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New Syntheses of the *Amaryllidacaea* Alkaloids Vasconine, Assoanine, Oxoassoanine, Pratosine and Ismine by Radical Cyclisation

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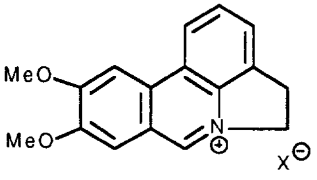
Abstract: N-(2-bromo-4,5-dimethoxybenzyl)-N-(2'-β-hydroxyethylphenyl)amine when subjected to the action of AIBN and tri-*n*-butyltin hydride (TBTH) in benzene, under reflux, yielded the corresponding β-4-phenanthridinylethyl alcohol. While reduction of the tetracyclic quaternary salt obtained by treatment of this alcohol with PBr_3 gave assoanine, its oxidation with alkaline ferricyanide led to a separable mixture of pratosine and oxoassoanine. The σ radical, similarly generated from 2-bromo-4,5-methylenedioxybenzyl-2'-aminophenylether, afforded the biphenyl alcohol, N-norismine. Copyright © 1996 Elsevier Science Ltd

Vasconine[1] (**1**), assoanine[2] (**2**), oxoassoanine[2] (**3**), pratosine[3] (**4**) and ismine[4] (**5**) are a few examples of a variety of alkaloids isolated from plants belonging to the *Amaryllidacaea* family. In view of the interesting biological properties[5] exhibited by some member of this group of alkaloids there has been a recent interest in the development of new synthetic method[6] for the pyrrolophenanthridines.



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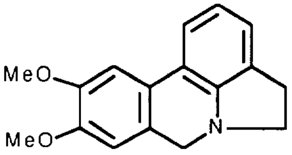

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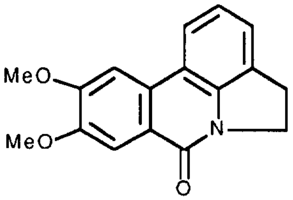

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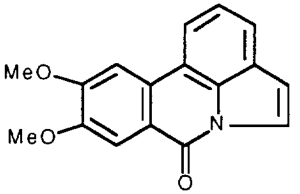

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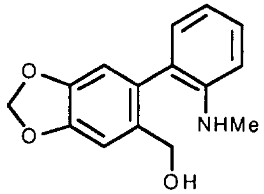

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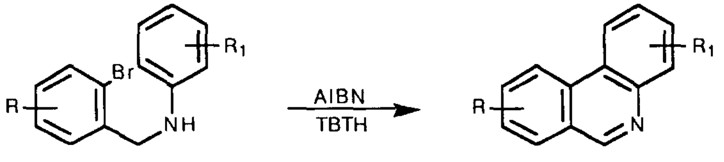
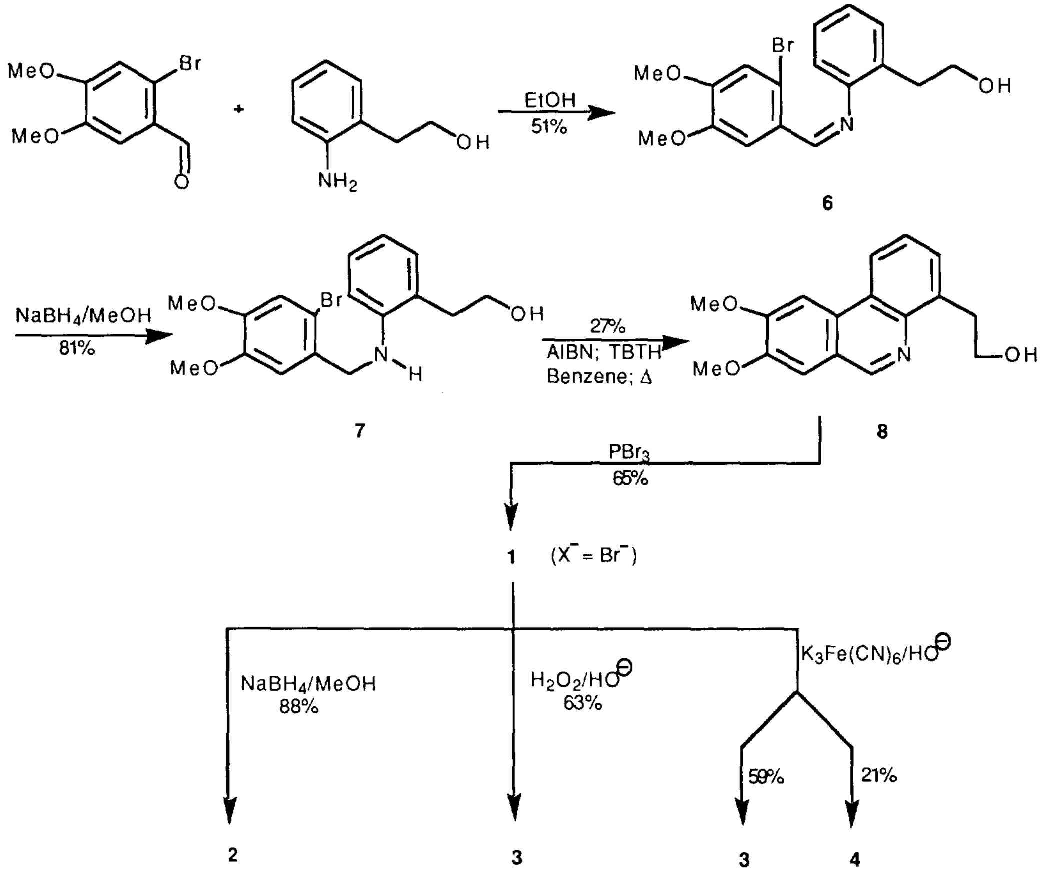
We report here a new approach[7] which utilises radical cyclisation as the key step in the establishment of C_{aryl}-C_{aryl} bond. It was shown (see previous two papers) that *o*-bromobenzylanilines when treated with AIBN and TBTH afford the corresponding phenanthridines in good yields (Scheme 1).



