Tetrahedron Vol. 49, No. 1, pp. 151-164, 1993
Printed in Great Britain

0040-4020/93 $5.00+.00

Synthesis of Pyrrolophenanthridones By Aryl-Aryl Coupling Reactions

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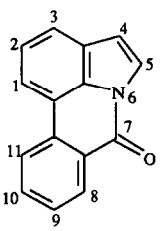
(*Received in UK* 6 *October* 1992)

Keywords: Indoles, pyrrolophenanthridones, alkaloids, palladium acetate, aryl-aryl coupling.

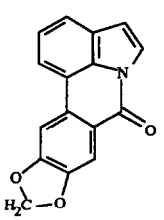
Abstract: The N-aroyl-4,6-dimethoxyindoles (15-21), prepared from 4,6-dimethoxyindole (14), were converted by palladium acetate in acetic acid into the pyrrolophenanthridones (22-28) in moderate yields (30-65%). These products are related to some pyrrolophenanthridone alkaloids, which lack the methoxyl groups. Similar aryl-aryl coupling reactions of N-benzylindoles could not be effected.

Pyrrolo[3,2,1-de]phenanthridin-7-one (1) (with numbering system shown) is formally the benzo-analog of 4-oxo-pyrroloquinoline.[1]



(1)

The importance of the pyrrolophenanthridones emerged with the isolation of three examples, hippadine (2), pratorinine (3) and a dihydro example, anhydrolycorin-7-one (4) from the bulbs of *Crinum pratense* collected at flowering time[2].



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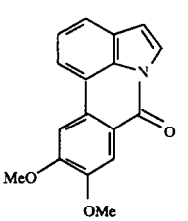

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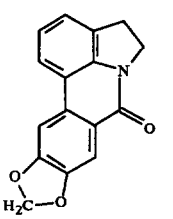
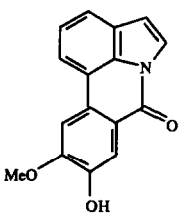


(4)

Subsequent isolation of other pyrrolophenanthridones from other *Amaryllidaceae* species has resulted in a wider range of alkaloids which also include pratorimine (5), pratosine (6)[3] and kalbretorine (7)[4], and oxoassoamine[5], the dihydro analog of pratorine. Early confusion with the correct assignment of the two

structural isomers pratorimine and pratorinine has been clarified with the advent of an X-ray crystal structure of pratorinine[6].

The physiological activity of hippadine has been investigated. Hippadine-treated male rats showed a reversible inhibition in fertility with a significant loss of testis tissue weight and testis DNA content. There was no anti-mitotic activity which suggests that the effects are being exerted at the genetic level and thus may be useful in future fertility control[7]. This has prompted various attempts at the synthesis of hippadine.



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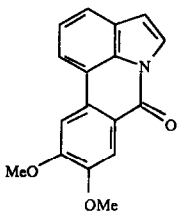

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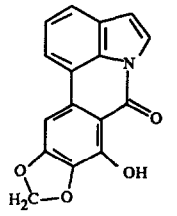
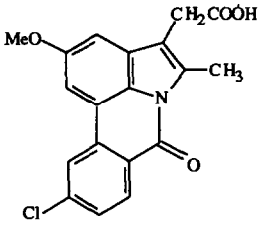


(7)

Early syntheses of pyrrolophenanthridones were investigated independently from the isolation of the alkaloids. Olsen *et al* synthesized the pyrrolophenanthridone (8) as a rigid analog of the 'nonsteroidal antiinflammatory agent' indomethacin (9)[8]. The key step involved an aryl-aryl coupling reaction via a diazonium cation (10) (Pschorr cyclisation).



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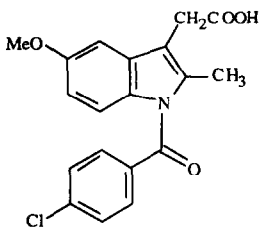

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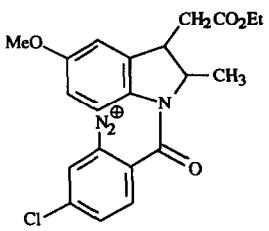
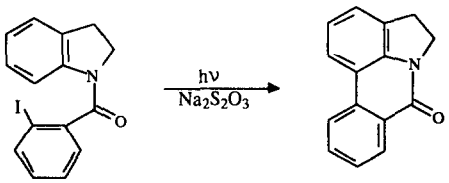


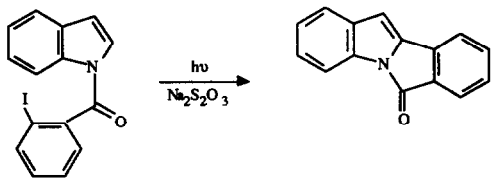
(10)

Investigation into the photochemical behaviour of N-benzoyl indole led to the synthesis of another pyrrolophenanthridone. This involved the irradiation of *o*-iodobenzoylindoline (11) which yielded the cyclic product (1) in 10% yield[9].



(11) (1)

An important result arising from these investigations is that a corresponding cyclisation using the indole (12) in place of the indoline (11) gave the product (13) resulting from cyclisation on the C2 position of the indole ring.



(12) (13)

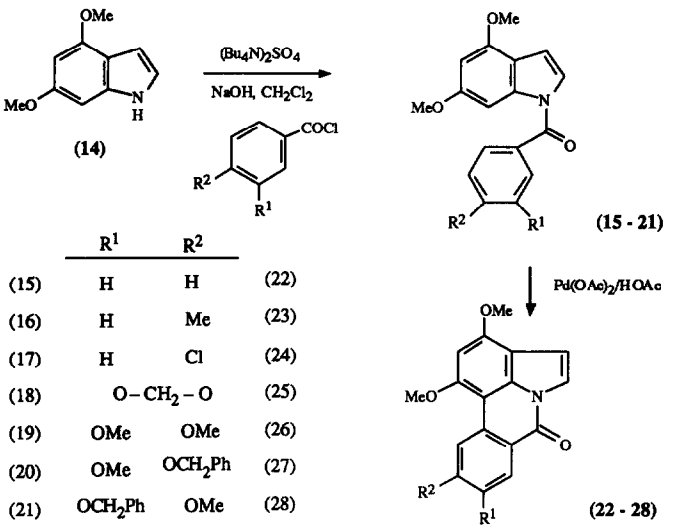
Hippadine was one of the first of the alkaloids to be synthesized due to its interesting biological activity. Successful syntheses include a long and reasonably complicated route involving indole ring formation by an intramolecular allene cycloaddition and cyclisation of a 7-(*o*-formylaryl)indole, to give the desired alkaloid in 2% overall yield[10]. Another method involves the formation of the pyrrole ring from an N-hydroxyphenanthridone *via* reaction with methyl propiolate followed by a [3,3] sigmatropic rearrangement to give hippadine in 18% yield.[11] Initial synthesis of pratosine (6) and pratorinine (3) involved the construction of a substituted indoline, which was subsequently cyclised by a Pschorr reaction. Oxidation to pratosine was achieved using DDQ and monodemethylation yielded the desired hydroxy product.[3]

