New Dibenz[*d,f*]azonine Alkaloids from *Cocculus laurifolius* DC [1]

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The structures of laurifonine (17) (6,7,8,9-tetrahydro-2,3,12-trimethoxy-7-methyl-5*H*-dibenz[*d,f*]azonine) laurifine (18) (its 7-demethyl analogue), and laurifinine (19) (its 2-de-*O*-methyl analogue) have been established by chemical and spectroscopic studies. The biogenesis of dibenz[*d,f*]azonine bases is discussed.

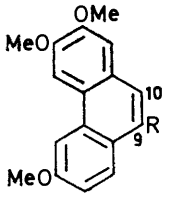
Cocculus laurifolius DC (Menispermaceae) has been a source of a variety of 1-benzyltetrahydroisoquinoline-derived alkaloids. Our interest in the alkaloids of *C. laurifolius* DC arose when hypotensive activity was observed in the 50% aqueous ethanolic extract of the leaves of the plant during a programme of screening of Indian plants over a wide range of biological activities.[2] In further studies the hypotensive activity was concentrated in the alkaloid fraction. A search for the active principle(s) from this fraction resulted in the isolation of three new dibenz[*d,f*]azonine bases, laurifine, laurifonine, and laurifinine, assigned the structures (18), (17), and (19) respectively.[1] We now present a full account of the work leading to these structures.

The alkaloids were isolated by column chromatography over neutral alumina of the non-phenolic fraction of the alkaloidal mixture from the leaves of the plant. The i.r. spectrum [$\nu_{max.}$ (KBr) 1 605, 1 510,

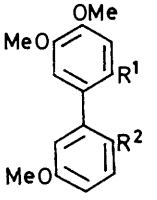
[1] Preliminary report, H. Uprety and D. S. Bhakuni, *Tetrahedron Letters*, 1975, 1201.

[2] D. S. Bhakuni, M. L. Dhar, M. M. Dhar, B. N. Dhawan, and B. N. Mehrotra, *Indian J. Expt. Biol.*, 1969, **7**, 250.

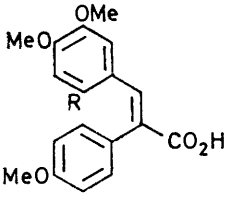
1 450, 1 240, 1 030, and 820 cm^{-1}] of laurifonine (17) ($C_{20}H_{25}NO_3$) (M^+ 327) in conjunction with the u.v. absorption maxima at 221 and 283 nm (log ε 4.30 and 3.90), unchanged in alkali, suggested the presence of a substituted biphenyl system as in erybidine,[3] a dibenz-[*d*,*f*]azonine base from *Erythrina* species. Laurifonine did not give an *N*-methyl derivative with formic acid–formaldehyde or formaldehyde–sodium borohydride, indicating the absence of an NH function. The n.m.r. spectrum ($CDCl_3$) had signals for one *N*-methyl and



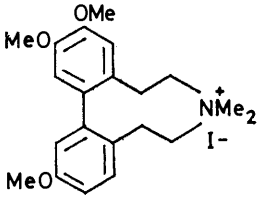
(1) R = H
(2) R = CO_2H
(3) R = CO_2Me



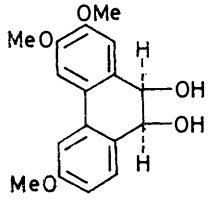
(4) R^1 = $[CH_2]_2$·NMe_2, R^2 = CH_2:CH
(5) R^1 = CH_2:CH, R^2 = $[CH_2]_2NMe_2$
(6) R^1R^2 = CH_A:CH_BH_C
(7) R^1 = R^2 = CHO



(8) R = NO_2
(9) R = NH_2



(10)



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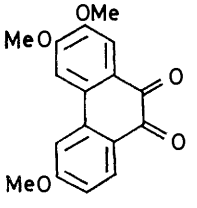


(12)

three aromatic methoxy-groups. Of the 5 protons in the aromatic region 2 *para*-oriented protons resonated at τ 3.28 and 3.32, respectively, whereas the remaining 2 *ortho*- and 1 *meta*-coupled proton signals appeared between τ 2.82 and 3.20 (J_{AB} 0.2, J_{AC} 2.5, J_{BC} 8.5 Hz).

Distillation of laurifonine with zinc dust yielded the phenanthrene derivative (1), identified from spectral data and by comparison with the product of decarboxylation of 2,3,6-trimethoxyphenanthrene-9-carboxylic acid [4] (2) in the presence of quinoline and copper powder.

