6.62 (1 H, dd, *J* 8.0 and 1.1, 6-H), 6.83 (1 H, dt, *J* 8.0 and 1.0, 8-H) and 7.15 (1 H, t, *J* 8.0, 7-H); $\delta_C(CDCl_3)$ 26.5, 27.9, 76.3 (C-2), 116.4 (C-8*), 117.4 (C-6*), 119.6 (C-4a), 121.0 (C-3), 129.4 (C-7), 133.4 (C-4), 135.4 (C-5), 154.1 (C-8a) and 172.7 (CO) (Found: C, 69.6; H, 6.4; N, 5.5%; M^+, 259.11227. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%; *M*, 259.1208).

2-*Methylbut*-3-*yn*-2-*yl* 3,5-*Dinitrophenyl Ether* **3**.—3,5-Dinitrophenol was prepared from 1,3,5-trinitrobenzene *via* 3,5-dimethoxyanisole.[13] A mixture of 3,5-dinitrophenol (0.500 g, 2.72 mmol), 3-chloro-3-methylbutyne (0.560 g, 5.44 mmol) and anhydrous potassium carbonate (0.450 g, 3.2 mmol) was boiled under reflux overnight with mechanical stirring. The mixture was filtered, the residues washed well with acetone, and the combined filtrates evaporated. The residue was dissolved in ethyl acetate and the solution washed with NaOH (1 mol dm^{-3}; 2 × 20 cm^3) and brine and then dried (Na_2SO_4). The residue left after evaporation of the solvent was purified by flash chromatography (10% ethyl acetate–light petroleum as eluent) to give the title yellow dinitroether (0.520 g, 76%) obtained as pale yellow *prisms*, m.p. 92 °C (from methanol), ν_{max}(KBr)/cm^{-1} 3283 (≡CH), 2117 (C≡C), 1544 and 1347; $\delta_H(CDCl_3)$ 1.79 (6 H, s, gem-Me_2), 2.82 (1 H, s, HC≡), 8.40 (2 H, d, *J* 2.0, 2- and 6-H) and 8.69 (1 H, t, *J* 2.0, 4-H); $\delta_C(CDCl_3)$ 29.4 (gem-Me_2), 74.8 (C-Me_2), 77.0 (HC≡), 83.6 (C≡CH), 112.2 (C-4), 120.4 (C-2 and -6), 148.9 (C-3 and -5) and 157.2 (C-1) (Found: C, 52.5; H, 3.8; N, 11.1%; M^+, 235.0362. $C_{11}H_{10}N_2O_5$ requires C, 52.8; H, 4.0; N, 11.2%; *M*, 235.0354).

2,2-*Dimethyl*-5,7-*dinitro*-2H-*chromene* **11**.—The above 3,5-dinitrophenyl ether **3** (1.00 g, 4.0 mmol) in *o*-xylene (20 cm^3) was boiled under reflux overnight. The solvent was evaporated and the residue purified by flash chromatography (7.5% ethyl acetate–light petroleum as eluent) to give the chromene (0.792 g, 79%), obtained as yellow *plates*, m.p. 92–93 °C (from toluene–light petroleum), ν_{max}(KBr)/cm^{-1} 1543, 1525 and 1341; $\delta_H(CDCl_3)$ 1.55 (6 H, s, gem-Me_2), 6.15 (1 H, d, *J* 10.3, 3-H), 7.02 (1 H, dd, *J* 10.3 and 0.5, 4-H), 7.85 (1 H, dd, *J* 2.3 and 0.5, 8-H) and 8.35 (1 H, d, *J* 2.3, 6-H); $\delta_C(CDCl_3)$ 27.8, 77.9 (C-2), 112.3 (C-6), 116.0 (C-3*), 116.6 (C-8*), 121.4 (C-4a), 138.5 (C-4), 145.7 (C-5[n]), 146.7 (C-7[n]) and 155.1 (C-8a) (Found: C, 52.6; H, 4.1; N, 11.1%; M^+, 250.0588. $C_{11}H_{10}N_2O_5$ requires C, 52.8; H, 4.0; N, 11.2%; *M*, 250.0589).

Thermolysis of the Dinitroether **3** *in Dimethyl Sulfoxide*.—The above 3,5-dinitrophenyl ether **3** (0.109 g, 0.530 mmol) in degassed [$^2H_6$]-dimethyl sulfoxide was heated at 145 °C (boiling *o*-xylene) until TLC and NMR indicated that all starting material had disappeared (8 h). The solvent was evaporated (0.1 mmHg) and the residue purified by flash chromatography (dichloromethane as eluent) to give 2-isopropyl-4,6-dinitrobenzofuran **12** (0.067 g, 61%) as thick yellow *needles*, m.p. 81–82 °C (from ether), ν_{max}(KBr)/cm^{-1} 1528 and

1342; $\delta_H(CDCl_3)$ 1.45 (6 H, d, *J* 7.0, gem-Me_2), 3.25 (1 H, septet, *J* 7.0), 7.27 (1 H, t, *J* 0.8, 3-H), 8.61 (1 H, dd, *J* 1.9 and 0.8, 7-H) and 9.08 (1 H, d, *J* 1.9, 5-H) (Found: C, 52.8; H, 4.3; N, 10.9%; M^+, 250.0583. $C_{11}H_{10}N_2O_5$ requires C, 52.8; H, 4.0; N, 11.2%; *M*, 250.0589).

