The synthesis of benzo[*h*]quinolines as topoisomerase inhibitors

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Received (in Cambridge) 28th April 1999, Accepted 23rd June 1999

A range of benzo[*h*]quinolines of potential biological interest have been prepared by way of the 2-chloro- and the 4-chlorobenzo[*h*]quinoline-3-carbaldehyde isomers.

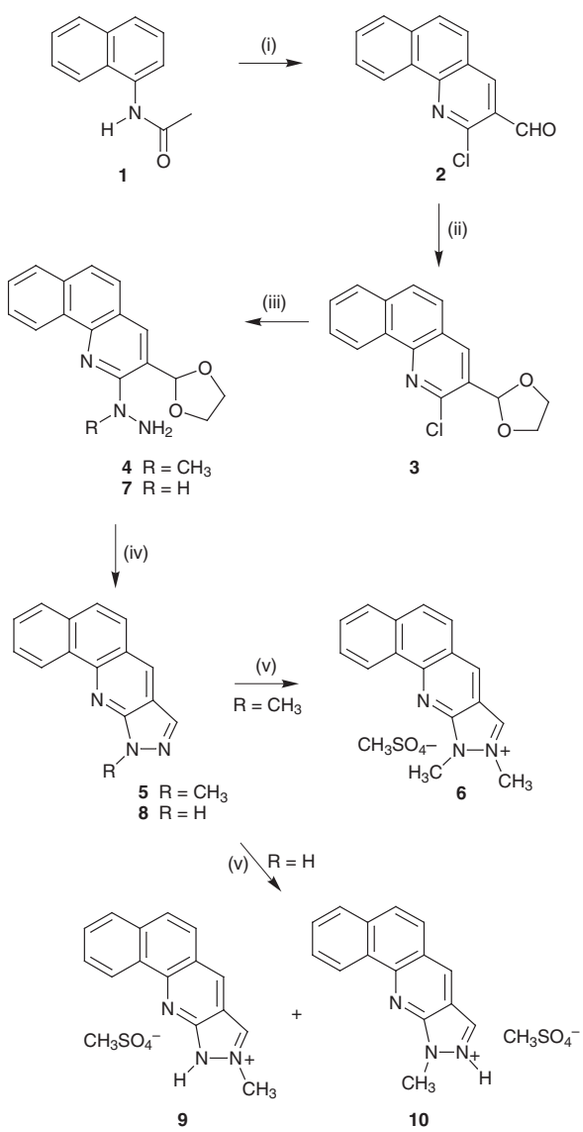
Introduction

Numerous tri- and tetracyclic planar nitrogen heterocycles, such as amsacrine, the benzo[*c*]phenanthridines, the ellipticines, intoplicine and coralyne are well known as topoisomerase inhibitors and have been investigated as potential anticancer agents.[1–5] The benzo[*h*]quinolines can be viewed as being structurally related to the antitumour benzo[*c*]phenanthridines by deletion of a ring, or as heterocyclic isomers of the above-mentioned acridine and phenanthridine based antitumour agents. Consequently, given routes to 2-chlorobenzo[*h*]quinoline-3-carbaldehyde, and to the 4-chloro-isomer, a range of benzo[*h*]quinolines of potential biological interest will become available.

The synthetic methodologies that have been used to create the benzo[*h*]quinoline nucleus are generally adaptations of the commonly used methods of quinoline synthesis (*e.g.* Skraup, and Doebner and von Miller),[6–9] although other routes involving Diels–Alder reactions[10] and Friedlander condensations[11] provide alternative, multistep approaches. We have used the Vilsmeier reaction previously to provide access to a variety of 2,3-substituted and 2,3-fused quinolines[12,13] by reacting *N*,*N*-dimethylformamide (DMF) with an appropriate *N*-arylacetamide in the presence of phosphorus oxychloride ($POCl_3$) to yield, for example, 2-chloroquinoline-3-carbaldehyde. Acetylation of α-naphthylamine provided us with an alternative nucleophilic species **1** for reaction with DMF which under the same conditions yielded the 2-chlorobenzo[*h*]quinoline-3-carbaldehyde **2** (Scheme 1). This appropriately substituted heterocycle along with the corresponding 3,4-substituted benzo[*h*]quinoline **17** was recognised as a potential precursor to analogues of a number of agents with anticancer activity.[14–17]

Results and discussion

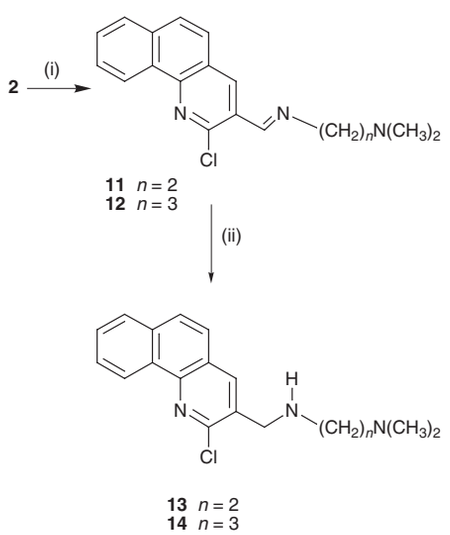
Our first target was annelation of a pyrazole ring to the benzo[*h*]quinoline nucleus. This was envisaged to occur *via* reaction of the precursor **3** with methylhydrazine. Initial conversion of the aldehyde group in **2** to the acetal **3** was required in order to prevent formation of the hydrazone which does not undergo cyclisation,[18] presumably due to the adoption of the unfavourable *E*-configuration. Consequently, after the acetal was refluxed with methylhydrazine to yield the hydrazine-acetal **4**, cyclisation to the corresponding 10-methyl-10*H*-benzo[*h*]-pyrazolo[3,4-*b*]quinoline **5** was achieved in hot alcoholic acidic conditions. The structure was confirmed by NOE experiments. Irradiation of the N-CH_3 signal (4.33 ppm) failed to enhance any aromatic signals indicating that the secondary amino group of the *N*-methylhydrazine had substituted the 2-chloro-group of the benzo[*h*]quinoline nucleus. Methylation to give the quaternary benzo[*h*]pyrazolo[3,4-*b*]quinolinium salt **6** was achieved by refluxing the pyrazoloquinoline **5** with dimethyl sulfate in toluene. If hydrazine was utilised in place of



Scheme 1 *Reagents and conditions*: (i) DMF, $POCl_3$, 75 °C, 6 h, 69%; (ii) ethylene glycol, toluene-*p*-sulfonic acid, toluene, reflux, 5 h, 75%; (iii) N_2 atmosphere, reflux, 3 h; *N*-methylhydrazine (**4**), 86%; hydrazine (**7**), 86%; (iv) ethanol, 2 M HCl (aq), reflux, 5 min; (**5**) 96%; (**8**) 86%; (v) dimethyl sulfate, xylene–nitrobenzene, 130 °C, 15 min; (**6**) 96%; (**9**) 36%; (**10**) 22%.

N-methylhydrazine, the resulting demethyl 10*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline **8** gave a mixture of both the 9-methyl and 10-methyl salts **9** and **10** on methylation which were separated by flash chromatography and the positions of the respective methyl groups were confirmed by NOE experiments. The structure of **10** was also established by treatment with base, which confirmed **5** as its free base form. The quinolinium salt **6** possesses an electrophilic iminium group and resembles the pharmacophoric heterocyclic nucleus of the antitumour benzo[*c*]phenanthridines[16,19] and has served as a model synthesis for other related analogues which are now being assessed for activity. Annelation of a heterocyclic six-membered ring to the benzo[*h*]quinoline system by replacement of methylhydrazine with either urea or guanidine in the above scheme proved unsuccessful, yielding only the chloro-acetal starting material. This result is in agreement with earlier studies performed with the corresponding quinoline analogues.[13]

Without prior acetalisation of the 2-chlorobenzo[*h*]quinoline-3-carbaldehyde **2**, nucleophilic attack takes place at the formyl group. Analogues of the antitumour agent *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA)[15,17] were produced by treatment of the 2-chlorobenzo[*h*]quinoline-3-carbaldehyde **2** with the *N*,*N*-dimethylaminoalkylamine [ethyl and propyl homologues] followed by reduction of the resulting imines **11**, **12** with sodium borohydride (Scheme 2) gave the corresponding amines **13**, **14**.