Treatment of laurifonine with methyl iodide gave the methiodide (10), Hofmann degradation of which furnished a mixture of biphenyls (4) and (5), which was not separated. Treatment of the mixture with methyl iodide followed by second Hofmann elimination afforded the styrene derivative (6). The n.m.r. spectrum of (6) showed three aromatic methoxy-groups. The signals for the non-equivalent olefinic protons of the vinylic groupings consisted of two double doublets for H_C and H_B centred at τ 4.56 and 5.07 (J_{AB}, J_{AC}, and J_{BC} 11.0, 17.0, and 2.0 Hz respectively) and a double doublet centred at τ 3.65 for H_A. Of the 5 aromatic protons, signals for 2 *para*-oriented protons appeared at τ 3.39, a poorly resolved doublet for *ortho*-coupled protons was at τ 2.49 (*J* 9.0 Hz), a doublet for a *meta*-coupled proton was at τ 3.33 (*J* 2.6 Hz), and a poorly resolved double doublet for a *meta*- and *ortho*-coupled proton was centred at τ 2.87 (*J* 2.6 and 9.0 Hz).

Cleavage of the styrene (6) with osmium tetraoxide–sodium periodate in aqueous t-butyl alcohol yielded 4,4′,5-trimethoxy-2,2′-bibenzaldehyde (7), identified from spectral data and by synthesis as follows. Treatment of 2,3,6-trimethoxyphenanthrene (1) in benzene with osmium tetraoxide–pyridine afforded a complex which on decomposition with an aqueous solution of mannitol and potassium hydroxide furnished the diol (11). Cleavage of (11) with periodate in tetrahydrofuran afforded a mixture of the dialdehyde (7) and 2,3,6-trimethoxyphenanthrenequinone (12), separated by column chromatography on silica gel.

Laurifine (18) ($C_{19}H_{23}NO_3$) (M^+ 313) showed i.r. absorption [$\nu_{max.}$ (KBr) 3 450 cm^{-1}] indicating the presence of an NH or OH function. Its u.v. spectrum [$\lambda_{max.}$ (MeOH) 221 and 284 nm (log ε 4.34 and 3.90)], which remained unchanged on addition of alkali, excluded the presence of a phenolic hydroxy-group. In its n.m.r. ($CDCl_3$) spectrum, there was no *N*-methyl signal, but the spectrum was otherwise similar to that of laurifonine (17).

Treatment of laurifine with formaldehyde–sodium borohydride afforded *N*-methyl-laurifine which was identical with laurifonine (17).

Laurifinine (19) ($C_{19}H_{23}NO_3$) (M^+ 313) formed a crystalline perchlorate. Its i.r. spectrum [$\nu_{max.}$ (KBr) 3 400 cm^{-1}] indicated the presence of a hydroxy-function. Its u.v. spectrum [$\lambda_{max.}$ (MeOH) 223 and 284 nm (log ε 4.24 and 3.84)] underwent a bathochromic shift on addition of alkali, suggesting that the OH group was phenolic. The base did not react with formaldehyde–formic acid or formaldehyde–sodium borohydride, indicating the absence of an NH function. Its n.m.r. spectrum ($CDCl_3$) showed an *N*-methyl signal at τ 7.68, only two aromatic methoxy-signals, and a broad exchangeable OH signal at τ 5.18.

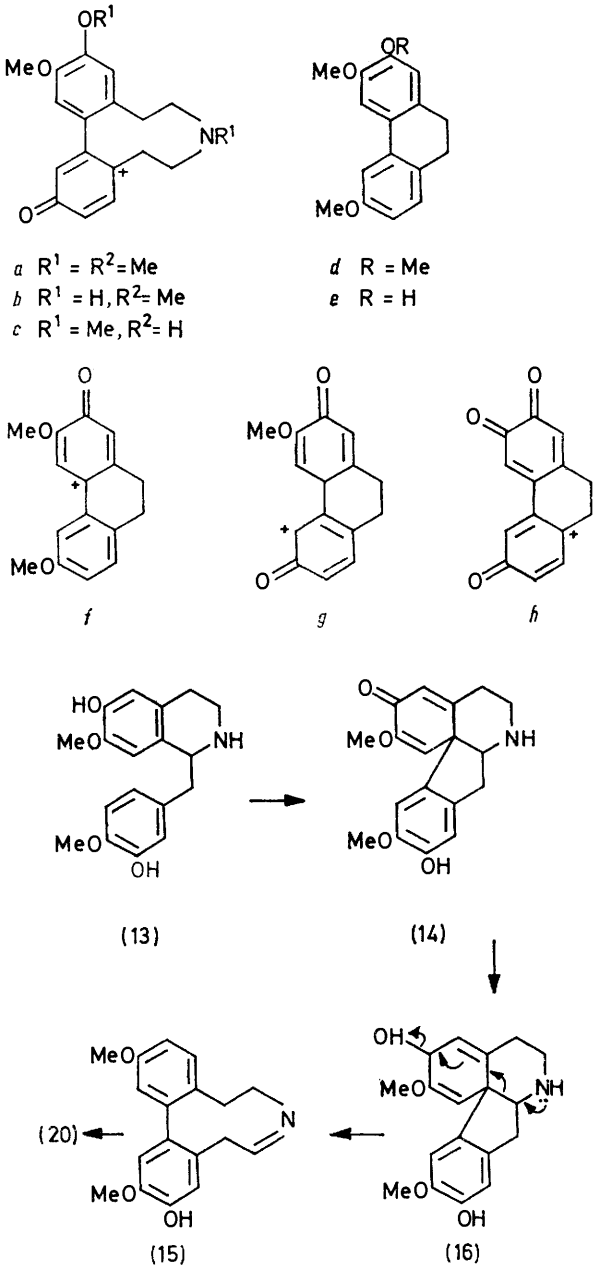
Treatment of laurifinine in methanol with ethereal diazomethane furnished *O*-methyl-laurifinine, identical with laurifonine (17).

