A Novel Ring Closure leading to 3,9-Dihydroxyaporphines (3,9-Dihydroxy-4*H*-dibenzo[*de,g*]quinolines). Part 2†

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3,9-Dihydroxyaporphines are formed by a novel and efficient ring closure when certain 1-benzyl-1,2,3,4-tetrahydro-5,8-dimethoxyisoquinolines are demethylated in refluxing hydrobromic acid. In accordance with a mechanism proposed in Part 1, it has been shown that such a ring closure is facilitated by a labile 3-alkoxy group on the benzyl moiety but inhibited by the stable 3-phenoxy group. The general principle of the aporphine ring closure is further confirmed by an alternative, unambiguous, albeit less efficient, synthesis of 3,9-dihydroxyaporphine.

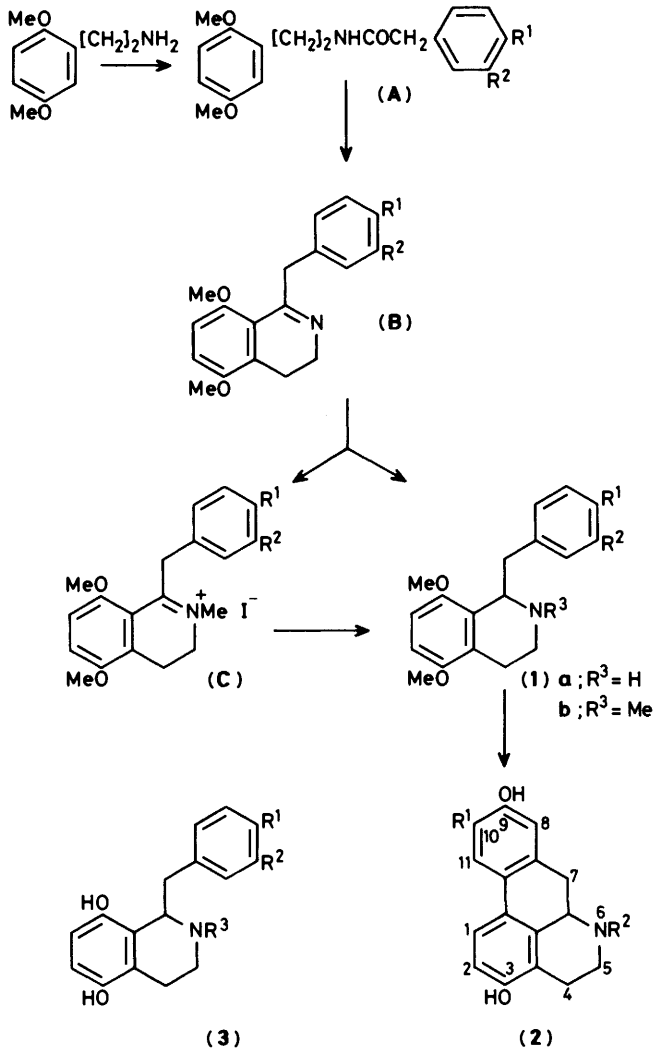
A variety of aporphines have been reported to exhibit an important range of pharmacological,[1] therapeutic,[2] and antibiotic[3] properties which has stimulated considerable interest in these compounds. Numerous methods[4] have been devised for their synthesis although, to date, these have proved less than satisfactory due to competing side-reactions. Therefore, any efficient and convenient procedure leading to this class of compound would be of interest.

In a preliminary communication,[5] evidence was presented for a novel cyclisation which gave 3,9-dihydroxyaporphines in high yield. We reported that the vigorous demethylation, in boiling hydrobromic acid, of 1,2,3,4-tetrahydro-1-(3,4-dimethoxybenzyl)-5,8-dimethyoxyisoquinoline (**1a**; $R^1 = R^2 = OMe$) and its *N*-methyl analogue (**1b**; $R^1 = R^2 = OMe$) yielded the respective aporphine derivatives (**2**; $R^1 = OH$, $R^2 = H$ or Me) rather than the simple demethylation products (**3**; $R^1 = R^2 = OH$, $R^3 = H$ or Me) (Scheme 1).

Although the sequence of events leading to cyclisation has not been fully elucidated, it was suggested[5] that this reaction proceeds by the mechanism shown in Scheme 2. It is implicit that the driving force for this putative mechanism must be the activation of one aromatic ring towards nucleophilic attack by another. Such activation could be achieved through the protonation of the relatively electron-rich 5-methoxy group[6] and the nucleophilic attack by bromide ion on the labile[7] 3′-methoxy group. This would initiate the first step in the cyclisation process leading to the quinone methide (**5**), *via* the loss of methanol from (**4**), and ultimately to the aporphine (**2**). Whether the reaction proceeds in a stepwise fashion with an initial formation of the intermediate 3′-hydroxybenzyl species (**1**; $R^2 = OH$) or in a concerted manner remains to be established. However, it is inferred that the 4′-methoxy group of compound (**1**; $R^1 = OMe$) is not essential to the ring-forming process. It is also inferred that, in combination with a correctly substituted 1,2,3,4-tetrahydroisoquinoline moiety, a labile 3′-alkoxy group by itself will facilitate the ring closure, but that a non-labile 3′-phenoxy group will not do so.

We now present further work which supports the validity of these initial conclusions. The formation of the 3,9-dihydroxyaporphine system (**2**) is further confirmed by an alternative, unambiguous, synthesis of compound (**2**; $R^1 = H$, $R^2 = Me$).

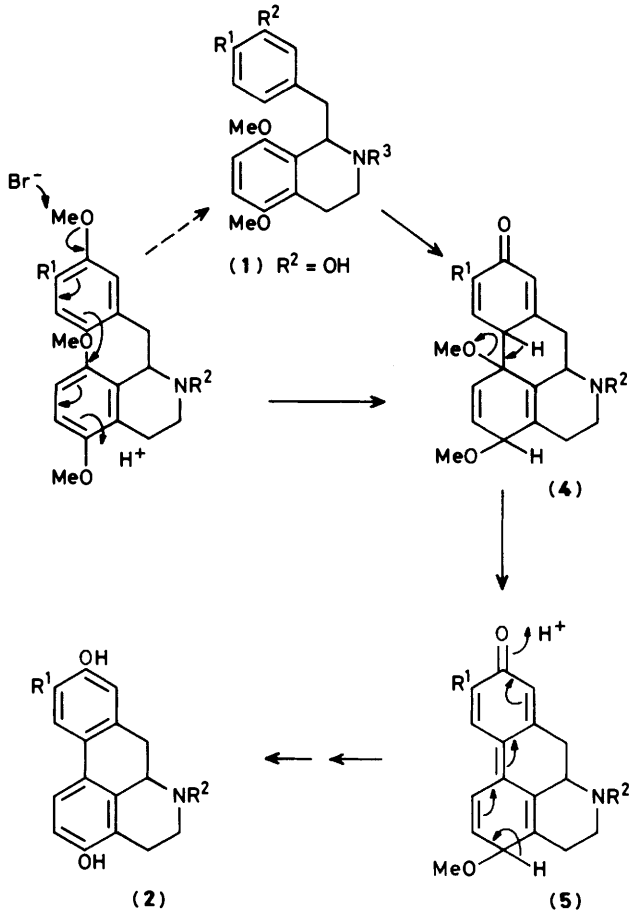
Thus, treatment of 1,2,3,4-tetrahydro-5,8-dimethoxy-1-(3-methoxybenzyl)isoquinoline (**1a**; $R^1 = H$, $R^2 = OMe$), prepared according to standard procedures (Scheme 1), with refluxing hydrobromic acid under nitrogen afforded 3,9-dihydroxynoraporphine (**2**; $R^1 = R^2 = H$).‡ Similarly, the *N*-methyl analogue (**1b**; $R^1 = H$, $R^2 = OMe$) gave 3,9-dihydroxyaporphine (**2**; $R^1 = H$, $R^2 = Me$), both cyclisations being accomplished in high yield (*ca.* 95%). The 3-ethoxy



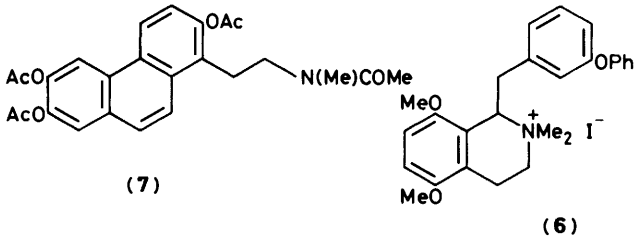
Scheme 1.