The demethylated product was originally reported as pratorimine but the X-ray crystal analysis mentioned previously corrects an earlier assignment and deems this product to be pratorinine. Any confusion is further clarified by an independent synthesis of pratorimine utilizing similar methodology to that described above.[12]

Our current work on 4,6-dimethoxyindoles has shown that 7-substitution can be achieved directly and easily, and furthermore, that cyclisation processes can lead to new rings between C7 and N1. Therefore, 4,6-dimethoxyindoles might be suitable starting materials for the synthesis of the dimethoxy analogs of the known pyrrolophenanthridone alkaloids.

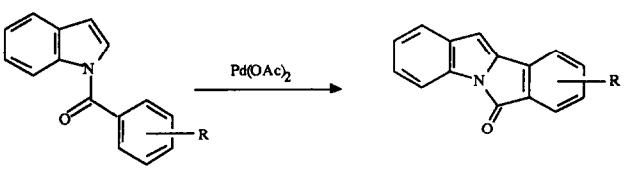
Retrosynthetic analysis would indicate that the crucial C7 bond could be achieved by a biaryl coupling of an N-benzoyl indole, itself available from the relevant acid chloride and indole.

A range of N-benzoyl indoles was prepared from 4,6-dimethoxyindole (14) and the relevant series of acid chlorides. A phase transfer catalyst in conjunction with sodium hydroxide in dichloromethane was used to generate the indole nucleophile because of the sensitivity of the acid chlorides to base. By this method, the N-aroyl indoles (15) - (21) were prepared.



	R^1	R^2	
(15)	H	H	(22)
(16)	H	Me	(23)
(17)	H	Cl	(24)
(18)	O–CH_2–O		(25)
(19)	OMe	OMe	(26)
(20)	OMe	OCH_2Ph	(27)
(21)	OCH_2Ph	OMe	(28)

The indole (14), which is unsubstituted at C2 and C3 was deliberately chosen as the alkaloids themselves do not have substituents as these positions. However, this does raise a problem with the biaryl coupling in that there is competition between the dimethoxy activated C7 position and the active indole C2 position. It has already been shown that N-benzoyl indole undergoes a light-induced cyclisation to the C2 position[9] and there are numerous examples in the literature of similar types of reactions. One example is the synthesis of 6-oxo-6H-isoindole [2,1-a]indole (30) via a palladium acetate coupling of N-aroyl indoles (29).[13]

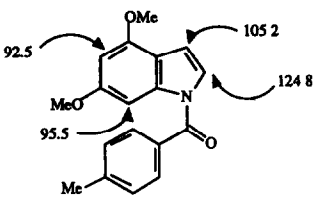


(29) (30)

It was anticipated that the activation of the methoxy groups would be sufficient to encourage cyclisation at C7 at the expense of C2. Another factor is that such a C7-linked product would contain a new six-membered ring which would probably be less strained than the five-membered ring in the alternative product.

Several reagents are available for biaryl coupling but experiments were confined to the widely established palladium coupling in acetic acid. Under the conditions, the N-aroyl indoles were converted into the pyrrolophenanthridones (22)-(28) in yields ranging from 30-65%.

The most striking evidence for the production of the pyrrolophenanthridones and not the product resulting from cyclisation onto C2 was provided by ^{13}C n.m.r. spectroscopy. A comparison of the ^{13}C chemical shifts of the indole C2, C3, C5 and C7 carbon atoms of starting materials and products establishes the site of reaction. For example, the chemical shift values are indicated below for compounds (16) and (23).



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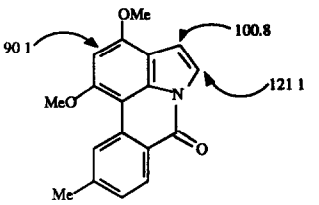
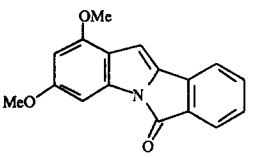


(23)

Clearly a protonated indole C2 position is still present in the product (23) whereas the C7 carbon is now quaternary. This evidence is consistent throughout the series of pyrrolophenanthridones produced here.

The infra-red spectra of the series of N-benzoyl indole starting materials reveal the amide carbonyl stretching frequencies in the acceptable amide range 1682-1690 cm^{-1}. Upon cyclisation to the dimethoxy-pyrrolophenanthridone series of products reported here, the corresponding amide stretching frequencies increase to the range of 1715-1763 cm^{-1}. Although these absolute values for amides seem to be high, they are consistent with the change from an N-substituted indole to a pyrrolophenanthridone, or of an open chain amide to a lactam. It is noteworthy that the presence of the dimethoxy substituents also has an effect on these amide values. Comparison between an authentic pratosine sample and the dimethoxy derivative show amide stretching frequencies at υ_{max} 1675 cm^{-1} [3] and 1715 cm^{-1} respectively. A similar comparison between an authentic hippadine sample and the dimethoxy derivative shows respectively υ_{max} 1715 cm^{-1} [11] in contrast to 1731 cm^{-1}. Presumably this effect arises from the twist from planarity of the dimethoxy-pyrrolophenanthridones arising from steric hindrance between the indole C6-methoxy group and the *ortho* proton on the benzoyl group. Any twist would result in some disruption of conjugation between the carbonyl and adjacent benzene rings.