Scheme 1

The requisite starting material for the synthesis of pyrrolophenanthridine alkaloids, the substituted aniline derivative 7 (Scheme 2) was obtain as follows: condensation of 2-bromo-4,5-dimethoxybenzaldehyde and the

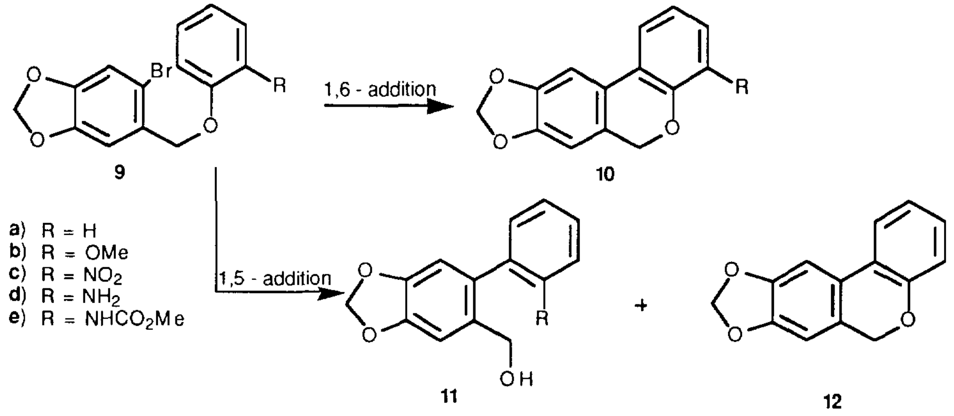


Scheme 2

commercially available 2-β-hydroxyethylaniline[8] provided the aldimine **6** which was reduced with $NaBH_4$ in methanol to the aminoalcohol 7. 7 and TBTH in benzene under reflux, was treated slowly with AIBN in benzene until the reaction was complete (12-13 h; tlc control). Crystallisation of the tin-free residue obtained after chromatography gave the phenanthridine alcohol **8** (27%) as a colourless solid. Examination of the mother-liquor (tlc) revealed that it consisted of debromocompound, small amounts of **7** and the phenanthridine **8**. The isolation of more of the latter once the bulk of it had been removed by crystallisation by standard laboratory techniques such as ptlc, fractional crystallisation or sublimation, however, proved to be very difficult.

