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Nucleophilic Additions to Fused Benzimidazole *N*-Oxides

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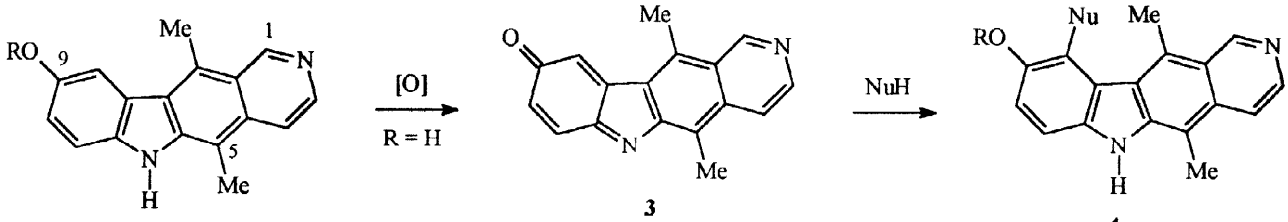
Abstract: The benzimidazoles **16a-f** have been prepared from *N*-oxides **15a-d**. Treatment of *N*-oxides **15c** and **15d** with a mixture of acetic anhydride and sodium acetate gave the corresponding acetoxy derivatives **26** and **27** *via* a regiospecific nucleophilic substitution reaction. *N*-Oxides **15c** and **15d** were also deoxygenated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Ellipticine, and its 9-oxygenated derivatives such as 9-hydroxyellipticine **1** and 9-methoxyellipticine **2** have attracted considerable attention as potential anti-cancer agents.[1-4] Several modes of anti-cancer action have been proposed for ellipticine and its derivatives; for example they have been described as bioalkylating agents, intercalating agents, inhibitors of the enzyme topoisomerase II and in the case of 9-hydroxyellipticine **1**, the corresponding phenoxy radical has been suggested to cause DNA damage either directly or indirectly by reduction of molecular oxygen to superoxide ions.



1 R = H
2 R = Me

3

4

Scheme 1

Two broad mechanisms[1] by which ellipticine and its derivatives can act as bioalkylating agents have been proposed. In the first mechanism (Scheme 1), 9-hydroxyellipticine **1** (which may be formed *in vivo* by oxidation of ellipticine or demethylation[5,6] of 9-methoxyellipticine **2**) is oxidised to the quinone-imine **3** which then undergoes regiospecific Michael-type addition of bionucleophiles at the 10-position yielding the products **4**. Adducts of general structure **4**, and other compounds derived from these primary adducts, have been

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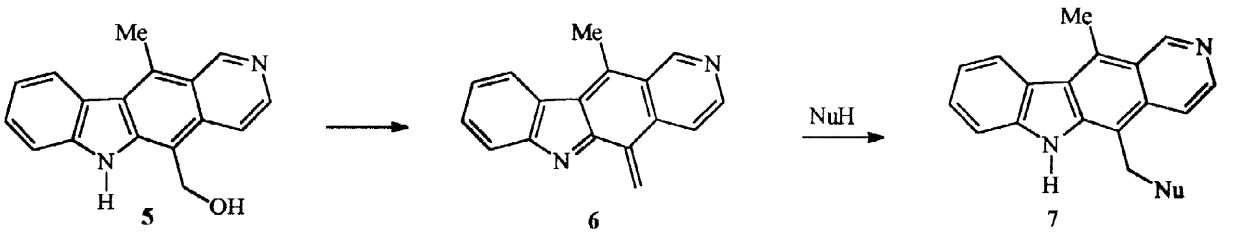
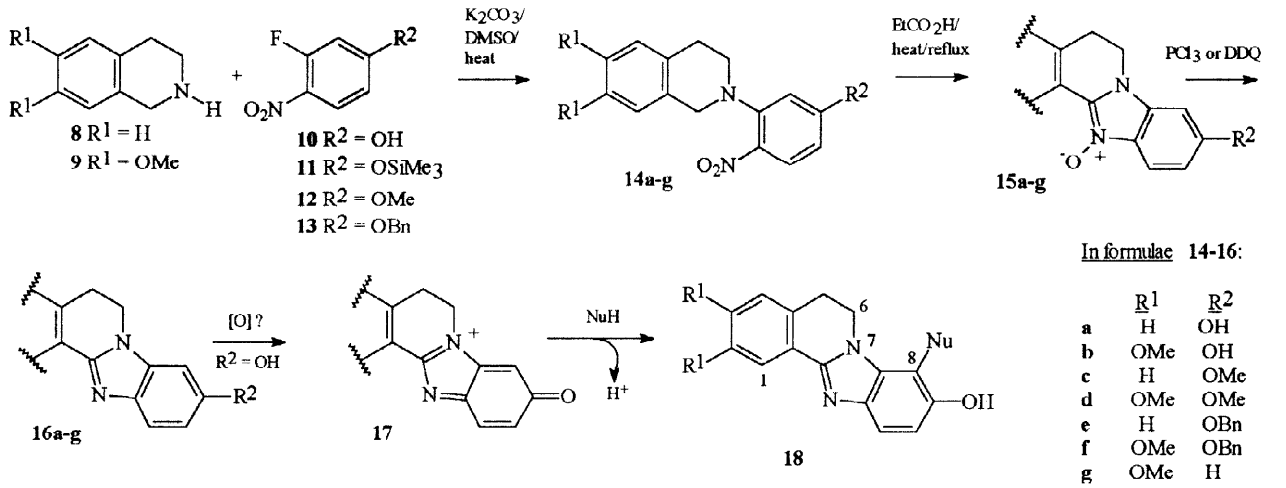
chemically prepared by oxidation of 9-hydroxyellipticine **1** in the presence of nucleophiles by both Potier's[7-9] and Meunier's[10-12] research groups. In an alternative mechanism[13] (Scheme 2), Archer's research group has provided evidence that the 5-methyl group of ellipticine derivatives is oxidised to the alcohol **5** which (as its sulfate or phosphate ester) acts as the precursor to the vinylogous imine intermediate **6**. Michael-type addition of bionucleophiles to this vinylogous imine **6** then yields products **7**.