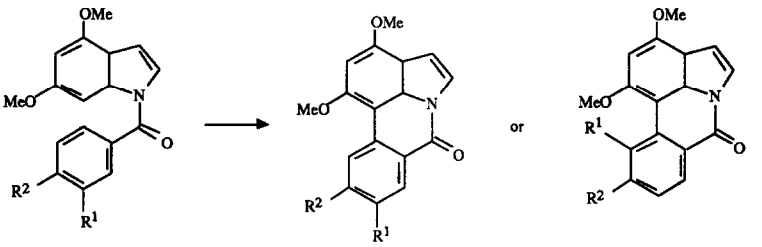


(31)

The overall effect of the change in chemical nature of the N-benzoyl indoles to the pyrrolophenanthridones is further supported by ultraviolet spectroscopy which shows an increase to higher wavelengths extending into the visible region for the final products. All the dimethoxy pyrrolo-phenanthridones are deep yellow in colour.

The cyclisation of the N-benzoylindole (15) yielded mostly the desired pyrrolophenanthridone. In the ^1H n.m.r. spectrum of this product the two methoxy peaks coincide, appearing as a singlet at 3.88 ppm. A minor product was also isolated and was partially characterised The evidence suggests that this product is the result of cyclisation on to the C2 position producing the 9,11-dimethoxy-6-oxo-6H-isoindolo[2,1-a]indole (31). An amide carbonyl peak is present (υ_{max} 1781 cm^{-1}) and the ^1H n.m.r. spectrum clearly shows the presence of the indole H5 and H7 protons at 6.23 (*J* 2.1Hz) and 7.07 ppm (*J* 2.0Hz) respectively. This product was isolated in 18% crude yield but could not be obtained analytically pure

There is some evidence for the formation of the C2-cyclised products in all the examples. Thin layer chromatographic analysis shows distinct and separate fluorescent yellow spots for both products. However, in all cases, the unwanted indolo[2,1-*a*]indole product was present only in minor quantities and was impractical to isolate and purify. In the examples where the benzoyl ring is disubstituted, there are two possible modes of cyclisation, as illustrated below.



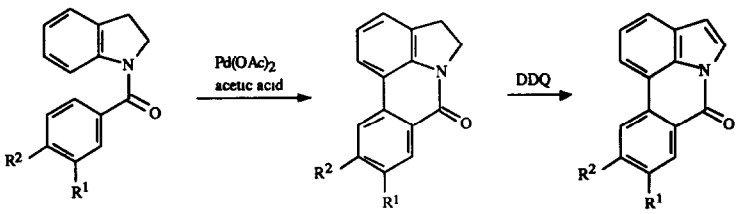
In the methylene-dioxy substituted case (18), both products are formed but were unable to be separated. The ratio of products, based on ^{1}H n.m.r. spectroscopic analysis was 2.5:1 with dimethoxy hippadine (25) the major product. This type of ratio is to be expected as the minor product would have a greater degree of interaction between the benzoyl substituents and the adjacent methoxy group and therefore buttressing effects would affect its formation.

The cyclisation of the N-(dimethoxybenzoyl)indole (19) to yield the dimethoxy derivative (26) of pratosine proceeded with formation of only a negligible amount of the second isomeric product. The final two examples containing the benzyloxy and methoxy substituents showed no sign of the formation of these alternative products. This is probably due to the combined buttressing effects of the indole methoxy groups and the bulky benzoyl ring substituents. These two products were designed with the benzyl groups to be used as protecting groups. All that remains to be done is to remove the benzyl groups to yield the dimethoxy derivatives of pratorimine and pratorinine.

All the dimethoxy-pyrrolophenanthridones were difficult to obtain analytically pure. They all required extended periods of drying under reduced pressure. The examples (27) and (28) analysed as partial hydrates and a satisfactory elemental analysis could not be obtained for compound (23).

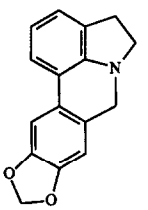
The presence of the dimethoxy groups on the indoles results in sufficient activation of the C7 position for reaction to take place there and only an insignificant quantity of product resulted from cyclisation on to C2. Thus these indoles represent an easy and quick access to the pyrrolophenanthridones.

The successful synthesis of this series of dimethoxy pyrrolophenanthridones led to an extension to produce the desired natural products. The reactions involve the cyclisation of N-benzoyl indolines with palladium acetate in glacial acetic acid followed by oxidation using DDQ[14]. This offers a truly general synthetic route to the pyrrolophenanthridone alkaloids



Since publication of this natural product synthesis, two further reports have described syntheses of hippadine. One involves arylboronic acid-aryl halide cross coupling methodology[15] and the other a coupling of two iodo-arenes initiated by palladium acetate and hexamethyl ditin.[16]

The related pyrrolophenanthridines are also known and some natural products of this type have been isolated.[17,18] These are usually synthetically prepared by a reduction of the corresponding pyrrolophenanthridones. For example, anhydrolycorine (32) can be prepared from hippadine by lithium aluminium hydride reduction[19] via the formation of a stable azomethine ylid intermediate. A direct approach can be proposed on the basis of the successful synthesis of the pyrrolophenanthridones. It would involve a biaryl coupling, utilizing a suitably substituted N-benzyl indole or indoline. Consideration of this type of reaction led to the preparation of a variety of potential starting materials (35)-(38) from the indole (33)[20] or its 7-bromo-analog (34).[21] A range of coupling experiments was then investigated in an attempt to produce the desired pyrrolophenanthridines.



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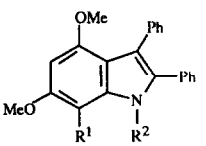

	R^1	R^2
(33)	H	H
(34)	Br	H
(35)	H	CH_2Ph
(36)	H	CH_2–*o*–BrPh
(37)	Br	CH_2Ph
(38)	Br	CH_2–*o*–BrPh

A direct coupling of (35) using palladium acetate in acetic acid heated at reflux could not be achieved. Presumably the *ortho* activation of the carbonyl group was sufficient to induce cyclisation to the pyrrolophenanthridones whereas in the absence of the *ortho* activation, as in the N-benzyl examples, no reaction occurred. Preliminary investigations of a Heck-type reaction[22] on both the monobrominated starting materials (36) and (37) also failed. Potentially a more desirable reaction would be a photochemical coupling of the dibromo compound (38). Despite the use of light sources at 305 nm and 254 nm in solvents such as benzene and absolute ethanol, with or without an initiator, benzophenone, all attempts failed.

The N-benzyl indole (35) was also treated with thallium trifluoroacetate and boron trifluoride etherate in trifluoroacetic acid and dichloromethane at 0°C but biaryl coupling could not be confirmed.

