Pergamon

Tetrahedron Vol. 50, No. 26, pp. 7879-7888, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00392-0

Synthesis of a 1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline

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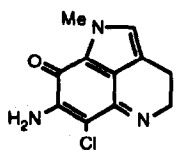
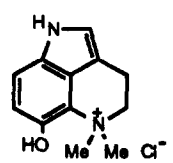
Key Words: Damirones; batzellines; isobatzellines; dehydrobufotenine; 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline.

Abstract: 6-Methoxy-4-methylquinoline was converted into 8-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline by a six reaction sequence in which the last step was the formation of the indole ring.

	R^1	R^2
damirone B	H	H
batzelline C	Cl	Me



isobatzelline C



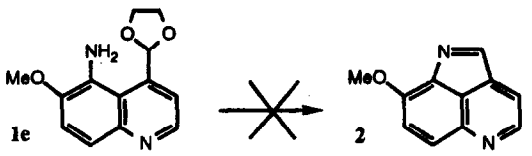
dehydrobufotenine chloride

The 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system was first recognised as a component of a natural product when the structure of the toad poison, dehydrobufotenine was elucidated.[1] Much more recently, several marine alkaloids[2] such as the tricyclic batzellines,[3] isobatzellines,[4] and damirones,[5] (the simplest example from each of these groups is shown above) and more complex molecules such as the discorhabdines,[6] and prianosines,[7] wayakin,[8] the makaluvamines,[9] and the fungal substance, haematopodin,[10] have been described which are also based on a 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus.

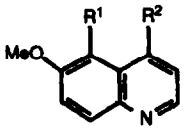
In most of the synthetic work so far described, relating to these natural products, including preparations of the unsubstituted-[11,12] and 1-methyl-[13] tricyclic system, of *O*-methylnordehydrobufotenine,[14] of dehydrobufotenine itself[15], and then later of batzelline C and isobatzelline C,[16] discorhabdin C,[17] and damirones A and B,[18] and the makaluvamines,[19] the tricyclic heterocycle has been constructed *from an indole*, *i.e.* by forming the six-membered nitrogen-containing ring as a late step, by cyclisation either of a 4-aminoindole carrying a two-carbon chain at its C-3,[12-17,19] or of a tryptamine quinone.[18] We are investigating an alternative strategy in which a quinoline is used as a starting point, and have given a preliminary report of one route,[20] and a full description[21] of another; here we document the detail of the former.

6-Methoxy-4-methylquinoline[22] was chosen as a suitable starting material in having both a carbon (the methyl) for the production of the pyrrole ring, and a methoxy at the position at which the natural targets are oxygenated and which we hoped would direct nitration to the desired position, for the introduction of the future pyrrole nitrogen atom, and indeed low temperature nitration did produce 6-methoxy-5-nitro-4-methylquinoline, **1a**, cleanly and efficiently.[23]

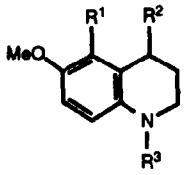
The formation of a fused pyrrole required conversion of the quinoline 4-methyl to the oxidation level of aldehyde. Although selenium dioxide has been used in the past for this purpose, we found that the oxidation of **1a** by Vismara's method[24] produced the corresponding aldehyde, **1b**, efficiently. Before attempting any adjustment of ring oxidation levels, the aldehyde was protected, as an acetal: **1c** and **1d** were prepared, the latter because the former proved more difficult to hydrolyse selectively at a later stage (see however below). Hydrogenation of the ethylene acetal **1c** gave amine **1e**, but all attempts to bring about five-membered ring formation by releasing the aldehyde failed, complex dark-coloured materials being produced. In all of our work in this series we have found it impossible to produce tricyclic materials of the type, **2**; it seems that such structures are too unstable to be isolable. We also failed in various attempts to produce 1,2-dihydro-**2**, for example attempts to achieve a nitrene insertion into a 4-methyl were not successful.



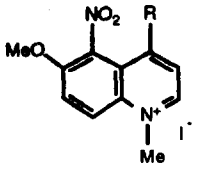
Reduction of the ethylene acetal with sodium cyanoborohydride in acetic acid resulted in saturation of the heterocyclic ring and the formation of **3a** and **3b**; longer reaction times led to the formation of increased quantities of the corresponding *N*-ethyl product **3b**.[25] Comparable reduction in formic acid produced *N*-methyl-derivative **3c** and catalytic reduction of this gave *N*-methylated acetal-amine **3d**, but this could be produced more conveniently as described below. Initial experiments with this acetal, using aqueous acid and aimed at releasing the aldehyde for pyrrole ring formation, met with no success, dark-coloured mixtures being produced. Because this suggested that the conditions necessary for hydrolysing the ethylene acetal were detrimental to the final product, we turned to the use of a more easily hydrolysed acetal – the dimethyl acetal.