Conversion of the alcohol **8** into phenanthridinium bromide **1** was achieved by the use of PBr_3.[9] The product, mp: 238-240°C, obtained in 65% yield, possessed ^1H NMR and IR spectra virtually identical with those reported for vasconine,[1,6d] mp: 233-235°C. $NaBH_4$ reduction of **1** provided the air sensitive amine, identical with assoanine[6d] (**2**) (mp; IR; ^1H NMR). Whilst oxidation of **1** with alkaline hydrogen peroxide yielded the lactam, oxoassoanine[6d,e,f,g,h] (**3**), the use of $K_3Fe(CN)_6$ resulted in the formation not only of **3** but also, interestingly the dehydrolactam **4**. The mp of the latter and its spectral data (^1H NMR and IR) were coincident with those recorded for the alkaloid pratosine.[3,6f,6i]

Our results obtained with various *o*-bromobenzylphenylethers (see previous paper) showed that the σ radicals generated from them did not exclusively yield the benzopyran derivatives. Instead the nature of the products formed was found to be largely determined by the position occupied by the alkoxyl substituent in the phenyl ring (Scheme 3).

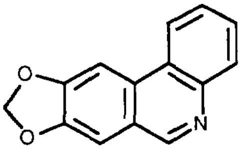


Scheme 3

Thus for substance **9a**, the benzopyran **10** (R=H) was the only isolable product. However, with compound **9b** the products obtained were **11** (R=OMe) and **12** (both resulting from a 1,5 substitution; see previous two papers) as well as compound **10** (R=OMe).

It was therefore anticipated that an amino group similarly positioned would encourage to a greater extent the 1,5-attack and lead to a simple synthesis of N-norismine **11d**. The necessary starting material, the aminobenzylether **9d** was readily obtained by catalytic hydrogenation (Pt/C) of the benzylphenylether **9c** prepared by alkylation of *o*-nitrophenol with 2-bromo-3,4-methylenedioxybenzylchloride (NaH; CH_3CN).

On exposure to the combined action of AIBN and TBTN, the compound **9d** yielded a mixture of products from which the following substances were isolated by preparative tlc: i) the aminopyran **10** ($R=NH_2$; 10%), ii) the phenanthridine **13** (10%), iii) *the debromo compound* **14** (24%) and N-norismine[10] **11** ($R=NH_2$; 27%). In an attempt to improve the yield of N-norismine, the urethane **9e** was subjected to standard cyclisation conditions. However, neither the N-norismine derivative **11** ($R=NHCO_2Me$) nor the debromo compound **14** ($R=CO_2Me$) could be detected in the reaction mixture. Instead, the pyrancarbamate **10** ($R=NHCO_2Me$; 26%) and the phenanthridine **13** (43%) were the two compounds that could be isolated. The formation of the same phenanthridine **13** from two different but related substrates is interesting, the crucial difference between the two reactions being the isolation of the debromo compound **14** (R=H) in significant amounts (24%) only when the free amine **9d** was utilised.



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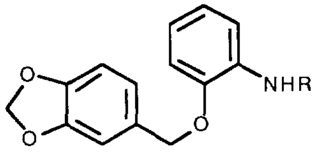

