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The Vilsmeier Synthetic Route to Indolylpyrroles

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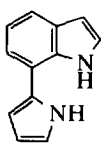
Abstract: Some 2-(7-indolyl)pyrroles have been synthesised from the 4,6-dimethoxyindoles **4, 19** and **20** using the modified Vilsmeier reaction. The indolylpyrrole **8** was formed by dehydrogenation of the 2-(7-indolyl)pyrroline **7**, which was obtained from indole **4**, methyl pyrrolidin-2-one-5-carboxylate and phosphoryl chloride. However, a more generally effective sequence uses a combination of 3-bromopyrrolidin-2-one **11** and phosphoryl chloride to give the 3-chloro-2-(7-indolyl)pyrrolines **12, 29** and **30**, which undergo subsequent dehydrohalogenation to give the indolylpyrroles **13, 33** and **34**.

The structural fragment of the 2-(7-indolyl)pyrrole ring system **1** is of particular interest because of its presence in benzoporphyrins and in its direct comparison with related 2,2'-dipyrrolylmethane and 2,2'-dipyrrolylmethene systems **2** and **3** respectively.



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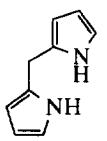

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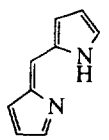

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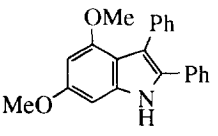
The synthetic limitations of the Nef reaction in the previously described[1] Paal-Knorr synthesis of a 2-(7-indolyl)pyrrole required that a more general alternative approach be developed. We now describe an approach using the Vilsmeier reaction applied to pyrrolidinone derivatives to give intermediate indolylpyrrolines, which could subsequently be converted into indolylpyrroles. We have already described the use of the Vilsmeier reaction methodology in the formation of indolylimines, including some examples of indolylpyrrolines.[2] In this work, pyrrolidin-2-one and 5-methylpyrrolidin-2-one were combined with phosphoryl chloride to generate an iminium electrophile capable of reaction at the 7-position of suitably activated indoles. The initial experiments in this approach were focussed on the indole **4**, in which there was only one potential site of reactivity, namely the C7 position. Thus 4,6-dimethoxy-2,3-diphenylindole **4** was converted into the indolylpyrrolines **5** and **6**. Similar reactions have also been carried out with pyrroles.[3,4] In order to develop an effective synthetic route to indolylpyrroles, the dehydrogenation of the pyrroline ring must be achieved.

The attempted dehydrogenation of indolylpyrroline **5** using either 10% or 30% palladium on charcoal failed to produce any of the related pyrrole. Similar attempts to achieve dehydrogenation of pyrrolylpyrrolines have been reported to give only very limited success.[3] However, significant improvements could be achieved through the installation of an electron-withdrawing substituent on the pyrroline ring.[5] Methyl pyroglutamate[4] was therefore reacted with the indole **4** and phosphoryl chloride to give the indolylpyrroline **7** in 60% yield. Treatment of this ring activated indolylpyrroline with 10% palladium on carbon in di-*n*-hexyl ether at 200°C gave the related indolylpyrrole **8** as a highly fluorescent colourless solid in 60% yield. Formation of the pyrrole ring was confirmed by NMR spectroscopy and the indolic and pyrrolic NH protons appeared at 8.58 and 10.02 ppm respectively. There are shortcomings in the palladium-based dehydrogenation of the pyrroline ring, especially because of the non-catalytic nature of the reaction.[3,4,6] Consequently the two unsaturated pyrrolidinones **9** and **10** were investigated, but gave no pyrrolic product, despite the earlier observation of successful reactions with pyrroles.[7-9] Attention was then directed towards the use of 3-bromopyrrolidin-2-one **11**, available from the bromination of 2-methoxypyrroline followed by treatment with hydrogen bromide.[10]



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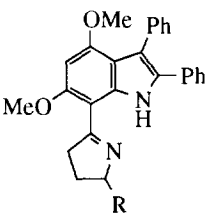
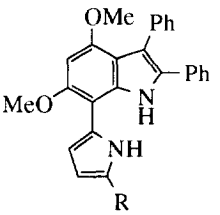


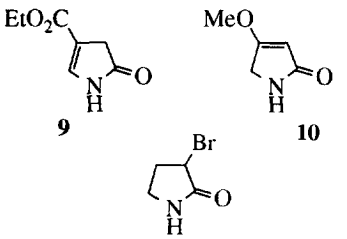
5 R = H
6 R = Me
7 R = CO_2Me



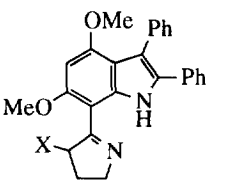
8 R = CO_2Me
13 R = H

The increased polarisation of the lactam carbonyl bond of 3-bromopyrrolidin-2-one **11** created by the presence of the bromine atom resulted in a dramatic increase in reactivity. Treatment of indole **4** with lactam **11** and phosphoryl chloride resulted in formation of the 2-(7-indolyl)pyrroline **12** in only 3 hours in moderate conditions. The structure of the product was confirmed by NMR spectroscopy and mass spectroscopy, the latter confirming the replacement of the bromine atom by chlorine, a phenomenon noted previously in similar reactions.[10] An accurate carbon analysis could not be obtained because of the presence of a trace of the bromo analog. Although recent use has been made of sodium ethoxide,[11] the best reagent for the elimination of hydrogen chloride from the chloropyrroline **12** was found to be a suspension of lithium carbonate and lithium bromide in dimethylformamide,[12] and the indolylpyrrole **13** was formed in 77% yield. Elimination is proposed to be encouraged *via* polarisation of the ring halide through coordination with a lithium cation.[13] The H4 and H5 pyrrolic protons appear in the ^1H NMR spectrum as complex multiplets at 6.60 and 6.95 ppm, with H3 appearing as a doublet of doublets at 6.40 ppm. The pyrrolic NH is again distinguishable from the indole NH by a broader meta coupled signal and appears at 9.45 ppm. The mass spectrum reflects the stability of the 2-(7-indolyl)pyrrole structure, showing a strong parent ion signal at *m/z* 394 and a peak corresponding to loss of a methyl group from one of the two indole methoxy groups. Compound **13** was sensitive to both light and acids, presumably because of the absence of stabilising electron-withdrawing groups on the pyrrole ring.