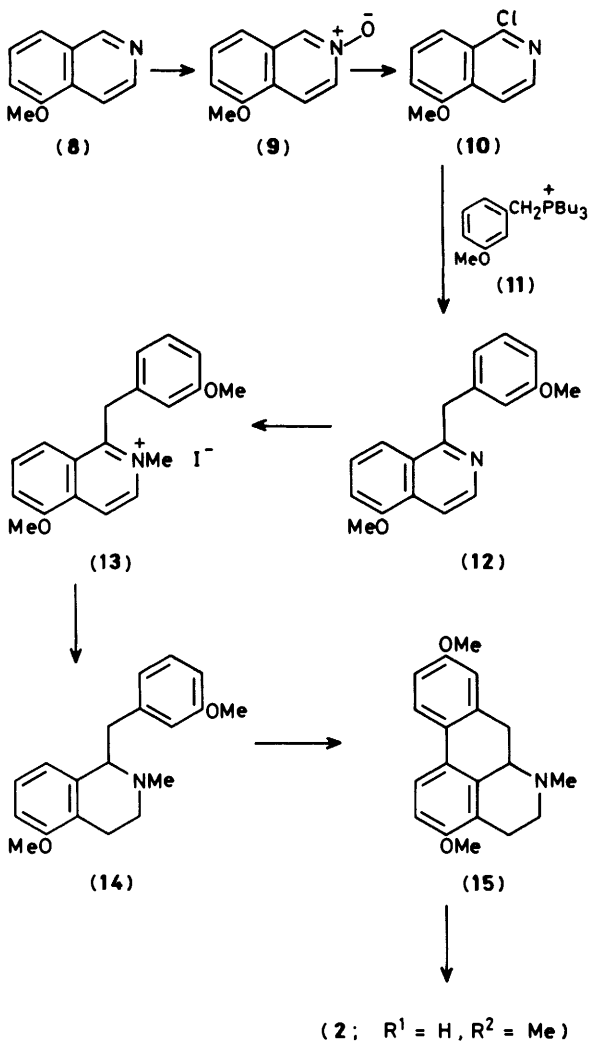
† Part 1, ref. 5.

‡ Unless stated otherwise, all products of demethylation with hydrobromic acid were isolated as their hydrobromide salts.



Scheme 2.





Scheme 3.

analogues, (**1a**, and **b**; R^1 = H, R^2 = OEt), also afforded equally high yields of the identical products (**2**; R^1 = R^2 = H) and (**2**; R^1 = H, R^2 = Me) respectively. In contrast, treatment of the 1,2,3,4-tetrahydro-1-(4-methoxybenzyl)isoquinoline (**1**; R^1 = OMe, R^2 = R^3 = H) under identical conditions gave the normal demethylation product (**3**; R^1 = OH, R^2 = R^3 = H). Thus these experiments support our original thesis that a 4′-alkoxy substituent does not participate in the ring-forming process.

Implicit in our postulated mechanism is the need for a labile C–O ether bond *para* to the position of ring closure. Consequently, a non-labile ether would not be expected to undergo a similar aporphine-forming cyclisation. Evidence in support of this was provided by the 3′-phenoxy derivatives (**1a**; R^1 = H, R^2 = OPh) and (**1b**; R^1 = H, R^2 = OPh) which, in boiling hydrobromic acid, afforded only the corresponding 1,2,3,4-tetrahydroisoquinolines (**3**; R^1 = R^3 = H, R^2 = OPh) and (**3**; R^1 = H, R^2 = OPh, R^3 = Me).

Failure to achieve cyclisation cannot be attributed to the steric effects of the bulky phenoxy substituents as the close analogue 1,2,3,4-tetrahydro-5,8-dimethoxy-1-(3-methoxy-4-phenoxybenzyl)-2-methylisoquinoline (**1b**; R^1 = OPh, R^2 = OMe) in boiling hydrobromic acid afforded the expected aporphine (**2**; R^1 = OPh, R^2 = Me) in high yield.

Treatment of compounds (**1**) with boron tribromide in place of hydrobromic acid did not effect the aporphine cyclisation and compounds (**1a**; R^1 = H, R^2 = OEt) and (**1a**; R^1 = H, R^2 = OPh) afforded only the 1,2,3,4-tetrahydroisoquinolines (**3**; R^1 = R^3 = H, R^2 = OH) and (**3**; R^1 = R^3 = H, R^2 = OPh), respectively. The latter compound on treatment with iodomethane in the presence of sodium hydride afforded the quaternary ammonium compound (**6**) which was identical with that prepared by the reaction of the isoquinoline (**1a**; R^1 = H, R^2 = OPh) with iodomethane.

The aporphine structures have been confirmed by established physicochemical criteria and substantiated by degradation of compound (**2**; R^1 = OH, R^2 = Me) with acetic anhydride[8] to the expected[9] phenanthrene derivative (**7**). Additional evidence for the validity of our general conclusion has been obtained by the alternative, unambiguous, synthesis of the aporphine (**2**; R^1 = H, R^2 = Me) outlined in Scheme 3. Reaction of 1-chloro-5-methoxyisoquinoline (**10**),[10] prepared from the *N*-oxide (**9**), with the ylide generated from the phosphonium salt (**11**) according to the method of Taylor and Martin[11] gave 5-methoxy-1-(3-methoxybenzyl)isoquinoline (**12**), which was

quaternised with iodomethane to give the salt (**13**) which was reduced with sodium borohydride in aqueous methanol to the 1,2,3,4-tetrahydroisoquinoline (**14**). Oxidative coupling of compound (**14**) with thallium(III) trifluoroacetate according to the procedure of McKillop[12] afforded 3,9-dimethoxyaporphine (**15**), albeit in low yield. This product was demethylated with refluxing hydrobromic acid to afford our target molecule (**2**; R^1 = H, R^2 = Me) which was identical with that obtained using the procedure outlined in Scheme 1. The overall yield of 3.6% based upon the starting material 5-methoxyisoquinoline (**8**) contrasts sharply with an overall yield of 38.4% based upon 2-(2,5-dimethoxyphenyl)ethylamine (Scheme 1) with the cyclisation steps giving 20 and 96% yield respectively.

It can be concluded, therefore, that the procedure described does lead to aporphines and, in contrast to published procedures,[4] is efficient and convenient. Our present observations identify certain structural features which are apparently essential for this novel ring closure.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 1579 spectrophotometer using KBr discs unless otherwise stated, u.v.–visible spectra on Acta CV or Hitachi-Perkin-Elmer 124 spectrophotometers, mass spectra on A.E.I. MS 902 or A.E.I. MS30 spectrometers, and ^{1}H n.m.r. spectra on a Perkin-Elmer R12B (60 MHz) or Brucker HFX-90 (90 MHz) spectrometers. Chemical shifts are reported in p.p.m. (δ) relative to tetramethylsilane. M.p.s (uncorrected) were recorded on Gallenkamp or Electrothermal heated block apparatus. Unless specified, all reagents and solvents were used as commercially available. Light petroleum refers to that fraction boiling in the range 40—60 °C.