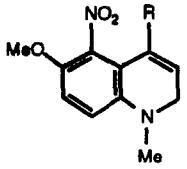
1a $R^1 = NO_2$, $R^2 = CH_3$
1b $R^1 = NO_2$, $R^2 = CHO$
1c $R^1 = NO_2$, $R^2 = CH(OCH_2)_2$
1d $R^1 = NO_2$, $R^2 = CH(OMe)_2$
1e $R^1 = NH_2$, $R^2 = CH(OCH_2)_2$
1d $R^1 = NHAc$, $R^2 = CH(OCH_2)_2$



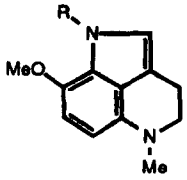
3a $R^1 = NO_2$, $R^2 = CH(OCH_2)_2$, $R^3 = H$
3b $R^1 = NO_2$, $R^2 = CH(OCH_2)_2$, $R^3 = Et$
3c $R^1 = NO_2$, $R^2 = CH(OCH_2)_2$, $R^3 = Me$
3d $R^1 = NH_2$, $R^2 = CH(OCH_2)_2$, $R^3 = Me$
3e $R^1 = NHAc$, $R^2 = CH(OCH_2)_2$, $R^3 = Me$
3f $R^1 = NHTs$, $R^2 = CH(OCH_2)_2$, $R^3 = Me$
3g $R^1 = NH_2$ $R^2 = CH(OMe)_2$ $R^3 = Me$



4a R= $CH(OCH_2)_2$
4b R= $CH(OMe)_2$

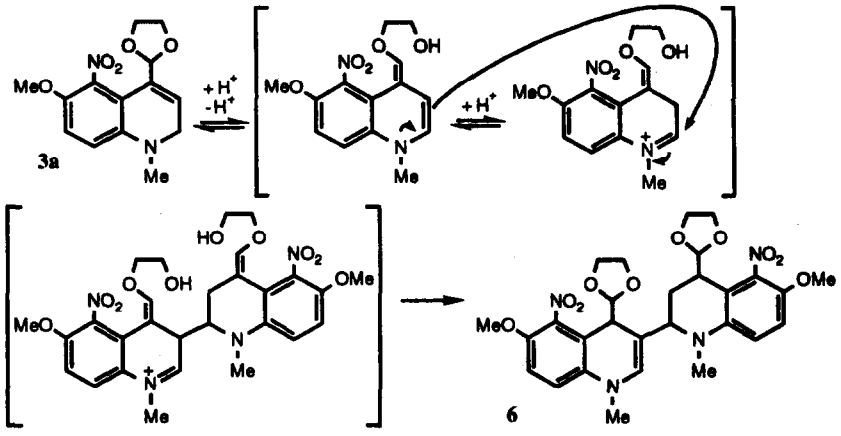


5a R= $CH(OCH_2)_2$
5b R= $CH(OMe)_2$



7a R=H
7b R=Ts

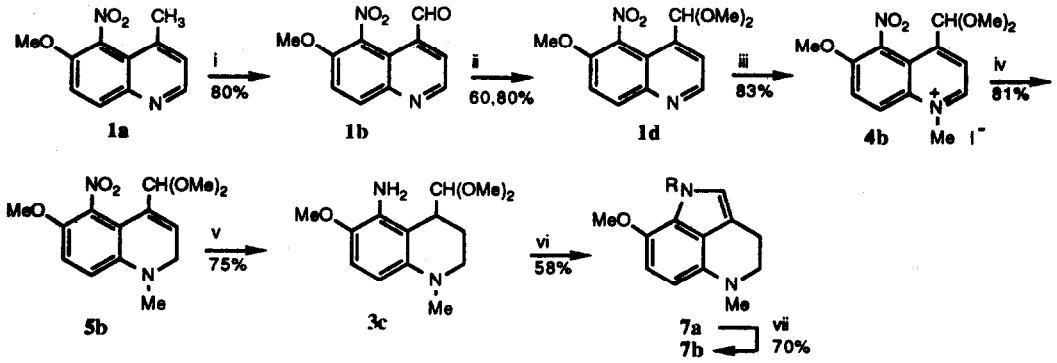
Each of the two acetals was quaternised by reaction with iodomethane giving salts **4a** and **b**. Exposure of salt **4a** to borohydride afforded a dihydro-derivative which was shown to have structure **5a** by ^{1}H-NMR analysis, specifically that the acetal methine was a singlet, showing the double bond to be located at the 3,4-position. On one ocasion, chromatographic purification of this substance over silica gel resulted in its loss and the formation of a dimeric material, **6**. Acid-catalysed dimerisation of 1,4-dihydroquinolines is a well recognised process,[26] but the isomerisation[27] of 1,2- to 1,4-dihydroquinolines generally requires rather vigorous conditions. In the present situation one can picture isomerisation of the ring double bond as involving proton-catalysed elimination of acetal oxygen, followed by dimerisation, and finally reclosure of the acetal (Scheme 1).



Scheme 1

Reduction of the methiodide, **4b**, of the dimethyl acetal, also produced a 1,2-dihydro-derivative, **5b**. Catalytic reduction of each of the dihydroquinolines achieved two desirable objectives: saturation of both the quinoline 3,4-double bond *and* reduction of the nitro group, and thus formation of amines **3d**, and **3g**. The scene was now set for the deprotection of the aldehyde and intramolecular interaction with the amine function to produce the pyrrole ring: the acetal-amines were rather unstable in chloroform solution and were therefore used directly for this purpose.

Hydrolysis of the dimethyl acetal was easier than that of the ethylene acetal, the optimum conditions being *p*-toluenesulfonic acid in hot THF, when the indole **7a** was isolated in 58% yield. After some experimentation, it was found that the ethylene acetal could be converted, less efficiently, into this same product, using comparble conditions. The electron-rich indole, carrying as it does amino and alkoxy substituents, was found to be rather sensitive, but could be cleanly characterised as its *N*-tosyl derivative **7b**. The preferred route is summarised in Scheme 2.



Scheme 2. Reagents: i, I_2, *t*-BuI, $FeCl_2.4H_2O$ TFA, DMSO, 80°C; ii, $HC(OMe)_3$/MeOH/reflux or dry HCl/MeOH/reflux; iii, MeI/MeCN/50°C; iv, $NaBH_4$/MeOH/20°C; v, H_2/Pt-C/20°C; vi, aq. 1N HCl/THF/40 °C/24 h or *p*-TsOH/THF/reflux/3 h; vii, $TsCl/CH_2Cl_2/Bu_4N^+ HO^-$.