Scheme 2

We have been interested in identifying and synthesising novel heterocyclic compounds which might act as precursors for quinone-imine intermediates similar in structure to **3** with the objective of developing novel bioalkylating agents. In this paper we report our work on the synthesis of the derivatives of 5,6-dihydro-9-hydroxybenzimidazo[2,1-*a*]isoquinoline **16a-f** which we reasoned might be a suitable precursor to the quinone-imines of general structure **17** and hence adducts **18** after Michael-type addition to nucleophiles (Scheme 3)

The synthetic route chosen to the target heterocycles **16** is shown in Scheme 3. The cyclodehydration of *N,N*-disubstituted 2-nitroaniline derivatives giving benzimidazole *N*-oxides is well-known (the *t*-amino effect)[14] and we have previously used this reaction to prepare substituted 5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxides.[15] We therefore envisaged a similar route to the 9-oxygenated 5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline *N*-oxides **15a-f** by a similar cyclodehydration of the nitro-compounds **14a-f** respectively from which heterocycles **16a-f** might then be obtained by deoxygenation.



In formulae **14-16**:

	R1	R2
a	H	OH
b	OMe	OH
c	H	OMe
d	OMe	OMe
e	H	OBn
f	OMe	OBn
g	OMe	H

Scheme 3

The preparation of nitro-compound **14a** was firstly investigated. Commercially available 3-fluoro-4-nitrophenol **10** was treated with a mixture of triethylamine and trimethylsilyl chloride to yield the silylated

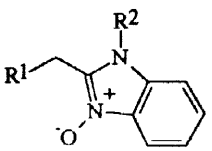
derivative **11** which was not isolated but was reacted directly with 1,2,3,4-tetrahydroisoquinoline **8** under basic conditions giving, after an acidic work-up, the nitrophenol derivative **14a** in low (16 %) yield. However, when compound **14a** was heated in propionic acid at reflux a complex mixture was produced and no compound **15a** was obtained. We therefore turned our attention to the synthesis of the *O*-protected derivatives **14c** and **14e** of compound **14a**. Both compounds **14c** and **14e** were readily prepared in excellent yields by heating a mixture of heterocycle **8** and fluoro-compounds **12** and **13** respectively under basic conditions. When these two compounds were heated in boiling propionic acid the required *N*-oxide derivatives **15c** (68 % yield) and **15e** (54 % yield) respectively were produced. Similarly prepared were the 6,7-dimethoxy analogues **14d** (93 % yield) and **14f** (86 % yield) from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **9** and fluoro-compounds **12** and **13** respectively. Nitro-compounds **14d** and **14f** gave the corresponding *N*-oxides **15d** (50 % yield) and **15f** (72 % yield) as expected. In view of the failure to obtain compound **15a**, the synthesis of the dimethoxy derivative **15b** *via* its precursor **14b** was not attempted.

Deoxygenation of compounds **15c-f** afforded heterocycles **16c-f** respectively and was achieved with phosphorus trichloride in boiling chloroform. Heterocycles **16c-e** were obtained in good yield (61–78 %) but compound **16f** was only isolated in poor yield (14 %). Hydrogenation of heterocycles **16e** and **16f** then gave the phenolic derivatives **16a** and **16b** respectively, but disappointingly in low yield (13-14 %). Although compounds **16e** and **16f** have been successfully prepared, in view of their low yields, this avenue was not pursued further and their chemistry was not investigated.

We were also interested in preparing benzimidazo[2,1-*a*]isoquinolines and benzimidazo[2,1-*a*]isoquinoline *N*-oxides in which the 5,6-positions are unsaturated. Literature precedent[16] suggested that dehydrogenation of benzimidazo[2,1-*a*]isoquinolines would not provide a satisfactory method of preparing these compounds because 2,3,9,10-tetramethoxybenzimidazo[2,1-*a*]isoquinoline had only been obtained in 10% yield by Pd/C mediated dehydrogenation of its corresponding 5,6-dihydro derivative. We therefore attempted two alternative methods of dehydrogenating benzimidazo[2,1-*a*]isoquinoline *N*-oxides as described below.

