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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—CDLXXXIV[1]

ONE-STEP SYNTHESIS OF DIBENZOINDOLIZINIUM SALT AND PHENOLIC APORPHINE BY BENZYNE REACTION

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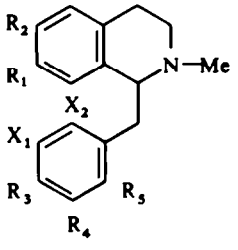
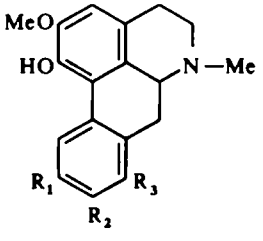
Abstract— An indisputable benzyne reaction of 1-(5-bromo-2,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**1**) with $NaNH_2$ in liquid NH_3 afforded 1-hydroxy-2,8,10-trimethoxy-6-methylaporphine (**4**) and 5,6,12,12a-tetrahydro-2-hydroxy-3,9,11-trimethoxy-7-methyldibenzo[*b*,*g*]indolizinium salt (**6**).

RECENTLY, Kessar[2] and Kametani[3] reported independently the synthesis of the phenolic aporphine (domesticine) (**5**) by treatment of the phenolic 2'-bromoisoquinoline (**2**) with $NaNH_2$ in liquid NH_3, and proposed the benzyne mechanism for this type of reaction without positive evidence. On the other hand, the formation of phenolic dibenzoindolizinium ion by the benzyne reaction of phenolic bromoisoquinoline is unknown. Gibson[4] reported the formation of an unidentified product from the bromoisoquinoline (**3**) by this type of reaction, in which the dibenzoindolizinium ion (**7**) was presumed as a possible intermediate.