N-[2-(2,5-*Dimethoxyphenyl*)*ethyl*]*phenylacetamides* (**A**).—*General procedure.* A mixture of 2-(2,5-dimethoxyphenyl)ethylamine (0.05 mol), a substituted phenylacetic acid (0.05 mol), and dry toluene (150 ml) was heated under reflux (12—20 h) until the theoretical amount of water had been azeotroped into a Dean–Stark trap. The resulting solution was cooled to 55—60 °C, light petroleum was added until a faint cloudiness was observed, and the mixture was kept at 2 °C for several hours. The crystalline deposit was collected, washed with toluene–light petroleum (1 : 5) followed by light petroleum, and dried at 50 °C. Analytically pure amides were produced. The relevant physicochemical data are given in Table 1.

Substituted 1-*Benzyl*-3,4-*dihydro*-5,8-*dimethoxyisoquinolines* (**B**): *General Procedure.*—A solution of an appropriately substituted *N*-[2-(2,5-dimethoxyphenyl)ethyl]phenylacetamide (**A**) (0.05 mol) in dry, ethanol-free chloroform (80 ml) and phosphoryl trichloride (40 ml) was heated under reflux until evolution of hydrogen chloride had ceased (5—12 h). The deep yellow-red reaction mixture was evaporated to dryness under reduced pressure to give a red gum which was treated cautiously with ice–water (150—200 ml) and stirred at 60 °C for 30 min, and the resulting solution was treated with 60% perchloric acid (20 ml). After several hours at 2 °C, the slurry was filtered and the solid residue was washed with ether. Crystallisation from an appropriate solvent afforded analytically pure 1-benzyl-3,4-dihydro-5,8-dimethoxyisoquinoline perchlorates: the physicochemical data for these are given in Table 2. All compounds were homogenous by t.l.c. and gave satisfactory ^{1}H n.m.r. spectra.

Substituted 1-*Benzyl*-3,4-*dihydro*-5,8-*dimethoxy*-2-*methylisoquinolinium Iodines* (**C**): *General Procedure.*—A suspension of an appropriately substituted 1-benzyl-3,4-dihydro-5,8-dimethoxyisoquinoline perchlorate (10 mmol) in water (50 ml) was basified with ammonia solution (*d* 0.88; 10 ml) and the liberated base was rapidly extracted into ether (3 × 50 ml). The combined extracts were washed with water (50 ml), dried over sodium sulphate, filtered, and evaporated under reduced pressure to give a pale yellow oil or solid. The base dissolved in butan-2-one (20 ml) and benzene (20 ml), was treated with iodomethane (10 ml) and the mixture was kept at 50 °C for 5—7 h. After being diluted slowly to twice its original volume with ether whilst being stirred, the slurry was filtered and the crude 1-benzyl-3,4-dihydro-5,8-dimethoxy-2-methylisoquinolinium iodide was washed with ether and recrystallised from a suitable solvent. All compounds were homogeneous by t.l.c. and their physicochemical data are given in Table 2.

Table 1. Substituted *N*-[2-(2,5-dimethoxyphenyl)ethyl]phenylacetamides (**A**)

Product (Formula)	R^1	R^2	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N
$C_{20}H_{25}NO_5$	OMe	OMe	83.0	95—96	66.4 (66.85)	7.1 (6.97)	3.7 (3.90)
$C_{19}H_{23}NO_4$	H	OMe	84.5	92—93	69.4 (69.30)	7.1 (6.99)	4.35 (4.26)
$C_{20}H_{25}NO_4$[a]	H	OEt	71.2	97—98	70.0 (69.95)	7.3 (7.34)	4.2 (4.08)
$C_{19}H_{23}NO_4$	OMe	H	88.2	88—89	69.4 (69.30)	7.2 (6.99)	4.2 (4.26)
$C_{24}H_{25}NO_4$[b]	H	OPh	62.3	74—75	73.8 (73.64)	6.4 (6.44)	3.6 (3.58)
$C_{25}H_{27}NO_5$[c]	OPh	OMe	71.0	135—136	71.5 (71.24)	6.55 (6.46)	3.3 (3.32)

[a] (3-Ethoxyphenyl)acetic acid, m.p. 92—93 °C. [b] (3-Phenoxyphenyl)-acetic acid, m.p. 84—86 °C. [c] (3-Methoxy-4-phenoxyphenyl)acetic acid, m.p. 70—72 °C. These 3 phenylacetic acids were prepared by standard procedures.

Substituted 1-*Benzyl*-1,2,3,4-*tetrahydro*-5,8-*dimethoxyisoquinolines* (**1a**) *and* 1-*Benzyl*-1,2,3,4-*tetrahydro*-5,8-*dimethoxy*-2-*methylisoquinolines* (**1b**): *General Procedure.*—A solution/suspension of the 3,4-dihydroisoquinoline perchlorate (10 mmol) or 3,4-dihydro-2-methylisoquinolinium iodide (10 mmol) in ethanol (50 ml) was treated with sodium borohydride (2 g) during 30 min. The resulting solution was stirred for 30 min, evaporated to dryness under reduced pressure, and the semisolid residue was treated with 0.5M-NaOH solution (50 ml). The liberated base was extracted into ether (3 × 50 ml) and the combined extracts were dried over magnesium sulphate, filtered, and evaporated to leave an oil. The 1-benzyl-1,2,3,4-tetrahydro-5,8-dimethoxyisoquinolines (**1a**) and 1-benzyl-1,2,3,4-tetrahydro-5,8-dimethoxy-2-methylisoquinolines (**1b**) were converted into appropriate salts and characterised. The physicochemical data for compounds (**1a**) and (**1b**) are given in Table 3. All compounds were homogeneous by t.l.c. and gave satisfactory ^{1}H n.m.r. spectra.

Demethylation of Substituted 1-*Benzyl*-1,2,3,4-*tetrahydro*-5,8-*dimethoxyisoquinolines* (**1**) *with Hydrobromic Acid*

(*A*) *Preparation of Substituted* 5,6,6a,7-*Tetrahydro*-4H-*dibenzo*[de,g]*quinolines* (**2**): *General Procedure.*—A suspension of an appropriately substituted 1-benzyl-1,2,3,4-tetrahydro-5,8-dimethoxyisoquinoline (**1**) (5 mmol) under nitrogen in 48% hydrobromic acid (20 ml) was heated rapidly to reflux using an

Table 2. Substituted 1-benzyl-3,4-dihydro-5,8-dimethoxyisoquinolines (**B**) and substituted 1-benzyl-3,4-dihydro-5,8-dimethoxy-2-methylisoquinolinium iodides (**C**)