Treatment of *N*-oxide **15c** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gave a product which was not the corresponding 5,6-dihydro derivative but was the deoxygenation product **16c** (55 % yield). The fate of the DDQ in this reaction has not been determined but it is possibly epoxidised *via* a Michael-type addition followed by an elimination process. Similarly, *N*-oxide **15d** afforded heterocycle **16d** in 47 % yield when treated with DDQ.

Benzimidazole *N*-oxides of general structure **19** can be transformed into the acetates **20** by heating in the presence of acetic anhydride.[17] We envisaged that fully conjugated benzimidazo[2,1-*a*]isoquinolines **22** (R^1 = H, OMe) might be obtained in a similar reaction from *N*-oxides **15c** and **15d**. Thus, a vinylogous equivalent of the transformation **19** → **20** might yield acetates **21** (R^1 = H, OMe) from which compounds **22** (R^1 = H, OMe) would be obtained by elimination of acetic acid.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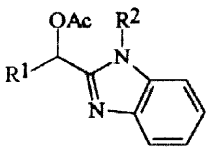
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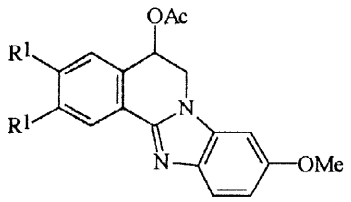
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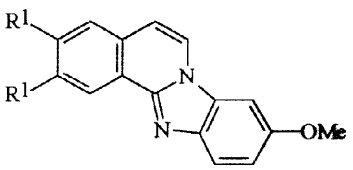
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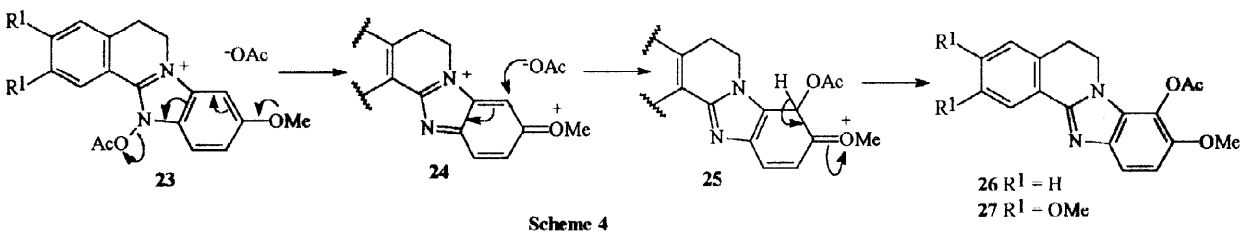
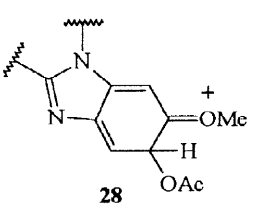
When the *N*-oxides **15c** and **15d** were heated with a mixture of acetic anhydride and sodium acetate, the acetoxy derivatives **26** (40 % yield) and **27** (15 % yield) were unexpectedly isolated. We have rationalised the formation of these compounds by the mechanism depicted in Scheme 4. Thus, reaction of acetic anhydride at the *N*-oxide substituent gives intermediates **23** which then expel acetate giving the quinone-imine intermediates **24**. A regiospecific Michael-type addition at the 8-position of compounds **24** with acetate then yields the structures **25** from which the products are derived by loss of a proton. The C-9 methoxy group is an essential structural requirement for this reaction since the lone pair of electrons associated with this methoxy group is necessary to assist the departure of acetate (arrows, structure **23**). In support of this argument, the *N*-oxide **15g** did not react under similar conditions.



Scheme 4

Nucleophilic substitution in benzimidazole *N*-oxides was reported by Takahashi and Kano in 1966[18] and further investigated in 1973 by Kielden, Meth-Cohn and Suschitzky.[19] In these nucleophilic substitutions, the *N*-oxide group is firstly transformed into a potential leaving group before the nucleophile attacks by an S_N2' mechanism. The reaction shown in Scheme 4 is unusual since it is believed to occur by an elimination-addition process and requires an appropriately positioned electron-rich substituent, in this case a methoxy group.

The mechanism shown in Scheme 4 also accounts for the regioselectivity of the reaction. When acetate is added at the 8-position, the resulting intermediates **25** possess aromatic imidazole fragments. If the addition of acetate were to occur at the 10-position giving structures **28**, an aromatic imidazole moiety cannot be drawn.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The unexpected nucleophilic substitution reactions of the *N*-oxides described above has been rationalised in terms of the quinone-imine intermediates **24** or their equivalents. These quinone-imines are in fact the methylated analogues of the compounds **17** that we had originally intended to investigate. Our studies of the reaction of the benzimidazo[2,1-*a*]isoquinoline *N*-oxides with acetic anhydride reported in this paper have therefore produced the desired nucleophilic substitution reactions.

Experimental

^{1}H-nmr spectra (60 or 270 MHz) were determined in $CDCl_3$ solution unless otherwise stated. Infra-red spectra were recorded as KBr discs unless otherwise stated.