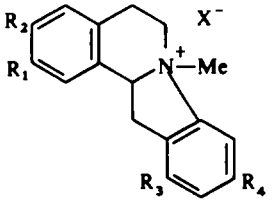
SCHEME 1



	R_1	R_2	R_3	R_4	R_5	X_1	X_2
1	OH	OMe	OMe	H	OMe	Br	H
2	OH	OMe	OCH_2O		H	H	Br
3		OCH_2O	OMe	H	H	Br	H



	R_1	R_2	R_3
4	OMe	H	OMe
5		OCH_2O	H

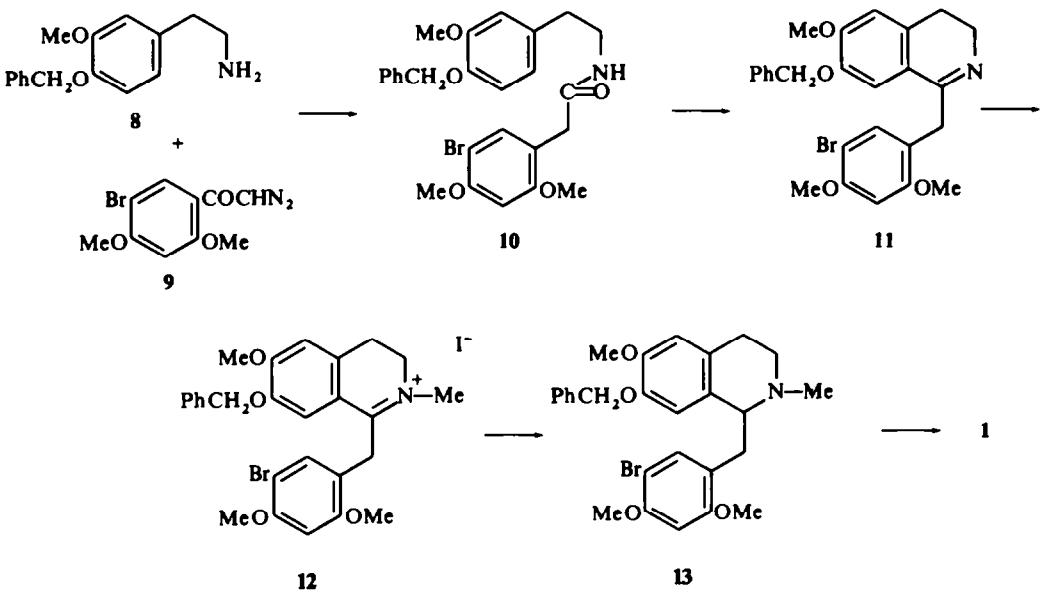


	R_1	R_2	R_3	R_4
6	OH	OMe	OMe	OMe
7		OCH_2O	H	OMe

We investigated the reaction of the phenolic 5'-bromoisoquinoline (**1**) with $NaNH_2$ in order to prove the formation of phenolic aporphine by the benzyne reaction, and also confirmed the formation of phenolic dibenzoindolizinium ion in this reaction.

The phenolic 5'-bromoisoquinoline (**1**) was synthesised as follows. The reaction of the amine (**8**) with the diazoketone[5] (**9**) afforded the amide (**10**), the cyclization of which with $POCl_3$ gave the corresponding 3,4-dihydroisoquinoline (**11**). Treatment of **11** with MeI, followed by the reduction of the methiodide (**12**), afforded the tetrahydroisoquinoline (**13**). Debenzylation of **13** gave the phenolic bromoisoquinoline (**1**).

SCHEME 2



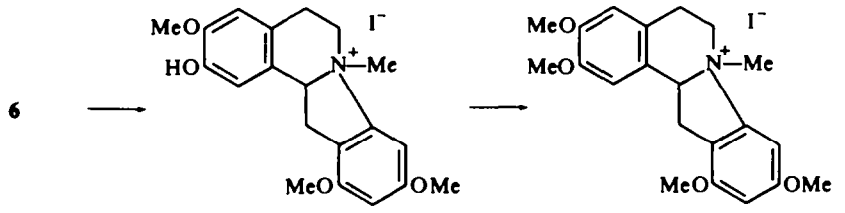
The benzyne reaction of the phenolic bromoisoquinoline (**1**) with $NaNH_2$ in liquid NH_3 was carried out. The crude products obtained by the usual work-up were chromatographed on silica gel to give two products together with the other unidentified materials.

The first compound, m.p. 146–148°, showed the molecular formula $C_{20}H_{23}NO_4$ by microanalysis and mass spectrum (*m/e* 341). The UV spectrum indicated this product to be an aporphine (λ_{max} 270, 277 and 304 nm),[6] which was also supported by mass spectrum showing a typical aporphine type fragmentation pattern[7] at *m/e* 340 (M–1), 339, 326, 310 and 298. The NMR (τ) ($CDCl_3$) spectrum revealed the expected four Me resonances at 7·44, 6·18 (6H) and 6·15, and the signals for three aromatic protons at 3·60 (d, *J* 2·5 Hz), 3·47 (s) and 2·40 (d, *J* 2·5 Hz).[8] These data indicated the first compound to be 1-hydroxy-2,8,10-trimethoxy-6-methylaporphine (**4**).

The microanalysis of the corresponding iodide (**14**), m.p. 157–159°, derived from the second compound, showed the molecular formula $C_{20}H_{24}O_4NI$. The UV spectrum showed the benzylisoquinoline system at 283 nm and the NMR (τ) ($CDCl_3$) spectrum

of the second compound revealed four Me resonances at 6·17, 6·14 (6H) and 6·04, one of which was considered to be a NMe resonance shifted to downfield and it was confirmed by the fact that the resonance was observed at 6·45 in CF_3COOH–$CDCl_3$. Moreover, four aromatic protons were observed at 3·50 (d, J 2·5 Hz), 3·27 (s), 3·08 (s) and 2·56 (d, J 2·5 Hz). The mass spectrum of **6** showed a typical fragmentation pattern[9, 10] of dibenzoindolizinium ion at m/e 327 ($M-CH_3X$), 326 and 325. These data suggested the second compound to be **6**.