Scheme 2 *Reagents and conditions*: (i) *N*,*N*-dimethylaminoalkylamine, ethanol, reflux, 4 h; (**11**) 75%; (**12**) 100%; (ii) sodium borohydride, ethanol, rt, 48 h, ethereal HCl; (**13**) 52%; (**14**) 15%.

Preparation of the 3,4-substituted benzo[*h*]quinolines was achieved by modifying the Gould–Jacobs synthesis of quinolines.[20] Reaction of α-naphthylamine with diethyl ethoxymethylenemalonic ester followed by cyclisation in the high boiling point solvent Dowtherm 'A' yielded ethyl 4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate **15** and provided a route to [*c*]-fusion of the pyrazolo ring with the benzo[*h*]quinoline system (Scheme 3). The structural isomer of **2** was prepared by initially chlorinating the quinolone **15** with $POCl_3$ to yield ethyl 4-chlorobenzo[*h*]quinoline-3-carboxylate **16**. Reduction of the ester with DIBAL-H in dichloromethane at −70 °C produced a mixture of both the alcohol and aldehyde **17**, which could be separated by flash chromatography. However, for preparative purposes, the resulting mixture was oxidised with activated manganese dioxide to produce the aldehyde **17** exclusively. The corresponding quaternary 2,3-dimethyl-3*H*-benzo[*h*]pyrazolo[4,3-*c*]quinolinium salt **18** was prepared *via* the route described for compound **6**.

Table 1 IC_{50} values for the inhibition of topoisomerase I

	6	**18**	**20**	**21**
IC_{50}/μM	13.9	34.8	12.9	5.16

Annelation of a heterocyclic 6-membered ring to the benzo[*h*]quinolines **16** and **17** with either urea or guanidine also proved unsuccessful. Treatment of the chloro-ester **16** with guanidine using ethylene glycol as the solvent actually produced the 2-hydroxyethyl ester **19** in 45% yield, the solvent acting as the reactant. Conversely, reaction with the *N*,*N*-dimethylaminoalkylamines does not result in reaction with the ester group to produce the corresponding amides, but in a nucleophilic aromatic substitution reaction at the 4-chloro position to produce the two amines **20** and **21** (both recognised as analogues of DACA).

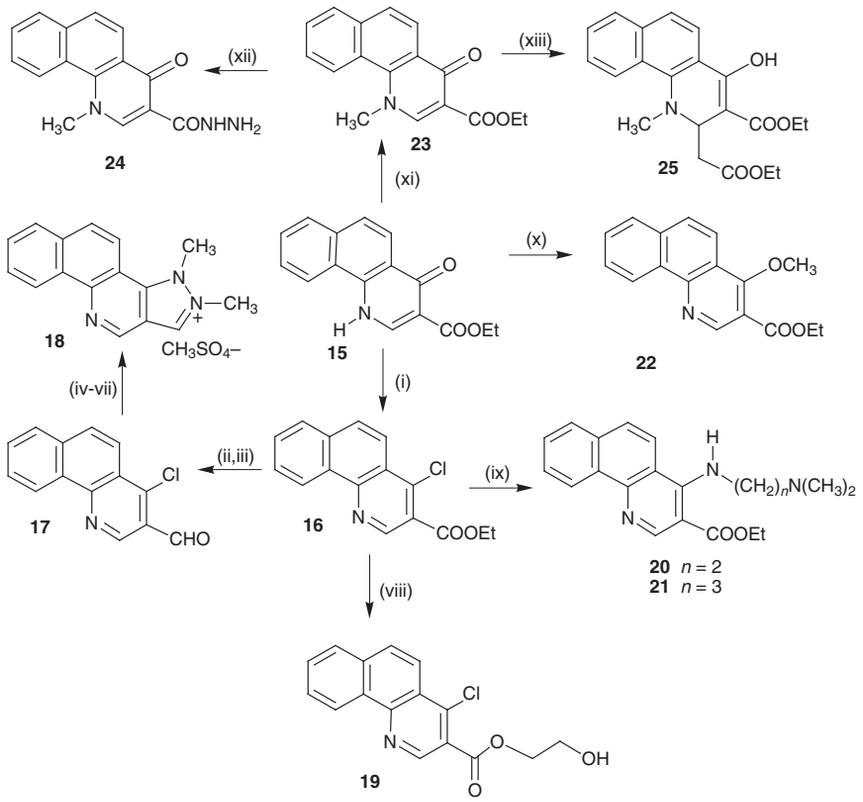
Refluxing the quinolone-ester **15** with dimethyl sulfate and potassium carbonate in acetone produced the 4-methoxy analogue **22**. Confirmation of the position of attachment of the methyl group was achieved by NOE. Irradiation of the methyl signal (4.16 ppm) resulted in the enhancement of the H-5 signal at 8.14 ppm. Furthermore, the absence of the quinolone C=O stretch in the IR spectrum supported this assignment. *N*-Methylation to give ethyl 1-methyl-4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate **23** was achieved using methyl iodide in the presence of sodium hydride. NOE enhancement of the proton signals for H-2 and H-10 (8.46 and 8.42 ppm, respectively) resulted from irradiation of the *N*-methyl signal at 4.27 ppm, confirming the proposed structure.

Reaction of the *N*-methylquinolone ester **23** with hydrazine produced the hydrazide **24**. Subsequent cyclisation to the pyrazolone with $POCl_3$ and isolation as the hexafluorophosphate salt produced a deep red–orange solid. The intractable nature of this salt precluded its full characterisation. The reaction of **23** with the softer nucleophile ethyl acetoacetate resulted in 1,4-Michael addition occurring at the 2-position with subsequent deacetylation to yield ethyl 1-methyl-4-hydroxy-2-(ethoxycarbonylmethyl)-1,2-dihydrobenzo[*h*]quinoline-3-carboxylate **25**. The structure was confirmed by the IR spectrum containing two C=O stretches at 1733 and 1643 cm^{-1}. The lower wavenumber C=O stretch is assigned to the 3-ester due to intramolecular hydrogen-bonding between the 3-ester and 4-hydroxy groups. ^1H NMR and $^1H^1H$ COSY allowed assignment of the diastereotopic splitting pattern associated with the ethoxycarbonyl methyl group attached at the chiral C-2 centre.

A number of the benzo[*h*]quinolines we have prepared bind to DNA with high affinity, inhibit topoisomerase I but not topoisomerase II and show varying cytotoxicity against the K562 and A2780 tumour cell lines. Inhibitory concentrations against topoisomerase I for those compounds demonstrating activity are shown in Table 1 and show comparable activity with the antitumour benzo[*c*]phenanthridine topoisomerase I inhibitors (fagaronine and nitidine) which formed the basis for their design (IC_{50} = 30 and 55 μM respectively).[3,23] A more detailed analysis of the biological data will be reported elsewhere.

Experimental

Melting points were determined on a Reichert Hotstage Microscope melting point apparatus and are uncorrected. All NMR spectra were recorded on a JEOL GSX 270-FT spectrophotometer operating at 270 MHz and 25 °C with tetramethylsilane as the internal reference standard unless otherwise stated. All coupling constants (*J* values) are quoted in hertz (Hz) and chemical shifts quoted in ppm. A UNICAM Research Series 1 FTIR spectrophotometer was used to record IR spectra using the sample preparation stated in the text. Mass spectra were recorded on a VG 302000.