4-Benzyloxy-2-fluoronitrobenzene **13**

To 3-fluoro-4-nitrophenol (4.90 g, 31.2 mmol) and K_2CO_3 (6.46 g, 46.8 mmol) in tetrahydrofuran (75 ml) was added benzyl bromide (5.04 ml, 32.7 mmol) and sodium iodide (few crystals) and the mixture was heated under reflux for 2 hours with stirring. After cooling the mixture was poured into water and extracted several times with DCM. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated yielding brown oil which was fractionated by column chromatography (silica gel, eluent petroleum ether b.p. 60-80°C : ethyl acetate 2:1) giving compound **13** (1.18 g, 15 %) as pale yellow crystals, m.p. 72-73 °C (ethanol). [Found: C, 63.2; H, 4.1; N, 5.7. $C_{13}H_{10}FNO_3$ requires C, 63.2; H, 4.0; N, 5.7 %]. $\nu_{max.}$ 1609, 1512, 1331, 1274 and 1091 cm^{-1}. δ 8.10 (1H, m, Ar-H), 7.45-7.35 (5H, s, Ar-H), 6.85-6.75 (2H, m, Ar-H), 5.15 (2H, s, -OCH_2Ph).

N-(5-Hydroxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14a**

Trimethylsilyl chloride (3.38 ml, 26.6 mmol) was added to a mixture of 3-fluoro-4-nitrophenol (4.00 g, 25.5 mmol), toluene (75 ml) and triethylamine (3 ml, 21.5 mmol). The mixture was heated at 80 °C overnight with stirring under a nitrogen atmosphere and then allowed to cool to room temperature. Triethylamine (3 ml, 21.5 mmol) and 1,2,3,4-tetrahydroisoquinoline (3.56 g, 26.7 mmol) were added and the mixture was refluxed for 4 hours with stirring. After cooling to room temperature the mixture was poured into dilute hydrochloric acid and extracted several times with with ethyl acetate. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated yielding compound **14a** (1.07 g, 16 %) as an orange solid, m.p. 152-155 °C (ethanol). [Found: C, 66.5; H, 5.4; N, 10.3; M$^+$, 270.1015. $C_{15}H_{14}N_2O_3$ requires C, 66.7; H, 5.2; N, 10.4 %; M, 270.1004]. $\nu_{max.}$ 3500-3200 (broad), 1614, 1514, 1307, 1182 and 1088 cm^{-1}. δ 7.92 (1H, d, *J* 9 Hz, Ar-H), 7.25-7.00 (4H, m, Ar-H), 6.58 (1H, d, *J* 2 Hz, Ar-H), 6.40 (1H, dd, *J* 9 and 2 Hz, Ar-H), 4.28 (2H, s, -CH_2-), 3.36 (2H, t, *J* 6 Hz, C(5)H_2) and 3.02 (2H, t, *J* 6 Hz, C(6)H_2). The –OH proton was too broad to be located.

Compounds **14c-g**. *General Method*.

A mixture of 1,2,3,4-tetrahydroisoquinoline (THIQ) or 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, K_2CO_3 and the appropriate halonitroaryl compound were heated (100 °C) in DMSO (4 hours) with stirring. The mixture was poured into water and the product was extracted several times with DCM. The combined organic layers were washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. The following compounds were prepared.

N-(5-Methoxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14c**

THIQ (4.12 g, 30.9 mmol), K_2CO_3 (4.93 g, 46.4 mmol) and 3-fluoro-4-nitroanisole[20] (5.37 g, 31.4 mmol) gave compound **14c** (8.05g, 91 %) as an orange oil. [Found: C ,67.5; H ,5.9; N, 9.8; M$^+$, 267.1141. $C_{16}H_{16}N_2O_3$ requires C, 67.6; H, 5.7; N, 9.9 %; M, 267.1134]. $\nu_{max.}$ 1607, 1505, 1251, and 1091 cm^{-1}(liquid film). δ 7.96 (1H, d, *J* 9 Hz, Ar-H), 7.20-7.00 (4H, m, Ar-H), 6.60 (1H, d, *J* 2 Hz, Ar-H), 6.46 (1H, dd, *J* 7 and 2 Hz, Ar-H), 4.30 (2H, s, -CH_2-), 3.86 (3H, s, -OCH_3), 3.41 (2H, t, *J* 6 Hz, C(5)H_2) and 3.03 (2H, t, *J* 6 Hz, C(6)H_2).

6,7-Dimethoxy-N-(5-methoxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14d**

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (6.64 g, 31.3 mmol), K_2CO_3 (6.91 g, 44.7 mmol) and 3-fluoro-4-nitroanisole[20] (5.10 g, 29.8 mmol) gave compound **14d** (10.1 g, 93 %) as orange crystals, m.p. 130-132 °C (ethanol). [Found: C, 62.7; H, 5.7; N, 8.05. $C_{18}H_{20}N_2O_5$ requires C, 62.8; H, 5.85; N, 8.1 %]. $\nu_{max.}$ 1610, 1518, 1301, 1175 and 1114 cm^{-1}. δ 7.95 (1H, d, *J* 8 Hz, Ar-H), 6.70-6.35 (4H, m, Ar-H), 4.20 (2H, s, -CH_2-), 3.80 (9H, s, 3 x -OCH_3), 3.30 (2H, t, *J* 8 Hz, C(5)H_2) and 2.90 (2H, t, *J* 8 Hz, C(6)H_2).