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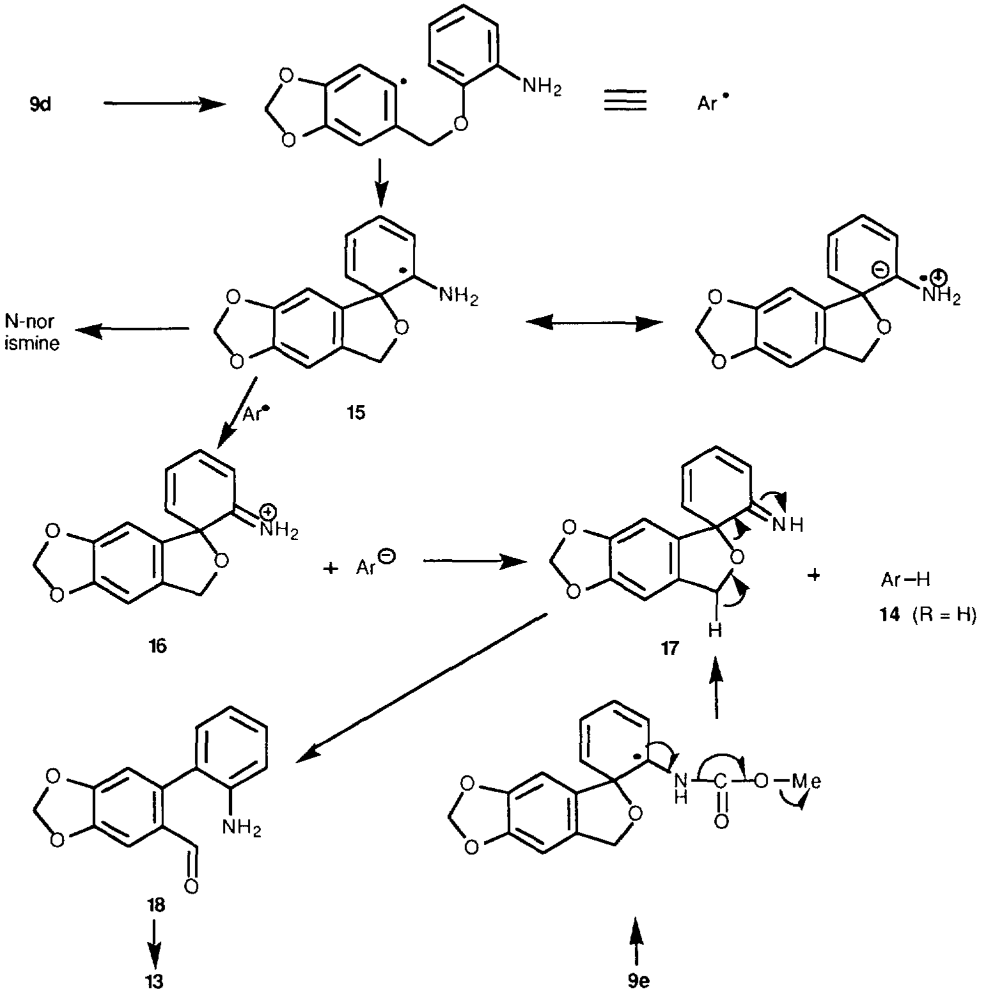
A plausible mechanism[11] (Scheme 4) that explains the results would be to invoke the involvement of the imine **17** as the common precursor of **13**. The stabilised radical **15** on transferring one electron to Ar• generates



Scheme 4

the carbanion Ar⁻ and the protonated imine **16**. A proton exchange between the two would lead to the imine **17** and the debromo compound **14** (R=H). In the case of the urethane **9e** the corresponding spirocyclohexadienyl radical formed from it could unimolecularly fragment[12] to **17** without the concomitant production of **14**

($R=CO_2Me$). Collapse of **17** in a thermochemically favoured process would result in the formation[13] of the aminoaldehyde **18** and thence to the phenanthridine **13**.

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EXPERIMENTAL

General. Melting points were either determined with a microscopic hot-stage Reichert Thermovar and are uncorrected. Preparative thin layer chromatography (PTLC) were performed on plates precoated with silica gel (0.5 mm or 2 mm). Infrared (IR) spectra were obtained on potassium bromide discs with a Perkin-Elmer 157G and 683 grating infrared spectrophotometer and the frequencies reported in cm^{-1}. Proton nuclear magnetic resonance spectra (^1H NMR) were obtained at 300 MHz with a Brücker CXP 380 or General Electric GE-NMR and those at 60 MHz with a Perkin Elmer R12 B instrument. Chemical shifts are reported in ppm down field from tetramethylsilane and $CDCl_3$ used as solvent unless stated otherwise. High and low resolution mass spectra (HREIMS and EIMS) were measured in a Kratos MS-25RF instrument using electron impact at 70 e V. All solvents were purified by standard methods.

N-(2'-Bromo-4',5'-dimethoxybenzylidene)-2-(β-hydroxyethyl)aniline (6). A mixture of 2-bromo-4,5-dimethoxybenzaldehyde (5 g) and 2-(β-hydroxyethyl)aniline (3.84 g) in ethanol (5 ml) was heated in a steam-bath until the completion of the reaction (tlc control). The crystals that separated on cooling (ice-bath) were collected by filtration to give the title compound (3.77 g; 51%), mp: 103-105°C; IR (KBr) 1616 (C=N); ^1H NMR (60 MHz) δ 3.05 (t, 2H, J = 6.5 Hz), 3.50-4.40 (m, 9H, 2xOCH_3, CH_2 and OH), 7.00-7.50 (m, 5H, Ar-H), 7.70 (s, 1H, Ar-H), 8.75 (s, 1H, CH=N). HREIMS Calcd. for $C_{17}H_{18}BrNO_3$: 365.0449. Found: 365.0449.