Product (Formula) (**B**)	R^1	R^2	Yield (%)	M.p. (°C)	Crystallisation solvent	Found (%) (Requires) C	H	N
$C_{20}H_{23}NO_4 \cdot HClO_4$	OMe	OMe	54.0	214—215 (decomp.)	MeOH	54.1 (54.36)	5.5 (5.44)	3.2 (3.17)
$C_{19}H_{21}NO_3 \cdot HClO_4$	H	OMe	64.9	178—179	MeOH–DMSO–Et_2O	55.5 (55.41)	5.4 (5.35)	3.4 (3.40)
$C_{20}H_{23}NO_3 \cdot HClO_4$	H	OEt	52.2	166—168	EtOH–Et_2O	56.6 (56.41)	5.8 (5.68)	3.3 (3.29)
$C_{19}H_{21}NO_3 \cdot HClO_4$	OMe	H	40.8	186—187	EtOH–Et_2O	55.6 (55.41)	5.6 (5.35)	3.4 (3.40)
$C_{24}H_{23}NO_3$	H	OPh	56.4	155—157	MeOH–light petroleum	60.9 (60.83)	5.2 (5.10)	2.9 (2.96)
$C_{25}H_{25}NO_4$	OPh	OMe	69.0	165—166	MeOH–Et_2O	59.5 (59.59)	5.2 (5.20)	2.8 (2.78)
(**C**)								
$C_{21}H_{26}INO_4$	OMe	OMe	96.5	202—203 (decomp.)	MeOH	52.4 (52.17)	5.5 (5.38)	2.9 (2.90)
$C_{20}H_{24}INO_3$	H	OMe	86.5	152—153 (resolidifies)	MeOH–Et_2O	52.9 (52.98)	5.5 (5.30)	2.9 (3.09)
$C_{21}H_{26}INO_3$	H	OEt	76.4	128—130	Me_2CO–Et_2O	53.6 (53.97)	5.6 (5.61)	3.0 (3.00)
$C_{25}H_{26}INO_3$	H	OPh	92.3	155—156	MeOH–Et_2O	58.2 (58.26)	4.95 (5.08)	2.7 (2.72)

Table 3. Substituted 1-benzyl-1,2,3,4-tetrahydro-5,8-dimethoxyisoquinolines (**1a**) and (**1b**)

Product (Formula) (**1a**)	R^1	R^2	Yield (%)	M.p. (°C)	Crystallisation solvent	Found (%) (Requires) C	H	N
$C_{20}H_{25}NO_4 \cdot HCl \cdot 0.25H_2O$	OMe	OMe	98.7	183—184	EtOH–Et_2O	62.7 (62.50)	6.9 (6.90)	3.6 (3.64)
$C_{19}H_{23}NO_3 \cdot HCl$	H	OMe	98.1	164—165	MeOH–Et_2O	65.4 (65.24)	7.0 (6.87)	3.9 (4.01)
$C_{20}H_{25}NO_3 \cdot HCl$	H	OEt	88.9	203—205	MeOH–Et_2O	66.1 (66.02)	7.25 (7.20)	4.5 (4.85)
$C_{19}H_{23}NO_3 \cdot HCl$	OMe	H	86.3	225—226	MeOH–Et_2O	65.2 (65.24)	7.1 (6.87)	4.0 (4.01)
$C_{24}H_{25}NO_3 \cdot HCl$	H	OPh	94.8	188—190	MeOH–Et_2O	69.65 (69.98)	6.4 (6.36)	3.4 (3.40)
$C_{25}H_{27}NO_4 \cdot HCl$	OPh	OMe	61.3	205—207	MeOH–Et_2O	67.9 (67.94)	6.5 (6.39)	3.1 (3.17)
(**1b**)								
$C_{21}H_{27}NO_4 \cdot HCl$	OMe	OMe	97.0	193—194	EtOH–Et_2O	64.1 (64.04)	7.2 (7.12)	3.6 (3.56)
$C_{20}H_{25}NO_3 \cdot HClO_4$	H	OMe	82.4	149—150	EtOH–Et_2O	56.1 (56.14)	6.3 (6.08)	3.1 (3.27)
$C_{21}H_{27}NO_3 \cdot HClO_4 \cdot \frac{1}{4}Me_2CO$	H	OEt	97.0	135—137	Me_2CO–Et_2O	56.9 (57.27)	6.6 (6.51)	3.1 (3.07)
$C_{25}H_{27}NO_3 \cdot HCl \cdot H_2O$	H	OPh	86.0	128—130	MeOH–Et_2O	67.6 (67.64)	6.7 (6.76)	3.2 (3.16)

oil bath at 140 °C. A clear solution quickly formed followed, after 2—4 h, by the gradual separation of a crystalline solid. After 7—9 h at reflux, the mixture was kept at 2 °C for several hours. The product was collected, washed with acetone–ether (1:4), dried and, if necessary, recrystallised. The ^1H n.m.r. spectra are given in Table 4.

5,6,6a,7-*Tetrahydro*-3,9,10-*trihydroxy*-4H-*dibenzo*[de,g]-*quinoline* (**2**; R^1 = OH, R^2 = H) *hydrobromide*. The *noraporphine* was prepared from the isoquinoline (**1a**; R^1 = R^2 = OMe) and the product was isolated from 48% hydrobromic acid as pale cream prisms (90.3%), m.p. 282—284 °C (decomp.); t.l.c. (HCl–MeOH, 1:99) one spot, R_F 0.56; $\bar{\nu}_{max.}$ 3 280, 3 200, 3 070, 2 920, 2 880, 1 610, 1 600, 1 485, 1 215, and 810 cm^{-1}; *m/z* 269 ($M^{+\cdot}$, 78%), 268 [$(M - 1)^{+\cdot}$, 100], 240 ($C_{15}H_{12}O_3^{+\cdot}$, 27), 222 ($C_{15}H_{10}O_2^{+\cdot}$, 8), 165 (9), and 152 (4.5); $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 236.7 infl (9 840), 281.7 (17 270), and 301.2 nm (14 880) (Found: C, 54.75; H, 4.6; N, 3.85. $C_{16}H_{15}NO_3 \cdot HBr$ requires C, 54.86; H, 4.57; N, 4.00%).

5,6,6a,7-*Tetrahydro*-3,9,10-*trihydroxy*-6-*methyl*-4H-*dibenzo*-[de,g]*quinoline* (**2**; R^1 = OH, R^2 = Me) *hydrobromide*. The

Table 4. ^{1}H N.m.r. data for substituted 5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinolines (**2**)

Product (**2**)	R^1 = OH, R^2 = H	R^1 = OH, R^2 = Me	R^1 = R^2 = H	R^1 = H, R^2 = Me
4- and 5-H_2	2.79—3.64 (4 H, m)	2.76—3.88 (6 H, m)	2.82—3.78 (4 H, m)	2.77—3.83 (6 H, m)
7-H_2	2.84 (dd), 3.56 (dd) (J_{gem} 12.0 Hz)		2.97 (dd), 3.65 (dd) (J_{gem} 14.1 Hz)	
6-R^2		3.10 (s)		3.04 (s)
6a-H	4.36 (d,d) (J_{cis} 12.6, J_{trans} 6.7 Hz)	4.42 (d,d) (J_{cis} 13.0, J_{trans} 4.0 Hz)	4.42 (d,d) (J_{cis} 12.2, J_{trans} 6.8 Hz)	4.45 (d,d) (J_{cis} 13.4, J_{trans} 2.5 Hz)
1-H	7.33 (d) ($J_{1,2}$ 8.6 Hz)	7.34 (d) ($J_{1,2}$ 8.5 Hz)	7.45 (d) ($J_{1,2}$ 8.6 Hz)	7.9 (d) ($J_{1,2}$ 8.6 Hz)
2-H	6.88 (d)	6.87 (d)	6.88 (d)	6.91 (d)
8-H	6.69 (s)	6.77 (s)	6.71 (d) ($J_{8,10}$ 2.4 Hz)	6.78 (d) ($J_{8,10}$ 1.9 Hz)
10-H			6.77 (dd) ($J_{10,11}$ 8.9 Hz)	6.79 (dd) ($J_{10,11}$ 9.1 Hz)
11-H	7.10 (s)	7.09 (s)	7.52 (d)	7.51 (d)
Other features	8.60 (v, br), 9.45 (br) (3 OH + NH_2^+)	9.00 (br), 9.78 (sh), 10.22 (br) (3OH + NH^+)	9.36 (br), 9.51 (br) (2OH + NH_2^+)	9.48 (br), 10.31 (br), 10.91 (br) (2 OH, NH^+)