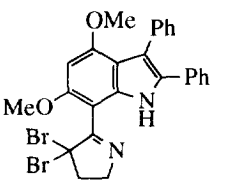
Although the synthesis of the chloropyrrolidine **12** established a convenient, high-yielding procedure for preparation of the indolylpyrrole **13**, the alternative possibility of bromination of the indolylpyrroline **5** was worthy of investigation. Reaction with *N*-bromosuccinimide in carbon tetrachloride gave a mixture of the desired monobromopyrroline **14** and the dibromopyrroline **15**. These could be separated, but only the former was obtained analytically pure, as the dibromo compound was relatively unstable. Use of the combination of freshly recrystallised *N*-bromosuccinimide and *t*-butylhydroperoxide gave the monobromopyrroline **14** selectively in 65% yield. Dehydrobromination of this product afforded the indolylpyrrole **13** in 85% yield.



9 **10** **11**



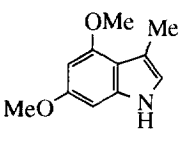
12 X = Cl
14 X = Br



15

The utility of 2-(7-indolyl)pyrroles for further synthesis would be greatly enhanced by the presence of another nucleophilic site on the indole. Consequently, the methodology for pyrrole attachment was investigated for a range of 3-substituted indoles. Regioselectivity of reaction thus becomes an important issue. Previous indications are that both C2 and C7 positions of activated 3-substituted indoles are reactive towards electrophiles, but that C7 is the preferred site for Vilsmeier reactions to occur.[2, 14-17]

The dimethoxy skatole **16**[18] underwent reaction with 2-pyrrolidinone and phosphoryl chloride at 60° to give a mixture of the 7- and 2-indolylpyrrolines **17** and **18** respectively in isolated yields of 36% and 12%.



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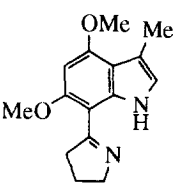

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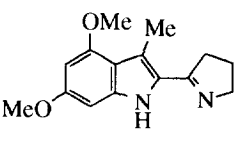
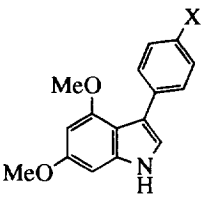


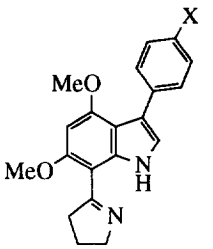
18

Attempts to gain selectivity of reaction at lower temperatures were unsuccessful. In an attempt to enhance selective reaction at C7, the electron-donating 3-methyl group of indole **16** was replaced with several electron-withdrawing 4-halophenyl groups. Thus the indoles **19-21** [19] were treated with 2-pyrrolidinone and phosphoryl chloride and gave mixtures of the 7- and 2-indolylpyrrolines with at least a 6:1 preference for the 7-isomers **22-24** over the 2-isomers **25-27**. A small amount of a third fluorescent product was isolated from the reaction involving the chlorophenyl indole **20** and was shown by the spectroscopic evidence to be the 2,7'-biindolyl **28**. This structurally important product[15] was presumably formed by chlorination of indole **20** at C3, followed by attack of another molecule of **20** at C2, and finally dehydrochlorination. In the presence of acid, nucleophilic addition of a simple indole at C2 of a 3-bromoindole, followed by dehydrobromination has

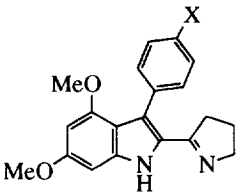
been demonstrated to lead to 2,3'-biindolyls.[20,21] Unfortunately, all attempts to improve the yield of biindolyl **28** were unsuccessful.



19 X = Br
20 X = Cl
21 X = F

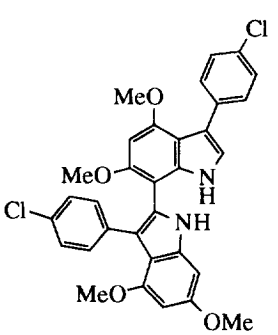


22 X = Br
23 X = Cl
24 X = F



25 X = Br
26 X = Cl
27 X = F

Treatment of the indoles **19** and **20** with the 3-bromopyrrolidinone **11** and phosphoryl chloride gave the corresponding 7-indolylpyrrolines **29** and **30** in 65% yield, with the respective 2-isomers **31** and **32** being detected in only trace amounts and only compound **32** could be isolated. Independent dehydrohalogenation of the halopyrrolines **29** and **30** gave the respective 7-indolylpyrroles **33** and **34** in 85% yield. Both NH protons appear as doublets in the ^{1}H NMR spectrum of indolylpyrrole **34**, with coupling to the indole H2 confirming assignment of the indole NH to the resonance at 10.65 ppm. A ^{1}H-^{13}C correlation experiment was conducted on indolylpyrrole **33** in order to assign unambiguously a number of key proton and carbon resonances.