Experimental

1-Benzoyl-4,6-dimethoxyindole (15)

A solution of 4,6-dimethoxyindole (14) (0.213 g, 1.20 mmol) in dry dichloromethane (30 mL) with crushed sodium hydroxide (0.12g, 3.00 mmol) and tetrabutylammonium hydrogen sulphate (0.01g) was stirred at room temperature for 15 min. Benzoyl chloride (0.15 mL, 1.29 mmol) was added dropwise and the whole stirred for a further 30 min. The mixture was then filtered, the filtrate evaporated and the residue recrystallized from ethanol to yield the N-benzoyl indole (15) (0.22g, 65%) as white *crystals*, m.p. 101-102° (Found: C, 72.4; H, 5.4; N, 5.0. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%). υ_{max} 1687, 1608, 149s, 1422, 1344, 1321, 1309, 1221, 1209, 1065, 823, 722 cm^{-1}. λ_{max} 223 (ε16,200), 253nm (22,200).^{1}H n.m.r. δ 3.89, 3.92, 2s, OMe; 6.43, d, *J* 2.1Hz, H5; 6.65, d, *J* 3.8 Hz, H3; 7.07, d, *J* 3.8 Hz, H2; 7.56, 7.73, m, aryl; 7.64, d, *J* 1.9 Hz, H7 .^{13}C n.m.r. δ 55.5, 55.8, OMe; 92.6, C5; 95.6, C7; 105.5, C3; 115.3, 134.7, 137.6, 153.1, 159.5, aryl C; 124.7, C2; 128.5, 129.1, 131.6, aryl CH; 169.2, CO. *m/z* 281 (M, 40%), 105 (100).

1-(4-Methylbenzoyl)-4,6-dimethoxyindole (16)

A solution of 4-methylbenzoic acid (0.401g, 2.95 mmol) in thionyl chloride (20 mL) was heated at reflux for 0.5 h before the solvent was removed and the residue dried on a vacuum pump. This residue was then dissolved in dry dichloromethane (10 mL) and added dropwise to a mixture of 4,6-dimethoxyindole (14) (0.502g, 2.84 mmol), sodium hydroxide (0.381g, 9.53 mmol) and tetrabutylammonium hydrogen sulphate (0.02g) in dry dicholoromethane (30 mL) which had already been stirring at room temperature for 0.5 h. After a further 2 h of stirring, the mixture was filtered, the filtrate evaporated, the residue flash chromatographed (1:1 dichloromethane/light petroleum) and then recrystallized from ethanol to yield the N-benzoyl indole (16) (0.210g, 25%) as light yellow *crystals*, m.p. 88-89° (Found: C, 72.8; H, 5.8; N, 4.7. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; 4.7%). υ_{max} 1682, 1603, 1501, 1424, 1357, 1335, 1308, 1217, 1190, 1071, 893, 829, 744, 709 cm^{-1}. λ_{max} 222nm (ε21,300). ^{1}H n.m.r. δ 2.46, s, CH_3; 3 89, 3.92, 2s, OMe; 6.42, d, *J* 2.0 Hz, H5; 6.63, d, *J* 3.8 Hz, H3; 7.10, d, *J* 3.8 Hz, H2; 7.32, d, *J* 8.1Hz, aryl, 7.64, bd, *J* 8.1 Hz, aryl and H7. ^{13}C n.m.r. δ 21.6, CH_3; 55.5 and 55.8, OMe; 92.5, C5; 95.5, C7; 105.2, C3; 115.0, 131.8, 137.6, 142.5, 153.1, 159.5, aryl C; 124.8, H2; 129.2, 129.4, aryl CH; 169.2, CO. *m/z* 295 (M 52%), 119 (100), 91 (26).

1-(4-Chlorobenzoyl)-4,6-dimethoxyindole (17).

This was prepared as described for the N-benzoyl indole (15) from 4,6-dimethoxyindole (14) (0.304g, 0.96 mmol), 4-chlorobenzoyl chloride (0.22 mL, 1.73 mmol), sodium hydroxide (0.10g, 2.5 mmol) and tetrabutylammonium hydrogen sulphate (0.01g) with a reaction time of 2 h. Recrystallization from ethanol resulted in the N-benzoyl indole (17) (0.40g, 74%) as light yellow *crystals*, m.p. 157-158° (Found: C, 64.5; H, 4.4; N, 4.5. $C_{17}H_{14}ClNO_3$ requires C, 64.7; H, 4.5; N, 4.4%). υ_{max} 1683,1606, 1498, 1431, 1350, 1315, 1224, 1210, 897, 847 cm^{-1}. λ_{max} 226 (ε18,800), 253nm (26,400) ^{1}H n.m.r. δ 3.89, 3.92, 2s, OMe; 6.43, d, *J* 2.0 Hz, H5; 6.66, d, *J* 3.8 Hz, H3; 7.02, d, *J* 3.8 Hz, H2; 7.50, d, *J* 8.4 Hz, aryl; 7.61, d, *J* 1.8 Hz, H7; 7.68, d, *J* 8.4 Hz, aryl. ^{13}C n.m.r. δ 55.5, 55.8, OMe; 92.6, C5; 95.7, C7; 106.0, C3; 115.0, 133.0, 137.6, 138.3, 153.1, 159.1, aryl C; 124.3, C2; 128.9, 130.6, aryl CH; 168.0, CO. *m/z* 317 (M ^{37}Cl, 26%), 315 (M ^{35}Cl, 74), 176 (23), 141 (53), 139 (100).

1-(3,4-Methylenedioxybenzoyl)-4,6-dimethoxyindole (18).