ACKNOWLEDGEMENTS

We thank the Royal Swedish Academy of Sciences, the Wenner-Gren Center Foundation, the Royal Society, UK (LV), and CIRIT, Generalitat de Catalunya (QF N 92-4315), Spain for generous financial support.

EXPERIMENTAL

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer, or when indicated, on a Brüker AC-300 instruments; chemical shifts are reported in ppm downfield (d) from Me_4Si as internal standard. IR spectra were taken with a Perkin-Elmer 1430 or Nicolet 205 spectrophotometer and only noteworthy absortions (cm^{-1}) are listed. Low resolution mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer and high-resolution measurements made on a MS-9 AEI mass spectrometer updated by VG. TLC was carried out on SiO_2 (silica Gel 60 F254, Merck 0.063-0.200 mm); the spots were located with iodoplatinate reagent or UV light. Column chromatography was carried out on SiO_2 (silica gel 60, SDS 0.060-0.2 mm); flash chromatography was carried out on SiO_2 (silica gel 60, 60, SDS 0.040-0.060 mm). Organic extracts were dried over anhydrous Na_2SO_4.

6-Methoxy-4-methylquinoline. A solution of $FeCl_3.6H_2O$ (5.4 g, 20 mmol) and *p*-anisidine (1.23 g, 10 mmol) in AcOH (32 ml) was heated to 55-70°C while methyl vinyl ketone (0.74 g, 0.88 ml, 10.5 mmol) was added during 5 min. After refluxing for 3 h and standing at room temperature overnight the solvent was removed under vaccuum, the residue made basic with aq. NaOH (50%) and then the H_2O removed by evaporation under water-pump vaccuum. The resulting solid was extracted with CH_2Cl_2 (6x40 ml), the combined extracts filtered through a pad of celite, the filtrate washed with aq. K_2CO_3 (10%), dried and evaporated to give the crude quinoline (1.13 g) as an oil, which solidifed, but was further purified by chromatography over silica (hexane/EtOAc; 1:2) producing pure 6-methoxy-4-methylquinoline (1.0 g, 58%).

4-Formyl-6-methoxy-5-nitroquinoline (1b). To a solution of 4-methyl-6-methoxy-5-nitroquinoline[23] (500 mg, 2.29 mmol) in DMSO (20 ml) F_3CCO_2H (314 mg, 2.75 mmol), I_2 (600 mg, 2.36 mmol), *t*-BuI (170 mg, 0.92 mmol) and $FeCl_2.4H_2O$ (catalytic amount) under nitrogen. The mixture was stirred for 6 h at 80 °C, diluted

with H_2O (60 ml) and saturated $Na_2S_2O_3$ (5 ml) was added. The resulting solution was basified with $NaHCO_3$ and extracted with EtOAc. The organic solution was washed with H_2O, dried and evaporated to give **1b** (432 mg, 80%) of **1b**: ν_{max} (KBr): 1708, 1530; δ_H (200 MHz, $CDCl_3$): 4.12 (s, 3H, OCH_3), 7.70 (d, J=9.5 Hz, 1H, H-7), 7.87 (d, J=4.3 Hz, 1H, H-3), 8.42 (d, J=9.5 Hz, 1H, H-8), 9.07 (d, J=4.3 Hz, 1H, H-2), 10.26 (s, 1H, CHO); δ_C (200 MHz, $CDCl_3$): 63.14 (q, CH_3), 122.88 (d, C-7), 130.17 (d, C-8), 140.81 (d, C-3), 154.68 (d, C-2), 195.5 (d, CHO); *m/z* (e.i.) 232 (M, 12%), 218 (100%), 201 (58%), 186 (30%), 171 (22%), 157 (24%), 142 (36%), 128 (43%), 115 (35%), 75 (26%); Accurate m.s.: $C_{11}H_8N_2O_4$ requires *m/z* 232.0484, peak at *m/z* 232.0491.

4-(1,3-Dioxolan-2-yl)-6-methoxy-5-nitroquinoline (1c). To a solution of 4-formyl-6-methoxy-5-nitroquinoline (**1b**, 440 mg, 1.90 mmol) in dry C_6H_6 (100 ml), ethane-1,2-diol (4.44 g, 71.6 mmol) and *p*-TsOH (catalytic amount) were added. The mixture was stirred at reflux temperature for 14 h with azeotropic removal of water in a Dean-Stark apparatus. The organic solution was washed with a saturated solution of $NaHCO_3$, dried and evaporated to give a solid (467 mg) which was purified by column chromatography on silica eluting with *n*-hexane-CH_2Cl_2 (40:60) then giving **1c** (373 mg, 71%): ν_{max} (film): 1536, 1376, 1348, 1269; δ_H (200 MHz, $CDCl_3$): 4.03 (s, 3H, OCH_3), 3.82-4.20 (m, 4H, $O(CH_2)_2O$), 6.22 (s, 1H, OCHO), 7.58 (d, J= 9.5 Hz, 1H, H-7), 7.86 (d, J= 4.5 Hz, 1H, H-3), 8.28 (d, J= 9.5 Hz, 1H, H-8), 8.82 (d, J= 4.5 Hz, 1H, H-2); δ_C (200 MHz, $CDCl_3$): 57.03 (q, OCH_3), 61.78 (t, $O(CH_2)_2O$), 99.29 (d, OCHO), 115.67 (d, C-3), 120.56 (d, C-7), 134.69 (d, C-8), 148.67 (d, C-2); *m/z* (e.i.): 276 (M,13%), 259 (21%), 218 (12%), 201 (9%), 86 (66%), 84 (100%); Accurate m.s.: $C_{13}H_{12}N_2O_5$ requires *m/z* 276.0746, peak at *m/z* 276.0753.