The location of the hydroxy-group in laurifinine was

[3] K. Ito, H. Furukawa, and H. Tanaka, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 1509.

[4] C. K. Bradsher and H. Berger, *J. Amer. Chem. Soc.*, 1957, **79**, 3287.

proved as follows. In the n.m.r. spectrum of laurifinine the *para*-oriented aromatic proton at τ 3.34 gave a

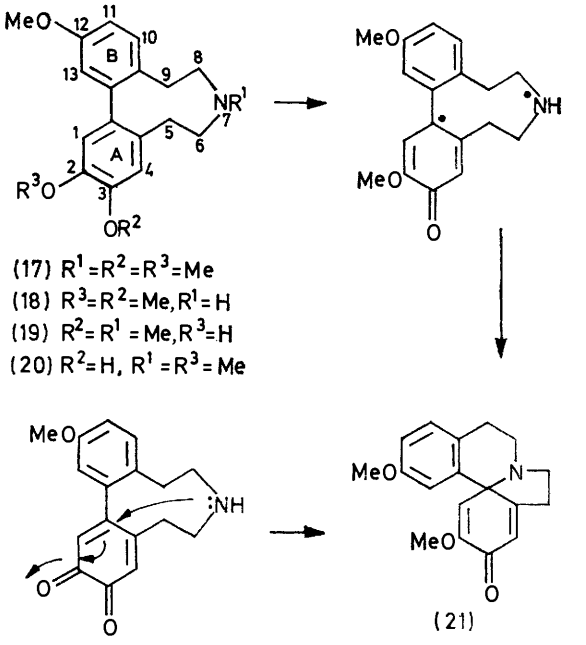


SCHEME 1

broader signal than that at τ 3.24. Irradiation at τ 6.75 (benzylic region) caused the high-field signal to sharpen and had no effect on the other. Irradiation >10 Hz to either side of τ 6.75 had no effect. It follows that the signals at τ 3.34 and 3.24 correspond to H-4 and H-1, respectively. Laurifine was heated in D_2O with potassium t-butoxide at 100 °C for 96 h to give $[^2H_1]$-laurifinine (M^+ 314). Since base-catalysed deuterium exchange of laurifinine, in which the positions *para* to the oxygen functions are substituted, furnished exclusively a $[^2H_1]$-compound, the phenolic hydroxy-group could occupy position 2 or 3 in ring A. The n.m.r. spectrum of the $[^2H_1]$-compound confirmed that the hydroxy-function was at C-2, since the signal at τ 3.24 for H-1 was reduced in intensity (64%).

The mass spectra of the alkaloids (17)—(19) were consistent with the proposed structures. In each case the molecular ion was the base peak. The ions *a*, *b*, and *c* could arise by loss of a methyl radical, and the ions *d* and *e* by loss of C_3H_7N and C_2H_5N from the molecular ion, respectively. Stepwise loss of three methyl radicals from the ion *d* could yield the ions *f*, *g*, and *h* respectively.