This was prepared as described for the N-benzoyl indole (16) from 4,6-dimethoxyindole (14)(1.003g, 5.67 mmol) in dry dichloromethane (30 mL), sodium hydroxide (0.574g, 14.35 mmol) and tetrabutylammonium hydrogen sulphate (0.02g) with piperonylic acid (1.010g, 6.08 mmol) and thionyl chloride (20 mL). After filtration, the filtrate was concentrated and the residue recrystallized from methanol to yield the N-benzoyl indole (18) (1.491g, 81%) as a white *solid*, m.p. 150-151° (Found: C, 66.8; H, 4.7; N, 4.2. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.7; N, 4.3%). υ_{max} 1684, 1500, 1347, 1312, 1272, 1225 cm^{-1}. λ_{max} 221 (ε14,800), 257 (15,300), 306nm (8,600). ^1H n.m.r. δ 3.88, 3.92, 2s, OMe; 6.09, s, CH_2; 6.41, d, *J* 2.1 Hz, H5; 6.64, d, *J* 3.8 Hz, H3; 6.91, d, *J* 8.1 Hz, H5'; 7.13, d, *J* 3.8 Hz, H2; 7.24, d, *J* 1.6 Hz, H2'; 7.31, dd, *J* 1.7, 8.1 Hz, H6'; 7.58, d, *J* 2.0 Hz, H7. ^{13}C n.m.r. δ 55.5, 55.6, OMe; 92.4, C5; 95.4, C7; 101.9, CH_2; 105.2, C3; 108.1, 109.6, 124.7, 125.1, aryl CH and C2; 115.0, 128.2, 137.7, 147.9, 150.9, 153.1, 159.5, aryl C; 168.2, CO. *m/z* 325 (M, 37%), 149 (100).

1-(3,4-Dimethoxybenzoyl)-4,6-dimethoxyindole (19)

This was prepared as described for the N-benzoyl indole (16) from 4,6-dimethoxyindole (14)(1.001g, 5.65 mmol) in dry dichloromethane (30mL) and sodium hydroxide (0.603g, 15.07 mmol), tetrabutylammonium hydrogen sulphate (0.01g) and 3,4-dimethoxybenzoic acid (1.200g, 6.59mmol) in thionyl chloride (30mL). Recrystallization of the residue from methanol gave the N-benzoyl indole (19) (0.543g, 28%) as yellow *crystals*, m.p. 140-141° (Found: C, 66.9; H, 5.7; N, 4.0. $C_{19}H_{19}NO_5$ requires C, 66.9; H, 5.6, N, 4.1%). υ_{max} 1690, 1605, 1519, 1498, 1426, 1344, 1311, 1281, 1270, 1240, 1223, 1211, 1177, 1144, 1068, 1026, 821, 809 753 cm^{-1}. λ_{max} 219 (ε29,400), 257 (22,000), 293nm (8,800). ^1H n.m.r. δ 3.88, 3.92. 3.93. 3.97, 4s, OMe; 6.41, d, *J* 2.1 Hz, H5; 6.65, d, *J* 3.8 Hz, H3; 7.0, d, *J* 8.3Hz, H5'; 7.17, d, *J* 3.8 Hz, H2; 7.33, d, *J* 2.1 Hz, H2'; 7.36, dd, *J* 2.1, 8.3 Hz, H6'; 7.59, d, *J* 2.0 Hz, H7. ^{13}C n.m.r. δ 55.4, 55.7, 56.1, OMe; 92.3, C5; 95.3, C7; 105.0, C3; 110.2, 112.4, 123.5, 124.8m, aryl CH and C2; 114.9, 126.7, 137.7, 148.9, 152.3, 153.0, 159.4, arylC; 168.6, CO. *m/z* 341 (M, 22%), 165 (100).

1-(4'-Benzyloxy-3'-methoxy-benzoyl)-4,6-dimethoxyindole (20).

This was prepared as described for the N-benzoyl indole (16) from 4,6-dimethoxy indole (14) (0.704g, 3.98mmol), sodium hydroxide (0.403g, 10.08mmol) and tetrabutylammonium hydrogen sulphate (0.02g) in dry dichloromethane (30mL) with 4-benzyloxy-3-methoxy benzoic acid (1.221g, 4.73mmol) and thionyl chloride (30mL). Recrystallization of the residue gave the N-benzoyl indole (20) (0.524g,32%) as a lemon yellow *solid*, m.p. 95-96° (Found: C, 72.0; H, 5.8; N, 3.3. $C_{25}H_{23}NO_5$ requires C, 71.9; H, 5.6; N, 3.4%). υ_{max} 1690, 1605, 1521, 1499, 1427, 1347, 1310, 1282, 1243, 1222, 1136, 816 cm^{-1}. λ_{max} 221 (ε34,400), 257 (27,500), 297nm (11,600). ^1H n.m.r. δ 3.87, 3.92, 3.94, 3s, OMe; 5.25, s, CH_2; 6.41, d, *J* 2.1 Hz, H5; 6.64, d, *J* 3.7 Hz, H3; 6.96, d, *J* 8.3 Hz, H5'; 7.16, d, *J* 3.8 Hz, H2; 7.28, dd, J, 2.1, 8.3 Hz, H6'; 7.40, m, H2' and aryl; 7.57, d, *J* 2.0 Hz, H7. ^{13}C n.m.r. δ 55.4, 55.7, 56.1, OMe; 70.9, CH_2; 92.3, 95.3, C5 and C7; 105.0, C3; 112.5, 112.8, 123.3, H2', H5' and H6'; 114.9, 127.0; 136.2, 137.6, 149.5, 151.4, 153.0, 159.4, aryl C; 124.8, C2; 127.2, 128.1, 128.7, aryl CH; 168.6,CO. *m/z* 417 (M, 31%), 241 (52), 91 (100%).

1-(3-Benzyloxy-4-methoxybenzoyl)-4,6-dimethoxyindole (21)

This was prepared as described for the N-benzoyl indole (16) from 4,6-dimethoxyindole (14) (0.703g, 3.97 mmol), sodium hydroxide (0.401g, 10.02 mmol) and tetrabutylammonium hydrogen sulphate (0.02g,) in dry dichloromethane (30 mL) with 3-benzyloxy-4-methoxy-benzoic acid (1.221g, 4.73 mmol) and thionyl chloride (30 mL). Recrystallization from ethanol yielded the N-benzoyl indole (21) (0.844g, 51%) as a pale yellow *solid,* m.p. 109-110° (Found: C, 71.9; H, 5.4; N, 3.2. $C_{25}H_{23}NO_5$ requires C, 71.9; H, 5.6; N, 3.4%). υ_{max} 1685, 1603, 1520, 1498, 1423, 1345, 1310, 1269, 1237, 1220, 1210, 1136, 1065 cm^{-1}. λ_{max} 219 (ε29,600), 258nm (21,000). ^1H n.m.r. δ 3.88, 3.92, 3.98, 3s, OMe; 5.20s, CH_2; 6.41, d, *J* 2.0 Hz, H5; 6.57, d, *J* 3.7 Hz, H3; 6.95, d, *J* 3.7 Hz, H2; 7.21, m, aryl; 7.58, d, *J* 2.1 Hz, H7. ^{13}C n.m.r. δ 55.4, 55.8, 56.1, OMe; 71.0, CH_2; 92.4, C5; 95.4, C7; 105.0, 110.9, 115.1, 124.1, 124.8, 127.4, 128.1, 128.7, C2, C3 and aryl CH; 114.9, 125.4, 126.5, 136.3, 137.6, 147.6, 153.0, 159.4, aryl C; 168.4, CO. *m/z* 417 (M, 40%), 341 (100), 181 (20).