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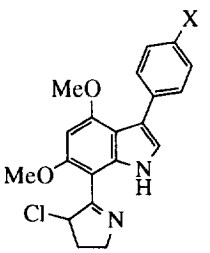
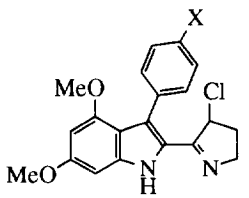
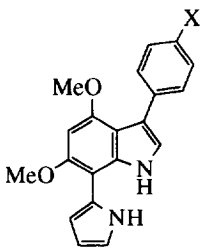


29 X = Br
30 X = Cl



31 X = Br
32 X = Cl



33 X = Br
34 X = Cl

The Vilsmeier route to 7-indolylpyrroles appears to be particularly effective because of the relatively high reactivity of the 3-bromopyrrolidinone, combined with the smooth dehydrohalogenation in the ultimate step. Its application to more complex systems will be the subject of further reports.

EXPERIMENTAL

General Information

^{1}H NMR spectra were recorded at 300 MHz with a Bruker CXP-300 or at 500 MHz with a Bruker AM-500 spectrometer, and refer to deuterochloroform solutions with chloroform (7.26 ppm) as an internal standard. Signals due to exchangeable protons (NH) were identified by exchange with deuterium oxide. The usual notational conventions are used. ^{13}C NMR spectra were recorded at 125.77 MHz with a Bruker AM-500 spectrometer, and refer to deuterochloroform solutions with chloroform (77.0 ppm) as an internal standard. Low resolution mass spectra were obtained on an A.E.I. MS12 spectrometer at 70eV and 8000V accelerating potential at 210 °C ion source temperature. Infrared spectra were recorded with a Perkin Elmer 580B and refer to paraffin mulls or KBr disks of solids. Ultraviolet spectra were measured using a Hitachi UV-3200 spectrophotometer. Microanalyses were performed by Dr. H.P. Pham of the UNSW Microanalytical Unit.

Methyl 2-(4',6'-dimethoxy-2',3'-diphenylindol-7'-yl)-1-pyrroline-5-carboxylate (7)

Indole **4** (0.30g, 0.9mmol) was added in small portions to a chloroform solution (30mL), containing methyl 2-pyrrolidinone-5-carboxylate (0.26g, 1.8mmol) and phosphoryl chloride (0.28g, 1.8mmol, 0.17mL.) at 0°C. After being allowed to reach room temperature slowly, the solution was then refluxed for 24h. Neutralisation with sodium bicarbonate solution followed by extraction with dichloromethane gave the crude product which was flash chromatographed and eluted with dichloromethane to give the pure indolylpyrroline ester (0.25g, 60%) as a yellow solid. m.p. 138-140°C. (Found: C, 74.1; H, 5.7; N, 6.2. $C_{28}H_{26}N_2O_4$ requires C, 74.0; H, 5.8; N, 6.2%). ν_{max} 3290, 3286, 1740, 1600, 1320, 1249, 1140, 1000, 795, 780, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.75 and 3.98, each s, OMe; 3.88, s, CO_2Me; 6.37, s, H5'; 6.62, bt, H4; 7.08, bt, H3; 7.22-7.41, m, ArH; 8.58, s, indole NH; 10.02, bs, pyrrole NH. ^{13}C NMR ($CDCl_3$): δ 26.44, C4; 39.34, C3; 52.01, $CO_2\underline{C}H_3$; 55.27 and 56.58, OMe; 72.30, C5; 88.21, C5'; 99.72, 113.21, 114.26, 132.67 133.11, 136.33, 137.54, ArC; 125.95, 126.74, 127.38, 127.74, 128.36, 131.52, ArCH; 157.76 and 158.47, $\underline{C}$OMe; 174.28, C=N; 175.59, $\underline{C}O_2CH_3$. Mass spectrum: *m/z* 453(M+1, 28%), 452(M, 100%), 421(22), 420(77), 405(58), 210(29), 139(22).

Methyl 5-(4',6'-dimethoxy-2',3'-diphenylindol-7'-yl) pyrrole-2-carboxylate (8)

The indolylpyrroline **7** (0.1g, 0.25mmol) was dissolved in di-*n*-hexyl ether (15ml) under an inert atmosphere. Palladium on charcoal (10%) was then added and the temperature raised to 200°C for 24h. The hot reaction mixture was filtered to separate the catalyst, and the filtrate collected and cooled overnight in the refrigerator during which time the indolylpyrrole crystallised as colourless prisms (0.06g, 60%). m.p. 214-216°C. (Found: C, 72.5; H, 5.2; N, 5.9. $C_{28}H_{24}N_2O_4.0.5H_2O$ requires C, 72.9; H, 5.4; N, 6.0%). ν_{max} 3440, 3340, 1715, 1695, 1600, 1375, 1340, 1260, 1130, 1000, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.75, s, $CO_2\underline{C}H_3$; 3.90 and 3.98, each s, OMe; 6.37, s, H5'; 6.62, dd, J 2.61, J 3.87Hz, H3 ; 7.08, dd, J 2.61, J 3.87Hz, H4; 7.21-7.41, m, ArH; 8.58, s, indole NH; 10.02, bs, pyrrole NH. ^{13}C NMR ($CDCl_3$): δ 51.45, $CO_2\underline{C}H_3$, 55.50 and 57.01, OMe; 89.47, 108.00, 116.02, 126.14, 127.31, 127.40, 127.98, 128.59, 131.42, ArCH; 97.07, 114.00, 115.29, 121.55,

132.64, 133.05, 135.44, 135.66, ArC; 153.59, 154.92, CCOMe; 161.54, $\underline{C}O_2CH_3$. Mass spectrum: *m/z* 454, (M+2, 30%), 453(M+1, 30), 452(M, 100), 421(30), 420(90), 404(55).

