Pergamon

*Tetrahedron*, Vol. 52, No. 13, pp. 4687-4696, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00140-8

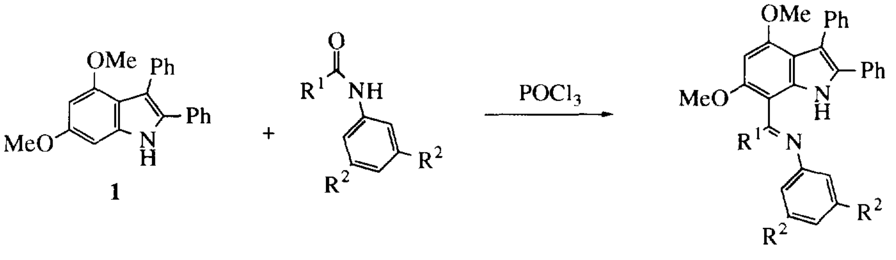
# Synthesis of 7-Indolyl-Imines by the Reaction of 4,6-Dimethoxyindoles with Secondary Amides and Phosphoryl Chloride

**David StC. Black,* Michael C. Bowyer, Andrew J. Ivory, Katrina A. Jolliffe and Naresh Kumar**

School of Chemistry, The University of New South Wales, Sydney, 2052, Australia.

***Abstract*:** 4,6-Dimethoxy-2,3-diphenylindole **1** undergoes reaction with formanilide, acetanilide, benzanilide and several dimethoxy analogs in the presence of phosphoryl chloride to give the corresponding 7-imino derivatives **2-6**. This reaction has been extended to include the synthesis of 7-indolyl-pyrrolines and tetrahydropyridines **7-9**, **11** and oxazolines **14**,**15**.

Recent work has drawn attention to the ability of 4,6-dimethoxyindoles to undergo electrophilic substitution at C7.[1-4] One of the most effective of these reactions is Vilsmeier formylation. Replacement of dimethylformamide in this reaction by a secondary amide leads to formation and isolation of an imine derivative. We now describe reactions involving anilides, pyrrolidinones, piperidinone and 4,4-dimethyl-2-oxazolidinone, which give rise to the corresponding imine derivatives.[5] Synthesis of the five imines **2-6** in yields of 63-92% was carried out using standard Vilsmeier conditions with freshly distilled phosphoryl chloride.

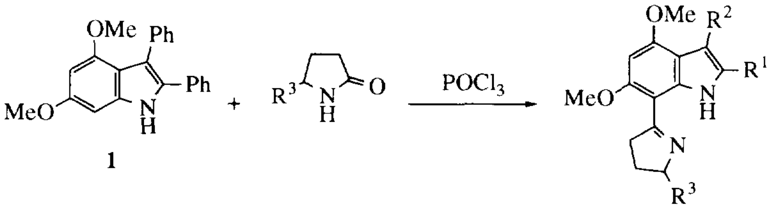


|   | $R^1$ | $R^2$ |
|---|---|---|
| **2** | H | H |
| **3** | Me | H |
| **4** | Me | OMe |
| **5** | $CH_2Ph$ | OMe |
| **6** | Ph | H |

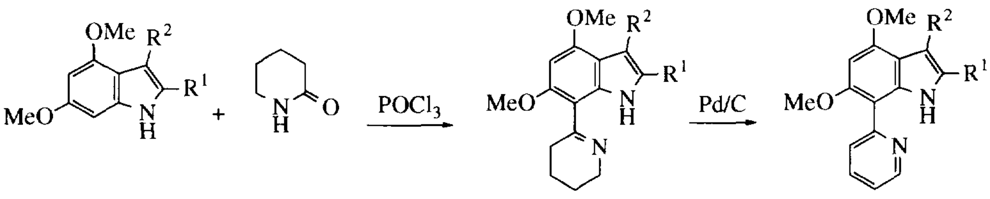
Hydrogen bonding between the indole NH and the imine nitrogen atom was indicated in the $^1H$ n.m.r. spectra by NH proton chemical shift values in the region of 11 and 12ppm. In the case of the benzanilide derivative **6**, both *E*- and *Z*-isomers were observed, but not separated.

Formation of imines by this method appears to be quite general and to provide an effective alternative to the more usual condensation between a primary amine and carbonyl compound. Indeed, although the aldimine **2** has been synthesised from 4,6-dimethoxy-2,3-diphenylindole-7-carbaldehyde (the 7-formyl derivative of **1**) and aniline, the methyl ketimine **3** could not be obtained from the related 7-acetylindole and aniline.[5] One restriction on the generality of the modified Vilsmeier approach is the inability to form a diimine from diamides derived from 1,2-diaminobenzene. Because of the proximity of the activated groups, benzimidazole formation occurs.[5]