6-Methoxy-4-dimethoxymethyl-5-nitroquinoline (1d). Method A. To a solution of **1b** (192 mg, 0.82 mmol) in dry MeOH (4 ml), $HC(OMe)_3$ (6.79 g, 64 mmol) and *p*-TsOH (catalytic amount) were added, and the mixture refluxed for 21 h under nitrogen. The solvent was removed and the residue dissolved in CH_2Cl_2 and washed with saturated aq. $NaHCO_3$. The organic solution was dried and evaporated to give **1d** (136 mg, 60%): m.p. 110-112°C (from MeOH); ν_{max} ($CHCl_3$): 1621, 1536, 1510, 1269; δ_H (200 MHz, $CDCl_3$): 3.39 (s, 6H, 2xOCH_3), 4.07 (s, 3H, OCH_3), 5.66 (s, 1H, OCHO), 7.61 (d, J=9.4 Hz, 1H, H-7), 7.91 (d, J=4.5 Hz, 1H, H-3), 8.30 (d, J=9.4 Hz, 1H, H-8), 8.90 (d, J=4.5 Hz, 1H, H-2); δ_C (200 MHz, $CDCl_3$): 53.59 (q, OCH_3), 57.10 (q, OCH_3), 99.85 (d, OCHO), 115.59 (d, C-3), 121.65 (d, C-7), 134.87 (d, C-8), 148.72 (d, C-2); *m/z* (e.i.) 278 (M, 4%), 247 (18%), 216 (20%), 201 (16%), 116 (15%), 75 (100%). Accurate m.s.: $C_{13}H_{14}N_2O_5$, requires *m/z* 278.0903, peak at *m/z* 278.0911. Elemental analysis: C, 56.1; H, 5.0; N, 9.9 % Calc.: C, 56.1; H, 5.1; N, 10.1%. Method B. To a solution of **1b** (3.28 g, 14.1 mmol) in MeOH (250 ml), HCl (19 ml, 1.0M in Et_2O) was added, and the mixture refluxed for 24 h. The solvent was removed and the residue dissolved in CH_2Cl_2 and washed with aq. K_2CO_3 (10%). The dried organic solution was evaporated to give crude material (3.99 g), flash chromatography of which (hexane/EtOAc; 1:2), produced pure acetal (3.03 g, 77%).

5-Acetylamino-4-(1,3-dioxolan-2-yl)-6-methoxyquinoline (1f) and 5-amino-4-(1,3-dioxolan-2-yl)-6-methoxyquinoline (1e). To a solution of **1c** (1.41 g, 5.11 mmol) in MeOH (200 ml), Pd-C (10% Pd, 141 mg) was added and the mixture was hydrogenated at 1 atm. The catalyst was removed by filtration through celite and the solvent evaporated to give 5-amino-4-(1,3-dioxolan-2-yl)-6-methoxyquinoline (**1e**) (1.20 g) as an oil. An analytical sample purified by column chromatography on silica, eluting with dry CH_2Cl_2-MeOH (99:1) had ν_{max} (film): 3430, 3350; δ_H (200 MHz, $CDCl_3$): 4.16 (s, 3H, OCH_3), 4.19-4.22 (m, 4H, $O(CH_2)_2O$), 6.87 (s, 1H, CH), 7.43 (d, J=9.1 Hz, 1H, H-7), 7.59 (d, J=4.4 Hz, 1H, H-3), 7.62 (d, J=9.1 Hz, 1H, H-8), 8.71 (d, J=4.4 Hz, 1H, H-2); δ_C (200 MHz, $CDCl_3$): 56.59 (q, OCH_3), 65.47 (t, $O(CH_2)_2O$), 101.17 (d, OCHO), 115.53 (d, C-3), 116.09 (d, C-7), 119.88 (d, C-8), 147.79 (d, C-2). A solution of the crude amine was stirred in Ac_2O (10 ml) for 16 h at

20ºC. The mixture was poured onto ice, basified with NaOH, and extracted with EtOAc. The organic solution was dried and evaporated to give 1.34 g of a residue which was purified by column chromatography on silica. Elution with CH_2Cl_2 gave **1c** (441 mg) and elution with CH_2Cl_2-MeOH (99:1) gave **1f** (535 mg, 53%): ν_{max} (film): 3300, 1670; δ_H (200 MHz, $CDCl_3$): 1.77, 2.23 (2xs, 3H, $COCH_3$), 3.94 (s, 3H, OCH_3), 4.05-4.12 (m, 4H, $O(CH_2)_2O$), 6.55, 6.61 (2xs, 1H, OCHO), 7.50, 7.52 (2xd, J=9.5 Hz, 1H, H-7), 7.67, 7.80 (2xd, J=4.5 Hz, 1H, H-3), 8.09, 8.15 (2xd, J=9.5 Hz, 1H, H-8), 7.86, 8.35 (2xbrs, 1H, NH), 8.71, 8.79 (2xd, J=4.5 Hz, 1H, H-2); δ_C (200 MHz, $CDCl_3$): 20.53, 23.87 (2xq, $COCH_3$), 56.83, 57.09 (2xq, OCH_3), 65.61, 66.16 (2xt, $O(CH_2)_2O$), 100.90, 101.34 (2xd, OCHO), 116.39, 116.90 (2xd, C-3), 119.14, 119.70 (2xd, C-7), 131.54, 132.24 (2d, C-8), 148.16, 148.73 (2xd, C-2), 169.83, 174.20 (2xs, C=O); *m/z* (e.i.) 288 (M, 35%), 246 (15%), 218 (23%), 185 (100%), 174 (28%), 159 (23%). Accurate m.s.: $C_{15}H_{16}N_2O_4$ requires *m/z* 288.1110, peak at *m/z* 288.1118.