3-Chloro-2-(4',6'-dimethoxy-2',3'-diphenylindol-7'-yl)-1-pyrroline (12)

A solution of freshly distilled phosphoryl chloride (0.76g, 5.0mmol, 0.47mL) was added over a 15min period to a suspension of indole **4** (1.0g, 3.0mmol) and 3-bromo-2-pyrrolidinone **11** (1.17g, 7.0mmol) in dry chloroform at 0°C under a nitrogen atmosphere. The solution was slowly brought to room temperature before being warmed to 60°C for 4h. Upon cooling, the solution was washed with 10% potassium hydroxide solution, dried over magnesium sulfate and chromatographed to give an orange/yellow solid (0.85g, 65%). m.p.194-197°C (dec.). (Found: C, 72.0; H, 5.4; N, 6.2. $C_{26}H_{23}ClN_2O_2$ requires C, 72.5; H, 5.4; N, 6.5%). ν_{max} (KBr) 3440, 1600, 1549, 1364, 1315, 1246, 1223, 1163, 1141cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.40, m, H4; 3.82 and 4.10, each s, OMe; 4.25, m, H5; 5.80, t, H3; 6.25, s, H5'; 7.20-7.50, m, ArH; 11.75, bs, NH. ^{13}C NMR ($CDCl_3$): δ 34.73, C4; 55.23 and 56.94, OMe; 57.16, C5; 63.31, C3; 88.49, C5'; 99.36, 113.27, 114.44, 132.72, 133.06, 136.16, 137.91, ArC; 125.93, 126.82, 127.36, 127.92, 128.36, 131.49, ArCH; 157.79, CCOMe; 170.77, C=N; Mass spectrum: *m/z* 432, (M+2, 35%), 431(M+1, 30), 430(M, 100), 394(30), 379(50).

3-Bromo-2-(4',6'-dimethoxy-2',3'-diphenylindol-7'-yl)-1-pyrroline (14)

Indolylpyrroline **5** (1.0g, 2.5mmol) was suspended in carbon tetrachloride containing *N*-bromosuccinimide (0.44g, 2.5mmol) together with 5 drops of *t*-butyl hydroperoxide to act as a low temperature radical initiator. The solution was then warmed (60°C) for 1h whilst being monitored by thin layer chromatography. Upon completion of the reaction, the succinimide was removed by filtration and the single product chromatographed to give the desired bromopyrroline (0.78g, 50%). m.p. 114-118°C (dec.). (Found: C 65.9; H 4.9; N 5.7. $C_{26}H_{23}BrN_2O_2$ requires C 65.7; H 4.9; N 5.9%). ν_{max} (KBr) 3441, 3313, 1601, 1509, 1469, 1454, 1432, 1385, 1365, 1314, 1245, 1223, 1207, 1195, 1163, 1139, 1029,1072, 1024, 1000cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.42, m, H4; 3.75 and 4.02, each s, OMe; 4.20, m, H5; 5.82, d, H3; 6.20, s, H5'; 7.20-7.50, ArH; 11.75, bs, NH. ^{13}C NMR. ($CDCl_3$): δ 35.67, C4; 54.04, C3; 55.23 and 56.83, OMe; 57.09, C5; 88.34, C5'; 97.19, 113.25, 114.4, 132.73, 133.08, 136.17, 137.91, ArC; 125.94, 126.83, 127.37, 127.94, 128.37, 131.50, ArCH; 157.81, CCOMe, 171.44, C=N. Mass spectrum: *m/z* 394(M-HBr, 100%), 379(70), 316(40).

3,3-Dibromo-2-(4',6'-dimethoxy-2',3'-diphenylindol-7'-yl)-1-pyrroline (15)

The indolylpyrroline **5** (1.0g, 2.5mmol) was suspended in carbon tetrachloride containing *N*-bromosuccinimide (0.44g, 2.5mmol) and the reaction initiated by irradiation from a 200 Watt bulb. After 1h reflux, the reaction mixture was allowed to cool and the precipitated succinimide removed by filtration. Column chromatography (dichloromethane/petroleum ether) gave the dibromoindolylpyrroline as a pale yellow-brown solid **15** (0.34g, 24%) which discoloured rapidly, together with the monobromoindolylpyrroline **14** (0.48g, 50%). m.p. 282°C (dec.). ν_{max} (KBr) 3437, 3434, 1597, 1547, 1468, 1455, 1433, 1380, 1363, 1310, 1290, 1272, 1245, 1225, 1169, 1149, 701cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.43, t, H4; 3.91 and 4.10, each s, OMe; 4.15, t, H5; 6.20, s, H5'; 7.43, m, ArH; 11.0, bs, NH. ^{13}C NMR ($CDCl_3$): δ 53.43, C4; 55.29 and 55.41, OMe; 55.51, C5; 88.12, C5'; 96.15, C3; 113.25, 114.98, 132.47, 132.85, 135.92, 137.57, ArC; 126.05, 126.95, 127.38, 127.90, 128.421, 131.44, ArCH; 158.08 and 158.59, CCOMe; 171.95, C=N. Mass spectrum: *m/z* 556(M+2, 50%), 554(M, 95), 552(50).