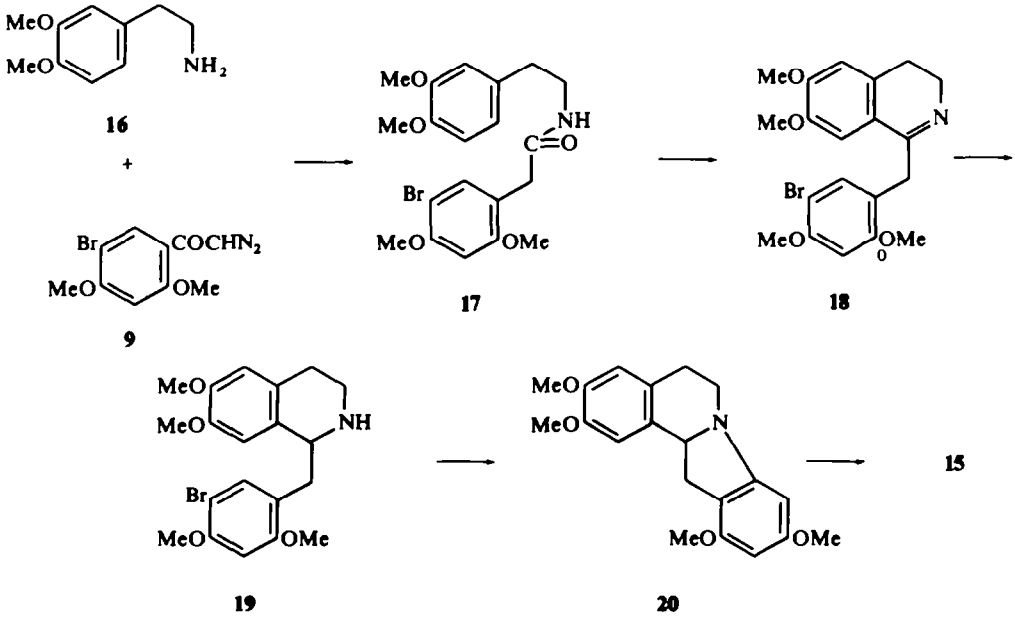
SCHEME 3



14 **15**

Furthermore, the suggested structure (**6**) was proved as follows. Methylation of **14** with diazomethane gave the tetramethoxydibenzoindolizinium ion (**15**) as needles, m.p. 193–197°, which was identical with the authentic sample given by an alternative synthesis in IR spectral comparisons. The authentic sample (**15**) was synthesised by the following route. Treatment of the amine (**16**) with diazoketone[5] (**9**) afforded the amide (**17**), the cyclization of which with $POCl_3$ gave the corresponding 3,4-dihydroisoquinoline (**18**). Reduction of **18** with $NaBH_4$ afforded the tetrahydroisoquinoline (**19**), which was treated with $NaNH_2$ in liquid NH_3 to give the expected indolizine (**20**)

SCHEME 4



in good yield, m.p. 162–164°. The methylation of **20** with MeI gave the corresponding methiodide (**15**).

Thus, we have succeeded in synthesising the phenolic aporphine (**4**) and the dibenzoindolizinium salt (**6**) by the benzyne reaction. This fact is the first example that an aporphine and dibenzoindolizinium ion were synthesised by an undoubted benzyne reaction.

EXPERIMENTAL

IR spectra were measured with a Hitachi EPI-3 recording spectrophotometer, UV spectra with a Hitachi EPS-3 recording spectrophotometer, and NMR spectra with a Hitachi R-20 spectrometer with tetramethylsilane as an internal reference. Mass spectra were taken with a Hitachi RMU-7 spectrometer.