aporphine was prepared from compound (**1b**; R^1 = R^2 = OMe) and the crude product was crystallised from ethanol–dimethyl sulphoxide–ether to give small off-white prisms (95.8%), m.p. 297—299 °C (decomp.); t.l.c. (HCl–MeOH, 1:99) one spot, R_F 0.55; $\tilde{\nu}_{max.}$ 3 545, 3 500, 3 250, 2 930, 2 820, 1 630, 1 610, 1 495, 1 340, 1 270, and 835 cm^{-1}; *m/z* 283 ($M^{+\bullet}$, 85), 282 [(M − 1)$^{+\bullet}$, 100], 265 [(M − H_2O)$^{+\bullet}$, 53], 240 ($C_{15}H_{12}O_3^{+\bullet}$, 67), 222 ($C_{15}H_{10}O_2^{+\bullet}$, 3), 165 (10), and 152 (4); $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 241.0 infl (8 350) and 280.9 nm (16 130) (Found: C, 56.0; H, 4.9; N, 4.1. $C_{17}H_{17}NO_3$·HBr requires C, 56.04; H, 4.95; N, 3.85%).

5,6,6a,7-*Tetrahydro*-3,9-*dihydroxy*-4H-*dibenzo*[de,g]*quinoline* (**2**; R^1 = R^2 = H) *hydrobromide*. (i) *From* (**1a**; R^1 = H, R^2 = OMe). The *noraporphine* was prepared from compound (**1a**; R^1 = H, R^2 = OMe) and crystallisation of the crude product from methanol gave beige plates (94.8%), m.p. 295—296 °C (decomp.); t.l.c. (HCl–MeOH, 1:99) one spot, R_F 0.58; $\tilde{\nu}_{max.}$ 3 295, 3 200, 3 040, 2 940, 2 800, 1 615, 1 600, 1 485, 1 220, and 815 cm^{-1}; *m/z* 253 ($M^{+\bullet}$, 73), 252 [(M − 1)$^{+\bullet}$, 100], 224 ($C_{15}H_{12}O_2^{+\bullet}$, 39), 165 (8.5), and 152 (5.5); $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 285.7 nm (23 700) (Found: C, 57.7; H, 4.9; N, 4.2. $C_{16}H_{15}NO_2$·HBr requires C, 57.50; H, 4.79; N, 4.19%).

(ii) *From* (**1a**; R^1 = H, R^2 = OEt). The noraporphine, prepared from compound (**1a**; R^1 = H, R^2 = OEt), was obtained as off-white needles (86.0%) from 48% hydrobromic acid, m.p. 292—293 °C (decomp.), admixture with product from reaction (i) m.p. 292—293 °C (decomp.) (Found: C, 55.1; H, 4.8; N, 4.0. Calc. for $C_{16}H_{15}NO_2$·HBr·0.75H_2O: C, 55.25; H, 5.04; N, 4.03%). The i.r., u.v., ^{1}H n.m.r., and mass spectra are consistent with those obtained for the product from reaction (i).

5,6,6a,7-*Tetrahydro*-3,9-*dihydroxy*-6-*methyl*-4H-*dibenzo*-[de,g]*quinoline* (**2**; R^1 = H, R^2 = Me) *hydrobromide*. (i) *From* (**1b**; R^1 = H, R^2 = OMe). The *aporphine* was prepared from compound (**1b**; R^1 = H, R^2 = OMe) and the product was isolated from 48% hydrobromic acid as an off-white crystalline powder (95.7%), m.p. 285—288 °C (decomp.); t.l.c. (HCl–MeOH, 1:99) one spot, R_F 0.57; $\tilde{\nu}_{max.}$ 3 480, 3 310, 3 260, 2 800, 1 620, 1 610, 1 600, 1 475, 1 280, 1 210, and 815 cm^{-1}; *m/z* 267 ($M^{+\bullet}$, 77), 266 [(M − 1),$^{+\bullet}$ 100], 249 [(M − H_2O)$^{+\bullet}$, 3], 224 ($C_{15}H_{12}O_2^{+\bullet}$, 64), 165 (5), and 152 (1); $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 284.9 nm (21 930) (Found: C, 58.5; H, 5.33; N, 3.9. $C_{17}H_{17}NO_2$·HBr requires C, 58.62; H, 5.21; N, 4.02%).

(ii) *From* (**1b**; R^1 = H, R^2 = OEt). The aporphine prepared from compound (**1b**; R^1 = H, R^2 = OEt)* was obtained as a white microcrystalline solid (76.0%) from 48% hydrobromic acid, m.p. 290—291 °C (decomp.); admixture with product from method (i) m.p. 290—291 °C (decomp.) (Found: C, 58.0; H, 5.3; N, 4.0. Calc. for $C_{17}H_{17}NO_2$·HBr: C, 58.62; H, 5.21; N, 4.02%). The i.r., u.v., ^{1}H n.m.r., and mass spectra are identical with those obtained from the product from method (i).

5,6,6a,7-*Tetrahydro*-3,9-*dihydroxy*-10-*phenoxy*-4H-*dibenzo*-[de,g]*quinoline* (**2**; R^1 = OPh, R^2 = H) *hydrobromide*. The *noraporphine* was prepared from compound (**1a**; R^1 = OPh, R^2 = OMe) and the product was isolated from 48% hydrobromic acid as a microcrystalline solid (50.0%), m.p. 293—295 °C (decomp.); $\tilde{\nu}_{max.}$ 3 532, 3 314, 2 800, 2 462, 1 338, and 1 213 cm^{-1}; *m/z* 345 ($M^{+\bullet}$, 100), 344 [(M − 1)$^{+\bullet}$, 96], 343 ($C_{22}H_{17}NO_3^{+\bullet}$, 65), 328 ($C_{22}H_{18}NO_2$, 15), 316 ($C_{21}H_{16}O_3$, 18), 251 (43), 223 (23), 165 ($C_{13}H_9^{+\bullet}$, 10), 164 ($C_{13}H_8^{+\bullet}$ 12), and 152 ($C_{12}H_8^{+\bullet}$, 7); $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 218.0 (31 000), 280.5 (21 000), and 293.0 nm (18 000); δ_H [$(CD_3)_2SO$; 90 MHz] 2.62—3.92 (6 H, br m, Ar$CH_2CH_2N^+$ and CCH_2Ar), 4.50 (1 H, br s, ArCHN^+), 6.79—7.49 (9 H, m, ArH), 8.60—9.97 (2 H, br s, N^+H_2), and 9.67 and 9.84 (2 H, 2 s, Ar*OH*) (Found: C, 62.0; H, 4.8; N, 3.3. $C_{22}H_{19}NO_3$·HBr requires C, 61.98; H, 4.73; N, 3.29%).