Scheme 3 *Reagents and conditions*: (i) $POCl_3$, 90 °C, 25 min, 85%; (ii) DIBAL-H, dry ether, −70 °C, N_2 atmosphere, 2 h; (iii) activated MnO_2, dichloromethane, rt, 30 min, overall yield for (ii) and (iii) 69%; (iv) ethylene glycol, toluene-*p*-sulfonic acid, toluene, reflux, 5 h, 53%; (v) *N*-methylhydrazine, N_2 atmosphere, reflux, 4 h; (vi) ethanol, 2 M HCl (aq), reflux, 15 min, 75%; (vii) dimethyl sulfate, xylene–nitrobenzene, 130 °C, 15 min, 59%; (viii) guanidine carbonate, ethylene glycol, 50 °C, 5 h, 45%; (ix) *N*,*N*-dimethylaminoalkylamine, rt, 1 h, ethereal HCl; (**20**) 90%; (**21**) 79%; (x) dimethyl sulfate, K_2CO_3, acetone, reflux, 24 h, 23%; (xi) methyl iodide, NaH, toluene, 50 °C, 16 h, 86%; (xii) hydrazine, reflux, 30 min, 93%; (xiii) ethyl acetoacetate, NaH, toluene, reflux, 20 h, 67%.

Elemental analysis was carried out using a Carlo Erba 1106 Elemental Analyser and a Mettler MT5 Microbalance was used to weigh samples. Accurate masses were performed on a Kratos MS80RF spectrometer.

Thin-layer chromatography (TLC) was carried out using Merck silica 60 F254 plates and visualised under short-wave UV light. Flash chromatography was performed using Acros silica (35–70 μm particle size) in the specified solvent mixture.

All chemicals were supplied by either Aldrich, Merck or Lancaster Chemicals and were used as received, unless otherwise stated.

N-Acetyl-1-naphthylamine 1

A mixture of 1-naphthylamine (43.0 g, 0.3 mol) in acetic anhydride (76.5 g, 0.75 mol) was heated under reflux for 10 min after which water (50 cm^3) was added and the mixture was refluxed for a further 5 min. The warm solution was then poured directly onto crushed ice (~30 g). The resulting white precipitate (49.8 g, 90%) was filtered, washed with water, and dried in air, and was pure enough for further use. A sample was recrystallised from ethanol to give the title compound **1** as white needles, mp 159–160 °C (lit.[21] 159 °C); ν_{max} (KBr disk) 3270 (NH), 1656 (CO), 1548, 1398 cm^{-1}; δ_H (d_6-DMSO, 50 °C) 2.17 (3H, s, COCH-3), 7.46 (1H, t, *J* 8, H-3), 7.52 (2H, m, H-6,7), 7.68 (1H, d, *J* 8, H-2), 7.74 (1H, d, *J* 8, H-4), 7.91 (1H, m, H-5), 8.07 (1H, m, H-8).

2-Chlorobenzo[*h*]quinoline-3-carbaldehyde 2

To a solution of *N*-acetyl-1-naphthylamine **1** (1.0 g, 5.4 mmol) in dry DMF (0.99 g, 14 mmol) was added $POCl_3$ (9.5 cm^3, 102 mmol) and the mixture stirred at 75 °C for 6 h. The mixture was poured onto crushed ice (~50 g) and the resulting solid (0.90 g, 69%) filtered, washed with water and dried in an oven. A sample was recrystallised from ethyl acetate–petroleum ether 60–80 °C to give the title compound **2** as yellow needles, mp 210–212 °C (Found: C, 70.0; H, 3.1; N, 5.9. $C_{14}H_8ClNO$ requires C, 69.7; H, 3.35; N, 5.8%); ν_{max} (KBr disk) 1685 (CO), 1579, 1365, 1054 cm^{-1}; δ_H ($CDCl_3$) 7.77 (1H, d, *J* 8, H-6), 7.79 (2H, m, H-8,9), 7.89 (1H, d, *J* 8, H-5), 7.94 (1H, m, H-7), 8.72 (1H, s, H-4), 9.24 (1H, m, H-10), 10.58 (1H, s, CHO); *m*/*z* 242 (M^+ 100%).

2-Chloro-3-(1,3-dioxolan-2-yl)benzo[*h*]quinoline 3

A solution of 2-chlorobenzo[*h*]quinoline-3-carbaldehyde **2** (2.0 g, 8.3 mmol) in toluene (100 cm^3) containing ethylene glycol (1.55 g, 25 mmol) and a trace amount of toluene-*p*-sulfonic acid was heated under reflux for 5 h using a Dean–Stark water separator. The cooled solution was treated with saturated aqueous sodium carbonate (50 cm^3), dried ($MgSO_4$), and evaporated to leave an orange solid (1.78 g, 75%). Recrystallisation from ethyl acetate–petroleum ether 60–80 °C gave the title compound **3** as yellow cuboids, mp 134–136 °C (Found: C, 67.1; H, 4.2; N, 5.1. $C_{16}H_{12}ClNO_2$ requires C, 67.3; H, 4.2; N, 4.9%); ν_{max} (KBr disk) 1592, 1478, 1359, 1089, 1051 cm^{-1}; δ_H ($CDCl_3$) 4.11–4.28 (4H, m, 2 × CH_2), 6.30 (1H, s, CH), 7.73 (3H, m, H-6,8,9), 7.83 (1H, d, *J* 9, H-5), 7.91 (1H, m, H-7), 8.42 (1H, s, H-4), 9.21 (1H, m, H-10); *m*/*z* 286 (M^+ 100%).

2-(1-Methylhydrazino)-3-(1,3-dioxolan-2-yl)benzo[*h*]quinoline 4

A solution of 2-chloro-3-(1,3-dioxolan-2-yl)benzo[*h*]quinoline **3** (2.0 g, 7 mmol) in *N*-methylhydrazine (15.0 g, excess) was refluxed under nitrogen while stirring for 3 h. *N*-Methylhydrazine was removed under reduced pressure to leave an orange oil which was dissolved in dichloromethane (50 cm^3). The organic phase was washed with water (2 × 20 cm^3), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to

give the title product (1.77 g, 86%). Recrystallisation from ethyl acetate–petroleum ether 60–80 °C gave the pure product **4** as orange cuboids, mp 133–134 °C (Found C, 69.2; H, 5.7; N, 14.1. $C_{17}H_{17}N_3O_2$ requires C, 69.1; H, 5.8; N, 14.2%); ν_{max} (KBr disk) 3328 (NH), 3027 (NH), 2861 (NCH_3), 1610 cm^{-1}; δ_H ($CDCl_3$) 3.39 (3H, s, NCH_3), 4.14 (4H, m, 2 × CH_2), 6.63 (1H, s, CH), 7.65 (2H, m, H-5,6), 7.66 (2H, m, H-8,9), 7.86 (1H, m, H-7), 8.37 (1H, s, H-4), 9.16 (1H, m, H-10).