4-(1,3-Dioxolan-2-yl)-1,2,3,4-tetrahydro-6-methoxy-5-nitroquinoline (3a) and 4-(1,3-dioxolan-2-yl)-1-ethyl-1,2,3,4-tetrahydro-6-methoxy-5-nitroquinoline (3b). To a solution of **1c** (344 mg, 1.25 mmol) in AcOH (8 ml), $NaB(CN)H_3$ (321 mg, 5.10 mmol) was added in portions under argon. The mixture was stirred at room temperature for 4 h and then heated at 50ºC for 1 h, then diluted with H_2O, basified with aq. NaOH (50%) and extracted with CH_2Cl_2. The organic extract was dried and evaporated to gave an oil, purified by flash column chromatography (CH_2Cl_2-MeOH (99:1)). The first fractions gave **3b** (60 mg, 16%): δ_H (200 MHz, $CDCl_3$): 1.12 (t, 3H, J=7 Hz, CH_2CH_3), 1.75-1.95 (m, 1H, H-3_{ax}), 2.15-2.30 (m, 1H, H-3_{eq}), 3.1-3.55 (m, 5H, $CH_3CH_2NCH_2$, H-4), 3.79 (s, 3H, OCH_3), 3.8-4.0 (m, 4H, $O(CH_2)_2O$), 4.99 (d, 1H, J=5.5 Hz, OCHO), 6.67 (d, 1H, J=9.3 Hz, H-7), 6.86 (d, J=9.3 Hz, H-8); successive fractions gave 80 mg (23%) of an oil identified as **3a:** δ_H (200 MHz, $CDCl_3$): 1.7-1.95 (m, 1H, H-3_{ax}), 2.1-2.25 (m, 1H, H-3_{eq}), 3.2-3.55 (m, 3H, NCH_2 and H-4), 3.79 (s, 3H, OCH_3), 3.7-3.95 (m, 4H, $O(CH_2)_2O$), 4.99 (d, 1H, J=4.6 Hz, OCHO), 6.56 (d, 1H, J=9 Hz, H-7), 6.80 (d, 1H, J=9 Hz, H-8).

4-(1,3-Dioxolan-2-yl)-1,2,3,4-tetrahydro-6-methoxy-1-methyl-5-nitroquinoline (3c) and 1,2-dihydro-4-(1,3-dioxolan-2-yl)-6-methoxy-1-methyl-5-nitroquinoline (5a). To a solution of **1c** (600 mg, 2.17 mmol) in THF (10 ml), $NaBH_4$ (625 mg, 16.5 mmol) was added, the solution was cooled in an ice bath, then formic acid (7 ml) added dropwise under argon. The reaction mixture was stirred for 16 h at room temperature. Water was added and the resulting solution was basified with aq. NaOH (50%) and extracted with CH_2Cl_2. The organic solution was dried and evaporated to gave an oil which was purified by flash chromatography (CH_2Cl_2). The first fractions gave **3c** (95 mg, 15%): δ_H (200 MHz, $CDCl_3$): 1.75-2.0 (m, 1H, H-3_{ax}), 2.1-2.3 (m, 1H, H-3_{eq}), 2.90 (s, 3H, NCH_3), 3.05-3.5 (m, 3H, NCH_2 and H-4), 3.79 (s, 3H, OCH_3), 3.8-4.0 (m, 4H, $O(CH_2)_2O$), 5.00 (d, 1H, J=5.6 Hz, OCHO), 6.63 (d, 1H, J=9.1 Hz, H-7), 6.86 (d, 1H, J-9.1 Hz, H-8); Accurate m.s.: $C_{14}H_{18}N_2O_5$ requires *m/z* 294.1216, peak at *m/z* 294.1216; successive fractions gave 147 mg (23%) of an oil. An analytical sample was prepared from this by flash column chromatography with CH_2Cl_2 to give **5a:** δ_H (200 MHz, $CDCl_3$): 2.79 (s, 3H, N-CH_3), 3.40 ("t", 1H, H-2_{eq}), 3.68 ("d", J=4.9 Hz, 1H, H-2_{ax}), 3.82 (s, 4H, $O(CH_2)_2O$), 3.92 (s, 3H, OCH_3), 5.64 (br, 1H, OCHO), 6.50 ("t", 1H, H-3), 6.69 (d, J=8.9 Hz, 1H, H-7), 6.89 (d, J=8.9 Hz, 1H, H-8).