Assignment of the 5- and 7-H signals follows from comparison with calculated values using standard additive data (δ 9.15 and 8.50 respectively) and from the observed long-range coupling between 7- and 3-H analogous to that between 4- and 8-H of chromenes.[12]

3,4-*Epoxy*-2,2-*dimethyl*-5,7-*dinitrochroman* **13**.—A mixture of the 5,7-dinitrochromene **11** (0.200 g, 0.80 mmol), potassium carbonate (0.020 g), and 3-chloroperbenzoic acid (0.275 g, 1.6 mmol) in dichloromethane (7 cm^3) was boiled under reflux overnight. After it had cooled the mixture was diluted with more dichloromethane and washed with aqueous sodium sulfite and then aqueous sodium hydrogencarbonate (3 ×), dried (Na_2SO_4) and the solvent removed by evaporation. Flash chromatography of the residue (20% ethyl acetate–light petroleum as eluent) gave the title epoxide (0.155 g, 71%) obtained as pale yellow hexagonal *plates*, m.p. 110–111 °C (from ether), ν_{max}(KBr)/cm^{-1} 1542 and 1346; λ_{max}(EtOH)/nm 218 (ε 17 800 dm^3 mol^{-1} cm^{-1}), 254 (13 600) and 341 (3450); $\delta_H(CDCl_3)$ 1.37 (3 H, s), 1.64 (3 H, s), 3.64 (1 H, d, *J* 4.4, 3-H), 4.68 (1 H, dd, *J* 4.4 and 0.6, 4-H), 7.89 (1 H, dd, *J* 2.3 and 0.6, 8-H) and 8.38 (1 H, d, *J* 2.3, 6-H); $\delta_C(CDCl_3)$ 22.9, 25.3, 45.5 (C-3), 62.5 (C-4), 75.3 (C-2), 112.2 (C-6), 117.6 (C-8), 121.7 (C-4a), 147.9 (C-5*), 150.9 (C-7*) and 155.1 (C-8a) (Found: C, 49.4; H, 3.8; N, 10.3%; M^+, 266.0513. $C_{11}H_{10}N_2O_6$ requires C, 49.6; H, 3.8; N, 10.5%; *M*, 266.0539).

Partial Reduction of the Dinitrochromene **11**.—To a boiling suspension of the dinitrochromene **11** (1.07 g, 4.28 mmol) in water (5 cm^3) was added dropwise over 30 min a solution prepared from sodium sulfide (1.13 g, 4.71 mmol) and sulfur (0.274 g, 5.56 mmol) in water (4.4 cm^3). After the addition, the mixture was heated for 1 h. The solvent was evaporated and the residue subjected to flash chromatography (10–15% ethyl acetate–light petroleum as eluent). The first fraction eluted was the strongly red 5-nitro-2*H*-chromen-7-amine **14** (0.652 g, 69%) obtained as red *plates*, m.p. 107 °C (from dichloromethane–light petroleum), ν_{max}(KBr)/cm^{-1} 3460, 3670br, 1520 and 1330; λ_{max}(EtOH)/nm 227 (ε 22 900 dm^3 mol^{-1} cm^{-1}), 291 (15 200) and 418 (3000); $\delta_H(CDCl_3)$ 1.40 (6 H, s, gem-Me_2), 3.98 (2 H, br s, NH_2), 5.64 (1 H, d, *J* 10.2, 3-H), 6.34 (1 H, dd, *J* 10.7 and 2.3, 8-H), 6.80 (1 H, dd, *J* 10.1 and 0.7, 4-H) and 6.82 (1 H, d, *J* 2.4, 6-H); $\delta_C(CDCl_3)$ 27.6 (q), 76.2 (s, C-2), 103.3 (d, C-6), 107.3 (s, C-4a), 107.5 (d, C-8), 117.6 (d, C-3), 130.6 (d, C-4), 147.0 (2 unresolved s, C-5 and -7) and 155.5 (s, C-8a) (Found: C, 59.8; H, 5.35; N, 12.5%; M^+, 221.0846. $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.5; N, 12.7%; *M* + 1, 221.0926).