10-Methyl-10*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline 5

To a solution of 2-(1-*N*-methylhydrazino)-3-(1,3-dioxolan-2-yl)benzo[*h*]quinoline **4** (1.0 g, 3.4 mmol) in ethanol (30 cm^3) was added 2 M HCl (4 cm^3) and the mixture was refluxed for 5 min. The cooled solution was poured onto a stirred solution of 2 M NaOH (~50 cm^3) and the yellow precipitate (0.76 g, 96%) was filtered and washed well with water. Recrystallisation from ethanol gave the title compound **5** as orange plates, mp 130–132 °C (Found C, 77.3; H, 4.5; N, 17.7. $C_{15}H_{11}N_3$ requires C, 77.2; H, 4.75; N, 18.0%); ν_{max} (KBr disk) 2935 (NCH_3), 1602 cm^{-1}; δ_H ($CDCl_3$) 4.35 (3H, s, NCH_3), 7.66 (1H, d, *J* 9, H-6), 7.72 (2H, m, H-2,3), 7.76 (1H, d, *J* 9, H-5), 7.89 (1H, m, H-4), 8.24 (1H, s, H-7), 8.55 (1H, s, H-8), 9.44 (1H, m, H-1); NOE Experiments irradiating the NCH_3 proton (4.35 ppm) failed to enhance any other aromatic proton confirming the placement of the CH_3 group within the molecule; *m*/*z* 234 (M^+ 100%).

9,10-Dimethyl-10*H*-benzo[*h*]pyrazolo[3,4-*b*]quinolinium methyl sulfate 6

A solution of 10-methyl-10*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline **5** (1.50 g, 6.4 mmol) in nitrobenzene (50 cm^3) and xylene (25 cm^3) was heated to 130 °C. To the heated solution was added dimethyl sulfate (25 cm^3, excess) and the solution heated for a further 15 min. After this period the solution was cooled then triturated onto ether to give a fine orange precipitate. The precipitate (2.21 g, 96%) was filtered, washed with ether and dried in an oven. Recrystallisation from glacial acetic acid–ethyl acetate afforded the title compound **6** as orange needles, mp >300 °C (Found C, 57.0; H, 4.7; N, 11.6. $C_{17}H_{17}N_3O_4S$ requires C, 56.8; H, 4.8; N, 11.7%); ν_{max} (KBr disk) 3102–2923 (NCH_3), 1635 cm^{-1}; δ_H (D_2O) 3.62 (3H, s, NCH_3), 3.95 (3H, s, N^+CH_3), 7.03 (1H, d, *J* 8, H-5), 7.13 (1H, d, *J* 8, H-6), 7.29 (1H, t, *J* 6, H-2), 7.41 (1H, d, *J* 8, H-4), 7.50 (1H, t, *J* 6, H-3), 7.82 (1H, s, H-7), 7.97 (1H, d, *J* 8, H-1), 8.11 (1H, s, H-8); *m*/*z* (ESMS – positive ion mode) 248 (M^+), (ESMS – negative ion mode) 111 (counter ion) ($^-OSO_3CH_3$).

2-Hydrazino-3-(1,3-dioxolan-2-yl)benzo[*h*]quinoline 7

A solution of 2-chloro-3-(1,3-dioxolan-2-yl)benzo[*h*]quinoline **3** (1.0 g, 3.5 mmol) in hydrazine monohydrate (8.0 g, excess) was refluxed under nitrogen while stirring for 2.5 h. The product (1.77 g, 86%) was recovered *via* filtration and washed well with water. Recrystallisation from ethanol gave the pure product **7** as yellow needles, mp 154–156 °C (Found C, 68.5; H, 5.2; N, 14.8. $C_{16}H_{15}N_3O_2$ requires C, 68.3; H, 5.4; N, 14.9%); ν_{max} (KBr disk) 3290 (NH), 3190 (NH), 1611 cm^{-1}; δ_H ($CDCl_3$) 4.17 (4H, m, 2 × C*H*$_2$), 4.36 (2H, br s, N*H*$_2$), 5.89 (1H, s, C*H*), 6.92 (1H, br s, N*H*), 7.60 (2H, s, H-5,6), 7.64 (2H, m, H-8,9), 7.86 (1H, m, H-7), 8.02 (1H, s, H-4), 9.19 (1H, m, H-10).

10*H*-Benzo[*h*]pyrazolo[3,4-*b*]quinoline 8

To a solution of 2-hydrazino-3-(1,3-dioxolan-2-yl)benzo[*h*]-quinoline **7** (500 mg, 1.8 mmol) in methanol (15 cm^3) was added 2 M HCl (2 cm^3) and the mixture refluxed for 10 min. The cooled solution was poured onto a stirred solution of 2 M NH_4OH (~40 cm^3) and the orange precipitate (340 mg, 86%) filtered and washed well with water. Recrystallisation from ethyl acetate–petroleum ether 60–80 °C gave the title compound **8** as orange needles, mp 250–252 °C (Found C, 76.6; H, 3.9; N, 19.0. $C_{14}H_9N_3$ requires C, 76.7; H, 4.1; N, 19.2%); ν_{max} (KBr disk) 3178–2800 (NH), 1614 cm^{-1}; δ_H ($CDCl_3$) 7.62 (2H, m, H-2,3), 7.63 (1H, d, *J* 9, H-6), 7.81 (1H, d, *J* 9, H-5), 7.86 (1H, m, H-4), 8.26 (1H, s, H-7), 8.73 (1H, s, H-8), 9.20 (1H, m, H-1), 12.94 (1H, br s, NH).

Methylation of 10*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline 8

A solution of 10*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline **8** (1.72 g, 7.85 mmol) in nitrobenzene (25 cm^3) and xylene (12 cm^3) was heated to 130 °C and dimethyl sulfate (10 cm^3, excess) added and heating at 130 °C was continued for a further 10 min. The mixture was cooled to room temperature and then triturated onto rapidly stirred ether (~100 cm^3). The resultant orange precipitate was filtered, washed well with petroleum ether 60–80 °C and allowed to dry in air. TLC analysis of the solid (eluent: methanol–ethyl acetate–glacial acetic acid, 2 : 2 : 1) showed that it comprised of two compounds (R_f 0.79 and 0.13). Separation of the two compounds was achieved *via* flash chromatography (eluent: ethanol).

9-Methyl-10*H*-benzo[*h*]pyrazolo[3,4-*b*]quinolinium methyl sulfate 9. Yield 0.98 g, 36% δ_H (D_2O) 4.09 (3H, s, N^+CH_3), 7.27 (2H, m, H-3,4), 7.45 (1H, t, *J* 7, H-2), 7.59 (2H, m, H-5,6), 8.09 (1H, s, H-7), 8.25 (1H, d, *J* 8, H-1), 8.34 (1H, s, H-8); irradiation of N^+CH_3 protons (4.09 ppm) leads to the enhancement of the signal of H-8 (8.34 ppm); *m*/*z* (ESMS – positive ion mode) 234 (M^+), (ESMS – negative ion mode) 111 ($^-OSO_3CH_3$).

10-Methyl-10*H*-benzo[*h*]pyrazolo[3,4-*b*]quinolinium methyl sulfate 10. Yield 0.59 g, 22% δ_H (d_6-DMSO–35 °C) 4.36 (3H, s, N^+CH_3), 7.62 (1H, d, *J* 9, H-5), 7.72 (2H, m, H-2,3), 7.80 (1H, d, *J* 9, H-6), 7.92 (1H, m, H-4), 8.75 (1H, s, H-7), 8.88 (1H, s, H-8), 9.21 (1H, m, H-1); irradiation of N^+CH_3 protons (4.36 ppm) does not lead to the enhancement of any aromatic protons, confirming the placement of the methyl group on N-10; *m*/*z* (ESMS – positive ion mode) 234 (M^+), (ESMS – negative ion mode) 111 ($^-OSO_3CH_3$).

2-Chloro-3-[2-(*N*,*N*-dimethylamino)alkyliminomethyl]benzo-[*h*]quinolines 11,12

A solution of 2-chlorobenzo[*h*]quinoline-3-carbaldehyde **2** (3 g, 12 mmol) and the *N*,*N*-dimethylaminoalkylamine (13 mmol) in ethanol was refluxed for 4 h. After cooling and removal of the solvent under reduced pressure, the products were recrystallised from ethyl acetate–petroleum ether 60–80 °C.