2-(4',6'-Dimethoxy-2',3'-diphenylindol-7'-yl) pyrrole (13)

The bromoindolylpyrroline **14** (0.50g, 1.1mmol) was suspended in dimethylformamide (10mL) under a nitrogen atmosphere. Lithium carbonate (0.44g, 8.0mmol) and lithium bromide (0.52g, 6.0mmol) were added and the mixture heated to 90°C for 3h. Upon cooling, the reaction mixture was diluted with water and acidified to pH 5. The resulting precipitate was collected and washed before being dissolved in dichloromethane and chromatographed (dichloromethane/petroleum ether). Crystallisation from petroleum ether/dichloromethane gave the indolylpyrrole as a colourless solid (0.35g, 85%). m.p. 219-220°C. (Found: C, 78.2; H, 5.9; N, 6.7. $C_{26}H_{22}N_2O_2.0.25H_2O$ requires C, 78.3; H, 5.7; N, 7.0%). ν_{max} (KBr) 3447, 1605, 1509, 1469, 1453, 1429, 1346, 1266, 1207, 1144, 1120, 1074cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.75 and 3.90, each s, OMe; 6.38, s, H5'; 6.42, dd, J 6.3, J 2.9Hz, H3; 6.60, m, H4; 6.95, m, H5; 7.20-7.45, m. ArH; 8.75, bs, indole NH; 9.40, bs, pyrrole NH. ^{13}C NMR ($CDCl_3$): δ 55.58 and 57.25, OMe; 90.18, C5'; 98.82, 113.95, 115.08, 126.21, 132.84, 132.92, 135.25, 135.88, ArC; 105.87, 108.78, 117.27, 126.00, 127.15, 127.35, 127.98, 128.52, 131.47, ArCH; 152.63 and 153.78, COMe. Mass spectrum: *m/z* 395(M+1, 35%), 394(M, 100), 389(80).

2-(4,'6'-Dimethoxy-3'-methylindol-7'-yl)-1−pyrroline (17) and 2-(4',6'-dimethoxy-3'-methylindol-2'-yl)-1−pyrroline (18)

A chloroform solution of 4,6-dimethoxy-3-methylindole **16** (0.15g, 0.79mmol) was added dropwise to a chloroform solution (30mL) of 2-pyrrolidinone (0.084g, 1.0mmol) and phosphoryl chloride (0.152g, 1.0mmol, 0.1mL.) at 0°C. The solution was then heated to reflux for a further 3h. Neutralisation with bicarbonate solution yielded two products which were separated by flash chromatography (dichloromethane/petroleum ether, 70:30) to give two products.

(i) The 7-indolylpyrroline **17** was obtained as a yellow solid (0.073g, 36%). m.p. 72-75°C. (Found: C, 69.4; H, 7.1; N, 10.6. $C_{15}H_{18}N_2O_2$ requires C, 69.7; H, 7.0; N, 10.8%). ν_{max} (KBr) 3431, 3301, 2963, 2938, 2858, 1618, 1596, 1577, 1516, 1461, 1440, 1429, 1368, 1358, 1319, 1310, 1256, 1215, 790cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.90, m, H4; 2.50, s, Me; 3.20, t, H3; 3.85 and 3.90, each s, OMe; 3.97, t, H5; 6.20, s, H5'; 6.60, s, H2; 11.30, bs, NH. ^{13}C NMR ($CDCl_3$): δ 11.94, Me; 22.22, C3; 38.76, C4; 54.87 and 56.46, OMe; 59.09, C5; 87.14, C5'; 100.50, 110.00, 112.50, 139.70, ArC; 119.66, C2; 157.50 and 158.20, COMe. Mass spectrum: *m/z* 259(M+1, 20%), 258(M, 100), 243(45).

(ii) The 2-indolylpyrroline **18** was obtained as a yellow solid (0.025g, 12%). m.p. 180-182°C. (Found: C, 66.3; H, 7.1; N, 10.1. $C_{15}H_{18}N_2O_2.0.75H_2O$ requires C, 66.3; H, 7.2; N, 10.3%). ν_{max} 3448, 3436, 2940, 1628, 1598, 1521, 1456, 1435, 1309, 1220, 1208, 1153 1132, 809cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.00, m, H4; 2.60, s, Me; 3.00, t, H3; 3.85 and 3.90, each s, OMe; 3.97, t, H5; 6.10, d, H5'; 6.30, d, H7'; 11.20, bs, NH. ^{13}C NMR ($CDCl_3$): δ 11.99, Me; 23.11, C3; 36.01, C2; 55.13 and 55.52, OMe; 58.95, C5; 85.97, C5', 91.65, C7'; 114.56, 116.56, 127.00, 138.35, ArC; 156.58 and 159.25, COMe; 166.75, C=N. Mass spectrum: *m/z* 259(M+1, 20%), 258(M, 100), 243(95).

2-[3'-(4-Bromophenyl)-4',6'-dimethoxyindol-7'-yl]-1-pyrroline (22) and 2-[3'-(4-bromophenyl)-4',6'-dimethoxyindol-2'-yl]-1-pyrroline (25)

A dry chloroform solution of indole **19** (0.15g, 0.45mmol) was added dropwise to a solution (5mL), containing 2-pyrrolidinone (0.042g, 0.5mmol) and freshly distilled phosphoryl chloride (0.076g, 0.5mmol, 0.05mL) at 0°C. Upon warming to room temperature, the solution was refluxed under nitrogen for 24h. Neutralisation with bicarbonate solution yielded two products which were subsequently separated by column chromatography (dichloromethane/petroleum ether, 70:30).