The second fraction was the isomeric 7-nitro-2*H*-chromen-5-amine **15** (0.135 g, 14%) obtained as yellow *prisms*, m.p. 97 °C (from toluene–light petroleum), ν_{max}(KBr)/cm^{-1} 1640, 1510 and 1355; λ_{max}(EtOH)/nm 224 (ε 22 300 dm^3 mol^{-1} cm^{-1}) and 364 (7000); $\delta_H(CDCl_3)$ 1.44 (6 H, s, gem-Me_2), 3.87 (2 H, br s, NH_2), 5.78 (1 H, d, *J* 10.0, 3-H), 6.35 (1 H, d, *J* 9.9 with unresolved further coupling, 4-H) and 7.09 (2 H, ABdd, *J* 2.7, 6- and 8-H); $\delta_C(CDCl_3)$ 27.6, 76.3 (C-2), 102.7 (C-8*), 103.3 (C-6*), 113.2 (C-4a), 115.8 (C-3), 132.8 (C-4), 142.8 (C-5), 148.5 (C-7) and 154.0 (C-8a) (Found: C, 59.9; H, 5.3; N, 12.6%; M^+, 221.0849. $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.5; N, 12.7%; *M* + 1, 221.0926).

7-(*Ethoxycarbonylamino*)-2,2-*dimethyl*-5-*nitro*-2H-*chromene* **16**.—Triethylamine (0.168 g, 1.66 mmol) was added dropwise to a solution of the 5-nitro-2*H*-chromen-7-amine **14** (0.366 g, 1.66 mmol) and ethyl chloroformate (0.900 g, 8.3 mmol) in toluene (8 cm^3). The solution was stirred for 3 d, diluted with ethyl acetate and washed with water, dilute hydrochloric acid, and water and then dried (Na_2SO_4). Removal of the solvent left a yellow oil which on flash chromatography (10% ethyl acetate–light petroleum as eluent) gave the bright yellow title carbamate (0.494 g, 100%), m.p. 83–85 °C (from ether–light petroleum), ν_{max}(film)/cm^{-1} 1740, 1710, 1535 and 1235; $\delta_H(CDCl_3)$ 1.28 (3 H, t, *J* 7.1), 1.42 (6 H, s, gem-Me_2), 4.22 (2 H, q, *J* 7.1), 5.77 (1 H, d, *J* 10.2, 3-H), 6.85 (1 H, dd, *J* 10.2 and 0.7, 4-H), 7.03 (1 H, br s, NH), 7.17 (1 H, d, *J* 0.8, 8-H) and 7.59 (1 H, d, *J* 2.2, 6-H); $\delta_C(CDCl_3)$ 14.5 (CH_3CH_2), 27.7 (gem-Me_2), 61.8 (O-CH_2), 76.5 (C-2), 107.0 (C-6*), 111.4 (C-8*), 111.5 (C-4a), 117.3 (C-3), 133.1 (C-4), 138.5 (C-7#), 146.3 (C-5#), 153.3 (C-8a') and 155.0 (CO') (Found: C, 57.7; H, 6.7; N, 9.9%; M^+, 292.1086. $C_{14}H_{16}N_2O_5$ requires C, 57.5; H, 5.5; N, 9.6%; *M*, 292.1059).

trans-3-*Bromo*-7-(*ethoxycarbonylamino*)-2,2-*dimethyl*-5-*nitrochroman*-4-*ol*.—The *N*-ethoxycarbonyl chromene **16** (0.172 g, 0.59 mmol) was dissolved in THF (12 cm^3) and water (8 cm^3). *N*-Bromosuccinimide (0.105 g, 0.59 mmol) in THF (2 cm^3) was added with stirring at room temperature. The reaction was complete within a few minutes (TLC) whereupon the mixture was diluted with ethyl acetate and the separated organic phase washed with brine and dried (Na_2SO_4). The residue after removal of the solvent was flash chromatographed (60% ether–light petroleum as eluent) to give the title bromo alcohol (0.222 g, 97%), as an *oil*, ν_{max}(film)/cm^{-1} 1715 and 1540; $\delta_H(CDCl_3)$ 1.32 (3 H, t, *J* 7.1), 1.50 (3 H, s), 1.61 (3 H, s), 3.25 (1 H d, *J* 5.0, 3-H), 4.20 (1 H, d, *J* 7.0, OH), 4.24 (2 H, q, *J* 7.1, OCH_2), 5.38 (1 H, dd, *J* 7.0 and 5.0, 4-H), 6.70 (1 H, br s, NH), 7.20 (1 H, d, *J* 2.2, 8-H) and 7.61 (1 H, d, *J* 2.2, 6-H); (Found: M^+, 388.0231. $C_{14}H_{17}BrN_2O_6$ requires *M*, 388.0270).