2-Chloro-3-[2-(*N*,*N*-dimethylamino)ethyliminomethyl]benzo-[*h*]quinoline 11. Yield 2.81 g, 75%; mp 88.9–90.9 °C (Found C, 69.46; H, 5.83; N, 13.22. $C_{18}H_{18}N_3Cl$ requires C, 69.3; H, 5.8; N, 13.5%); ν_{max} (KBr) 1637 (C=N), 1056 (C–Cl) cm^{-1}; δ_H ($CDCl_3$) 2.29 (6H, s, CH_3 × 2), 2.66 (2H, t, *J* 7, CH_2), 3.81 (2H, t, *J* 7, =NCH_2), 7.64 (1H, d, *J* 8.91, H-5), 7.67 (2H, m, H-8,9), 7.73 (1H, d, *J* 8.91, H-6), 7.82 (1H, m, H-7), 8.76 (1H, s, H-4), 8.78 (1H, t, N=C-H), 9.11 (1H, m, H-10); *m*/*z* 312 (M^+ 100%).

2-Chloro-3-[3-(*N*,*N*-dimethylamino)propyliminomethyl]-benzo[*h*]quinoline 12. Yield 4.0 g, 100%; mp 89.7 °C (Found C, 70.26; H, 6.04; N, 12.86. $C_{19}H_{20}N_3Cl$ requires C, 70.0; H, 6.14; N, 12.9%); ν_{max} (KBr) 1637 (C=N), 1054 (C–Cl) cm^{-1}; δ_H ($CDCl_3$) 1.88 (2H, m, *J* 7, 7.3, 7.5, CH_2), 2.21 (6H, s, CH_3 × 2), 2.35 (2H, t, *J* 7.5, 7.6, CH_2N), 3.73 (2H, t, *J* 7, =NCH_2), 7.66 (1H, d, *J* 8.37, H-5), 7.67 (2H, m, H-8,9), 7.75 (1H, d, *J* 8.91, H-6), 7.85 (1H, m, H-7), 8.75 (1H, s, H-4), 8.78 (1H, t, N=C-H), 9.1 (1H, m, H-10); *m*/*z* 326 (M^+ 100%).

2-Chloro-3-[2-(*N*,*N*-dimethylamino)alkylaminomethyl]benzo-[*h*]quinoline dihydrochlorides 13,14

To a solution of the 2-chloro-3-[2-(*N*,*N*-dimethylamino)alkyl-

iminomethyl]benzo[*h*]quinoline **11**, **12** (3.2 mmol) in dry ethanol (20 cm^3) was added sodium borohydride (0.26 g, 6.8 mmol) and the mixture stirred for 48 h. Water was added to dissolve any excess sodium borohydride and the products extracted into dichloromethane and the organic layer dried ($MgSO_4$). Addition of ethereal hydrogen chloride precipitated out the hydrochloride salts which were recrystallised from ethanol–ethyl acetate.

2-Chloro-3-[2-(*N*,*N*-dimethylamino)ethylaminomethyl]benzo[*h*]quinoline dihydrochloride 13. Yellow needles (0.66 g, 52%); mp 204–209 °C (Found: C, 53.21; H, 5.73; N, 10.14. $C_{18}H_{20}N_3Cl{\cdot}2HCl{\cdot}H_2O$ requires C, 53.4; H, 5.9; N, 10.4%); ν_{max} (KBr) 3320 (N–H), 2699 (N^+–H), 1592 (N^+–H), 1056 (C–Cl) cm^{-1}; δ_H (DMSO) 2.9 (6H, s, $CH_3 \times 2$), 3.6 (4H, m, $N^+CH_2 \times 2$), 4.5 (2H, s, N^+CH_2Ar), 7.82 (2H, m, H-8,9), 7.90 (1 H, d, *J* 8.58, H-5), 8.09 (1H, d, *J* 7.26, H-6), 8.12 (1H, m, H-7), 8.87 (1H, s, H-4), 9.02 (1H, m, H-10), 10.11 (H, br s, N–H), 10.88 (1H, br s, N–H); *m*/*z* 314 (M^+ 100%).

2-Chloro-3-[3-(*N*,*N*-dimethylamino)propylaminomethyl]benzo[*h*]quinoline dihydrochloride 14. Yellow needle-like crystals (0.2 g, 15%); mp 205–207 °C (Found C, 54.34; H, 6.33; N, 9.91. $C_{19}H_{22}N_3Cl{\cdot}2HCl{\cdot}H_2O$ requires C, 54.5; H, 6.2; N, 10.0%); ν_{max} (KBr) 3394 (N–H), 3297 (N–H), 2711 (N^+–H), 1592 (N^+–H), 1056 (C–Cl) cm^{-1}; δ_H (DMSO) 2.2 (2H, m, CH_2), 2.75 (6H, s, $CH_3 \times 2$), 3.2 (4H, m, $2 \times CH_2N^+$), 4.50 (2H, s, N^+CH_2Ar), 7.82 (2H, m, H-8,9), 7.90 (1H, d, *J* 8.58, H-5), 8.09 (1H, d, *J* 8.58, H-6), 8.12 (1H, m, H-7), 8.88 (1H, s, H-4), 9.04 (1H, m, H-10), 9.84 (1H, br s, N–H), 10.61 (1H, br s, N–H); *m*/*z* 328 (M^+ 100%).

Diethyl 1-naphthylaminomethylenemalonate

A stirred mixture of 1-naphthylamine (10.0 g, 70 mmol) in diethyl ethoxymethylenemalonate (15.0 g, 70 mmol) was heated to 130 °C for a period of 2.75 h after which the solution was cooled to −70 °C. The solid (20.0 g, 91%) was filtered, washed well with petroleum ether 60–80 °C and left to dry. Recrystallisation from ethanol gave the product as white needles, mp 86–87 °C (lit.[20] 87.5–88.0 °C); ν_{max} (KBr disk) 1683 (CO), 1643 (CO) cm^{-1}; δ_H ($CDCl_3$) 1.35 (3H, t, *J* 8, CH_3), 1.43 (3H, t, *J* 8, CH_3), 4.28 (2H, q, *J* 8, CH_2), 4.39 (2H, q, *J* 8, CH_2), 7.35 (1H, d, *J* 7, H-2), 7.48 (1H, t, *J* 8, H-3), 7.58 (2H, m, H-6,7), 7.70 (1H, d, *J* 8, H-4), 7.88 (1H, dd, *J* 8 and 3, H-5), 8.04 (1H, d, *J* 8, H-8), 8.67 (1H, d, *J* 14, NCH=C), 11.49 (1H, br d, *J* 14, NH).

Ethyl 4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate 15

To stirred Dowtherm 'A' (50 cm^3) at 255 °C was added diethyl 1-naphthylaminomethylenemalonate (10.0 g, 32 mmol), and heating was continued at 255 °C for 30 min. The mixture was allowed to cool to room temperature and stand for 30 min. The resulting solid (6.64 g, 78%) was filtered, washed with petroleum ether 60–80 °C and dried in an oven. Recrystallisation from glacial acetic acid afforded the title compound **15** as white needles, mp 258–260 °C (lit.[20] 261–262 °C); ν_{max} (KBr disk) 2923, 1708 (ester CO), 1635 (amide CO) cm^{-1}; δ_H (d_6-DMSO) 1.42 (3H, t, *J* 7, CH_3), 4.38 (2H, q, *J* 7, CH_2), 7.88 (2H, m, H-8,9), 7.94 (1H, d, *J* 9, H-6), 8.16 (1H, m, H-7), 8.29 (1H, d, *J* 9, H-5), 8.64 (1H, br s, H-2), 8.78 (1H, br s, H-10).