Extension of the above reaction to include pyrrolidin-2-one, 5-methylpyrrolidin-2-one and piperidin-2-one led to the formation of the 7-indolyl-pyrrolines **7**,**8** and the tetrahydropyridine **9**. The further tetrahydropyridine **11** was also formed from the indole **10** [6] in a regioselective reaction, with only a trace of the 2-isomer being observed. The use of lactams in the modified Vilsmeier reaction provides a dimension that cannot be achieved by simple Schiff base formation, and this strategy has been used to combine pyrrolidinones and pyrroles, leading to the formation of bipyrroles and terpyrroles.[7,8]



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **7** | Ph | Ph | H |
| **8** | Ph | Ph | Me |



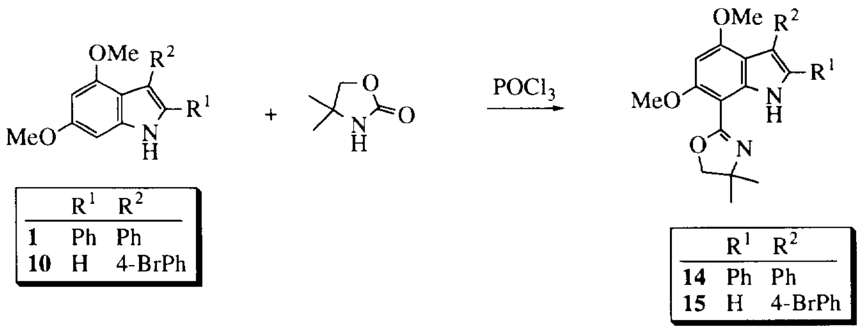
| | $R^1$ | $R^2$ |
|---|---|---|
| **1** | Ph | Ph |
| **10** | H | 4-BrPh |

| | $R^1$ | $R^2$ |
|---|---|---|
| **9** | Ph | Ph |
| **11** | H | 4-BrPh |

| | $R^1$ | $R^2$ |
|---|---|---|
| **12** | Ph | Ph |
| **13** | H | 4-BrPh |

The main interest in 7-indolyl-imines relates to their chelating ability, especially in comparison with the corresponding salicylaldimines and ketimines, and details of their metal complexing ability will be reported separately. It should be emphasised however, that modified Vilsmeier chemistry provides greater scope in dealing with electron-rich indole substrates, than is available from salicylaldehyde, which is restricted to amine condensation reactions. Furthermore, the formation of the tetrahydropyridines **9** and **11** offers the possibility to generate 2-(7-indolyl)pyridines, which would also be expected to show interesting chelating properties. Indeed, treatment with palladium/charcoal catalyst converted the tetrahydropyridine **9** into the indolyl-pyridine **12** in 60% yield, but only a 10% conversion to pyridine **13** could be achieved from tetrahydropyridine **11**, presumably because of the susceptibility for reaction of the unsubstituted 2-indolyl position or the 4'-bromo atom. Nevertheless, this approach could be of value in constructing a range of 2-(7-indolyl)pyridines. Previously only a few examples of this kind of compound have been prepared by lengthy syntheses from 2-(2-aminophenyl)pyridine [9]. We have also attempted to utilise pyridone in combination with phosphoryl chloride to form the pyridine derivative directly, but have not succeeded.

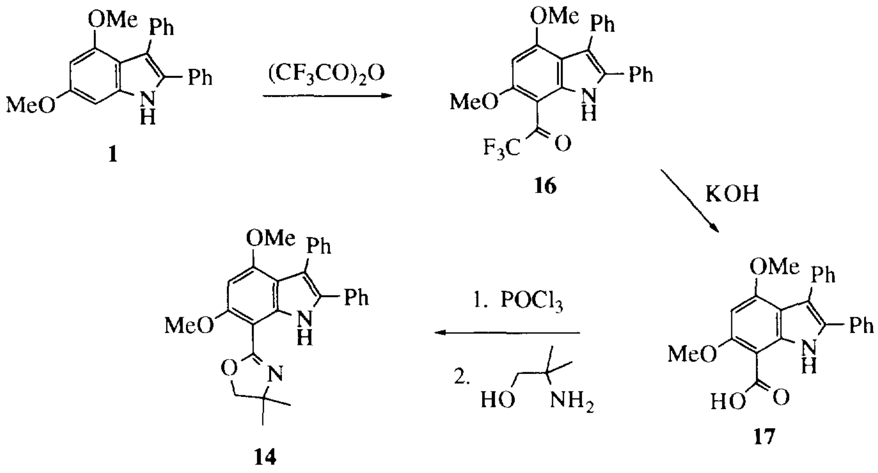
Oxazolines have been widely used in synthesis as protecting, activating and coordinating groups [10-12]. Therefore it was of interest to construct 2-(7-indolyl)oxazolines and to that end we investigated reaction of the indoles **1** and **10** with 4,4-dimethyl-2-oxazolidinone [13] in the presence of phosphoryl chloride. Imine formation took place and the 2-(7-indolyl)oxazolines **14** and **15** were isolated in approximately 50% yield.