N-(2'-Bromo-4,5'-dimethoxybenzyl)-2-(β-hydroxyethyl)aniline (7). The imine **6** (2.0 g) in dry MeOH (60 ml) was treated in portions with $NaBH_4$ (0.52 g). The solid obtained on the completion of reduction (tlc control) was collected and crystallised from EtOH to afford the amine **7**, (1.66 g) as white crystals, mp: 114-116°C; IR (KBr) 3360 (NH and OH); ^1H NMR (400 MHz) δ 2.81 (t, 2H, J = 7.3 Hz, CH_2CH_2OH), 3.76 (s, 3H, OCH_3), 3.87-3.90 (m+s, 6H, 1H exchangeable in D_2O, OCH_3, CH_2OH), 4.31 (bs, 2H, CH_2NH), 4.56 (bs, 1H, exchangeable in D_2O), 6.6-7.14 (m, 6H, Ar-H). HREIMS Calcd. for $C_{17}H_{20}BrNO_3$: 367.0606. Found: 367.0611.

4-(β-Hydroxyethyl)-8,9-methylenedioxyphenanthridine (8). The bromoalcohol **7** (1.0 g) and TBTH (0.98 g) in benzene (218 ml) under reflux was treated with a solution of AIBN (0.22 g) in benzene (55 ml) during 12 h. The residue obtained after evaporation of the solvent under reduced pressure was washed repeatedly with *n*-pentane to remove organotin compounds. The solid isolated by chromatography (silica; EtOAc), was further purified by crystallisation (EtOAc) to give the phenanthridine **8** (0.20 g), mp: 176-179°C;

^{1}H NMR (300 MHz) δ 3.512 (t, 2H, CH_2CH_2OH, *J* = 5.4 Hz), 4.06 (t, 3H, *J* = 5.4 Hz, CH_2-CH_2-O*H*, 1*H* exchangeable in D_2O), 4.073 (s, 3H, OCH_3), 4.142 (s, 3H, OCH_3), 7.331 (s, 1H, Ar-*H*), 7.538 (dd, 1H, *J* = 7.2 and 1.8 Hz, Ar-*H*), 7.591 (d, 1H, *J* = 7.2 Hz, Ar-*H*), 7.87 (s, 1H, Ar-*H*), 8.348 (dd, 1H, J_1 = 7.2 and J_2 = 1.8 Hz, Ar-*H*), 9.10 (s, 1H, C*H*=N). Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.22; H, 6.03; N, 4.89 %.

Vasconine (1). The phenanthridine alcohol **8** (1.0 g) in benzene (100 ml) was treated with PBr_3 (2 ml) in a 1:1 mixture of dry ether (10 ml) and *n*-hexane (10 ml). After the mixture had been heated under reflux (6 h 30 m), the solvents were evaporated under reduced pressure and the residue suspended in ether and refrigerated overnight. The solid that separated was collected by filtration and crystallised from MeOH to give the quaternary bromide **1** (0.80 g) mp: 238-240°C. The ^{1}H NMR spectrum ($CDCl_3/CD_3OD$, 1:1, 300 MHz) which contained resonances at δ 3.89 (t, 2H, *J* = 6.9 Hz, $N^+CH_2CH_2$), 4.14 (s, 3H, OCH_3), 4.28 (s, 3H, OCH_3), 5.38 (t, 2H, *J* = 6.9 Hz, $N^+CH_2CH_2$), 7.87 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 7.96 (s+t, 2H, *J* = 8.4 Hz, Ar-*H*), 8.14 (s, 1H, Ar-*H*), 8.60 (d, 1H, *J* = 8.4 Hz, Ar-*H*), 9.88 (s, 1H, C*H*=N) was virtually identical with that of vasconine.