N-(5-Benzyloxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14e**

THIQ (1.52 g, 11.4 mmol), K_2CO_3 (1.72 g, 17.1 mmol) and 4-benzyloxy-2-fluoronitrobenzene (2.57 g, 10.8 mmol) gave compound **14e** (2.97 g, 79 %) as yellow crystals, m.p. 96-97 °C (ethanol). [Found: C, 73.2; H, 5.45; N,7.7. $C_{22}H_{20}N_2O_3$ requires C, 73.3; H, 5.6; N, 7.8 %]. $\nu_{max.}$ 1618, 1484, 1288, 1174 and 1139 cm^{-1}. δ 7.96 (1H, d, *J* 8 Hz, Ar-H), 7.42-7.30 (5H, m, Ar-H), 7.18-7.00 (4H, m, Ar-H), 6.70 (1H, d, *J* 1 Hz, Ar-H), 6.55 (1H, dd, *J* 8 and 1 Hz, Ar-H), 5.10 (2H, s, -OCH_2Ph), 4.28 (2H, s, -CH_2-), 3.38 (2H, t, *J* 7 Hz, C(5)H_2) and 3.02 (2H, t, *J* 7 Hz, C(6)H_2).

N-(5-Benzyloxy-2-nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **14f**

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (1.59 g, 8.19 mmol), K_2CO_3 (1.62 g, 11.7 mmol) and 4-benzyloxy-2-fluoronitrobenzene (1.85 g, 7.81 mmol) gave compound **14f** (4.02 g, 86 %) as yellow crystals, m.p. 156-158 °C (ethanol). [Found: C, 68.4; H, 5.65; N, 6.5. $C_{24}H_{24}N_2O_5$ requires C, 68.6; H, 5.75; N, 6.7%]. $\nu_{max.}$ 1603, 1520, 1331, 1251 and 1117 cm^{-1}. δ 7.98 (1H, d, *J* 4 Hz, Ar-H), 7.45-7.30 (5H, m, Ar-H), 6.65 (2H, d, *J* 2 Hz, Ar-H), 6.59 (1H, s, Ar-H), 6.56 (1H, dd, *J* 3 and 1 Hz, Ar-H), 5.10 (2H, s, -OCH_2Ph), 4.20 (2H, s, -CH_2-), 3.82 (6H, s, 2 x -OCH_3), 3.37 (2H, t, *J* 6Hz, C(5)H_2) and 2.94 (2H, t, *J* 6 Hz, C(6)H_2).

6,7-Dimethoxy-N-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **14g**

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (3.50 g, 17.9 mmol), K_2CO_3 (3.71 g, 26.8 mmol) and 1-fluoro-2-nitrobenzene (2.78 g, 19.7 mmol) gave compound **14g** (2.45 g, 40%) as orange crystals, m.p. 132 °C (ethanol). [Found: C, 62.7; H, 5.65; N, 7.90. $C_{17}H_{18}N_2O_4$ requires C, 62.7; H, 5.85; N, 8.1 %]. $\nu_{max.}$ 1604, 1519, 1342, and 1115 cm^{-1}. δ 7.80 (1H, dd, *J* 8 and 1 Hz, Ar-H), 7.50-6.85 (4H, m, Ar-H), 6.60 (1H, dd, *J* 8 and 1 Hz, Ar-H), 4.20 (2H, s, -CH_2-), 3.80 (6H, s, 2 x -OCH_3), 3.35 (2H, t, *J* 8 Hz, C(5)H_2) and 2.90 (2H, t, *J* 8 Hz, C(6)H_2).

Compounds **15c-g**. *General Method*.

Compounds **14c-g** in either acetic or propionic acid were heated at reflux (20 – 24 hours) with stirring. After cooling to room temperature, the mixture was poured onto a mixture of ice and dilute sodium hydroxide solution (until alkaline) and the product was extracted into DCM. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. The following compounds were prepared:

5,6-Dihydro-9-methoxybenzimidazo[2,1-a]isoquinoline N-oxide **15c**

Compound **14c** (3.30 g, 11.6 mmol) in acetic acid (75 ml) yielded compound **15c** (2.09 g, 68 %) as brown crystals, m.p. 204-207 °C (acetone). [Found: M^+, 266.1052. $C_{16}H_{14}N_2O_2$ requires M, 266.1055]. $\nu_{max.}$ 1622, 1490, 1240 and 1136 cm^{-1}. δ 9.45 (1H, dd, *J* 4 and 1 Hz, Ar-H), 7.93 (1H, d, *J* 4 Hz, Ar-H), 7.55-7.30 (3H, m, Ar-H), 7.00 (1H, dd, *J* 4 and 1 Hz, Ar-H), 6.80 (1H, d, *J* 1 Hz, Ar-H), 4.30 (2H, t, *J* 6 Hz, C(5)H_2), 3.90 (3H, s, -OCH_3) and 3.35 (2H, t, *J* 6 Hz, C(6)H_2).