Dibenz[*d*,*f*]azonine bases are considered to be derived in nature from 1-benzylisoquinoline precursors.[5,6] Norprotosinomenine (13) has been demonstrated by tracer experiments to yield *in vivo* 6,7,8,9-tetrahydro-2,12-dimethoxy-5*H*-dibenz[*d*,*f*]azonine-3,11-diol, which in turn gives rise in nature to *Erythrina* alkaloids.[7] The trisubstituted dibenz[*d*,*f*]azonines which occur in *C. laurifolius* could also originate *in vivo* from norprotosinomenine (13) as shown in Scheme 1. The key dienone (21) from which hitherto known abnormal *Erythrina* alkaloids could be derived in nature by unexceptional



SCHEME 2

steps, could itself be formed [8] from the intermediate (20) as shown in Scheme 2.

[5] D. H. R. Barton, C. J. Potter, and W. A. Widdowson, *J.C.S. Perkin I*, 1974, 346.
[6] C. W. Thornber, *Phytochemistry*, 1970, 157.
[7] (*a*) D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1970, 1213; (*b*) D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *ibid.*, 1968, 1529; (*c*) D. H. R. Barton, R. D. Bracho, C. J. Potter, and D. A. Widdowson, *J.C.S. Perkin I*, 1974, 2278.
[8] D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1970, 1208.

EXPERIMENTAL

^{1}H N.m.r. spectra were determined with a Varian 60 or 100 MHz instrument, with tetramethylsilane as internal standard and deuteriochloroform as solvent except where otherwise stated.

Extraction.—Air-dried leaves (29 kg) of *C. laurifolius* DC collected in September from Dehra Dun, India, were pulverised and percolated with ethanol (4 × 45 l). The solvent from the extract was removed *in vacuo* below 40 °C to yield a dark green viscous mass (2.9 kg), which was extracted with 5% acetic acid (5 × 500 ml). The acidic solution was separated and the residual material was further treated with 15% acetic acid (5 × 500 ml). The total acidic solution was defatted with light petroleum and then basified with sodium carbonate to pH 9. The liberated bases were extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated to afford the crude alkaloid mixture (110 g).

Separation of the Phenolic and Non-phenolic Bases.—The foregoing alkaloid mixture (110 g) was extracted with ether. The ethereal extract was further extracted with 5% hydrochloric acid. The ether layer contained mostly non-basic material. The acidic extract containing the basic material was basified with sodium hydroxide to pH 9—10 and extracted with ether. This ethereal extract was concentrated to afford the non-phenolic bases (A) (50 g). The aqueous alkaline solution was adjusted to pH 7.0 with ammonium chloride and the liberated bases were extracted with chloroform. This extract was washed with water, dried (Na_2SO_4), and evaporated to afford the phenolic bases (B) (7.0 g).

Isolation of Bases.—The mixture (A) of non-phenolic bases (50 g) was chromatographed over a column of neutral alumina (2 kg). The column was eluted with hexane–benzene (1 : 1), benzene, benzene–chloroform (3 : 1, 1 : 1, and 1 : 3), chloroform, and chloroform–methanol containing an increasing proportion of the polar solvent. Elution was monitored by t.l.c. Fractions (313 × 250 ml) were collected.

Laurifonine (17). Fractions 211—235 [eluant $CHCl_3$–MeOH (99 : 1)], homogeneous on t.l.c. [SiO_2; MeOH–$CHCl_3$ (1 : 9)], afforded *laurifonine* (400 mg) as an amorphous powder, $\lambda_{max.}$ (MeOH) 221 and 283 nm (log ε 4.30 and 3.90); $\nu_{max.}$ 2 900, 1 605, 1 500, 1 450, and 1 240 cm^{-1}; τ ($CDCl_3$) 7.68 (3 H, s, NMe), 6.24 (3 H, s, OMe), 6.20 (3 H, s, OMe), 6.10 (3 H, s, OMe), 7.30—7.50 (8 H, m, 4 CH_2), 3.32 (1 H, s, 4-H); 3.28 (1 H, s, 1-H), 3.20 (1 H, dd, *J* 2.5 and 8.5 Hz, 11-H), 2.95 (1 H, d, *J* 2.5 Hz, 13-H), and 2.82 (1 H, d, *J* 8.5 Hz, 10-H); *m/e* 327 (M^+, base peak), 312 ($M^+ - 15$), 284 ($M^+ - 43$), 270 ($M^+ - 57$), 255 ($M^+ - 72$), 240 ($M^+ - 87$), 225 ($M^+ - 102$), and 163.5 (M^{2+}) (Found: C, 69.3; H, 8.1; N, 3.55. $C_{20}H_{25}NO_3,H_2O$ requires C, 69.55; H, 7.8; N, 4.05%).

A solution of laurifonine (20 mg) in 2% hydrochloric acid (0.3 ml) was treated with saturated aqueous sodium perchlorate. An oily residue separated which was washed with water, dried and crystallised from methanol–ether; yield 15 mg, m.p. 182—185°.