1,3-Dimethoxypyrrolo[3,2,1-de]phenanthridin-7-one (22)

A mixture of the N-benzoyl indole (15) (0.253g, 0 899 mmol) and palladium acetate (0.202g, 0.900 mmol) in glacial acetic acid (30 mL) was heated at reflux for 1 h. The reaction mixture was then filtered, water (100 mL) added to the filtrate and the resulting solution extracted with dichloromethane (3 x 50 mL). The combined organic layers were back extracted with saturated sodium bicarbonate solution (50 mL), dried ($MgSO_4$), flash chromatographed (dichloromethane) and then radially chromatographed. Elution with dichloromethane/light petroleum (1:1) yielded two fractions. Concentration and recrystallization of the first fraction from ethanol yielded the pyrrolophenanthridone (22) (0.163g, 65%) as yellow *crystals,* m.p. 176-177°(from ether). (Found: C, 73.2; H, 4.8; N 5.0. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.7; N, 5.0%). υ_{max} 1735, 1620, 1501, 1467, 1451, 1429, 1294, 1275, 1240, 1218, 1149, 812 cm^{-1}. λ_{max} 243 (ε33,700), 273 (24,300), 218 (24,200), 306 (11,800), 315 (13,100), 413nm (6,900). ^1H n.m.r. δ 3.88, s, OMe; 6.24, d, *J* 2.2 Hz, H4; 6.64, s, H2; 7.06, d, *J* 2.0 Hz, H5; 7.49, m, aryl. ^{13}C n.m.r. δ 55.5, 56.0, OMe; 90.3, C2; 95.3, 101.3, 120.5, 125.3, 127.6, 133.8, C4, C5, C8, C9, C10 and C11; 116.0, 133 3, 135.2, 135.3, 135.7, 154.3, 161.1, aryl C; 163.1, CO. *m/z* 279 (M, 100%), 264 (54), 236 (28), 221 (26).

The second fraction was recrystallized from ethanol to yield 9,11-dimethoxy-6-oxo-6H-isoindolo[2,1-*a*]indole (31) (0.045g, 18%). as yellow crystals, m.p. 209-210° υ_{max} (KBr disk) 1781, 1733, 1617, 1590, 1507, 1472, 1454, 1436, 1304, 1288, 1251, 1223, 1203 cm^{-1}. λ_{max} 243 (ε27,800), 273 (16,400), 281 (17,200), 304 (9,000), 313 (10,800), 409nm (6,500). ^1H n.m.r. δ 3.84, 3 88, 2s, OMe; 6.23, d, *J* 2.1 Hz, H7; 7.07, d, *J* 2.0, H5; 7.51, m, H3 and aryl.

1,3-Dimethoxy-10-methylpyrrolo[3,2,1-de]phenanthridin-7-one (23).

This was prepared as described for the pyrrolophenanthridone (22) from the N-benzoyl indole (16) (0.145g, 0.49 mmol) in glacial acetic acid (30 mL) Recrystallization from ethanol gave the pyrrolophenanthridone (23) (0.088g, 61%) as yellow *crystals*, m.p. 183-184°. υ_{max} 1731, 1719, 1617, 1504, 1430, 1288, 1273, 1244, 1223 cm^{-1}. λ_{max} 239 (21,500), 246 (24,900), 273 (17,200), 283 (15,700), 304 (7,800), 315 (8,300), 407nm (3,800). ^1H n.m.r. δ 2.41, s, 10-Me, 3.88, s, OMe; 6.24, d, *J* 2.0 Hz, H4; 6.61, s, H2; 7.07, m, H5 and H9; 7.26, d, *J* 2.0 Hz, H11; 7.61, d, *J* 7.7 Hz, H8. ^{13}C n m.r. δ 22.0, 10-Me; 55.4, 55.9, OMe; 90.1,

C2; 95.1, 125.0, 128.6, C8, C9 and C11; 100.8, 121.1, C4 and C5; 117.9, 130.7, 135.3, 135.4, 135.7, 154.1, 161.0, aryl C; 163.1, CO. *m/z* 293 (M, 100%) 278 (42), 250 (18), 235 (20)

10-Chloro-1,3-dimethoxypyrrolo[3,2,1-de]phenanthridin-7-one (24).

This was prepared as described for the pyrrolophenanthridone (22) from the N-benzoyl indole (17) (0.350g, 1.11 mmol) and palladium acetate (0.251g, 1.12 mmol) in glacial acetic acid (30 mL). The residue was flash chromatographed and the fraction eluted with dichloromethane/light petroleum (1:1) was recrystallized from ethanol to yield the pyrrolophenanthridone (24) (0.185g, 53%) as a yellow *solid*, m.p. 225-226° (Found: C, 64.7; H, 3.7; N, 4.1. $C_{17}H_{12}ClNO_3$ requires C, 65.1; H, 3.9; N, 4.5%). υ_{max} 1735, 1613, 1507, 1423, 1280, 1225, 1066, 922, 818 cm^{-1}. λ_{max} 249 (ε16,200), 270 (11,300), 321 (5,000), 415nm (2,400). ^1H n.m.r. δ 3.88, s, OMe; 6.24, d, *J* 2.1 Hz, H4; 6.66, s, H2; 7.03, d, *J* 2.1 Hz, H5; 7.21, dd, *J* 2.0, 8.1 Hz, H9; 7.41, d, *J* 1.9 Hz, H11; 7.64, d, *J* 8.1 Hz, H8. ^{13}C n.m.r. δ 55.5, 56.0, OMe; 90.2, 126.4, 127.8, C8, C9 and C11; 95.5, C2; 102.5, C4; 117.9, 131.5, 134.2, 135.4, 136.6, 140.3, 154.5, 161.5, aryl C; 120.8, C5; 162.1, CO. *m/z* 315 (M ^{37}Cl, 34%), 313 (M ^{35}Cl, 100), 300 (14), 298 (39), 270 (21), 255 (19).