Ethyl 4-chlorobenzo[*h*]quinoline-3-carboxylate 16

A stirred solution of ethyl 4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate **15** (500 mg, 1.9 mmol) in $POCl_3$ (0.3 cm^3, 3.2 mmol) was heated to 90 °C for a period of 25 min. After this time, the mixture was cooled and poured into a 10% ammonium hydroxide solution (30 cm^3) while being kept cool by the addition of crushed ice to the solution. The aqueous solution was then extracted with ether (4×50 cm^3), dried ($MgSO_4$) and the ether was removed under reduced pressure to give an off white solid (452 mg, 85%). Recrystallisation from petroleum ether 60–80 °C gave the title compound **16** as a white solid, mp 119–120 °C (lit.[22] 120–121 °C); ν_{max} (KBr disk) 1725 (CO), 1241, 1168 cm^{-1}; δ_H ($CDCl_3$) 1.46 (3H, t, *J* 7, CH_3), 4.52 (2H, q, *J* 7, CH_2), 7.80 (2H, m, H-8,9), 7.94 (2H, m, H-6,7), 8.27 (1H, d, *J* 9, H-5), 9.30 (1H, m, H-10), 9.31 (1H, s, H-2); *m*/*z* 286 (M^+ 100%).

Reduction of ethyl 4-chlorobenzo[*h*]quinoline-3-carboxylate 16 with diisobutyl aluminium hydride (DIBAL-H)

A stirred solution of ethyl 4-chlorobenzo[*h*]quinoline-3-carboxylate **16** (1.0 g, 3.5 mmol) and dichloromethane (5 cm^3) was cooled to −70 °C in dry glassware while under an inert nitrogen atmosphere. To the cooled solution was added DIBAL-H [1.0 M solution in dichloromethane] (3.8 cm^3, 3.8 mmol) and the reaction was left for 2 h. After this time 4 drops of glacial acetic acid were added to deactivate the DIBAL-H and the reaction was allowed to warm to room temperature. Saturated ammonium chloride solution (100 cm^3) was added to the reaction which was extracted with dichloromethane (4×50 cm^3), the organic aliquots combined, washed well with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow solid. Analysis of the solid *via* TLC (solvent: ethyl acetate–petroleum ether 60–80 °C, 1 : 1) showed that it was composed of two compounds which were separated by flash chromatography (eluent: ethyl acetate–petroleum ether 60–80 °C, 1 : 5).

4-Chlorobenzo[*h*]quinoline-3-carbaldehyde 17. Yield 319 mg, 39%, mp 195–196 °C (Found C, 69.6; H, 3.0; N, 5.8. $C_{14}H_8ClNO$ requires C, 69.6; H, 3.3; N, 5.8%); ν_{max} (KBr disk) 1685 (CO), 1577, 798 (C–Cl) cm^{-1}; δ_H ($CDCl_3$) 7.82 (2H, m, H-8,9), 7.97 (1H, m, H-7), 8.01 (1H, d, *J* 11, H-6), 8.23 (1H, d, *J* 11, H-5), 9.34 (1H, m, H-10), 9.36 (1H, s, H-2), 10.76 (1H, s, CHO); *m*/*z* 242 (M^+ 100%).

4-Chloro-3-hydroxymethylbenzo[*h*]quinoline. White needles (80 mg, 9%), mp 173–175 °C (Found C, 68.8; H, 4.0; N, 5.7. $C_{14}H_{10}ClNO$ requires C, 69.0; H, 4.1; N, 5.75%); ν_{max} (KBr disk) 3400–3200 (br, OH), 1400, 1085 cm^{-1}; δ_H ($CDCl_3$) 5.07 (2H, s, CH_2), 7.75 (2H, m, H-8,9), 7.93 (2H, m, H-6,7), 8.16 (1H, d, *J* 8, H-5), 9.05 (1H, s, H-2), 9.28 (1H, m, H-10); *m*/*z* 244 (M^+ 100%).

4-Chlorobenzo[*h*]quinoline-3-carbaldehyde 17

To 4-chloro-3-hydroxymethylbenzo[*h*]quinoline (1.75 g, 7.2 mmol) in dichloromethane (150 cm^3) was added activated manganese(IV) oxide (10.0 g, excess) and the solution stirred at room temperature for 30 min. The manganese(IV) oxide was then removed from the solution *via* filtration and washed well with dichloromethane. The dichloromethane was removed under reduced pressure to give a pale yellow solid (1.23 g, 71%). Recrystallisation from ethyl acetate–petroleum ether 60–80 °C gave the title compound **17** as pale yellow needles, mp 195–196 °C.

4-Chloro-3-(1,3-dioxolan-2-yl)benzo[*h*]quinoline

A solution of 4-chlorobenzo[*h*]quinoline-3-carboxylate **17** (1.18 g, 4.9 mmol) in toluene (50 cm^3) containing ethylene glycol (0.82 cm^3, 14.7 mmol) and a trace amount of toluene-*p*-sulfonic acid was heated under reflux for 10 h using a Dean–Stark water separator. The cooled solution was treated with saturated aqueous sodium carbonate (50 cm^3), washed well with several aliquots of water, dried ($MgSO_4$), and evaporated to leave an orange solid. Analysis of the solid *via* TLC (solvent system ethyl acetate–petroleum ether 60–80 °C, 1 : 1) showed the solid to contain one major spot (R_f 0.74) and two minor spots (R_f 0.83 and 0.61). Flash chromatography (eluent ethyl acetate–

petroleum ether 60–80 °C, 1 : 5) isolated the title compound as a white solid (740 mg, 53%). Recrystallisation from ethyl acetate–petroleum ether 60–80 °C gave the title compound as white needles, mp 110.8–111.8 °C (Found C, 67.4; H, 3.9; N, 4.9. $C_{16}H_{12}ClNO_2$ requires C, 67.3; H, 4.2; N, 4.9%); ν_{max} (KBr disk) 1390, 1110, 927 cm^{-1}; δ_H ($CDCl_3$) 4.15 (4H, m, 2 × CH_2), 6.38 (1H, s, CH), 7.68 (2H, m, H-8,9), 7.85 (2H, m, H-6,7), 8.11 (1H, d, *J* 11, H-5), 9.05 (1H, s, H-2), 9.23 (1H, m, H-10).

3-Methyl-3*H*-benzo[*h*]pyrazolo[4,3-*c*]quinoline

A solution of 4-chloro-3-(1,3-dioxolan-2-yl)benzo[*h*]quinoline (0.73 g, 2.6 mmol) in *N*-methylhydrazine (2 cm^3, excess) was refluxed under nitrogen for 4 h. *N*-Methylhydrazine was removed under reduced pressure to leave a brown oil. To this oil was added ethanol (20 cm^3) and 2 M HCl (10 cm^3, excess) and the mixture was refluxed for 15 min. The cooled solution was poured onto a stirred solution of 2 M NaOH (~50 cm^3) and the white precipitate was filtered, washed well with water and left to dry in air. The product (449 mg, 75%) was isolated *via* flash chromatography using an ethyl acetate–petroleum ether, 60–80 °C, 2 : 3, eluent system. Recrystallisation from ethyl acetate–petroleum ether 60–80 °C gave the title compound as white needles, mp 155–156 °C (Found C, 77.3; H, 4.5; N, 17.9. $C_{15}H_{11}N_3$ requires C, 77.2; H, 4.75; N, 18.0%); ν_{max} (KBr disk) 2942 (NCH_3), 1583 cm^{-1}; δ_H ($CDCl_3$) 4.59 (3H, s, NCH_3), 7.74 (2H, m, H-7,8), 7.97 (1H, dd, *J* 9 and 1, H-6), 7.99 (1H, d, *J* 9, H-5), 8.23 (1H, s, H-1), 8.38 (1H, d, *J* 9, H-4), 9.33 (1H, s, H-11), 9.42 (1H, d, *J* 9, H-9). An NOE experiment irradiating the NCH_3 protons (4.59 ppm) leads to an enhancement of H-6 (8.38 ppm) in the aromatic region, confirming the position of the *N*-methyl group in the cyclised product.