Laurifine (18). Fractions 264—270 [eluant $CHCl_3$–MeOH (95 : 5)] afforded *laurifine* (120 mg) as an amorphous powder, $\lambda_{max.}$ (MeOH) 221 and 284 nm (log ε 4.34 and 3.96); $\nu_{max.}$ (KBr) 3 450 (NH), 1 600 (Ar), 1 500, 1 450, and 1 240 cm^{-1}; τ ($CDCl_3$) 6.18 (3 H, s, OMe), 6.10 (3 H, s, OMe), 6.06 (3 H, s, OMe), 6.80—7.70 (8 H, m, 4 CH_2), 3.30 (1 H, s, 4-H), 3.28 (1 H, s, 1-H), 3.26 (1 H, dd, *J* 2.5 and 9.5 Hz, 11-H), 3.06 (1 H, d, *J* 2.5 Hz, 13-H), and 2.84 (1 H, d, *J* 9.5 Hz, 10-H); *m/e* 313 (M^+, base), 298 ($M^+ - 15$), 270 ($M^+ - 43$), 255 ($M^+ - 58$), 240 ($M^+ - 73$), 225 ($M^+ - 88$), and 156.5 (M^{2+}) (Found: C, 66.7; H, 8.05; N, 4.4. $C_{19}H_{23}NO_3,1.5H_2O$ requires C, 67.05; H, 7.65; N, 4.1%).

Laurifinine (19). Fractions 93—112 [eluant EtOAc–MeOH (90 : 10)], homogeneous on t.l.c. [SiO_2; $CHCl_3$–MeOH (90 : 10)] afforded *laurifinine* (160 mg) as an amorphous powder, $\lambda_{max.}$ (MeOH) 223 and 284 nm (log ε 4.24 and 3.84); $\nu_{max.}$ (KBr) 3 410 (OH), 1 610, 1 500, and 1 450 cm^{-1}; τ ($CDCl_3$) 7.68 (3 H, s, NMe), 6.20 (3 H, s, OMe), 6.18 (3 H, s, OMe), 6.75 (2 H, s, CH_2), 7.42 (6 H, m, 3 CH_2), 5.18br (1 H, s, exchangeable with D_2O, OH), 3.34br (1 H, s, 4-H), 3.24 (1 H, s, 1-H), 3.26 (1 H, dd, *J* 2.4 and 10.0 Hz, 11-H), 3.10 (1 H, d, *J* 2.4 Hz, 13-H), 2.84 (1 H, dd, *J* 1.4 and 10.0 Hz, 10-H); *m/e* 313 (M^+, base), 298 ($M^+ - 15$), 270 ($M^+ - 43$), 256 ($M^+ - 57$), 255 ($M^+ - 58$), 225 ($M^+ - 68$), 195 ($M^+ - 118$), and 156.5 (M^{2+}) (Found: C, 65.05; H, 7.55; N, 4.35. $C_{19}H_{23}NO_3,2H_2O$ requires C, 65.35; H, 7.75; N, 4.0%).

A solution of laurifinine (20 mg) in 2% hydrochloric acid (0.2 ml) was treated with aqueous sodium perchlorate and the resulting mixture was worked up as described earlier to afford laurifinine perchlorate (14 mg), m.p. 243—245° (from methanol–ether).

N-*Methyl-laurifine* (17).—A solution of laurifine (60 mg) in methanol (10 ml) was treated with formaldehyde (1 ml) followed by sodium borohydride (40 mg). After stirring for 2 h the solvent was removed. The residue was acidified with 5% hydrochloric acid and extracted with ether. The acidic layer was basified with sodium carbonate to pH 8—9. The liberated base was extracted with chloroform and the extract washed with water, dried (Na_2SO_4), and evaporated to afford *N*-methyl-laurifine (45 mg) as an amorphous powder, identical with laurifonine (17) (t.l.c. and u.v., i.r., n.m.r., and mass spectral data).

O-*Methyl-laurifinine* (17).—A solution of laurifinine (40 mg) in methanol (10 ml) was treated with excess of diazomethane at room temperature for 24 h. The resulting mixture was worked up to afford *O*-methyl-laurifinine (28 mg) as an amorphous powder, identical with laurifonine (t.l.c. and u.v., i.r., n.m.r., and mass spectral data).