5-Amino-4-(1,3-dioxolan-2-yl)-1,2,3,4-tetrahydro-1-methyl-6-methoxyquinoline (3d) and 1,2-dihydro-4-(1,3-dioxolan-2-yl)-6-methoxy-1-methyl-5-nitroquinoline (5a). To a solution of **1c** (620 mg, 2.25 mmol) in dry CH_2Cl_2 (70 ml) $Me_3O.F_4B$ (550 mg, 3.72 mmol) was added at 0ºC under nitrogen and the mixture was stirred for 5 min at 0ºC and 3 h at rt. The solvent was evaporated, the residue obtained dissolved in dry MeOH (70 ml), cooled at 0ºC and $NaBH_4$ (1.5 g, 39.69 mmol) added, then the reaction mixture was stirred 5 min to 0ºC and 16 h at rt under nitrogen. The solvent was removed under reduced pressure and the residue was dissolved in

water and extracted with EtOAc. The organic layer was dried and evaporated to give 560 mg of an oil. An analytical sample was prepared by flash column chromatography with CH_2Cl_2 to give **5a**. Crude **5a** was dissolved in dry MeOH (40 ml) and PtO_2 (150 mg) was added, and the mixture was hydrogenated at rt and atmospheric pressure. The catalyst was removed by filtration and the solvent evaporated to give 440 mg (74%) of **3d**: ν_{max} (film): 3439, 3357, 1616, 1519, 1502, 1467, 1225; δ_H (200 MHz, $CDCl_3$): 1.75-1.96 (m, 1H, H-3 ax.), 2.10-2.20 (m, 1H, H-3 eq.), 2.86 (s, 3H, NCH_3), 3.05-3.20 (m, 2H, H-2 eq. and H-4), 3.23-3.42 (m, 1H, H-2 ax.), 3.77 (s, 3H, OCH_3), 3.80-4.02 (m, 4H, $O(CH_2)_2O$), 4.96 (d, J=6.8 Hz, 1H, OCHO), 6.06 (d, J=8.8 Hz, 1H, H-7), 6.67 (d, J=8.8 Hz, 1H, H-8), δ_C (200 MHz, $CDCl_3$): 23.83 (t, C-3), 36.20 (d, C-4), 39.40 (q, NCH_3), 46.79 (t, C-2), 56.40 (q, OCH_3), 64.32 and 65.12 (2t, $O(CH_2)_2O$), 100.28 (d, OCHO), 106.97 (d, C-8), 109.97 (d, C-7); *m/z* (e.i.) 264 (M, 100%), 249 (33%), 191 (71%), 127 (27%), 111 (31%), 99 (51%), 73 (73%), 45 (45%); Accurate m.s.: $C_{14}H_{20}N_2O_3$ requires *m/z* 264.1474, peak at *m/z* 264.1465.

5-Acetylamino-4-(1,3-dioxolan-2-yl)-1,2,3,4-tetrahydro-6-methoxy-1-methylquinoline (3e). To a solution of **1f** (225 mg, 0.78 mmol) in dry CH_3CN (10 ml), MeI (4.56 g, 320 mmol) was added in two portions with an interval of 10 min maintaining the solution at reflux temperature with stirring for 14 h. The solvent was evaporated, the residue dissolved in dry MeOH (20 ml), the resulting solution cooled at 0°C and $NaBH_4$ (103 mg, 2.73 mmol) was added. The resulting mixture was stirred for 5 min at 0°C and 5 h at 20°C under nitrogen. The solvent was removed under reduced pressure, H_2O was added to the residue and the aqueous solution was extracted with AcOEt. The organic extract was dried and evaporated to give a residue which was purified by a flash chromatography. Elution with CH_2Cl_2-MeOH (99.5:0.5) gave **3e** (51 mg, 21%): mp: 138-140°C (Me_2CO): ν_{max} (KBr): 3237, 1650, 1551, 1466, 1280; δ_H (200 MHz, $CDCl_3$): 1.82 and 2.14 (2xs, 3H, CH_3CO), 1.83 (m, 1H, H-3_{ax}), 2.70 (m, 1H, H-3_{eq}), 2.73 and 2.86 (2xs, 3H, NCH_3), 3.10 (m, 1H, H-2_{eq}), 3.45 (m, 1H, H-2_{ax}), 3.50-4.00 (m, 8H, H-4, OCH_3, $O(CH_2)_2O$), 4.86 (d, J=7.5 Hz, 1H, OCHO), 6.45 (d, J=9.5 Hz, 1H, H-7), 6.59 (d, J=9.5 Hz, 1H, H-8), 7.52 and 8.00 (2 bs, 1H, NH); δ_C (200 MHz, $CDCl_3$): 20.28 and 23.57 (q, $COCH_3$), 23.23 (t, C-3), 36.27 (d, C-4), 38.40 (q, N-CH_3), 46.48 (t, C-2), 56.19 (q, OCH_3), 64.91 (t, $O(CH_2)_2O$), 106.89 (d, OCHO), 109.60 (d, C-8), 112.28 (d, C-7), 134.68 (s, CO); *m/z* (e.i.) 306 (M, 65%), 231 (73%), 191 (59%), 175 (33%), 73 (72%), 43 (100%); Accurate m.s.: $C_{20}H_{20}NO_2$ requires *m/z* 306.1494, peak at *m/z* 306.1507.