(B) *Dealkylation Reactions giving Non-aporphine Derivatives*.—1,2,3,4-*Tetrahydro*-5,8-*dihydroxy*-1-(4-*hydroxybenzyl*)-*isoquinoline* (**3**; R^1 = OH, R^2 = R^3 = H) *hydrobromide*. *Procedure A*. A suspension of 1,2,3,4-tetrahydro-5,8-dimethoxy-1-(4-methoxybenzyl)isoquinoline hydrochloride (**1a**; R^1 = OMe, R^2 = H)·HCl (3.5 g, 10 mmol) in 48% hydrobromic acid (40 ml) under nitrogen was heated rapidly to reflux. After 4 h at reflux, the pale tan solution was cooled to 2 °C. After 2 h, the *title product* (**3**; R^1 = OH, R^2 = R^3 = H) was collected, washed with acetone–ether (1:4), and recrystallised from ethanol–acetone–ether to give pale pink prisms (3.21 g, 90.0%), m.p. 297—299 °C (effervesc.); t.l.c. (HCl–MeOH, 1:99) one spot, R_F 0.48; $\tilde{\nu}_{max.}$ 1 590, 1 490, 1 280, 1 270, 1 070, 810, 790, and 745 cm^{-1}; δ_H [$(CO_3)_2SO$; 90 MHz; 333 K] 2.68—3.45 (6 H, m), 4.66 (1 H, dd, *J cis* 11.5, *J* trans 3.1 Hz, 1-H), 6.67 (2 H, s, 6- and 7-H), 6.76 (2 H, d, 3′- and 5′-H), 7.15 (2 H, d, 2′- and 6′-H), ($J_{2',3'}$ = $J_{5',6'}$ = 8.5 Hz), and 8.74 and 9.10 (each br, N^+H_2 and OH); *m/z*) 271 ($M^{+\bullet}$, absent), 164 ($C_8H_{10}O_2^{+\bullet}$, 100%), and 107 ($C_7H_7O^{+\bullet}$, 14) (Found: C, 54.5; H, 5.1; N, 4.0. $C_{16}H_{17}NO_3$·HBr requires C, 54.56; H, 5.15; N, 3.98%).

1,2,3,4-*Tetrahydro*-5,8-*dihydroxy*-1-(3-*hydroxybenzyl*)*iso*-

* (The base, regenerated from the perchlorate salt using standard procedure, was used).

quinoline (3; $R^1 = R^3 = H, R^2 = OH$) *hydrobromide. Procedure B.* To a stirred solution of 1-(3-ethoxybenzyl)-1,2,3,4-tetrahydro-5,8-dimethoxyisoquinoline hydrochloride (**1a**; $R^1 = H$, $R^2 = OEt$)·HCl (0.50 g, 1.4 mmol) in dry dichloromethane (15 ml) at −60 °C was added a solution of boron tribromide (0.95 ml, 10 mmol) in dichloromethane (5 ml). The colourless solution was allowed to warm to room temperature overnight and was then treated slowly with 48% (w/w) hydrobromic acid (11 ml). After 5 min, the solid was collected by filtration, washed with cold water, and dried to give a white powder (0.05 g), m.p. 279—280 °C. The filtrates were evaporated under reduced pressure to 1—2 ml and the resulting suspension was treated with water (20 ml). After a few minutes the off-white microcrystalline solid was collected by filtration, washed with water, and dried; m.p. 280—281 °C, total yield 0.25 g (52%); $\bar{\nu}_{max.}$ 3 260br, 1 262br, and 1 215 cm^{-1}; $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 284 (4 900) and 295 nm (5 000); δ_H [$(CD_3)_2SO$; 60 MHz; 298 K] 2.66—4.05 (6 H, br m, $ArCH_2CH_2N^+$ and CCH_2Ar), 4.67 (1 H, br s, $ArCHN^+$), 6.71—6.84 and 7.10—7.45 (total 6 H, m, ArH), 8.41 (2 H, br s, N^+H_2), and 9.38 (3 H, br s, 3 ArOH); *m/z* 271 ($M^{+\bullet}$, trace), 2.53 [$(M - H_2O)^{+\bullet}$, trace], 236 ($C_{16}H_{14}NO^{+\bullet}$, trace), 164 ($C_9H_{10}NO_2^{+\bullet}$, 100), 147 ($C_9H_9NO^{+\bullet}$,1), 107 ($C_7H_7O^{+\bullet}$, 4), and 91 ($C_7H_7^{+\bullet}$, 1) (Found: C, 54.4; H, 5.3; N, 3.9. $C_{16}H_{17}NO_3$·HBr requires C, 54.56; H, 5.15; N, 3.98%).

1,2,3,4-*Tetrahydro*-5,8-*dihydroxy*-2-*methyl*-1-(3-*phenoxybenzyl*)*isoquinoline* (3; $R^1 = H$, $R^2 = OPh$, $R^3 = Me$) *hydrobromide.* Demethylation of 1,2,3,4-tetrahydro-5,8-dimethoxy-2-methyl-1-(3-phenoxybenzyl)isoquinoline hydrochloride (1.83 g) using *procedure A* afforded the *title product* (3; $R^1 = H$, $R^2 = OPh$, $R^3 = Me$) (1.47 g, 77%) as an off-white amorphous solid which did not melt sharply, but sintered above 140 °C and became liquid at *ca.* 240 °C; $\bar{\nu}_{max.}$ 3 240br, 2 860br, and 1 274 cm^{-1}; $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 209 (32 000) and 285 nm (9 400); δ_H [$(CD_3)_2SO$; 60 MHz; 289 K] 2.76—4.10 (9 H, br m, $ArCH_2CH_2NCH_3$ and $ArCH_2$), 4.83 (1 H, br s, $ArCHN^+$), 6.70—7.82 (11 H, m, ArH), 8.98 (br), 9.15; 9.46 (br), and 9.75 (total 3 H, each s, 2 ArOH + N^+H) (Found: C, 61.6; H, 5.4; N, 3.1. $C_{23}H_{23}NO_3$·HBr·0.25H_2O requires C, 61.81; H, 5.49; N, 3.14%). A sample submitted for mass spectral analysis underwent aerial oxidation to the 1-benzoyl derivative, $C_{23}H_{21}NO_4$·HBr, which showed *m/z* 375 ($M^{+\bullet}$, absent), 206 ($C_{11}H_{12}NO_3^{+\bullet}$, 100), 191 ($C_{10}H_9NO_3^{+\bullet}$, 7), 174 ($C_{10}H_8NO_2^{+\bullet}$, 9), 149 ($C_8H_7NO_2^{+\bullet}$, 6), 121 ($C_7H_7NO^{+\bullet}$, 5), and 105 ($C_7H_7N^{+\bullet}$, 9).

1,2,3,4-*Tetrahydro*-5,8-*dihydroxy*-1-(3-*hydroxy*-4-*phenoxybenzyl*)*isoquinoline* (3; $R^1 = OPh$, $R^2 = OH$, $R^3 = H$) *hydrobromide.* Demethylation of 1,2,3,4-tetrahydro-5,8-dimethoxy-1-(3-methoxy-4-phenoxybenzyl)isoquinoline hydrochloride (**1a**; $R^1 = OPh$, $R^2 = OMe$) (1.01 g, 2.3 mmol) using *procedure B* afforded the *title compound* (3; $R^1 = OPh$, $R^2 = OH$, $R^3 = H$) (0.5 g, 47%) as a cream coloured amorphous solid, m.p. 205—210 °C; t.l.c. (methanol) one spot, R_F 0.73; $\nu_{max.}$ 3 680—2 100br, 1 268, and 1 213 cm^{-1}; $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 204 (46 000), 270 (10 000), 276.5 (11 000), and 283 nm (11 000); δ_H [$(CD_3)_2SO$; 60 MHz; 298 K] 2.60—3.59 (6 H, br m, $ArCH_2CH_2N^+$ + CCH_2Ar), 4.65 (1 H, br s, $ArCHN^+$), 6.67—7.45 (10 H, m, ArH) 8.43 (1 H, br s, N^+H_2), and 9.37 (3 H, br s, 3 ArOH); *m/z* 363 ($M^{+\bullet}$, trace), 361 [$(M - 2)^{+\bullet}$, 2%)], 345 ($C_{22}H_{19}NO_3^{+\bullet}$, trace), 200 ($C_{13}H_{12}O_2^{+\bullet}$, 6), 199 ($C_{13}H_{11}O_2^{+\bullet}$, 5), 164 ($C_9H_{10}NO_2^{+\bullet}$, 100), 162 ($C_9H_8NO_2^{+\bullet}$, 6), and 136 ($C_8H_{10}NO$, 16) (Found: C, 57.15, H, 5.1; N, 3.0. $C_{22}H_{21}NO_4$·HBr·H_2O requires C, 57.15; H, 5.23; N, 3.03%).