[1-^{2}H]*Laurifinine.*—A mixture of laurifinine (40 mg), D_2O (0.5 ml), and potassium t-butoxide (60 mg) was heated in a sealed tube (nitrogen atmosphere) at 100 °C for 100 h, then diluted with water. Ammonium chloride was added (pH 7) and the liberated base was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to afford [1-^{2}H]laurifinine (24 mg), $\lambda_{max.}$ (MeOH) 223 and 284 nm (log ε 4.24 and 3.84); $\nu_{max.}$ (KBr) 3 400, 1 610, 1 500, and 1 450 cm^{-1}; *m/e* 314 (M^+), 299 ($M^+ - 15$), 271 ($M^+ - 43$), and 256 ($M^+ - 58$); n.m.r. spectrum identical with that of laurifinine except that the singlet at τ 3.34 (1-H) was reduced in intensity (64%).

Hofmann Degradation of Laurifonine (17).—A solution of laurifonine (200 mg) in methanol (10 ml) was refluxed with methyl iodide (5 ml) for 4 h. The solvent and the excess of methyl iodide were removed *in vacuo* to afford laurifonine methiodide (10) (180 mg), m.p. 165—170°; τ ($CDCl_3$) 6.64 (6 H, s, $^+NMe_2$), 6.20 (3 H, s, OMe), 6.18 (3 H, s, OMe), 6.05 (3 H, s, OMe), 6.52—7.35 (8 H, m, 4 CH_2), 3.37 (1 H, s, 4-H), 3.34 (1 H, d, *J* 2.0 Hz, 13-H), 3.10 (1 H, s, 1-H), 2.95 (1 H, dd, *J* 1.8 and 9.0 Hz, 11-H), and 2.82 (1 H, d, *J* 9.0 Hz, 10-H).

A solution of the product (10) (180 mg) in methanol–water (4 : 1) was passed through a column of freshly regenerated Amberlite IR-410 anion-exchange resin (OH^-) (4.3 g) to afford laurifonine methohydroxide. The eluate was concentrated to 10 ml and refluxed for 2 h with a solution of potassium hydroxide (0.42 g) in water (1.0 ml). It was then cooled and extracted with ether–chloroform (3 : 1 v/v; 5 × 20 ml) and chloroform (5 × 25 ml). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to afford a mixture of biphenyls (4) and (5) as an oil (130 mg).

The mixture of (4) and (5) (120 mg) in methanol (10 ml) was refluxed with methyl iodide (3.0 ml) for 2 h. The solvent and the excess of reagent were then removed to afford a mixture of methiodides (125 mg) as an amorphous powder which was converted into the hydroxide form by passing through a column of freshly regenerated Amberlite IR-410 anion-exchange resin (OH^-). The resulting methohydroxides in methanol (5 ml) were refluxed with a solution of potassium hydroxide (0.3 g) in water (1.0 ml) for 2 h. The mixture was cooled and extracted with ether–chloroform (3 : 1 v/v; 5 × 50 ml). The combined extract was washed with water, dried (Na_2SO_4), and evaporated to afford an oil (70 mg), which showed two spots on t.l.c. (benzene). Elution with hexane–benzene (1 : 1) (fractions 3—5) monitored by t.l.c. afforded the styrene (6) (25 mg) as an oil, τ ($CDCl_3$) 6.21 (3 H, s, OMe), 6.20 (3 H, s, OMe), 6.10 (3 H, s, OMe), 5.07 (2 H, dd, $J_{AB} = J_{A'B'} = 11$, $J_{BC} = J_{B'C'} = 2$ Hz), 4.56 (2 H, dd, $J_{AC} = J_{A'C'} = 17$, $J_{BC} = J_{B'C'} = 2$ Hz), 3.65 (2 H, dd, $CH_A{=}CH_BH_C$ and $CH_A{=}CH_B$, H_C), 3.39 (2 H, s, 3- and 6-H), 3.33 (1 H, d, *J* 2.5 Hz, 6′-H), 2.87 (1 H, dd, *J* 2.6 and 9.0 Hz, 4′-H), and 2.49 (1 H, d, *J* 9.0 Hz, 3′-H).