4-(1,3-Dioxolan-2-yl)-1,2,3,4-tetrahydro-1-methyl-6-methoxy-5-tosylaminoquinoline (3f). To a solution of **3d** (56 mg, 0.21 mmol) in dry CH_2Cl_2 (10 ml) *p*-TsCl (48 mg, 0.25 mmol) and K_2CO_3 (5 mg, 0.04 mmol) were added. The mixture was refluxed for 2 h, cooled and washed with aq. saturated solution of $NaHCO_3$. The organic solution was dried and evaporated to give 87 mg of a residue which was purified by flash chromatography (CH_2Cl_2) giving **3f** (42 mg, 47%): ν_{max} (film): 3300, 1502, 1325, 1272, 1159, 1091; δ_H (200 MHz, $CDCl_3$): 1.70-1.90 (m, 1H, H-3_{ax}), 2.05-2.20 (dm, 1H, H-3_{eq}), 2.40 (s, 3H, Ar-CH_3), 2.85 (s, 3H, N-CH_3), 3.00-3.12 (m, 1H, H-2_{eq}), 3.20-3.35 (m, 1H, H-2_{ax}), 3.29 (s, 3H, OCH_3), 3.40-3.55 (m, 1H, H-4), 3.75-4.00 (dm, 4H, $O(CH_2)_2O$), 4.96 (d, J=6.2 Hz, 1H, OCHO), 6.47 (d, J=9.1 Hz, 1H, H-7), 6.63 (d, J=9.08 Hz, 1H, H-8), 7.24 (d, J=8.7 Hz, 2H, H-3' and H-5'), 7.43 (br, 1H, NH), 7.68 (d, J=8.4, 2H, H-2' and H-6'); δ_C (200 MHz, $CDCl_3$): 21.47 (q, CH_3-Ar), 22.99 (t, C-3), 36.05 (d, C-4), 39.22 (q, NCH_3), 46.80 (t, C-2), 55.38 (q, OCH_3), 64.61 and 64.98 (2t, $O(CH_2)_2O$), 106.47 (d, OCHO), 109.91 (d, C-7), 111.59 (d, C-8), 127.26 (2d, C-3' and C-5'), 128.84 (2d, C-2' and C-6'), *m/z* (e.i.) 419 (M-15, 19%), 356 (28%), 345 (37%), 264 (28%), 201 (66%), 191 (100%), 175 (52%) 147 (23%), 91 (41%).

5-Amino-4-dimethoxymethyl-1,2,3,4-tetrahydro-6-methoxy-1-methylquinoline (3g) and 5-amino-4-dimethoxymethyl-1,2-dihydro-6-methoxy-1-methylquinoline (5b). To a solution of **1d** (1.27 g, 4.57

mmol) in dry CH_2Cl_2 (95 ml), $Et_3O.BF_4$ (1.00 g, 6.76 mmol) was added at 0 °C under nitrogen. The mixture was stirred for 5 min at 0°C and 3 h at 20°C, the solvent was removed at reduced pressure, and the residue dissolved in dry MeOH (95 ml), the solution was cooled at 0°C, and $NaBH_4$ (1.72 g, 46 mmol) added then the whole stirred for 5 min at 0°C and 16 h at 20°C under nitrogen. The solvent was removed under reduced pressure and the residue was partitioned between H_2O and EtOAc. The organic solution was dried and evaporated to give an oil (1.18 g). An analytical sample was prepared by flash column chromatography (hexane-EtOAc (1:1)) to give **5b** as a red solid: m.p. 96-99°C; δ_H (200 MHz, $CDCl_3$): 2.82 (s, 3H, NCH_3), 3.28 (s, 7H, $(OCH_3)_2$ and H-2_{eq}), 3.66 (m, J=5.1 and 1.2 Hz, 2H, H-2_{ax}), 3.85 (s, 3H, OCH_3), 5.08 (m, 1H, OCHO), 6.49 (td, J=5.1 and 1.5 Hz, 1H, H-3), 6.72 (d, J=9.1 Hz, 1H, H-7), 6.92 (d, J=9.1 Hz, 1H, H-8); *m/z* (c.i.) 295 (M+1, 25%), 263 (100). Elemental analysis: C, 57.2; H, 6.3; N, 9.4 % Calc. for $C_{14}H_{18}N_2O_5$: C, 57.1; H, 6.2; N, 9.5 %. The dihydroquinoline **5b** in dry MeOH (100 ml) was hydrogenated with PtO_2 (120 mg) as catalyst at 20°C and atmospheric pressure. The catalyst was removed by filtration and the solvent evaporated under reduced pressure to give 0.91 g (72%) of **3g**: A sample purified by flash chromatography over silica (hexane/EtOAc; 1:1) had m.p. 57-59°C; ν_{max} (film): 3439, 3353, 1502, 1225; δ_H (200 MHz, $CDCl_3$): 1.60-1.85 (m, 1H, H-3_{ax}), 2.06-2.20 (m, 1H, H-3_{eq}), 2.88 (s, 3H, NCH_3), 3.04-3.15 (m, 1H, H-2_{eq}), 3.20-3.30 (m, 1H, H-4), 3.31 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.65-3.74 (m, 1H, H-2_{ax}), 3.79 (s, 3H, OCH_3), 4.33 (br, 2H, NH_2), 4.51 (d, J=8.7 Hz, 1H, OCHO), 6.06 (d, J=8.8 Hz, 1H, H-8), 6.69 (d, J=8.8 Hz, 1H, H-7); δ_C (200 MHz, $CDCl_3$): 23.81 (t, C-3); 35.46 (d, C-4), 39.78 (q, NCH_3), 47.44 (t, C-2), 51.40 (q, OCH_3), 57.07 and 57.20 (2q, OCH_3), 100.61 (d, OCHO), 107.46 (d, C-8), 111.21 (d, C-7). Accurate m.s.: $C_{14}H_{22}N_2O_3$ requires *m/z* 266.1630, peak at *m/z* 266.1636; Elemental analysis: C, 63.3; H, 8.3; N, 10.3% Calc.: C, 63.1; H, 8.3; N, 10.5%.

4-(1,3-Dioxolan-2-yl)-6-methoxy-1-methyl-5-nitroquinolinium iodide (4a). To a solution of **1c** (1.28 g, 4.3 mmol) in MeCN (35 ml), MeI (5 ml) was added and the reaction mixture was stirred at 50°C for 24 h. After this time, more MeI (5 ml) was added and the mixture stirred for a further 24 h at 50°C. The solvent was removed and the residue triturated with acetone to yield a yellow solid (1.10 g, 87%), identified as **4a**: δ_H (200 MHz, d_6-DMSO): 3.9-4.1 (m, 4H, $O(CH_2)_2O$), 4.21 (s, 3H, OCH_3), 4.72 (s, 3H, N^+CH_3), 6.26 (s, 1H, OCHO), 8.44 (d, 1H, J=9.7 Hz, H-7), 8.45 (d, 1H, J=6.7 Hz, H-3), 8.89 (d, 1H, J=9.7 Hz, H-8), 9.54 (d, 1H, J=6.1 Hz, H-2).