9,10-Methylenedioxy-1,3-dimethoxypyrrolo[3,2,1-de]phenanthridin-7-one (25).

This was prepared as described for the pyrrolophenanthridone (22) from the N-benzoyl indole (18) (1.359g, 4.17 mmol) and palladium acetate (0.940g, 4.19 mmol) in glacial acetic acid (40 mL). Recrystallization from ethanol yielded yellow *crystals*, which was a mixture (3:1) of the pyrrolophenanthridone (25) and its structural isomer (0.613g, 45%) and could not be separated, m.p. 246-247°(from isopropanol) (Found : C, 66.9; H, 4.2; N, 4.1. $C_{18}H_{13}NO_5$ requires C, 66.9; H, 4.1; N, 4.3%). υ_{max} 1731, 1506, 1279, 1260, 1242, 1222 cm^{-1}. λ_{max} 247 (ε12,400), 271 (12,500), 284 (10,200), 298 (9,500), 325nm (6,500). ^1H n.m.r. δ major product: 3.87, s, OMe; 6.05, s, CH_2; 6.22, d, *J* 2.0 Hz, H4; 6.51, s, H2; 6.87, 7.14, 2s, H8 and H11; minor product: 3.88, 3.89, 2s, OMe; 6.14, s, CH_2; 6.26, d, *J* 2.0 Hz, H4; 6.64, s, H2; 6.70, 7.35, 2d, *J* 7.9 Hz, H8 and H9; 7.08, d, *J* 1.8 Hz, H5. *m/z* 323 (M,100%), 308 (58), 280 (21), 265 (73), 237 (20).

1,3,9,10-Tetramethoxypyrrolo[3,2,1-de]phenanthridin-7-one (26).

This was prepared as described for the pyrrolophenanthridone (22) from the N-benzoyl indole (19) (0.467g, 1.37 mmol) and palladium acetate (0.310g, 1.38 mmol) in glacial acetic acid (30 mL). Recrystallization from ethanol gave the pyrrolophenanthridone (26) (0.284g, 61%) as yellow *crystals*, m.p. 210-211° (Found: C, 67.0; H, 5.3; N, 3.9. $C_{19}H_{17}NO_5$ requires C, 67.2; H, 5.0; N, 4.1%). υ_{max} 1716, 1610, 1491, 1437, 1424, 1317, 1271, 1247, 1234, 1218, 1153 cm^{-1}. λ_{max} 252 (ε20,000), 273 (20,200), 279 (19,500), 306 (13,700), 319 (13,400), 418nm (3,700) ^1H n.m.r. δ 3.88, 3.93, 3.98, 3s, OMe; 6.21, d, *J* 2.0 Hz, H4; 6.50, s, H2; 6.92, 7.21, 2s, H8 and H11; 7.00, d, *J* 1.5 Hz, H5. ^{13}C n.m.r. δ 55.4, 55.9, 56.2, OMe; 90.0, 94.6, 100.1, 103.1, 107.4, C2, C4, C5, C8 and C11; 117.8, 125.4, 128 6, 129.6, 130.7, 135.7, 149.3, 154.0, 160.8, aryl C; 163.1, CO. *m/z* 339 (M, 100%), 324 (53).

10-Benzyloxy-1,3,9-trimethoxypyrrolo[3,2,1-de]phenanthridin-7-one (27)

This was prepared as described for the phenanthridone (22) from the N-benzoyl indole (20) (0.407g, 0.975 mmol) and palladium acetate (0.224g, 0.996 mmol) in glacial acetic acid (30 mL). Recrystallization of the residue from dichloromethane/light petroleum gave the pyrrolophenanthridone (27) (0.202g, 49%) as a

yellow *solid*, m.p. 173-174° (from ether) (Found: C, 71.2; H, 5.3; N, 3.0. $C_{25}H_{21}NO_5.0.25\ H_2O$ requires C, 71.5; H, 5.2; N, 3.3%). υ_{max} 1723, 1616, 1319, 1273, 1239, 1220, 1155 cm^{-1}. λ_{max} 273 (ε32,800), 279 (31,400), 306 (24,400), 320 (23,500), 376 (8,700), 416nm (5,500). ^1H n.m.r. δ 3.86, 3.87, 3.93, 3s, OMe; 5.23, s, CH_2; 6.20, d, *J* 2.1 Hz, H4; 6.46, 7.24, 2s, H8 and H11; 7.00, d, *J* 2.1 Hz, H5; 7.40, m, aryl. ^{13}C n.m.r. δ 55.3, 55.8, 56.2, OMe; 71.0, CH_2; 89.9, 94.8, 100.1, 105.2, 107.7, C2, C4, C5, C8 and C11; 127.3, 128.2, 128.7, aryl CH; 118.0, 125.7, 129.3, 135.5, 135.6, 136.1, 149.8, 153.1, 154.0, 160.8, aryl C; 163.0, CO. *m/z* 415 (M, 100%), 325 (16), 324 (34), 296 (36), 295 (20).

9-Benzyloxy-1,3,10-trimethoxypyrrolo[3,2,1-de]phenanthridin-7-one (28).

This was prepared as described for the pyrrolophenanthridone (22) from the N-benzoyl indole (21) (0.306g, 0.73 mmol) and palladium acetate (0.165g, 0.73 mmol) in glacial acetic acid (30 mL). Recrystallization from ethanol gave the pyrrolophenanthridone (28) (0.092g, 30%) as yellow *crystals*, m.p. 174-176° (from ether) (Found: C, 71.4; H, 5.3; N, 3.2 $C_{25}H_{21}NO_5.0.125\ H_2O$ requires C, 71.9; H, 5.1; N, 3.4%). υ_{max} (KBr disk) 1763, 1724, 1704, 1615, 1500, 1470, 1454, 1322, 1289, 1275, 1239, 1210, 1155, 1107, 1086, 1068, 1047 cm^{-1}. λ_{max} 253 (ε13,300), 273 (13,500), 281 (12,400), 307 (8,600), 320 (8,600), 416nm (2,200). ^1H n.m.r. δ 3.87, 3.88, 3.98, 3s, OMe; 5.18, s, CH_2; 6.21, d, *J* 2.0 Hz, H4; 6.52, s, H2; 6.94, 7.68, 2s, H8 and H11; 7.00, d, *J* 2.1 Hz, H5; 7.34, m, aryl. ^{13}C n.m.r. δ 55.5, 56.0,56.4, OMe; 71.3, CH_2; 90.0, 94.9, 100.2, 103.6, 109.9, C2, C4, C5, C8 and C11; 117.8, 125.4, 130.0, 135.6, 135.7, 136.3, 148.4, 154.1, 154.8, 160.9, aryl C; 127.5, 128.2, 128.7, aryl CH; 163.2, CO. *m/z* 415 (M, 30%), 324 (100).