(i) The 7-indolylpyrroline **22** (0.054 g, 30%) was the major product. m.p.196-198°C. (Found: C, 60.4; H, 5.0; N, 6.8. $C_{20}H_{19}BrN_2O_2$ requires C, 60.2; H, 4.8; N, 7.0%). ν_{max} (KBr) 3433, 2958, 1632, 1604, 1591, 1540, 1520, 1489, 1310, 1210, 1157, 1137, 1016cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.80, qui, H4; 2.35, t, H3; 3.80 and 3.90, each s, OMe; 3.91, t, H5; 6.15, s, H5'; 7.10, s, H2'; 7.50, s, ArH; 12.02, bs, NH. ^{13}C NMR ($CDCl_3$): δ 22.38, C4; 39.02, C3; 59.27, C5; 55.13 and 56.78, OMe; 88.45, C5'; 121.56, C2'; 100.67, 110.17, 117.00, 119.46, 135.32, 138.66, ArC; 130.60, 131.08, ArCH; 156.61 and 157.87, COMe; 173.25, C=N. Mass spectrum: *m/z* 401(M+1, 25%), 400(M, 100), 398(100), 355(30).

(ii) The 2-indolylpyrroline **25** was formed as a yellow solid (0.01g, 5%). m.p. 179-180°C. (Found: C, 60.2; H, 4.7; N, 6.8. $C_{20}H_{19}BrN_2O_2$ requires C, 60.2; H, 4.8; N, 7.0%). ν_{max} (KBr) 3432, 3214, 1616, 1594, 1565, 1540, 1522, 1467, 1365, 1354, 1317, 1218, 1157, 1100, 1069, 969cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.85, qui, H4; 2.30, t, H3; 3.62 and 3.87, each s, OMe; 3.92, t, H5; 6.22, d, H5'; 6.42, d, H7'; 7.25 and 7.50, each d, ArH. ^{13}C NMR: δ 23.28, C4; 36.02, C3; 55.03 and 55.48, OMe; 59.22, C5; 86.05, C5'; 92.17, C7'; 113.17, 119.96, 120.96, 127.76, 135.26, 137.26, ArC; 130.05, 132.73, ArCH; 155.66 and 159.33, COMe; 167.25, C=N. Mass spectrum: *m/z* 401(M+1, 40%), 400(M, 100), 398(100).

2-[3'-(4-Chlorophenyl)-4',6'-dimethoxyindol-7'-yl]-1-pyrroline (23), 2-[3'-(4-chlorophenyl)-4',6'-dimethoxyindol-2'-yl]-1-pyrroline (26) and 2,7'-bi-[3-(4'-chlorophenyl)-4,6-dimethoxy]indolyl (28)

A dry chloroform solution of indole **20** (0.14g, 0.5mmol) was added dropwise to a chloroform solution (5mL), containing 2-pyrrolidinone (0.042g, 0.5mmol) and freshly distilled phosphoryl chloride (0.076g, 0.5mmol, 0.05ml.) at 0°C. Upon warming to room temperature, the solution was refluxed under nitrogen for 24h. Neutralisation with bicarbonate solution yielded two yellow products together with a trace amount of a fluorescent material, which were separated by column and plate chromatography.

(i) The 7-indolylpyrroline **23** (0.053g, 30%) was formed as a yellow solid. m.p. 125-127 °C. (Found: C, 67.9; H, 5.6; N, 7.7. $C_{20}H_{19}ClN_2O_2$ requires C, 67.7; H, 5.4; N, 7.9%). ν_{max} (KBr) 3692, 3464, 1740, 1594, 1565, 1540, 1522, 1447, 1345, 1280, 1220, 1197, 1096, 1069, 969cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.02, qui, H4; 3.20, t, H3; 3.85 and 3.90, each s, OMe; 4.10, t, H5; 6.30, s, H5'; 7.10, s, H2'; 7.40 and 7.60, each d, ArH; 12.00, bs, NH. ^{13}C NMR ($CDCl_3$): δ 22.38, C4; 39.02, C3; 55.13 and 56.78, OMe; 59.27, C5; 88.45, C5'; 121.56, C2'; 100.68, 110.23, 117.00, 131.31, 134.88, 138.65, ArC; 127.66, 130.69, ArCH; 156.66 and 157.83, COMe; 173.25, C=N. Mass spectrum: *m/z* 356(M+2, 37%), 354(M, 100).

(ii) The 2-indolylpyrroline **26** was obtained by chromatography (0.09g, 5%) as a yellow solid. m.p. 179-180°C. ν_{max} (KBr) 3432, 3214, 1616, 1594, 1565, 1540, 1522, 1467, 1365, 1354, 1317, 1218, 1157, 1100, 1069, 969cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.85, qui, H4; 2.30, t, H3; 3.62 and 3.87, each s, OMe; 3.92, t, H5; 6.15, d, H5'; 6.45, d, H7'; 7.36, s, ArH. ^{13}C NMR ($CDCl_3$): δ 23.10, C4; 35.70, C3; 55.13 and 55.70, OMe;

58.57, C5; 86.05, C5'; 92.53, C7'; 113.42, 127.00, 128.92, 132.97, 134.53, 138.21, ArC; 127.28, 132.28, ArCH; 155.81 and 159.88, COMe; 167.18, C=N.

(iii) The 2,7'-biindolyl **28** was separated in only trace amounts from the above reaction. Chromatography afforded sufficient material to allow only ^{1}H NMR data to be obtained and structural assignment was therefore made on this basis.

^{1}H NMR ($CDCl_3$): δ 3.80 and 3.90, each s, OMe; 6.25, d, J 2.1Hz) H5"; 6.37, s, H5; 6.50, d, J 2.1Hz, H7"; 6.72, d, J 2.6Hz; H2; 7.15, 7.27, 7.35 and 7.45, each d, ArH; 7.70, bs, NH; 8.45, bs, NH.