Cleavage of the Styrene (6) *with Osmium Tetraoxide and Periodate.*—To a stirred solution of compound (6) (50 mg) in purified t-butyl alcohol (5.0 ml) and water (3.0 ml), an aqueous solution of osmium tetraoxide (1.0 ml; 4%) was added, followed by sodium periodate (80 mg). More periodate (60 mg) was added after 2.5 h. Stirring was continued for another 2.5 h. After a total of 5 h the complex was decomposed with saturated aqueous arsenic trioxide (25 ml). The product was then extracted with chloroform (5 × 20 ml). The combined extract was washed with water, dried (Na_2SO_4), and evaporated to afford *4,4′,5-trimethoxy-2,2′-bibenzaldehyde* (7), as plates, m.p. 150—151° (from methanol), $\lambda_{max.}$ (MeOH) 227 and 271 nm; $\nu_{max.}$ (KBr) 2 820, 1 680, and 1 603 cm^{-1}; τ ($CDCl_3$) 6.08 (3 H, s, OMe), 6.05 (3 H, s, OMe), 5.98 (3 H, s, OMe), 3.2 (1 H, s, 3-H), 3.15 (1 H, d, *J* 2.0 Hz, 3′-*H*), 2.90 (1 H, dd, *J* 2.0 and 9.0 Hz, 5′-H), 2.43 (1 H, s, 6-H), 1.96 (1 H, d, *J* 9.0 Hz), 0.33 (1 H, s, CHO), and 0.30 (1 H, s, CHO); *m/e* 300 (M^+), 271 ($M^+ - 29$), 246 ($M^+ - 54$), 232 ($M^+ - 68$), 220 ($M^+ - 80$), and 208 ($M^+ - 94$) (Found: C, 68.55; H, 5.9. $C_{17}H_{15}O_5$ requires C, 68.0; H, 5.35%).

Distillation of Laurifonine (17) *with Zinc Dust.*—A mixture of laurifonine (120 mg) and zinc dust (1.0 g) in a glass tube in an atmosphere of hydrogen was distilled at 300 °C. The oily product was subjected to preparative t.l.c. [SiO_2; $CHCl_3$–MeOH (98 : 2)] to afford *2,3,6-trimethoxyphenanthrene* (1), m.p. 132—133° (from benzene–petroleum); $\nu_{max.}$ (KBr) 1 606, 1 600, 1 549, 1 230, and 1 040 cm^{-1}; τ ($CDCl_3$) 6.03 (3 H, s, OMe), 6.02 (3 H, s, OMe), 5.98 (3 H, s, OMe), 2.84 (1 H, dd, *J* 2.0 and 9.0 Hz, 7-H), 2.82 (1 H, s, 1-H), 2.50 (1 H, s, 9-H), 2.47 (1 H, s, 10-H), 2.22 (1 H, d, *J* 9.0 Hz, 8-H), and 2.17 (2 H, s, 4- and 5-H); *m/e* 268 (M^+), 267 ($M^+ - 1$, base), 253 ($M^+ - 15$), 225 ($M^+ - 43$), 195 ($M^+ - 73$), and 182 ($M^+ - 86$) (Found: C, 75.8; H, 6.2. $C_{17}H_{16}O_3$ requires C, 76.1; H, 5.95%).

Synthesis of 2,3,6-Trimethoxyphenanthrene (1).—A mixture of 6-nitroveratraldehyde (5.0 g), 4-methoxyphenylacetic acid (4.0 g), acetic anhydride (25 ml), and triethylamine (5.0 ml) was heated at 100 °C for 18 h. Work-up gave 3,4-dimethoxy-α-(4-methoxyphenyl)-6-nitrocinnamic acid (8) (6.2 g), m.p. 180—182° (lit.,[4] 185—186°). A warm solution of the acid (8) (10 g) in 14% ammonia (400 ml) was added dropwise to a stirred solution of ammoniacal iron(II) sulphate (300 ml; 28%) and water (300 ml) at 90—95 °C during 15 min. After 2 h the mixture was worked up to give 6-amino-3,4-dimethoxy-α-(4-methoxyphenyl)cinnamic acid (9) (6.1 g), m.p. 208—209° (lit.,[4] 206—207°). To a hot solution of the acid (9) (10 g) in dry acetone (800 ml), 20% sulphuric acid (53 ml) was added dropwise with stirring. The resulting mixture was cooled in ice and a white solid (amine sulphate) separated out. It was diazotised at 0 °C with n-butyl nitrite (10 ml) in dry acetone (20 ml). Freshly prepared copper powder (10 g) was added to the mixture and stirring was continued for 3 h at 0—5 °C and 2 h at 10—15 °C. The mixture was kept at room temperature overnight, then worked up to give 2,3,6-trimethoxyphenanthrene-9-carboxylic acid (2), which was purified through its methyl ester (3) as follows. An ice cooled solution of the acid (2) (1.0 g) in dimethylformamide (5.0 ml) was treated with an excess of ethereal diazomethane for 4 h. The solvent was removed and the residue crystallised from benzene–petroleum to afford the *ester* (3) (0.6 g), m.p. 165—166°; $\nu_{max.}$ (KBr) 1 706, 1 616, and 1 507 cm^{-1}; τ ($CDCl_3$) 6.07 (3 H, s, OMe), 6.02 (9 H, s, 3 OMe), 2.97 (1 H, s, 1-H), 2.81 (1 H, dd, *J* 3.0 and 9.0 Hz, 7-H), 2.43 (1 H, s, 4-H), 2.42 (1 H, d, *J* 3.0 Hz, 5-H), 1.97 (1 H, s, 10-H), and 1.47 (1 H, d, *J* 10.0 Hz, 8-H); *m/e* 326 (M^+), 311 ($M^+ - 15$), 295 ($M^+ - 31$), 283 ($M^+ - 43$), 224 ($M^+ - 102$), and 163 (M^{2+}) (Found: C, 70.1; H, 5.8. $C_{19}H_{18}O_5$ requires C, 69.95; H, 5.55%). A suspension of the ester (3) (1.0 g) in aqueous 5% sodium hydroxide (5.0 ml) and ethanol (20 ml) was refluxed for 2 h on a water-bath. The solvent was removed and the aqueous alkaline solution was acidified with 10% hydrochloric acid to give the acid (2) (900 mg), which crystallized from hot ethanol; m.p. 120—121° (lit.,[4] 122°).