5,6-Dihydro-2,3,9-trimethoxybenzimidazo[2,1-a]isoquinoline N-oxide **15d**

Compound **14d** (10.0 g, 30.3 mmol) in acetic acid (150 ml) yielded compound **15d** (5.29 g, 50 %) as off white crystals, m.p. 229-232 °C (acetone/ethanol). [Found: C, 59.6; H, 6.3; N, 7.7; M^+, 326.1268. $C_{18}H_{18}N_2O_4.2H_2O$ requires C, 59.7; H, 6.1; N, 7.7 %; M, 326.1267]. $\nu_{max.}$ 1620, 1496, 1245 and 1147 cm^{-1}. δ 9.20 (1H, s, Ar-H), 7.85 (1H, d, *J* 10 Hz, Ar-H), 7.00 (1H, dd, *J* 9 and 1 Hz, Ar-H), 6.82-6.70 (2H, m, Ar-H), 4.20 (2H, t, *J* 7 Hz, C(5)H_2), 4.00 (3H, s, -OCH_3), 3.80 (6H, d, *J* 9 Hz, 2 x -OCH_3) and 3.20 (2H, t, *J* 8 Hz, C(6)H_2).

5,6-Dihydro-9-benzyloxybenzimidazo[2,1-a]isoquinoline N-oxide **15e**

Compound **14e** (2.63 g, 7.51 mmol) in acetic acid (100 ml) yielded compound **15e** (1.39 g, 54 %) as brown crystals m.p. 185-189 °C (acetone/ethanol). [Found: M^+, 342.1358. $C_{22}H_{18}N_2O_2$ requires M, 342.1368]. $\nu_{max.}$ 1618, 1484, 1234 and 1174 cm^{-1}. δ 9.47 (1H, dd, *J* 7 and 1 Hz, Ar-H), 7.95 (1H, d, *J* 8 Hz, Ar-H), 7.55-7.30 (8H, m, Ar-H), 7.10 (1H, dd, *J* 8 and 1 Hz, Ar-H), 6.90 (1H, d, *J* 1 Hz, Ar-H), 5.15 (2H, s, -OCH_2Ph), 4.30 (2H, t, *J* 7 Hz, C(5)H_2) and 3.30 (2H, t, *J* 7 Hz, C(6)H_2).

9-Benzyloxy-5,6-dihydro-2,3-dimethoxybenzimidazo[2,1-a]isoquinoline N-oxide **15f**

Compound **14f** (4.02 g, 9.56 mmol) in acetic acid (75 ml) yielded compound **15f** (2.81 g, 72 %) as brown crystals, m.p. 237-240 °C (acetone/ethanol). [Found: C, 65.8; H, 5.7; N, 6.4; M^+, 402.1581. $C_{24}H_{22}N_2O_4.2H_2O$ requires C, 65.8; H, 6.0; N, 6.4 %; M, 402.1580]. $\nu_{max.}$ 1622, 1495, 1220 and 1152 cm^{-1}. δ 9.18 (1H, s, Ar-H), 7.85 (1H, d, *J* 7 Hz, Ar-H), 7.55-7.30 (5H, m, Ar-H), 7.05 (1H, dd, *J* 7 and 1 Hz, Ar-H), 6.86 (1H, d, *J* 1 Hz, Ar-H), 6.80 (1H, s, Ar-H), 5.15 (2H, s, -OCH_2Ph), 4.22 (2H, t, *J* 7 Hz, C(5)H_2), 4.05 (3H, s, -OCH_3), 3.95 (3H, s, -OCH_3) and 3.20 (2H, t, *J* 8 Hz, C(6)H_2).

5,6-Dihydro-2,3-dimethoxybenzimidazo[2,1-a]isoquinoline N-oxide **15g**

Compound **14g** (3.09 g, 9.82 mmol) in propionic acid (75 ml) yielded compound **15g** (2.13 g, 73 %) as creamy yellow crystals, m.p. 230 °C (acetone). $\nu_{max.}$ 1609, 1498, 1257 and 1147 cm^{-1}. δ 9.20 (1H, s, Ar-H), 7.95 (1H, m, Ar-H), 7.43-7.30 (3H, m, Ar-H), 6.83 (1H, d, *J* 1 Hz, Ar-H), 4.30 (2H, t, *J* 8Hz, C(5)H_2), 4.03 (3H, s, -OCH_3), 3.95 (3H, s, -OCH_3) and 3.23 (2H, t, *J* 8 Hz, C(6)H_2). This compound was characterised as its deoxygenated derivative, compound **16g**.

5,6-Dihydro-9-hydroxybenzimidazo[2,1-a]isoquinoline **16a**

A mixture of compound **16e** (0.10 g, 0.30 mmol), ammonium formate (0.02 g, 0.33 mmol), 5% palladium on carbon (0.05 g, 0.02 mmol) and methanol (10 ml) was heated under reflux (4 hours) with stirring. After cooling to room temperature the mixture was filtered, poured onto sodium hydroxide solution, neutralised with dilute hydrochloric acid and then extracted several times with dichloromethane (DCM). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated yielding **16a** (0.01 g, 14%) as brown oil. δ 8.22 (1H, m, Ar-H), 7.60 (1H, d, *J* 9 Hz, Ar-H), 7.40-7.20 (3H, m, Ar-H), 6.80-6.75 (2H, m, Ar-H), 4.23 (2H, t, *J* 8 Hz, C(5)H_2) and 3.23 (2H, t, *J* 8 Hz, C(6)H_2). The –OH proton was too broad to be located. In view of the low yield, this compound was not characterised further.