2-(3-'(4-Fluorophenyl)-4',6'-dimethoxyindol-7'-yl)-1-pyrroline (24) and 2-(3'-(4-fluorophenyl)-4',6'-dimethoxyindol-2'-yl)-1-pyrroline (27)

A dry chloroform solution of 4,6-dimethoxy-3-(4'-fluorophenyl) indole **29** (0.14g, 0.5mmol) was added dropwise to a solution (5mL), containing 2-pyrrolidinone (0.043g, 0.5mmol) and freshly distilled phosphoryl chloride (0.076g, 0.5mmol, 0.05mL.) at 0°C. Upon warming to room temperature, the solution was refluxed under nitrogen for 24h. Neutralisation with bicarbonate solution yielded two pale yellow products which were separated by column chromatography (dichloromethane).

(i) The 7-indolylpyrroline **24** (0.05g, 30%) was the major product. m.p. 170-172°C. (Found: C, 70.7; H, 5.7 N, 8.0. $C_{20}H_{18}FN_2O_2$ requires C, 71.0; H, 5.7; N, 8.3%)). ν_{max} (KBr) 3223, 2940, 1618, 1599, 1587, 1569, 1544, 1504, 1364, 1219, 1157, 1101, 1069, 841, 793cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.00, qui, H4; 3.20, t, H3; 3.90 and 4.00, each s, OMe; 4.10, t, H5; 6.30, s, H5'; 7.01, s, H2'; 7.01 and 7.60, d, ArH; 11.80, bs, NH. ^{13}C NMR ($CDCl_3$): δ 22.40, C4; 39.02, C3; 59.27, C5; 55.13 and 56.78, OMe; 88.33, C5'; 121.36, C2'; 100.65, 110.37, 114.20, 117.10, 132.33, 138.52, ArC; 130.83, 130.89, ArCH; 156.61 and 157.80, COMe; 160.50 and 162.43, d, C-F; 173.25, C=N. Mass spectrum: *m/z* 339(M+1, 30%), 338(M, 100), 323(40), 308(30).

(ii) The 2-indolylpyrroline **27** was the minor product but could not be crystallised. (0.005g, 3%). ^{1}H NMR ($CDCl_3$): δ 1.90, qui, H4; 2.30, t, H3; 3.60 and 3.80, each s, OMe; 4.02, t, H5; 6.15, d, H5'; 6.45, d, H7'; 7.03 and 7.42, m, ArH.

2-[3'-(4-Bromophenyl)-4',6'-dimethoxyindol-7'-yl]-3-chloro-1-pyrroline (29)

Freshly distilled phosphoryl chloride (0.076g, 0.5mmol, 0.05mL.) was added to 3-bromopyrrolidin-2-one **11** (0.12g, 0.75mmol) chilled to 0°C. The mixture was stirred for 20min prior to warming to room temperature. At this point, a suspension of indole **19** (0.17g, 0.5mmol) in chloroform (3.0mL) was added. After stirring at room temperature for 10min the reaction mixture was heated at 60°C for 2h. The solution was neutralised with bicarbonate solution and extracted with dichloromethane. Flash chromatography gave the desired 7-indolylpyrroline **29** (0.14g, 65%) as a pale orange solid. m.p. 186-189°C. ν_{max} (KBr) 3433, 3305, 2938, 1612, 1594, 1565, 1540, 1522, 1447, 1345, 1280, 1220, 1197, 1096, 1069, 969cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.43, m, H4; 3.90 and 4.00, each s, OMe; 4.20, m, H5; 5.80, t, H3; 6.30, s, H5'; 7.10, s, H2'; 7.45, s, ArH; 11.65, bs, NH. ^{13}C NMR ($CDCl_3$): δ 34.62, C4; 55.15 and 56.98, OMe; 57.01, C5; 63.27, C3; 88.40, C5'; 121.50, C2'; 97.72, 110.42, 117.37, 119.58, 135.45, 138.93, ArC; 130.61, 131.08, ArCH; 157.43 and 157.88, COMe; 170.76 C=N. Mass spectrum: *m/z* 480(M+2, 5%), 478(M, 15%), 476(5), 434(65), 432(50), 400(50), 398(100), 396(55).

3-Chloro-2-[3'-(4-chlorophenyl)-4',6'-dimethoxyindol-7'-yl]-1-pyrroline (30) and 3-chloro-2-[3'-(4-chlorophenyl)-4',6'-dimethoxyindol-2'-yl]-1-pyrroline (32)

Freshly distilled phosphoryl chloride (0.076g, 0.5mmol, 0.05mL.) was added to 3-bromo-2-pyrrolidinone **11** (0.12g, 0.75mmol) chilled to 0°C and the resulting mixture was stirred for 20min before being allowed to come to room temperature. Dry, distilled chloroform (3mL) was then added along with a suspension of indole **20** (0.143g, 0.5mmol) in 3mL of chloroform. Stirring was continued at room temperature for 10min prior to heating to a final temperature of 60°C. Upon formation of an orange salt, the reaction mixture was neutralised with bicarbonate solution and the resulting solid extracted with dichloromethane, dried and chromatographed to give the 7-indolylpyrroline **30** as the major product together with a small amount of the 2-isomer **32.**

(i) The 7-indolylpyrroline **30** (0.12g, 65%) had m.p. 186-188 °C. ν_{max} (KBr) 3433, 3305, 2938, 1612, 1594, 1565, 1540, 1522, 1447, 1345, 1280, 1220, 1197, 1096, 1069, 969cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.34, m, H4; 3.85 and 4.00, each s, OMe; 4.20, m, H5; 5.80, m, H3; 6.30, s, H5'; 7.10, s, H2'; 7.50, s, ArH; 11.60, bs, NH. ^{13}C NMR ($CDCl_3$): δ 34.62, C4; 55.15 and 56.98, OMe; 57.01, C5; 63.27, C3; 88.40, C5'; 121.50, C2'; 97.72, 110.42, 117.37, 119.58, 135.45, 138.93, ArC; 130.61, 131.08, ArCH; 157.43 and 157.88, COMe; 170.76 C=N. Mass spectrum: *m/z* 353(M-HCl, 100%).