N-(4-Benzyloxy-3-methoxyphenethyl)-5-bromo-2,4-dimethoxyphenylacetamide (**10**). To a stirred mixture of **8** (15.2 g) in dry dioxane (120 ml) and **9**[5] (14·1 g) in dry dioxane (300 ml) was added in small portions Ag_2O (21·0 g) during 1 hr at 60–65° (bath). After the stirring had been continued for 2·5 hr at the same temp, the temperature was raised to about 95°. The mixture was filtered while hot and the filtrate was evaporated *in vacuo*. The resulting residue was chromatographed on silica gel (50 g) using $CHCl_3$ [fractions (100 ml) 1–12, monitored by IR]. Fractions 2–12 were combined and evaporated to leave a red viscous oil (25 g) which was recrystallised from EtOH to give **10** (19·0 g) as yellow prisms, m.p. 116–118°. (Found: C, 60·92; H, 5·31; N, 2·99. $C_{26}H_{28}BrNO_5$ requires: C, 60·73; H, 5·49; N, 2·75%); IR cm^{-1} ($CHCl_3$): 3350 (NH) and 1655 (C=O); NMR τ ($CDCl_3$): 6·40 (3H, s, OMe), 6·38 (3H, s, OMe), 6·13 (3H, s, OMe), 4·90 (2H, s, $OC\underline{H}_2Ph$).

7-Benzyloxy-1-(5-bromo-2,4-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (**11**). A mixture of **10** (2·0 g), $POCl_3$ (2 ml) and dry benzene (30 ml) was refluxed for 1 hr, then cooled. After being set aside for 2 hr at about 10°, the ppt was collected by filtration and washed with n-hexane to afford a pale yellowish solid (1·7 g), which was recrystallised from EtOH to give **11** hydrochloride (1·5 g) as colourless prisms, m.p. 223–225°. (Found: C, 58·62; H, 4·75; N, 2·77. $C_{26}H_{26}BrNO_4 \cdot HCl$ requires: C, 58·61; H, 5·11; N, 2·63%); IR cm^{-1} ($CHCl_3$): 1650 ($>C=\overset{+}{N}-$). The free base from the above hydrochloride gave **11** (1·1 g) as colourless prisms, m.p. 127–128° (from EtOH). (Found: C, 63·17; H, 5·29; N, 2·97. $C_{26}H_{26}BrNO_4$ requires: C, 62·91; H, 5·28; N, 2·82%).

7-Benzyloxy-1-(5-bromo-2,4-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline methiodide (**12**). A mixture of the 3,4-dihydroisoquinoline [prepared from the above hydrochloride (9·5 g)], MeI (45 ml), MeOH (45 ml) and $CHCl_3$ (37 ml) was refluxed for 2 hr, and then the mixture was set aside overnight at room temp. The solvent was evaporated and the remaining residue was recrystallised from $CHCl_3$–Et_2O to give **12** (10·0 g) as pale yellowish needles, m.p. 244–245°. (Found: C, 50·86; H, 4·56; N, 2·26. $C_{26}H_{26}BrNO_4 \cdot CH_3I$ requires: C, 50·80; H, 4·58; N, 2·20%); IR cm^{-1} (KBr): 1630 ($>C=\overset{+}{N}-$).

7-Benzyloxy-1-(5-bromo-2,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**13**). To a stirred suspension of **12** (12·5 g) in MeOH (200 ml) was added $NaBH_4$ (12·5 g) in small portions during 50 min at 0–5°. After the stirring had been continued for 2 hr at room temp, the solvent was evaporated and the resulting residue was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The remaining viscous oil was recrystallised from EtOH to give **13** (7·6 g) as colourless needles, m.p. 122–123°. (Found: C, 63·59; H, 5·51; N, 2·84. $C_{27}H_{30}BrNO_4$ requires: C, 63·28; H, 5·90; N, 2·73%); NMR τ ($CDCl_3$): 7·54 (3H, s, NMe), 6·28 (3H, s, OMe), 6·19 (3H, s, OMe), 6·16 (3H, s, OMe), 5·20 (2H, s, $OC\underline{H}_2Ph$), 3·93, 3·60, 3·45 (3H, each s, 3 × aromatic protons), 2·92 (1H, s, 6′—H), 2·73 (5H, s, aromatic protons).