5,6-Dihydro-9-hydroxy-2,3-dimethoxybenzimidazo[2,1-a]isoquinoline **16b**

Following the procedure described above for the preparation of compound **16a**, compound **16f** (0.50 g) yielded compound **16b** (0.05g, 13 %) as brown crystals m.p. 267 °C (ethanol). [Found: M^+, 296.1162. $C_{17}H_{16}N_2O_3$ requires M, 296.1161]. $\nu_{max.}$ 1616, 1477, 1280, 1234 and 1171 cm^{-1}. δ 7.73 (1H, s, Ar-H), 7.61 (1H, d, *J* 9 Hz, Ar-H), 6.79 (3H, m, Ar-H), 4.23 (2H, t, *J* 7 Hz, C(5)H_2), 3.97 (3H, s, -OCH_3), 3.94 (3H, s, -OCH_3) and 3.20 (2H, t, *J* 7 Hz, C(6)H_2). The –OH proton was too broad to be located.

Compounds **16c-g**. *Method A*.

The appropriate *N*-oxide was dissolved in chloroform. Phosphorus trichloride was then added and the resulting mixture heated at reflux for 2 hours with stirring. The mixture was poured into a mixture of ice and dilute sodium hydroxide solution and the product extracted into DCM. The organic layer was washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. The following compounds were prepared:

5,6-Dihydro-9-methoxybenzimidazo[2,1-a]isoquinoline **16c**

N-Oxide **15c** (2.00 g, 7.51 mmol) and PCl_3 (0.79 ml, 9.01 mmol) gave compound **16c** (1.14 g, 61 %) as brown crystals, m.p. 203-206 °C (acetone). [Found: M^+, 250.1096. $C_{16}H_{14}N_2O$ requires M, 250.1106]. $\nu_{max.}$ 1624, 1493, 1245 and 1176 cm^{-1}. δ 8.20 (1H, m, Ar-H), 7.90 (1H, d, *J* 9 Hz, Ar-H), 7.50-7.30 (3H, m, Ar-H), 7.00-6.80 (2H, m, Ar-H), 4.30 (2H, t, *J* 9 Hz, C(5)H_2), 3.90 (3H, s, -OCH_3) and 3.30 (2H, t, *J* 9 Hz, C(6)H_2).

5,6-Dihydrobenzimidazo-2,3,9-trimethoxy[2,1-a]isoquinoline **16d**

N-Oxide **15d** (4.00 g, 12.3 mmol) and PCl_3 (3.15 ml, 14.7 mmol) gave compound **16d** (2.96 g, 78 %) as white plates, m.p. 244-246 °C (ethanol). [Found: M^+, 310.1315. $C_{18}H_{18}N_2O_3$ requires M, 310.1317]. $\nu_{max.}$ 1621, 1510, 1254 and 1177 cm^{-1}. δ 7.90 (1H, s, Ar-H), 7.70 (1H, d, *J* 10 Hz, Ar-H), 7.00-6.70 (3H, m, Ar-H), 4.30 (2H, t, *J* 9 Hz, C(5)H_2), 4.00 (3H, s, -OCH_3), 3.90 (6H, s, 2 x -OCH_3) and 3.20 (2H, t, *J* 9 Hz, C(6)H_2).

9-Benzyloxy-5,6-dihydrobenzimidazo[2,1-a]isoquinoline **16e**

N-Oxide **15e** (1.39 g, 4.06 mmol) and PCl_3 (0.42 ml, 4.87 mmol) gave compound **16e** (0.81 g, 62%) as brown crystals, m.p. 150-153 °C (ethanol). [Found: C, 80.9; H, 5.6; N, 8.5. $C_{22}H_{18}N_2O$ requires C, 81.0; H, 5.6; N, 8.6 %]. $\nu_{max.}$ 1623, 1481, 1237 and 1165 cm^{-1}. δ 8.25 (1H, d, *J* 5 Hz, Ar-H), 7.75 (1H, d, *J* 9 Hz, Ar-H), 7.55-7.35 (8H, m, Ar-H), 7.00 (1H, dd, *J* 9 and 1 Hz, Ar-H), 6.90 (1H, d, *J* 1 Hz, Ar-H), 5.15 (2H, s, -OCH_2Ph), 4.30 (2H, t, *J* 9 Hz, C(5)H_2) and 3.30 (2H, t, *J* 9 Hz, C(6)H_2).