3,4-*Epoxy*-7-(*ethoxycarbonylamino*)-2,2-*dimethyl*-5-*nitrochroman* **17**.—The above bromo alcohol (0.175 g, 0.45 mmol) in dry THF (10 cm^3) was added over 1 h by syringe to a suspension of sodium hydride (light petroleum washed) (0.090 g, 2.3 mmol) in dry THF (10 cm^3) in an atmosphere of nitrogen. After 5 h at room temperature the reaction was cooled to 0 °C, quenched with ice-cold sodium phosphate buffer (pH 7.2), and extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (10–20% ethyl acetate–light petroleum as eluent) gave the title epoxide (0.102 g, 74%) obtained as pale yellow *needles*, m.p. 154–156 °C (from ether), ν_{max}(KBr)/cm^{-1} 1730, 1635, 1595, 1540 and 1360; λ_{max}(EtOH)/nm 215 (ε 36 900 dm^3 mol^{-1} cm^{-1}), 245 (21 000), 294 (2600) and 343 (2400); $\delta_H(CDCl_3)$ 1.27 (3 H, s, 2-Me), 1.28 (3 H, t, *J* 7.2, CH_3CH_2), 1.54 (3 H, s, 2-Me'), 3.52 (1 H, d, *J* 4.6, 3-H), 4.20 (2 H, q, *J* 7.1, OCH_2), 4.59 (1 H, d, *J* 4.4, 4-H), 7.14 (1 H, d, *J* 2.1, 8-H), 7.20 (1 H, s, NH) and 7.65 (1 H, d, *J* 2.2, 6-H); $\delta_C(CDCl_3)$ 14.5 (CH_3CH_2), 22.9 (2-Me), 25.5 (2-Me'), 46.2 (OCH_2), 61.9 (C-3), 62.1 (C-4), 74.0 (C-2), 107.8 (C-8), 109.6 (C-4a), 112.4 (C-6), 139.7 (C-7), 151.1 (C-8a*), 153.2 (C-5*) and 154.7 (C=O*) (Found: C, 54.2; H, 5.1; N, 9.0%; M^+, 308.1050. $C_{14}H_{16}N_2O_6$ requires C, 54.5; H, 5.2%; N, 9.1, *M*, 308.1009).

7-[(2'-tert-*Butoxycarbonylamino*)*acetamido*]-2,2-*dimethyl*-5-*nitro*-2H-*chromene*.—A mixture of the chromene-7-amine **14** (0.371 g, 1.69 mmol), 1,3-dicyclohexylcarbodiimide (0.698 g, 3.38 mmol), and *N*-(*tert*-butoxycarbonyl)glycine (0.592 g, 3.38 mmol) in dry dichloromethane (15 cm^3) was stirred overnight at room temperature. Water (1.0 cm^3) was added and the mixture stirred for 5 min. The organic layer was filtered and evaporated. Flash chromatography of the residue (20% ethyl acetate–light petroleum as eluent) gave the title derivative (0.633 g, 99%), as

an *oil*, $\delta_H(CDCl_3)$ 1.43 (6 H, s, gem-Me_2), 1.47 (9 H, s), 3.96 (2 H, d, *J* 6.0, CH_2N), 5.60 (1 H, t, *J* 6.0, N*H*CH_2), 5.77 (1 H, d, *J* 10.5, 3-H), 6.90 (1 H, d, *J* 10.5, 4-H), 7.40 (1 H, br s, 8-H), 7.73 (1 H, d, *J* 2.0, 6-H) and 8.97 (1 H, br s, N*H*Ar) (Found: M^+, 377.1542. $C_{18}H_{23}N_3O_6$ requires *M*, 377.1587).

7-(2′-*Aminoacetamido*)-2,2-*dimethyl*-5-*nitro*-2H-*chromene* **18**.—The above *tert*-Boc derivative (0.370 g, 1.02 mmol) in aqueous hydrochloric acid (3 mol dm^{-3}, 10 cm^3) and ethyl acetate (4 cm^3) was stirred at room temperature overnight. The solution was basified with aqueous sodium hydroxide and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (10% methanol–dichloromethane as eluent) gave the title *N*-glycylaminochromene (0.253 g, 89%) as an *oil*, $\delta_H(CDCl_3)$ 1.44 (6 H, s, gem-Me_2), 1.68 (2 H, br s, NH_2), 3.47 (2 H, s, CH_2), 5.80 (1 H, d, *J* 10.2, 3-H), 6.88 (1 H, d, *J* 10.2, 4-H), 7.49 (1 H, d, *J* 2.0, 8-H), 7.73 (1 H, d, *J* 2.1, 6-H) and 9.63 (1 H, br s, NH) (Found: M^+, 277.1037. $C_{13}H_{15}N_3O_4$ requires *M*, 277.1062).

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