1-(5-Bromo-2,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**1**). A mixture of **13** (7·1 g), conc HCl (70 ml) and EtOH (70 ml) was refluxed for 40 min. The solvent was evaporated, and the remaining residue was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give a pale brown solid (6·5 g), which was recrystallised from EtOH to give **1** (5·0 g) as colourless needles, m.p. 128–130°. (Found: C, 56·53; H, 5·86; N, 3·36. $C_{20}H_{24}BrNO_4$ requires: C, 56·88; H, 5·73; N, 3·32%); IR cm^{-1} ($CHCl_3$): 3450 (OH); NMR τ ($CDCl_3$): 7·74 (3H, s, NMe), 6·30 (3H, s, OMe), 6·16 (6H, s, OMe), 3·63, 3·47, 3·34 (3H, each s, 3 × aromatic protons), 2·72 (1H, s, 6′—H), 1·53 (1H, broad s, OH).

Benzyne reaction of 1-(5-bromo-2,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**1**)

The synthesis of 1-hydroxy-2,8,10-trimethoxy-6-methylaporphine (**4**) and *5,6,12,12a-tetrahydro-2-hydroxy-*

3,9,11-*trimethoxy*-7-*methyldibenzo*[b,g]*indolizinium salt* (**6**). To a stirred solution of $NaNH_2$ [prepared from Na (1·1 g) in liquid NH_3 (200 ml)] was added a suspension of **1** (2·0 g) in dry dioxane (30 ml) and dry THF (30 ml). Stirring was continued for 3·5 hr, and the excess of $NaNH_2$ was then decomposed with crystalline NH_4Cl (4·0 g). The mixture was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried (K_2CO_3) and evaporated to give a brown solid (1·5 g), which was chromatographed on silica gel (50 g) using $CHCl_3$ [fractions (50 ml) 1–16, monitored by IR and UV spectra], MeOH–$CHCl_3$ (1:99) (fractions 17–30), MeOH–$CHCl_3$ (2:98) (fractions 31–33), and MeOH–$CHCl_3$ (5:95) (fractions 34–49) as eluants.

Fractions 24–25 were combined and evaporated to leave a brown solid (70 mg), which was recrystallised from EtOH–Et_2O to give **4** (40 mg) as pale greyish prisms, m.p. 146–148°. (Found: C, 70·22; H, 6·49; N, 4·05. $C_{20}H_{23}NO_4$ requires: C, 70·36; H, 6·79; N, 4·10%); IR cm^{-1} ($CHCl_3$): 3450 (OH); λ_{max}^{MeOH} (log ε) (free base); 270 (4·19), 277 (4·16) and 304 nm (3·88); NMR τ ($CDCl_3$): 7·44 (3H, s, NMe), 6·18 (6H, s, 2 × OMe), 6·15 (3H, s, OMe), 3·60 (1H, d, *J* 2·5 Hz, 9 —H), 3·47 (1H, s, 3 —H), 2·40 (1H, d, *J* 2·5 Hz, 11 —H)[8], *m/e* 341 (M^+), 340, 339, 326, 324, 310, 298.[7]

Fractions 42–48 gave the crude dibenzoindolizinium ion (410 mg) as a brown solid, which was recrystallised from MeOH–Et_2O to give **6** (320 mg) as a very hygroscopic pale brown solid; IR cm^{-1} ($CHCl_3$): 3470 (OH); λ_{max}^{MeOH}: 283 nm; NMR τ ($CDCl_3$); 6·17, 6·14 (6H), 6·04 (12H, each s, NMe, 3 × OMe), 4·67 (1H t, *J* 8 Hz, 12a —H), 3·50 (1H, d, *J* 2·5 Hz, 10 —H), 3·27 (1H, s, aromatic proton), 3·08 (1H, s, aromatic proton), 2·56 (1H, d, *J* 2·5 Hz, 8 —H); τ (CF_3COOH–$CDCl_3$): 6·45 (3H, s, NMe), 6·05 (9H, s, 3 × OMe), 4·90 (1H, t, *J* 8 Hz, 12a —H), 3·30 (1H, d, *J* 2·5 Hz, 10 —H), 3·26 (1H, d, *J* 2·5 Hz, 8 —H), 3·18, 3·13 (2H, each s, aromatic protons), *m/e* 327 ($M-CH_3X$), 326 ($M-CH_3X-1$), 325 ($M-CH_3X-2$).[9, 10]