1,2,3,4-*Tetrahydro*-5,8-*dihydroxy*-1-(3-*phenoxybenzyl*)-*isoquinoline* (3; $R^1 = R^3 = H$, $R^2 = OPh$) *hydrobromide. Procedure A.* Demethylation of 1,2,3,4-tetrahydro·5,8-dimethoxy-1-(3-phenoxybenzyl)isoquinoline hydrochloride (**1a**; $R^1 = H$, $R^2 = OPh$) (7.11 g, 17 mmol) using *procedure A* afforded the *title product* (3; $R^1 = R^3 = H$, $R^2 = OPh$) (7.18 g, 97%) as a white micro-crystalline solid, m.p. 268—270 °C; $\bar{\nu}_{max.}$ 3 330br, 2 780, 2 434, 1 613, 1 209, and 772 cm^{-1}; $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 282 (5 100) and 295 nm (5 600); δ_H [$(CO_3)_2SO$; 60 MHz; 298 K] 2.68—3.80 (6 H, br m, $ArCH_2CH_2N^+$ + CCH_2Ar), 4.79 (1 H, br s, $ArCHN^+$), 6.75—7.61 (11 H, m, ArH), 8.71 (1 H, br s, NH_2^+), and 9.37 (2 H, br s, 2 ArOH); *m/z* 347 ($M^{+\bullet}$, trace), 346 ($M^{+\bullet} - 1$,trace),329[$(M - H_2O)^{+\bullet}$,10%)],312($C_{22}H_{18}NO^{+\bullet}$,2),183 ($C_{13}H_{11}O^{+\bullet}$, 2), and 164 ($C_9H_{10}NO_2^{+\bullet}$, 100) (Found: C, 61.9; H, 5.12; N, 3.3. $C_{22}H_{21}NO_3$·HBr requires C, 61.69; H, 5.18; N, 3.27%).

Procedure B. Demethylation of compound (**1a**; $R^1 = H$, $R^2 = OPh$) using *procedure B* afforded the product (3; $R^1 = R^3 = H$, $R^2 = OPh$)·HBr in 65% yield as a buff coloured powder, m.p. 262—263 °C. Admixture with the product from *procedure A* gave mixed m.p. 261—262 °C (Found: C, 61.3; H, 5.2; N, 3.3%). The i.r., u.v., ^1H n.m.r., and mass spectra are consistent with those obtained for the product from procedure A.

1,2,3,4-*Tetrahydro*-5,8-*dimethoxy*-2,2-*dimethyl*-1-(3-*phenoxybenzyl*)*isoquinolinium Iodide* (**6**).—*Procedure A.* To a solution of 1,2,3,4-tetrahydro-5,8-dimethoxy-2-methyl-1-(3-phenoxybenzyl)isoquinoline (**1b**; $R^1 = H$, $R^2 = OPh$) (0.9 g, 2.3 mmol) in acetone (5 ml) was added iodomethane (3 ml) and the mixture was kept, with occasional warming, for 24 h. The solid deposit was collected, washed with acetone–ether (1:1), and dried to give the *title product* as an amorphous white powder (0.95 g, 76%), m.p. 203—205 °C; $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 211.5 (36 000), 280 (5 200), and 292 nm (4 900); δ_H (60 MHz; $CDCl_3$) 2.82—4.10 (6 H, m, $ArCH_2CH_2N^+$ + CCH_2Ar), 3.34 (3 H, s, N^+CH_3), 3.51, 3.62, and 3.78, (total 9 H, 3 s, N^+CH_3 and 2 OCH_3), 4.95 (1 H, br s, $ArCHN^+$), 6.72—7.52 (11 H, m, ArH); *m/z* 404 ($M^{+\bullet}$, trace), 403 [$(M - 1)^{+\bullet}$, trace], 388 [$(M - 15)^{+\bullet}$ trace], 206 ($C_{12}H_{16}NO^{+\bullet}$, 100), 191 ($C_{11}H_{13}NO^{+\bullet}$, 4), 176 ($C_{11}H_{14}NO^{+\bullet}$,9), and 142 ($CH_3I^{+\bullet}$,8) (Found: C, 58.7; H, 5.7; N, 2.8. $C_{26}H_{30}INO_3$ requires C, 58.76; H, 5.69; N, 2.64%).

Procedure B. A suspension of the hydrobromide of 1,2,3,4-tetrahydro-5,8-dihydroxy-1-(3-phenoxybenzyl)isoquinoline (3; $R^1 = R^3 = H$, $R^2 = OPh$) (1.0 g, 2.3 mmol) in a solution of sodium carbonate (5 g) in water (50 ml), previously flushed with nitrogen, was stirred for 2 h and the free base (3; $R^1 = R^3 = H$, $R^2 = Ph$) was collected by filtration and dried *in vacuo* to give a pale pink solid. A mixture of this 1,2,3,4-tetrahydroisoquinoline, tetrahydrofuran (50 ml), and iodomethane (5 ml) was treated with sodium hydride (1.0 g, 42 mmol) at room temperature. A vigorous effervescence occurred and the mixture colour changed from dark green to dark purple-brown. The mixture was kept overnight, then the excess of sodium hydride was destroyed with a few drops of methanol and the resultant solution was diluted with light petroleum. The precipitated solid was collected, washed with ether, and recrystallised from ethanol–ether to give a buff micro-crystalline powder (0.42 g, 34%), m.p. 201—203 °C. A mixture with the product from *procedure A* gave a mixed m.p. 203—204.5 °C (Found: C, 58.3; H, 5.65; N, 2.5%). ^1H N.m.r., i.r., u.v., and mass spectra are identical with those obtained for the product from *procedure A*.

2,6,7-*Triacetoxy*-1-(2-N-*methylacetamidoethyl*)*phenanthrene* (**7**).—A suspension of 3,9,10-trihydroxyaporphine (**2**; $R^1 = OH$, $R^2 = Me$) (0.1 g) in acetic anhydride (1.0 ml) was heated under reflux during 6 h. After evaporation to dryness, the residue was treated with water and the product was collected by filtration and crystallised from ethanol to give the *title compound* as needles (0.10 g), m.p. 176—177 °C; $\bar{\nu}_{max.}$ 1 760 (ester), 1 650 (NMeCO), 1 210, 1 200 cm^{-1} (ester); *m/z* 451 ($C_{25}H_{25}NO_7^{+\bullet}$) (Found: C, 66.4; H, 5.8; N, 3.1; acetyl, 38.1. $C_{25}H_{25}NO_7$ requires C, 66.52; H, 5.54; N, 3.10; acetyl, 38.14%).

Alternative Synthesis of 3,9-*Dihydroxyaporphine* (**2**; R^1 = H, R^2 = Me) *Hydrobromide.—Tri-n-butyl*-(3-*methoxybenzyl*)-*phosphonium chloride.* A solution of 3-methoxybenzyl chloride (20 g) and tri-n-butylphosphine (48 ml) in benzene (300 ml) was heated under reflux during 15 h. The reaction mixture was cooled to −5 °C and the resultant precipitate was collected and crystallised from benzene–chloroform to give the *title product* (44 g, 95%) as plates, m.p. 140—142 °C (Found: C, 66.75; H, 10.2. $C_{20}H_{36}ClOP$ requires C, 66.93; H, 10.11%).