2,3-Dimethyl-3*H*-benzo[*h*]pyrazolo[4,3-*c*]quinolinium methyl sulfate 18

A solution of 3-methyl-3*H*-benzo[*h*]pyrazolo[4,3-*c*]quinoline (508 mg, 2.2 mmol) in nitrobenzene (15 cm^3) and xylene (8 cm^3) was heated to 130 °C. To the heated solution was added dimethyl sulfate (8 cm^3, excess) and the solution was heated for a further 15 min. After this period the product (459 mg, 59%) was filtered, washed with ether and allowed to dry. Recrystallisation from methanol–acetonitrile afforded the title compound **18** as white needles, mp 264–266 °C (Found C, 57.0; H, 4.9; N, 11.5. $C_{17}H_{17}N_3O_4S$ requires C, 56.8; H, 4.8; N, 11.7%); ν_{max} (KBr disk) 3004 and 2958 (NCH_3), 1643, 1253 and 1214 (SO) cm^{-1}; δ_H (CF_3CO_2D) 4.77 (3H, s, NCH_3), 4.91 (3H, s, N^+CH_3), 8.12 (2H, m, H-7,8), 8.31 (1H, m, H-6), 8.59 (1H, d, *J* 9, H-5), 8.72 (1H, d, *J* 9, H-4), 8.94 (1H, m, H-9), 9.85 (1H, s, H-11), 10.26 (1H, s, H-1).

2-Hydroxyethyl 4-chlorobenzo[*h*]quinoline-3-carboxylate 19

A mixture of ethyl 4-chlorobenzo[*h*]quinoline-3-carboxylate **16** (1.0 mg, 3.5 mmol) and guanidine carbonate (648 mg, 3.6 mmol) in ethylene glycol (10 cm^3, excess) was heated to 50 °C for 5 h, after which the white precipitate (473 mg, 45%) was filtered, washed well with water and dried. Recrystallisation from ethyl acetate–petroleum ether 60–80 °C gave white needles of 2-hydroxyethyl 4-chlorobenzo[*h*]quinoline-3-carboxylate **19**, mp 151–153 °C (Found C, 63.8; H, 3.9; N, 4.6. $C_{16}H_{12}ClNO_3$ requires C, 63.8; H, 4.0; N, 4.65%); ν_{max} (KBr disk) 3471 (OH), 1720 (CO), 1243 cm^{-1}; δ_H ($CDCl_3$) 4.04 (2H, t, *J* 5, CH_2), 4.60 (2H, t, *J* 5, CH_2), 7.78 (2H, m, H-8,9), 7.95 (2H, m, H-6,7), 8.25 (1H, d, *J* 9, H-5), 9.30 (1H, m, H-10), 9.32 (1H, s, H-2); *m*/*z* 301 (M^+ 57%), 257 ($M^+ - 44$, 60), 240 ($M^+ - 61$, 100), 212 ($M^+ - 89$, 60). The filtrate was washed several times with water, dried ($MgSO_4$) and the ethylene glycol was removed under reduced pressure to leave a white solid (432 mg, 43%) which was confirmed as starting material *via* its melting point (114–117 °C) and IR analysis.

Ethyl 4-[2-(*N*,*N*-dimethylamino)alkylamino]benzo[*h*]quinoline-3-carboxylate hydrochlorides 20, 21

A mixture of ethyl 4-chlorobenzo[*h*]quinoline-3-carboxylate **16** (500 mg, 1.75 mmol) and *N*,*N*-dimethylaminoalkylamine (5 cm^3) was stirred at room temperature for a period of 1 h. Dichloromethane (30 cm^3) was added to the reaction mixture and the organic layer was washed well with saturated sodium carbonate solution (5 × 20 cm^3). The organic layer was then dried ($MgSO_4$) and an excess of ethereal hydrogen chloride was added until the hydrochloride salts of the final products precipitated out of solution. Recrystallisation from methanol–ethyl acetate gave the title compounds.

Ethyl 4-[2-(*N*,*N*-dimethylamino)ethylamino]benzo[*h*]quinoline-3-carboxylate hydrochloride 20. White needles (587 mg, 90%), mp 125 °C (softens) (Found C, 55.9; H, 6.8; N, 9.75. $C_{20}H_{24}ClN_3O_2 \cdot 3H_2O$ requires C, 56.1; H, 7.1; N, 9.8%); ν_{max} (KBr disk) 3415 (NH), 3056 and 2958 (CH), 1687 (CO) cm^{-1}; δ_H (D_2O) 1.35 (3H, t, *J* 7, $CO_2CH_2CH_3$), 2.82 (6H, s, $N(CH_3)_2$), 3.53 (2H, t, *J* 6, CH_2), 4.16 (2H, t, *J* 6, CH_2), 4.37 (2H, q, *J* 7, $CO_2CH_2CH_3$), 7.65 (2H, m, H-8,9), 7.69 (1H, d, *J* 8, H-7), 7.74 (1H, d, *J* 8, H-6), 7.81 (1H, d, *J* 7, H-5), 8.10 (1H, d, *J* 7, H-10), 8.54 (1H, s, H-2); *m*/*z* 338 (M^+ 100%).

Ethyl 4-[3-(*N*,*N*-dimethylamino)propylamino]benzo[*h*]quinoline-3-carboxylate hydrochloride 21. White needles (539 mg, 79%), mp 195–196 °C (Found C, 55.0; H, 7.2; N, 9.1. $C_{21}H_{26}ClN_3O_2 \cdot 4H_2O$ requires C, 54.8; H, 7.5; N, 9.1%); ν_{max} (KBr disk) 3409 (NH), 3050 and 2965 (CH), 1689 (CO) cm^{-1}; δ_H (D_2O) 1.39 (3H, t, *J* 7, $CO_2CH_2CH_3$), 2.16 (2H, t, *J* 6, CH_2), 2.89 (6H, s, $N(CH_3)_2$), 3.22 (2H, t, *J* 6, CH_2), 3.74 (2H, br t, *J* 6, CH_2), 4.33 (2H, q, *J* 7, $CO_2CH_2CH_3$), 7.59 (5H, m, H-5–9), 7.87 (1H, d, *J* 8, H-10), 8.17 (1H, s, H-2); *m*/*z* 352 (M^+ 100%).

Ethyl 4-methoxybenzo[*h*]quinoline-3-carboxylate 22

A stirred solution of ethyl 4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate **15** (2.0 g, 7.5 mmol), anhydrous potassium carbonate (1.5 g, excess) in acetone (10 cm^3) and dimethyl sulfate (700 μl, 7.5 mmol) was heated to reflux for 24 h, cooled to room temperature, and the acetone removed under reduced pressure. The remaining solid was filtered, washed well with petroleum ether 60–80 °C, water and dried. Flash chromatography (eluent: ethyl acetate–petroleum ether 60–80 °C, 1 : 4) revealed starting material (41 mg, mp 258–261 °C) and white needles (486 mg, 23%) which were recrystallised from ethyl acetate–petroleum ether 60–80 °C and identified as ethyl 4-methoxybenzo[*h*]-quinoline-3-carboxylate **22**, mp 53–54 °C (Found C, 72.75; H, 5.3; N, 5.1. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%); ν_{max} (KBr disk) 2973 and 2846 (CH), 1724 (CO), 1579, 1309 cm^{-1}; δ_H ($CDCl_3$) 1.48 (3H, t, *J* 5, CH_3), 4.16 (3H, s, OCH_3), 4.50 (2H, q, *J* 5, CH_2), 7.74 (2H, m, H-8,9), 7.86 (1H, d, *J* 8, H-6), 7.93 (1H, m, H-7), 8.14 (1H, d, *J* 8, H-5), 9.28 (1H, m, H-10), 9.32 (1H, s, H-2); *m*/*z* (EIMS) 281 (M^+); an NOE difference experiment confirmed the placement of the methyl on the oxygen due to irradiation of the methyl protons (4.16 ppm) enhancing the signal of H-5 at 8.14 ppm.