5,6,12,12a-*Tetrahydro*-2-*hydroxy*-3,9,11-*trimethoxy*-7-*methyldibenzo*[b,g]*indolizinium iodide* (**14**). To **6** (80 mg) in hot H_2O (3 ml) was added a soln of K I (0·5 g) in hot H_2O (1 ml). The mixture was heated under reflux overnight and then set aside for 10 hr at room temp. The crude iodide (68 mg) precipitated was collected by filtration and recrystallised from MeOH to give **14** as pale yellowish needles, m.p. 157–159°. (Found: C, 50·15; H, 5·30; N, 2·79. $C_{20}H_{24}INO_4 \cdot 1/2H_2O$ requires: C, 50·22; H, 5·26; N, 2·93%); IR cm^{-1} ($CHCl_3$) 3470 (OH).

5,6,12,12a-*Tetrahydro*-2,3,9,11-*tetramethoxy*-7-*methyldibenzo*[b,g]*indolizinium iodide* (**15**). Diazomethane [prepared from *p*-toluenesulphonyl-N-methyl-N-nitrosoamide (6 g) in the usual way] in Et_2O (50 ml) was added to a solution of **14** (50 mg) in MeOH (30 ml) and the mixture was set aside overnight at room temp. After the evaporation of the solvent, the resulting yellow oil was recrystallised from MeOH–Et_2O to give **15** (17 mg) as pale yellow needles, m.p. 193–197°, which was superimposable upon the following authentic sample obtained by an alternative synthesis in IR spectral comparisons.

N-(3,4-*Dimethoxyphenethyl*)-5-*bromo*-2,4-*dimethoxyphenylacetamide* (**17**). To a stirred mixture of 3,4-dimethoxyphenethylamine (6·4 g) in dry dioxane (50 ml) and **9**[5] (9·6 g) in dry dioxane (200 ml) was added in portions Ag_2O (13·7 g) at 55–60° (bath) within 1 hr. After the stirring had been continued for 2·5 hr at the same temp, the temp was raised to about 95°. The mixture was filtrated while hot, and the filtrate was evaporated *in vacuo*. The resulting residue was chromatographed on silica gel (50 g) using $CHCl_3$ [fractions (100 ml) 1–6, monitored by IR]. Fractions 2–3 were combined and evaporated to leave a yellow solid (14·0 g), which was recrystallised from EtOH to give **17** (10·2 g) as yellow prisms, m.p. 142–143°. (Found: C, 54·58; H, 5·49; N, 3·09. $C_{20}H_{24}BrNO_5$ requires: C, 54·80; H, 5·52; N, 3·20%); IR cm^{-1} ($CHCl_3$): 3350 (NH) and 1655 (C=O); NMR τ ($CDCl_3$): 6·27 (3H, s, OMe), 6·17 (3H, s, OMe), 6·13 (3H, s, OMe), 6·07 (3H, s, OMe).

1-(5-*Bromo*-2,4-*dimethoxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (**18**). A mixture of **17** (10·0 g), $POCl_3$ (10 ml) and dry benzene (150 ml) was refluxed for 1 hr and then cooled for 2 hr at about 10°. The ppt was filtered and washed with n-hexane to afford a pale brown solid (8·0 g), which was recrystallised from MeOH–Et_2O to give **18** hydrochloride (6·5 g) as colourless prisms, m.p. 231–233°. (Found: C, 50·59; H, 5·16; N, 3·15. $C_{20}H_{22}BrNO_4 \cdot HCl$ requires: C, 50·59; H, 5·31; N, 2·95%); IR cm^{-1} ($CHCl_3$): 1650 ($>C=\overset{+}{N}-$). The free base from the hydrochloride (5·2 g) gave **18** (4·8 g) as pale yellowish prisms, m.p. 171–173° (from EtOH). (Found: C, 56·93; H, 5·13; N, 3·50. $C_{20}H_{22}BrNO_4$ requires: C, 57·15; H, 5·28; N, 3·33%); NMR τ ($CDCl_3$): 3·50, 3·42, 2·91, 2·58 (4H, each s, aromatic protons).