6-Methoxy-4-dimethoxymethyl-1-methyl-5-nitroquinolinium iodide (4b). To a solution of **1d** (1.03 g, 3.7 mmol) in MeCN (35 ml), MeI (5 ml) was added and the reaction mixture was stirred at 50°C for 45 h, the solvent was removed, and the resulting residue triturated with acetone to give the iodide, **4b**, as a solid: m.p. (dec.) 141-142°C (acetone-hexane), δ_H (200 MHz, d_6-DMSO): 3.35 (s, 6H, 2xOCH_3), 4.20 (s, 3H, OCH_3), 4.72 (s, 3H, N^+CH_3), 5.61 (s, 1H, OCHO), 8.41 9d, 1H, J=6.3 Hz, H-3), 8.43 (d, 1H, J=10 Hz, H-7), 8.88 (d, 1H, J=10 Hz, H-8), 9.54 (d, 1H, J=6.3 Hz, H-2). Elemental analysis: C, 40.3; H, 4.1; N, 6.6%. Calc. for $C_{14}H_{17}IN_2O_5$: C, 40.0; H, 4.08; N, 6.67%.

1,3,4,5-Tetrahydro-8-methoxy-5-methyl-pyrrolo[4,3,2-*de*]quinoline (7a). Method A: To a solution of **3g** (16 mg, 0.06 mmol) in dry THF (8 ml), *p*-TsOH (60 mg, 0.31 mmol) was added and the reaction mixture was stirred at reflux temperature for 3 h. The solvent was removed and the residue was dissolved in CH_2Cl_2 the resulting solution was washed with saturated aqueous $NaHCO_3$. The organic layer was dried, filtered and evaporated to give **7a** (7 mg, 58%): ν_{max} (film): 1603, 1519, 1453, 1380, 1344, 1259, 1210; δ_H (200 MHz, $CDCl_3$): 2.96 (s, 3H, NCH_3), 3.09 (t, J=5.4 Hz, 2H, H-3), 3.27 (t, J=5.4 Hz, 2H, H-4), 3.93 (s, 3H, OCH_3), 6.14 (d, J=8.0 Hz, 2H, H-6), 6.56 (d, J=8.0 Hz, 1H, H-7), 6.77 (s, 1H, C-2), 8.05 (br, 1H, NH); δ_C (200 MHz, $CDCl_3$) 23.47 (t, C-3), 38.57 (q, NCH_3), 53.09 (t, C-4), 55.86 (q, OCH_3), 97.64 (d, C-2), 103.73 (d, C-7), 115.22 (d, C-6);

m/z (e.i.) 202 (M, 87%), 187 (100%), 91 (66%); Accurate m.s.: $C_{12}H_{14}N_2O$ requires *m/z* 202.1106, peak at *m/z* 202.1107. Method B: A solution of **3d** (31 mg, 0.12 mmol) and *p*-TsOH (60 mg, 0.31 mmol) in THF (3 ml) was stirred at reflux temperature for 3 h. The solvent was removed at reduced pressure, an aqueous solution of $NaHCO_3$ added, and product extracted with CH_2Cl_2. The organic solution was dried and evaporated to give 15 mg of a mixture of **3d** and **7a** (1:2 by ^{1}H-NMR). Yield of **7a** (49%).

1,3,4,5-Tetrahydro-8-methoxy-5-methyl-1-(4-methylphenylsulphonyl)pyrrolo[4,3,2-*de*]quinoline (7b). To a solution of **7a** (137 mg, 0.68 mmol), $Bu_4N.HSO_4$ (6 mg, 17 mmol) in CH_2Cl_2 (2 ml) powdered NaOH (100mg, 2.5 mmol) and a solution of TsCl (168 mg, 0.88 ml) in CH_2Cl_2 (1 ml) were added. The reaction mixture was stirred under argon for 4h. Water was added and the organic layer was collected, dried and evaporated to give crude product as a foam (223 mg), further purified by flash chromatography (CH_2Cl_2-MeOH (99:1)) giving **7b** (168 mg, 78%): ^{1}H-NMR (200 MHz, $CDCl_3$): 2.37 (s, 3H, $ArCH_3$), 2.88 (s, 3H, NCH_3), 3.00 (t, J=6.0 Hz, 2H, C-3-H_2), 3.20 (t, J=6.0 Hz, 2H, C-4-H_2), 3.71 (s, 3H, OCH_3), 6.28 (d, J=8.3 Hz, 1H, d, 6-H), 6.62 (d, J=8.3 Hz, 1H, H-7), 7.23 (d, J=8.3 Hz, 2H, ArH), 7.34 (s, 1H, H-2), 7.79 (d, J=8.3 Hz, 2H, d, ArH); m/z (c.i.) 357 (M+1, 100%), 203 (50%), 174 (20%). Accurate m.s.: $C_{19}H_{20}N_2O_3S$ requires *m/z* 357.1273, peak at *m/z* 357.1273. Elemental analysis: C, 63.7; H, 5.80; N, 7.70; S, 9.40% Calc. for $C_{19}H_{20}N_2O_3S$: C, 64.0; H, 5.66; N, 8.99; S, 8.99%.

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(*Received in UK* 7 *April* 1994; *accepted* 29 *April* 1994)