9-Benzyloxy-5,6-dihydrobenzimidazo-2,3-dimethoxy[2,1-a]isoquinoline **16f**

N-Oxide **15f** (2.80 g, 6.96 mmol) and PCl_3 (0.72 ml, 8.35 mmol) gave compound **16f** (0.37 g, 14%) as orange crystals, m.p. 160-162 °C (ethanol). [Found: M^+, 386.1619. $C_{24}H_{22}N_2O_3$ requires M, 386.1630]. $\nu_{max.}$ 1627, 1483, 1236 and 1135 cm^{-1}. δ 7.75 (1H, s, Ar-H), 7.65 (1H, d, *J* 10 Hz, Ar-H), 7.50-7.30 (5H, m, Ar-H), 7.00 (1H, dd, *J* 7 and 2 Hz, Ar-H), 6.90 (1H, d, *J* 2 Hz, Ar-H), 6.80 (1H, s, Ar-H), 5.15 (2H, s, -OCH_2Ph), 4.22 (2H, t, *J* 8 Hz, C(5)H_2), 4.00 (3H, s, -OCH_3), 3.90 (3H, s, -OCH_3) and 3.20 (2H, t, *J* 8 Hz, C(6)H_2).

5,6-Dihydro-2,3-dimethoxybenzimidazo[2,1-a]isoquinoline **16g**

N-oxide **15g** (0.50 g, 1.69 mmol) and PCl_3 (0.17 ml, 2.02 mmol) gave compound **16g** (0.19g, 41%) as orange crystals m.p. 191 °C (ethanol). [Found: C, 72.2; H, 5.75; N, 9.8. $C_{17}H_{16}N_2O_2$ requires C, 72.8; H, 5.75; N, 10.0 %]. $\nu_{max.}$ 1623, 1481, 1237 and 1165 cm^{-1}. δ 7.82 (2H, m, Ar-H), 7.36-7.24 (3H, m, Ar-H), 6.80 (1H, s, Ar-H), 4.32 (2H, t, *J* 7 Hz, C(5)H_2), 4.01 (3H, s, -OCH_3), 3.95 (3H, s, -OCH_3) and 3.23 (2H, t, *J* 7 Hz, C(6)H_2).

Compounds **16c** *and* **16d**. *Method B*.

A mixture of the appropriate *N*-oxide and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and anhydrous DCM was heated at reflux for 18 hours with stirring. The mixture was allowed to cool to room temperature

and was poured into dilute sodium hydroxide solution. The organic layer was separated and washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method *N*-oxide **15c** (0.02 g, 0.08 mmol) and DDQ (0.04 g, 0.15 mmol) gave compound **16c** (0.01 g, 55 %), identical with an authentic sample and *N*-oxide **15d** (0.10 g, 0.31 mmol) and DDQ (0.14 g, 0.61 mmol) gave compound **16d** (0.047 g, 47 %), identical with an authentic sample.

Compounds **26** *and* **27** *General Method*.

A mixture of the appropriate *N*-oxide, acetic anhydride and sodium acetate were heated at reflux (4 hours). After cooling to room temperature the mixture was poured into sodium hydroxide solution. After stirring overnight the mixture was extracted several times with DCM, the combined organic layers were washed several times with water, dried ($MgSO_4$) and evaporated yielding the product. By this method the following compounds were prepared.

8-Acetoxy-5,6-dihydro-9-methoxybenzimidazo[2,1-a]isoquinoline **26**

Compound **15c** (0.50 g, 1.88 mmol) in acetic anhydride (20 ml) and sodium acetate (0.30 g, 3.76 mmol) yielded compound **26** (0.28 g, 50 %) as brown crystals, m.p. 136–139 °C (ethanol). [Found: C, 67.0; H, 5.5; N, 8.7; M^+, 308.1147. $C_{18}H_{16}N_2O_3.0.8H_2O$ requires C, 67.05; H, 5.5; N, 8.7 %; M, 308.1161]. $\nu_{max.}$ 1762, 1638, 1263, 1174 and 1094 cm^{-1}. δ 8.22 (1H, m, Ar-H), 7.60 (1H, dd, *J* 6 and 1 Hz, Ar-H), 7.44-7.25 (3H, m, Ar-H), 7.00 (1H, dd, *J* 6 and 1 Hz, Ar-H), 4.43 (2H, t, *J* 7 Hz, C(5)H_2), 3.90 (3H, s, -OCH_3), 3.23 (2H, t, *J* 7 Hz, C(6)H_2) and 2.41 (3H, s, -$COCH_3$).

8-Acetoxy-5,6-dihydro-2,3,9-trimethoxybenzimidazo[2,1-a]isoquinoline **27**

Compound **15d** (0.10 g, 0.31 mmol), acetic anhydride (5.0 ml) and sodium acetate (0.049 g, 0.61 mmol) yielded compound **27** (0.023 g, 20 %) as brown crystals, m.p. 254-257 °C (ethanol). [Found: C, 65.0; H, 5.2; N, 7.3. $C_{20}H_{20}N_2O_5$ requires C, 65.2; H, 5.5; N, 7.6 %]. $\nu_{max.}$ 1764, 1638, 1264, 1163 and 1097 cm^{-1}. δ 7.75 (1H, s, Ar-H), 7.62 (1H, d, *J* 6 Hz, Ar-H), 7.00 (1H, d, *J* 6 Hz, Ar-H), 6.78 (1H, s, Ar-H), 4.48 (2H, t, *J* 7 Hz, C(5)H_2), 4.00 (3H, s, -OCH_3), 3.95 (3H, s, -OCH_3), 3.90 (3H, s, -OCH_3) and 3.20 (2H, t, *J* 7 Hz, C(6)H_2), 2.41 (3H, s, -$COCH_3$).

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