Assoanine (2). To the above compound **1** (0.1 g) in MeOH (10 ml) was added, in small portions, $NaBH_4$ (25 mg) and the mixture stirred under argon atmosphere at RT (15h). The solvent was evaporated under reduced pressure, water added and the product extracted with ether. Removal of solvent from the dried (Na_2SO_4) filtrate afforded assoanine (**2**) (68 mg), mp: 164-166°C (lit[2] mp: 175-176°C); ^{1}H NMR (300 MHz) δ 3.03 (t, 2H, *J* = 7.8 Hz, NCH_2CH_2), 3.45 (t, 2H, *J* = 7.8 Hz, NCH_2CH_2), 3.89 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.12 (s, 2H, $ArCH_2N$), 6.66 (s, 1H, Ar-*H*), 6.76 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.01 (d, 1H, *J* = 7.5 Hz, Ar-*H*), 7.19 (s, 1H, Ar-*H*), 7.33 (d, 1H, *J* = 7.5 Hz, Ar-*H*). The ^{1}H NMR and IR (KBr) spectra were identical with those of an authentic sample.

Oxoassoanine (3). The phenanthridinium bromide **1** (50 mg) in MeOH (3 ml) containing H_2O_2 (30%; 0.3 ml) and 2N NaOH (0.3 ml) was stirred at RT (24 h). The residue obtained on evaporation of solvent was treated with water and extracted with $CHCl_3$. Evaporation of the solvent from the dried (Na_2SO_4) filtrate gave **3** (26 mg), mp: 250-252°C (from EtOH; lit[2] mp: 247-250°C). Its ^{1}H NMR and IR spectra were identical with those of an authentic sample.

Pratosine (4) and Oxoassoanine (3). A mixture of the bromide **1** (50 mg) in H_2O (2 ml), $K_3Fe(CN)_6$ (100 mg), KOH (10 mg) and H_2O (5 ml) was heated under reflux (22 h). It was then cooled to RT and extracted with $CHCl_3$. Evaporation of solvent from the dried (Na_2SO_4) filtrate yielded a residue which consisted essentially of two compounds. Separation by preparative layer chromatography (SiO_2) using $CHCl_3$ as eluent yielded *oxoassoanine* (**3**) (24 mg, 59%) and *pratosine* (**4**) (8.5 mg; 21%), mp: 228-230°C (lit[3] mp: 232-233°C). The ^{1}H NMR spectrum of **4** contained proton resonances with δ and *J* values identical with those reported for the natural product.

2-Bromo-4,5-methylenedioxybenzyl-2'-nitrophenylether (9c). To *o*-nitrophenol (4.47 g) in acetonitrile (250 ml) was added NaH (60%; 1.28 g) and the resulting solution treated dropwise with 2-bromo-4,5-methylenedioxybenzyl chloride (8.0 g) in CH_3CN (150 ml). The mixture was heated under reflux (26h), cooled and bulk of solvent removed under reduced pressure. The residue was extracted into ether, washed several times with aq. NaOH solution, then with H_2O and dried (Na_2SO_4). Evaporation of solvent yielded a residue which was crystallised from CH_2Cl_2-*n*-hexane to give the phenylether **9c** (7.3 g), mp: 151-154°C; IR (KBr) 1518, 1336; ^1H NMR (60 MHz) δ 5.10 (s, 2H, C*H*$_2$O), 5.90 (s, 2H, OC*H*$_2$O), 6.80-8.00 (m, 6H, Ar-*H*). Anal. Calcd. for $C_{14}H_{10}BrNO_5$: C, 47.75; H, 2.86; N, 3.98. Found: C, 47.69; H, 2.90; N, 3.86%.

2-Bromo-4,5-methylenedioxybenzyl-2'-aminophenylether (9d). The above nitro compound (2 g) in EtOH (100 ml) was hydrogenated (4 h) in the presence of Pt/C (1%; 0.39 g) at 30 psi. The product worked-up in the usual manner, was crystallised (from Et_2O-*n*-hexane), to give **9d** (77%), mp: 85-88°C; IR (KBr) 3450, 3370; ^1H NMR (60 MHz) δ 3.55 (bs, 2H, N*H*$_2$, exchangeable in D_2O), 5.10 (s, 2H, C*H*$_2$O), 6.05 (s, 2H, OC*H*$_2$O), 6.85 (s, 4H, Ar-*H*), 7.05 (s, 1H, Ar-*H*), 7.10 (s, 1H, Ar-*H*). Anal. Calcd. for $C_{14}H_{12}BrNO_3$: C, 52.20; H, 3.75; N, 4.35. Found: C, 52.12; H, 3.78; N, 4.17%.