1-(5-*Bromo*-2,4-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**19**). To a stirred suspension of **18** hydrochloride (3·0 g) in MeOH (90 ml) was added in small portions $NaBH_4$ (6·0 g) under stirring during 1 hr at 0–5°. After the stirring had been continued overnight at room temp and the mixture then refluxed for 30 min, the solvent was evaporated and the resulting residue was diluted with H_2O. The mixture was

extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated to afford **19** (2·7 g) as a pale yellowish oil, the oxalate of which was recrystallized from MeOH–Et_2O to give colourless needles, m.p. 217–219°. (Found: C, 48·72; H, 5·06; N, 2·72. $C_{20}H_{24}BrNO_3 \cdot C_2H_2O_4 \cdot 1{\cdot}5\ H_2O$ requires: C, 48·99; H, 5·42; N, 2·60%); NMR τ ($CDCl_3$) (free base): 6·10, 6·15 (6H), 6·18 (12H, each s, 4 × OMe), 5·77 (1H, broad s, 1 —H), 3·52, 3·44, 3·38 (3H, each s, 3 × aromatic protons) 2·72 (1H, s, 6′ —H).

Benzyne reactions of 1-(*5-bromo-2,4-dimethoxybenzyl*)-1,2,3,4-*tetrahydro-6,7-dimethoxyisoquinoline* (**19**)

The synthesis of 5,6,12,12a-*tetrahydro*-2,3,9,11-*tetramethoxydibenzo*[b,g]*indoline* (**20**). To a stirred soln of $NaNH_2$ [prepared from Na (6·4 g) and liquid NH_3 (200 ml)] **19** (2·7 g) in dry THF (20 ml) was added. Stirring was continued for 2 hr and then the excess of $NaNH_2$ was decomposed with crystalline NH_4Cl (16·0 g). After the solvent was evaporated, the residue was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried (K_2CO_3), and evaporated to give a brown oil (3·3 g), which was chromatographed on silica gel (60 g) using $CHCl_3$ [fractions (50 ml) 1–12, monitored by IR and NMR spectra]. Fractions 5–12 were combined and evaporated to leave a brown solid (900 mg), which was recrystallised from EtOH to give **20** (650 mg) as colourless needles, m.p. 162–164°. (Found: C, 70·03; H, 6·83; N, 3·83. $C_{20}H_{23}NO_4$ requires: C, 70·35; H, 6·79; N, 4·10%); NMR τ ($CDCl_3$): 6·26, 6·24, 6·20, 6·15 (12H, each s, 4 × OMe), 5·13 (1H, q, *J* 4 and 8 Hz, 12a —H)[10], 4·13 (1H, d, *J* 2·5 Hz, 8 —H), 4·08 (1H, d, *J* 2·5 Hz, 10 —H), 3·53, 3·44 (2H, each s, 2 × aromatic protons); *m/e* 341 (M^+), 340 and 339.[9, 10]

5,6,12,12a-*Tetrahydro*-2,3,9,11-*tetramethoxy*-7-*methyldibenzo*[b,g]*indolizinium iodide* (**15**). A mixture of **20** (30 mg), MeI (1 ml) and MeOH (1 ml) was set aside overnight at room temp. The excess of MeI was then distilled off and the residue was recrystallised from MeOH–Et_2O to give **15** (35 mg) as pale yellowish needles, m.p. 199–200°. (Found: C, 51·70; H, 5·30; N, 2·65. $C_{21}H_{26}INO_4 1/4H_2O$ requires: C, 51·70; H, 5·42; N, 2·90%); NMR τ ($CDCl_3$): 6·18, 6·12 (9H), 6·04 (15H, each s, NMe, 4 × OMe), 4·52 (1H, t, *J* 8 Hz, 12a —H), 3·52 (1H, d, *J* 2·5 Hz, 10 —H), 3·30, 3·17 (2H, each s, 2 × aromatic protons), 2·55 (1H, d, *J* 2·5 Hz, 8 —H), *m/e* 341 ($M-CH_3I$), 340 and 339.[9, 10]

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