Ethyl 1-methyl-4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate 23

Using dry glassware, ethyl 4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate **15** (2.0 g, 7.5 mmol) and dry toluene (10 cm^3) were cooled to 0 °C in an ice bath and sodium hydride (60% dispersion with mineral oil, 900 mg, 22.5 mmol) was added slowly. The reaction was stirred at 0 °C for 10 min and then allowed to warm to room temperature. After 15 min methyl iodide (3.5 cm^3, excess) was added and then heated to 50 °C for 16 h. The reaction was cooled to room temperature and water was carefully added until no further effervescence was

observed. The solution was extracted with dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to leave ethyl 1-methyl-4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate **23** (1.81 g, 86%). Recrystallisation from ethyl acetate–petroleum ether 60–80 °C afforded the product as white needles, mp 143–145 °C (Found C, 72.6; H, 5.3; N, 5.0. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%); ν_{max} (KBr disk) 2923 and 2854 (CH), 1685 (CO), 1619, 1213 cm^{-1}; δ_H ($CDCl_3$) 1.40 (3H, t, *J* 7, CH_2CH_3), 4.27 (3H, s, NCH_3), 4.37 (2H, q, *J* 7, CH_2CH_3), 7.59 (2H, m, H-8,9), 7.69 (1H, d, *J* 8, H-7), 7.90 (1H, dd, *J* 8 and 2, H-6), 8.39 (1H, d, *J* 8, H-5), 8.42 (1H, d, *J* 9, H-10), 8.46 (1H, s, H-2); δ_C 14.38, 29.63, 47.68, 60.89, 112.97, 122.83, 123.98, 125.22, 125.63, 126.38, 127.92, 129.23, 136.62, 139.10, 151.02, 165.34 (CO), 173.39 (CO); *m*/*z* (EI) 281 (M^+ 100%). NOE difference experiments confirm the placement of the methyl on the nitrogen; irradiation of the methyl singlet (4.27 ppm) enhances the signals of H-10 and H-2 at 8.42 and 8.46 ppm respectively.

1-Methyl-3-hydrazinocarbonyl-4-oxo-1,4-dihydrobenzo[*h*]-quinoline 24

A mixture of ethyl 1-methyl-4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate **23** (2.0 g, 7.1 mmol) and hydrazine monohydrate (10 cm^3, excess) were heated to reflux for 30 min, after which the mixture was cooled and basified with saturated Na_2CO_3 solution. The resulting solid (1.76 g, 93%) was filtered, washed well with water and left to dry. Recrystallisation from ethanol afforded the product 1-methyl-3-hydrazinocarbonyl-4-oxo-1,4-dihydrobenzo[*h*]quinoline **24** as off-white needles, mp 235–237 °C (decomp.) (Found C, 67.2; H, 4.85; N, 15.5. $C_{15}H_{13}N_3O_2$ requires C, 67.4; H, 4.9; N, 15.7%); ν_{max} (KBr disk) ~3300 (br, NH), 2923 and 2854 (CH), 1666 (CO) cm^{-1}; δ_H (d_6-DMSO, 50 °C) 4.43 (3H, s, NCH_3), 4.59 (2H, br s, NH_2, D_2O exchangeable), 7.72 (2H, m, H-8,9), 7.91 (1H, d, *J* 9, H-7), 8.08 (1H, d, *J* 9, H-6), 8.29 (1H, d, *J* 9, H-5), 8.75 (1H, d, *J* 9, H-10), 8.80 (1H, s, H-2), 10.76 (1H, br s, NH, D_2O exchangeable); δ_C (d_6-DMSO, 50 °C) 48.00 (N*C*H_3), 112.30, 121.39, 125.66, 125.95, 126.13, 126.28, 128.27, 128.79, 136.08, 139.15, 149.49, 163.15 (CO), 173.91 (CO).

Attempted cyclisation of 1-methyl-3-hydrazinocarbonyl-4-oxo-1,4-dihydrobenzo[*h*]quinoline 24

1-Methyl-3-hydrazinocarbonyl-4-oxo-1,4-dihydrobenzo[*h*]-quinoline **24** (500 mg, 1.9 mmol) was heated to reflux in $POCl_3$ (4.0 cm^3, excess) and after 1 h the mixture was cooled to room temperature. The cooled mixture was poured onto ice–water and basified with ~50 cm^3 of saturated Na_2CO_3. Upon addition of NH_4PF_6 (305 mg, 1.9 mmol) a deep red solid (419 mg) precipitated out of solution which was collected by vacuum filtration and allowed to dry. The TLC of the solid (eluent: methanol–ethyl actetate–glacial acetic acid, 2:2:1) showed only a baseline orange spot. The IR spectrum indicated that a hexafluorophosphate salt may be present (844 cm^{-1}), however, the NMR spectrum in CF_3CO_2D was far too impure to characterise the compound. Attempted purification *via* recrystallisation in many different solvents failed to improve the purity of the compound significantly enough to allow the structure of the product to be determined.

Ethyl 1-methyl-4-hydroxy-2-(ethoxycarbonylmethyl)-1,2-dihydrobenzo[*h*]quinoline-3-carboxylate 25

A stirred solution of ethyl 1-methyl-4-oxo-1,4-dihydrobenzo[*h*]-quinoline-3-carboxylate (**23**) (200 mg, 0.71 mmol) and ethyl acetoacetate (92 mg, 0.71 mmol) in dry ether was cooled to 0 °C with the aid of an ice bath. Sodium hydride (60% dispersion in mineral oil, 100 mg, excess) was added carefully and allowed to stir for 10 min, before toluene (10 cm^3) was added and the temperature was raised to 100 °C for 20 h. The reaction was cooled to room temperature and water (50 cm^3) was added cautiously to the reaction until effervescence ceased. The aqueous layer was extracted with ether, dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a bright green oil. The oil was purified by flash chromatography (eluent: ethyl acetate–petroleum ether 60–80 °C, 2:3) and identified as ethyl 1-methyl-4-hydroxy-2-(ethoxycarbonylmethyl)-1,2-dihydrobenzo[*h*]-quinoline-3-carboxylate **25** (180 mg, 67%). A sample was prepared for analysis by distillation using Kugelröhr apparatus (bp 200 °C/0.02 mbar). ν_{max} (NaCl disk) 3060–2931 (CH), 1733 (CO), 1643 (CO), 1344 cm^{-1}; δ_H ($CDCl_3$) 1.19 (3H, t, *J* 8, CH_2CH_3), 1.39 (3H, t, *J* 8, CH_2CH_3), 2.39 (2H, dd, *J* 8 and 2, $NCHCH_2CO$), 2.95 (3H, s, NCH_3), 4.14 (2H, q, *J* 8, CH_2CH_3), 4.34 (2H, dq, *J* 8 and 3, CH_2CH_3), 4.67 (1H, dd, *J* 9 and 7, $NCHCH_2$), 7.50 (2H, m, H-8,9), 7.57 (1H, d, *J* 9, H-7), 7.81 (1H, m, H-5), 7.83 (1H, d, *J* 9, H-6), 8.11 (1H, m, H-10), 12.25 (1H, br s, OH - D_2O exchangeable); *m*/*z* 369.1570, $C_{21}H_{23}NO_5$ requires 369.1576; a 2D-COSY NMR experiment confirmed the structure of the product.

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Paper 9/03402A