1-Benzyl-4,6-dimethoxy-2,3-diphenylindole (35)

This was prepared from 4,6-dimethoxy-2,3-diphenyl indole (33) (0.503g, 1.53 mmol) in DMSO (1mL), potassium hydroxide (0.102g, 1.82 mmol) and benzyl bromide (0.20mL, 1.68 mmol). Recrystallization from ethanol yielded the N-benzyl indole (35) (0.530g, 83%) as white *crystals*, m.p. 130-131° (Found: C, 83.4; H, 6.3; N, 3.3. $C_{29}H_{25}NO_2$ requires C, 83.0; H, 6.0; N, 3.3%) υ_{max} 1577, 1503, 1349, 1337, 1263, 1219, 1201, 1181, 1144, 1060, 811, 771, 739, 724, 700 cm^{-1}. λ_{max} 221 (ε36,300), 239 (25,300), 301nm (10,500) ^1H n.m.r. δ 3.74, 3.76, 2s, OMe; 5.21, s, CH_2; 6.28, 6.32, 2 bs,H5 and H7; 7.16,m, aryl. *m/z* 419 (M, 100%), 328 (92).

1-(2'-Bromobenzyl)-4,6-dimethoxy-2,3-diphenylindole (36).

This was prepared from 4,6-dimethoxy-2,3-diphenyl indole (33) (1.003g, 3.05 mmol) and *o*-bromobenzyl bromide (0.788g, 3.15 mmol). Recrystallization from dichloromethane/ light petroleum yielded the N-benzyl indole (36) (1.21g, 80%) as a white *solid*, m.p. 163-164° (Found: C, 69.8; H, 4.6; N, 2.9. $C_{29}H_{24}BrNO_2$ requires C, 69.9; H, 4.9; N, 2.8%). υ_{max} 1611, 1592, 1506, 1334, 1270, 1218, 1199, 1149, 1048, 705 cm^{-1}. ^1H n.m.r. δ 3.75, 3.78, 2s, OMe; 5.23, s, CH_2; 6.24, 6.30, 2d, *J* 2.1 Hz, H5 and H7; 7.14, m, aryl. ^{13}C n.m.r. δ 48.2, CH_2; 55.2, 55.7, OMe; 86.1, 92.5, C7 and C5; 111.6, 116.0, 121.6, 131.6, 135.7, 136.0, 136.9, 138.4, 155.1, 157.6, aryl C; 125.4, 126.9, 127.7, 127.9, 128.2, 128.7, 131.0, 131.5, 132.6, aryl CH. *m/z* 499 (^{81}Br, M, 60%), 497 (^{79}Br, M, 60%), 328 (100).

1-Benzyl-7-bromo-4,6-dimethoxy-2,3-diphenylindole (37)

This was prepared from 7-bromo-4,6-dimethoxy-2,3-diphenyl indole (34) (1.003g, 2.46 mmol) and benzyl bromide (0.04 mL, 3.36 mmol). Recrystallization from ethanol gave the N-benzyl indole (37) (0.486g,

40%) as a white *solid*, m.p. 140-141° (Found: C, 70.2; H, 5.0; N, 2.6. $C_{29}H_{24}BrNO_2$ requires C, 69.9; H, 4.9; N, 2.8%). υ_{max} 1607, 1572, 1560, 1368, 1348, 1267, 1219, 1170, 1135, 1058, 732, 703 cm^{-1}. λ_{max} 233 (ε20,200), 300nm (7,800). ^1H n.m.r. δ 3.72, 3.93, 2s, OMe; 5.75, s, CH_2; 6.41, s, H5; 7.02, M, aryl. ^{13}C n.m.r. δ 48.7, CH_2; 55.5, 57.8, OMe; 86.1, 115.0, 116.3, 131.6, 134.9, 135.4, 139.2, 140.1, 153.2, 154.0, aryl; 91.1, C5; 125.5, 125.7, 126.6, 126.7, 127.9, 128.3, 131.4, 131.5, aryl CH. *m/z* 499 (^{81}Br, M, 68%), 497, (^{79}Br, M, 68), 408 (100), 406 (98).

7-Bromo-1-(2'-bromobenzyl)-4,6-dimethoxy-2,3-diphenylindole (38).

To a solution of the N-benzyl indole (36) (0.301g, 0.60 mmol) in dry THF (40 mL) was added phenyltrimethylammonium tribromide (0.230g, 0.61 mmol) and the mixture stirred for 5 min. The reaction was filtered, the solvent removed and the residue recrystallized from ethanol to give the bromoindole (38) (0.290g, 83%) as white *crystals*, m.p. 159-160° (Found:C, 60.5; H, 4.0; N, 2.3. $C_{29}H_{23}NO_2$ requires C, 60.3; H, 4.0; N, 2.4%). υ_{max} 1608, 1354, 1309, 1265, 1203, 1153, 1092, 1029, 758, 726, 701 cm^{-1} λ_{max} 225 (ε33,300), 257 (17,800), 307nm (10,100). ^1H n.m.r. δ 3.25, 3.82, 2s OMe; 5.26, s, CH_2; 6.46, s, H5; 7.12, m, aryl· ^{13}C n.m.r. δ 48.3, CH_2; 56.8, 61.1, OMe; 90.0, C5; 100.6, 115.2, 115.6, 121.7, 131.0, 134.6, 136.4, 137.4, 137.5, 151.6, 153.1, aryl C ; 125.9, 127.3, 127.6, 128.0, 128.1, 128.4, 128.9, 130.9, 131.4, 132.7, aryl CH. *m/z* 579 (^{81}Br, M, 53%), 578 (33), 576 (100), 408 (37), 406 (37).

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