A mixture of the acid (2) (500 mg), copper powder (1.5 g), and freshly distilled quinoline (30 ml) was refluxed for 6 h, cooled, and filtered. The filtrate was acidified with dilute hydrochloric acid and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue (200 mg) was chromatographed over silica (8 g). Elution with benzene yielded 2,3,6-trimethoxyphenanthrene (1) (120 g), m.p. 132—133° (from benzene–petroleum), identical (m.p. and mixed m.p., t.l.c., and n.m.r., i.r., u.v., and mass spectral data) with the phenanthrene derivative (1) from laurifonine.

Degradation of 2,3,6-Trimethoxyphenanthrene.—A solution of compound (1) (500 mg) in dry benzene (100 ml) was treated with a solution of osmium tetraoxide (500 mg) in dry benzene (5 ml) and pyridine (0.75 ml) for 1 week at room temperature. The supernatant liquid was decanted and the brown crystalline product was washed with dry benzene (2 × 5 ml). It was dissolved in dichloromethane (10 ml), treated with a solution of mannitol (5 g) and potassium hydroxide (500 mg) in water (50 ml), and

left for 2 h under nitrogen. The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (5 × 10 ml). The combined dichloromethane solution was washed with water (2 × 10 ml), dried (Na_2SO_4), and evaporated. The residue (280 mg) was chromatographed over silica (8.0 g). Elution with methanol–chloroform (1 : 99) furnished the diol (11) (200 mg), m.p. 166—167°; $\nu_{max.}$ 3 350, 1 603, and 1 570 cm^{-1}; *m/e* 302 (M^+), 284 ($M^+ - 18$, base), 271 ($M^+ - 31$), 269 ($M^+ - 33$), 255 ($M^+ - 47$), and 241 ($M^+ - 61$).

A solution of the diol (11) (200 mg) in tetrahydrofuran (20 ml) was treated with a solution of sodium periodate (150 mg) in water (10 ml) and left at room temperature overnight. The solvent was removed, water added, and the product extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The product [two spots on t.l.c. in $CHCl_3$–MeOH (99 : 1)] was chromatographed on a silica column. Elution with chloroform furnished the bibenzaldehyde (7) (80 mg) as needles, m.p. 150—151° (from methanol), identical (m.p., mixed m.p., and i.r., u.v., n.m.r., and mass spectral data) with the dialdehyde (7) obtained from laurifonine (17).

Further elution of the column with methanol–chloroform (1 : 99) gave 2,3,6-*trimethoxyphenanthrenequinone* (12) (50 mg), m.p. 210—211°; $\lambda_{max.}$ (EtOH) 212, 242, 289, and 352 nm; $\nu_{max.}$ (KBr) 1 705 cm^{-1} (C=O); τ ($CDCl_3$) 6.06 (6 H, s, 2 OMe), 5.98 (3 H, s, OMe), 3.25 (1 H, dd, *J* 2.0 and 9.0 Hz, 7-H), 2.95 (1 H, d, *J* 2.0 Hz, 5-H), 2.97 (1 H, s, 4-H), 2.59 (1 H, s, 1-H), and 2.05 (1 H, d, *J* 9.0 Hz, 8-H); *m/e* 298 (M^+), 270 ($M^+ - 28$), 255 ($M^+ - 43$), 227 ($M^+ - 71$), 212 ($M^+ - 86$), and 184 ($M^+ - 114$) (Found: C, 68.0; H, 5.2. $C_{17}H_{15}O_4$ requires C, 68.45; H, 4.7%).

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