5-*Methoxy*-1-(3-*methoxybenzyl*)*isoquinoline* (**12**) *hydrochloride.* A stirred suspension of the phosphonium chloride (**11**) (22.52 g, 0.063 mol) in dry 1,2-dimethoxyethane (250 ml) under dry nitrogen was cooled to −50 °C and treated with a 1.6M solution of n-butyl-lithium in hexane (40 ml, 0.064 mol). After 1 h, a solution of 1-chloro-5-methoxyisoquinoline (**10**) (5.8 g, 0.03 mol) in dry 1,2-dimethoxyethane (200 ml) was added during 10 min and the mixture was stirred at room temperature for 1 h and then under reflux during 20 h. The resultant orange-red solution was cooled, treated with a solution of sodium carbonate (3.22 g, 0.03 mol) in water (50 ml), and heated for a further 3 h. The cold solution was decanted and evaporated to dryness, and the residual oil was triturated with toluene–ether (2:1) (2 × 250 ml). The organic phase was extracted with 1M-hydrochloric acid (2 × 200 ml) and the combined acidic extracts were basified with ammonia (*d* 0.88; 40 ml) and extracted with toluene (3 × 100 ml). The combined extracts were dried over sodium sulphate, filtered, and evaporated to dryness under reduced pressure, and the straw coloured oil was dissolved in ether (100 ml). Treatment of the ethereal solution with hydrogen chloride afforded a gum which crystallised from acetone–ether to give the *hydrochloride* of *compound* (**12**) (5.16 g, 52%) as cream plates, m.p. 147—149 °C (Found: C, 66.4; H, 5.9; N, 4.2. $C_{18}H_{17}NO_2$·HCl·H_2O requires C, 66.56; H, 5.90; N, 4.31%).

5-*Methoxy*-1-(3-*methoxybenzyl*)-2-*methylisoquinolinium iodide* (**13**). A solution of the isoquinoline base (**12**) (7.5 g, 0.027 mol) in butan-2-one (150 ml) and toluene (150 ml), under nitrogen, was treated with iodomethane (100 ml) and the mixture was heated under reflux during 4 h. After the mixture had cooled, the precipitated solid was collected and recrystallised from methanol–ether to give the iodide (**13**) (10.5 g, 92%) as yellow-orange needles, m.p. 164—166 °C (Found: C, 54.1; H, 4.8; N, 3.3. $C_{19}H_{20}INO_2$ requires C, 54.17; H, 4.79; N, 3.32%).

1,2,3,4-*Tetrahydro*-5-*methoxy*-1-(3-*methoxybenzyl*)-2-*methylisoquinoline* (**14**) *hydrochloride.* A mixture of the isoquinolinium iodide (**13**) (10.17 g, 0.024 mol) and sodium borohydride (13.1 g, 0.34 mol), under nitrogen, was treated with aqueous methanol [methanol (120 ml) + water (12 ml)] in 3 portions. When the vigorous reaction had subsided, the mixture was heated under reflux for 15 min, cooled, poured into water (500 ml), and extracted with chloroform (4 × 100 ml). The combined extracts were dried over sodium sulphate, filtered, and evaporated to dryness under reduced pressure and the resultant oil was dissolved in ether (200 ml), treated with ethereal hydrogen chloride, and the semi-solid precipitate was collected. Crystallisation from methanol–ether afforded the *title product* (7.1 g, 88%) as prisms, m.p. 191—193 °C (Found: C, 68.2; H, 7.3; N, 4.1. $C_{19}H_{23}NO_2$·HCl requires C, 68.36; H, 7.25; N, 4.20%).

5,6,6a,7-*Tetrahydro*-3,9-*dimethoxy*-6-*methyl*-4H-*dibenzo*-[de,g]*quinoline* (**15**) *hydrochloride.* A solution of the 1,2,3,4-tetrahydroisoquinoline hydrochloride (**14**)·HCl (0.3 g, 0.9 mmol) and boron trifluoride–diethyl ether (3 ml) was added during 2 min to a solution of thallium(III) trifluoroacetate (0.56 g, 1.03 mmol) in trifluoroacetic acid (250 ml) at −4 °C under dry nitrogen. The resultant green mixture was stirred for 2 h and evaporated to dryness under reduced pressure, the residue was treated with water, and the solution was basified with 5% aqueous ammonia. The resultant brown oily suspension was extracted with chloroform (4 × 50 ml), and the combined extracts were dried, filtered, and evaporated to dryness. Separation by preparative t.l.c. (silica; chloroform–methanol, 9:1) afforded an oil which was dissolved in acetone (2 ml) and treated with ethereal hydrogen chloride. Crystallisation of the precipitated solid (151 mg) from methanol–acetone gave the *title product* (140 mg, 20%) as off-white needles, m.p. 263—264 °C (decomp.); $\bar{\nu}_{max.}$ 2 838, 2 650, 2 534, 2 480, 1 241, 1 052, and 801 cm^{-1}; $\lambda_{max.}$ (ε/l mol^{-1} cm^{-1}) 210 (33 000) and 284 nm (27 000); *m/z* 295 ($M^{+\bullet}$, 78), 294 [$(M-1)^{+\bullet}$, 100], 293 [$(M-2)^{+\bullet}$, 34], 264 ($C_{18}H_{18}NO^{+\bullet}$, 20), 252 ($C_{17}H_{16}O_2^{+\bullet}$, 62), 237 ($C_{16}H_{13}O_2^{+\bullet}$, 19), 221 ($C_{16}H_{13}O^{+\bullet}$, 24), 165 ($C_{13}H_9^{+\bullet}$, 10), and 152 ($C_{12}H_8^{+\bullet}$, 8); δ_H($CDCl_3$ + CF_3CO_2D) 3.18—4.55 (9 H, br m, (Ar$CH_2CH_2N^+Me$ + CCH_2Ar), 3.86 and 3.90 (total 6 H, 2 s, 2 OMe), 4.25 (1 H, dd, J_{cis} 11.3 J_{trans} 6.0, ArC*H*N^+ Hz), 6.85—7.05 (3 H, m, 2-, 8-, and 10-H) and 7.55 and 7.61 (total 2 H, 2 d, $J_{1,2}$ = $J_{10,11}$ = 8.6 Hz, 1- and 11-H) (Found: C, 68.3; H, 6.7; N, 4.2. $C_{19}H_{23}NO_2$·HCl requires C, 68.77; H, 6.68; N, 4.22%).

5,6,6a,7-*Tetrahydro*-3,9-*dihydroxy*-6-*methyl*-4H-*dibenzo*-[de,g]*quinoline* (**2**; R^1 = H, R^2 = Me) *hydrobromide by demethylation of compound* (**15**). Demethylation of the aporphine (**15**) (151 mg) with 48% hydrobromic acid (3 ml) as previously described afforded the title compound (**2**; R^1 = H, R^2 = Me) (115 mg, 73%) as an off-white powder, m.p. 276—278 °C (decomp.) Admixture with material prepared by the action of hydrobromic acid on the 1,2,3,4-tetrahydroisoquinoline (**1b**; R^1 = H, R^2 = OMe) (*see above*) gave mixed m.p. 277—278 °C (decomp.) (Found: C, 57.3; H, 5.25; N, 3.9%). ^{1}H N.m.r., i.r., u.v., and mass spectra are similar to those obtained for the product described earlier.

Acknowledgements

One of us (J. G.) acknowledges receipt of an S.R.C. CASE Studentship. We thank Dr. H. T. Openshaw for his interest and Prof. A. McKillop for details of the use of thallium(III) trifluoroacetate prior to publication.

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Received 18*th March* 1985; *Paper* 5/440