(ii) The 2-indolylpyrroline **32** was isolated by thin layer chromatography (dichloromethane) as a pale orange solid (0.006g, 3%). m.p. 78-81°C. ν_{max} (KBr) 2920, 2880, 1585, 1520, 1375, 1305, 1200, 1150, 1130, 1050, 1020, 987, 960, 810, 740cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.35, m, H4; 3.60 and 3.80, each s, OMe; 3.95-4.05, m, H5; 4.50, d, H3; 6.20, d, H5'; 6.40, d, H7'; 7.40, bs, ArH; 10.30, bs, NH. ^{13}C NMR ($CDCl_3$): δ 36.21, C4; 49.47, C3; 55.00 and 55.44, OMe; 57.34, C5; 86.00, C5'; 92.41, C7'; 113.21, 120.38, 124.86, 133.08, 133.95, 138.23, ArC; 127.21, 132.36, ArCH; 155.73 and 159.20, COMe; 166.40, C=N. Mass spectrum: *m/z* 391(M+2, 33%), 389(M, 39), 96(100).

2-[3'-(4-Bromophenyl)-4',6'-dimethoxyindol-7'-yl]pyrrole (33)

Indolylpyrroline **29** (1.0g, 2.1mmol) was suspended in dry dimethylformamide under a nitrogen atmosphere and lithium carbonate (1.2g, 16.8mmol) and lithium bromide (1.1g, 12.6mmol) were added and the reaction mixture warmed to 110°C for 2h. Upon cooling, water was added to precipitate the product. The resulting suspension was then neutralised with 2M hydrochloric acid, collected and washed. The crude material was dissolved in dichloromethane and passed through a short plug of silica to remove baseline impurities. Recrystallisation from petroleum ether/dichloromethane gave the indolylpyrrole **33** (0.69g, 85%) as a colourless solid. m.p. 210-212°C. (Found: C, 60.6; H, 4.4; N, 6.9. $C_{20}H_{17}BrN_2O_2$ requires C, 60.5; H, 4.3; N, 7.0%). ν_{max} (KBr) 3437, 1614, 1543, 1513, 1465,1414, 1336, 1210, 1207, 1141, 1118, 1101, 1071, 797, 721cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.75 and 3.76, each s, OMe; 6.20, dd, J 2.5, J 4.1Hz, H3; 6.35, m, H4; 6.50, s, H5'; 6.75, dd, J 2.3, J 4.5Hz, H5; 7.20, d, H2'; 7.45, s, ArH; 10.65, d, indole NH; 10.70, d, pyrrole NH. ^{13}C NMR ($CDCl_3$): δ 55.40 and 57.33, OMe; 89.94, C5'; 99.21, 111.06, 118.04, 119.74, 126.01, 135.00, 136.28, ArC; 105.96, 108.60, 117.41, 121.47, 130.67, 131.18, ArCH; 152.75 and 153.43, COMe. Mass spectrum: *m/z* 398(M+2, 100%), 396(M, 100), 383(60), 381(60).

2-[3'-(4-Chlorophenyl)-4',6'-dimethoxyindol-7'-yl]pyrrole (34)

The 7-indolylpyrroline **30** (1.0g, 2.6mmol) was suspended in dimethylformamide under a nitrogen atmosphere and lithium carbonate (1.2g, 16.8mmol) and lithium bromide (1.1g, 12.6mmol) were added and the reaction mixture warmed to 110°C for 2h. Upon cooling, water was added to precipitate the product. The suspension was then neutralised with 2M hydrochloric acid, collected and washed. The solid was dissolved in dichloromethane and chromatographed through a short plug of silica. Crystallisation from petroleum ether/dichloromethane gave the indolylpyrrole **34** (0.76g, 85%) as a colourless solid. m.p. 197-199°C. (Found: C, 67.7; H, 5.0; N, 7.6. $C_{20}H_{17}ClN_2O_2$ requires C, 68.1; H, 4.9; N, 7.9%). ν_{max} (KBr) 3437, 1614, 1543, 1513, 1465, 1414, 1336, 1210, 1207, 1141, 1118, 1101, 1071, 797, 721cm^{-1}. ^{1}H NMR (d^6 DMSO): δ 3.75 and 3.76, each s, OMe; 6.20, s, H3; 6.35, s, H4; 6.52, s, H5'; 6.75, s, H5; 7.23 d, H2'; 7.45 and 7.55, each s, ArH; 10.65, d, indole NH; 10.70, d, pyrrole NH. ^{13}C NMR (d^6 DMSO): δ 58.79 and 60.33, OMe; 93.32, C5'; 103.21, 113.79, 119.26, 127.79, 133.36, 138.78, 139.73, ArC; 93.27, 110.80, 111.26, 121.09, 126.79, 131.00, 134.18, ArCH; 155.97 and 156.17, COMe. Mass spectrum: *m/z* 354(M+2, 36%), 352(M, 100), 337(60%).

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