Methyl-*o*-(2-bromo-4,5-methylenedioxybenzyloxy)phenylcarbamate (9e). The amine **9d** (1 g), K_2CO_3 (0.164 g) in a mixture of THF (40 ml) and H_2O (10 ml) was cooled to 0° and treated with methyl chloroformate (0.381 g) in THF (2 ml). After 2 h stirring at RT, the bulk of the solvent was removed under reduced pressure, water added and the product extracted into ether. Evaporation of solvent from the dried (Na_2SO_4) filtrate led to a residue which crystallised from CH_2Cl_2-*n*-hexane to afford the carbamate **9e** mp: 123-124°C; IR (KBr) 3320, 1700; ^1H NMR (60 MHz) δ 3.80 (s, 3H, OC*H*$_3$), 5.10 (s, 2H, C*H*$_2$O), 6.05 (s, 2H, OC*H*$_2$O), 6.90-7.20 (m, 6H, Ar-*H*), 8.15 (bs, 1H, N*H*). Anal. Calcd. for $C_{16}H_{14}BrNO_5$: C, 50.55; H, 3.71; N, 3.68. Found: C, 50.68; H, 3.80; N, 3.50%.

N-norismine 11 (R=NH$_2$). The aminoether (**9d**) (0.8 g) and TBTH (1.65 ml) in benzene (200 ml) under reflux, was treated with a solution of AIBN (0.2 g) in benzene (50 ml) during 13 h. Evaporation of solvent under reduced pressure led to an oil which was dissolved in ether and washed with aqueous KF (10%). The mixture was filtered and the filtrate, after drying (NO_2SO_4) evaporated to dryness and the residue purified by chromatography on silica using *n*-hexane-ethylacetate (4:1) as the eluent. The following compounds were isolated: a) 4-Amino-8,9-methylenedioxy-6H-dibenzo[*b*,*d*]-pyran (**10**; R=NH$_2$) (0.06 g; 10% yield) as a viscous oil; ^1H NMR (300 MHz) δ 3.60 (bs, 2H, N*H*$_2$ exchangeable in D_2O), 5.015 (s, 2H, C*H*$_2$O), 5.967 (s, 2H, OC*H*$_2$O), 6.625 (s, 1H, Ar-*H*), 6.65 (dd, 1H, J = 7.8 and 1.2 Hz, Ar-*H*), 6.85 (t, 1H, J = 7.8 Hz, Ar-*H*), 6.993 (dd, 1H, J = 7.8 Hz and 1.2 Hz, Ar-*H*), 7.142 (s, 1H, Ar-*H*). HREIMS Calcd for $C_{14}H_{11}NO_3$: 241.0739. Found: 241.0742. b) 8,9-Methylenedioxyphenanthridine (**13**) (0.044 mg; 7.9% yield) mp: 132-134°C. The mp was undepressed on admixture with an authentic sample. The ^1H NMR and IR spectra were identical with those an authentic sample[14] of **13**. c) 3,4-Methylenedioxybenzyl-2'-aminophenylether (**14**) (R=H) (0.14 g; 23% yield) as colourless oil. d) *2-Hydroxymethyl-4,5-methylenedioxy-2'-aminobiphenyl* (N-norismine; **11**, R=NH$_2$) (0.16 g; 26% yield) as a colourless oil, picrate 150-154°C, lit[10] mp: 150-154°C, mixed mp: 150-154°C.

The urethane derivative **9e** (0.75 g) on similar treatment yielded 8,9-methylenedioxyphenanthridine (**13**) (0.19 g; 43% yield) and the pyran carbamate **10** (R=NHCO$_2$Me) (0.16 g; 26% yield), mp: 194-196°C (from CH_2Cl_2-*n*-hexane); IR (KBr) 3430 (NH) 1738 (C=O); ^1H NMR (300 MHz) δ 3.795 (s, 3H, OC*H*$_3$), 5.026 (s, 2H, C*H*$_2$O), 5.989 (s, 2H, OC*H*$_2$O), 6.633 (s, 1H, Ar-*H*), 7.025 (t, 1H, J = 8.1 Hz, Ar-*H*), 7.247 (dd, 2H, J = 8.4 and 1.5 Hz, Ar-*H*), 7.996 (bs, 1H, N*H*). Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.08; H, 4.26; N, 4.41%.

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