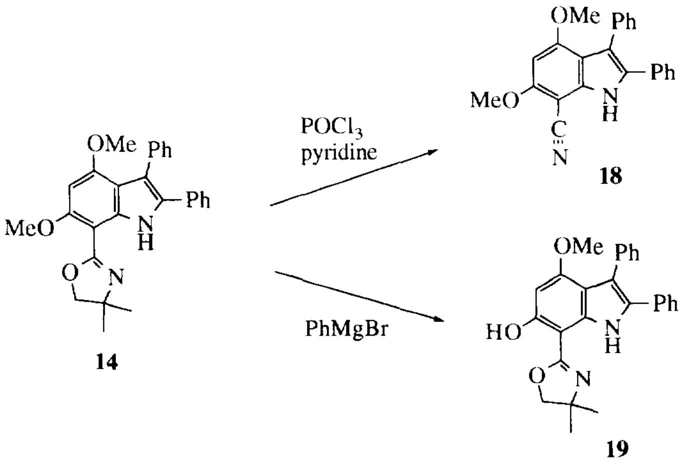
|  | R¹ | R² |
|---|---|---|
| **1** | Ph | Ph |
| **10** | H | 4-BrPh |

|  | R¹ | R² |
|---|---|---|
| **14** | Ph | Ph |
| **15** | H | 4-BrPh |

The conventional method for preparation of oxazolines involves the conversion of a carboxylic acid to its acid chloride, then its amide in combination with a 2-hydroxyamine, followed by cyclisation of the amide. As the indole-7-carboxylic acid **17** was available [4] *via* the 7-trifluoroacetyl derivative **16**, the conventional approach was also tried. Attempts to form the acid chloride by reaction of the acid with oxalyl chloride were unsuccessful, but it has been found that amides can be prepared from the indole-7-carboxylic acid **17** using phosphoryl chloride to generate the acid chloride *in situ*, followed by the addition of an appropriate amine. Reaction of the acid **17** with phosphoryl chloride at 0 °C and subsequent addition of 2-amino-2-methyl-1-propanol gave a white solid, which was expected to be the related amide. However, the $^1H$ n.m.r. spectrum showed the product to be the oxazoline **14**, indicating that cyclisation occurred spontaneously in the reaction mixture. However, the yield of oxazoline **14** was only 15% and therefore the modified Vilsmeier reaction is preferable.



The oxazoline system is useful as a synthetic intermediate for conversion into a number of functional groups, including nitriles, oxazoles and aldehydes [12,14]. The indolyl-oxazoline **14** was converted to the nitrile **18** by reaction with phosphoryl chloride and pyridine. The cyano group was identified by the appearance of an infrared stretching vibration at $2200 cm^{-1}$. Metal complexes can be formed from oxazoline systems, often in combination with other donor atoms [15,16]. Recently, some bis-oxazoline metal complexes have been used to effect in enantioselective synthesis [17-24] Attempts to form metal complexes of the indolyl-oxazoline **14** failed, presumably as a result of steric hindrance provided by the *gem*-dimethyl group of the oxazoline ring and the indole 2-phenyl group. In similar systems where one or both of these groups are removed, it should be possible to form complexes with the indolyl-oxazoline system.



Meyers and others have explored the use of oxazolines as directing groups for both electrophilic and nucleophilic substitution. For example, it has been found that methoxy groups *ortho* to an oxazoline ring can be displaced by a wide range of nucleophilic reagents [25-28]. Reaction of the oxazoline **14** with phenylmagnesium bromide, in an attempt to generate a 6-phenylindole, resulted in formation of the 6-hydroxy compound **19**. Although no OH stretching frequency could be observed in the infrared spectrum, the compound was identified by the presence of a broad peak at 12.2ppm in the $^1H$ n.m.r.spectrum, resulting from hydrogen bonding. A molecular ion at m/z 412 confirmed the loss of the methyl group. This demethylation process has been observed as a general side reaction in the substitution process, especially using Grignard reagents [26]. However, in the reaction of oxazoline **14**, no substitution product was observed. The proposed substitution mechanism involves an addition-elimination sequence requiring the nitrogen atom of the oxazoline ring to be planar with and adjacent to the methoxy group to be substituted.[26] In the case of oxazoline **14**, the preferred hydrogen bonding links the oxazoline nitrogen atom to the indole NH, as shown by the $^1H$ n.m.r. chemical shift of 11.5ppm. After demethylation, the opposite configuration is observed, as the indole NH signal of the oxazoline **19** appears at 9.2ppm, indicating only weak hydrogen bonding with the oxazoline oxygen atom.

## EXPERIMENTAL

### *General Information*

$^1H$ n.m.r. spectra were recorded at 100 MHz with a Bruker CXP-100, at 300 MHz with a Bruker CXP-300 and a Bruker AC-300F 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. $^{13}C$ n.m.r. spectra were recorded at 75.48 MHz with a Bruker AC-300F or at 125.77 MHz with a Brucker 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. Microanalyses were performed by Dr. H.P. Pham of the UNSW Microanalytical Unit.

### *General procedure for the synthesis of imines, pyrrolines, tetrahydropyridines and oxazolines*

The indole 1 (1mmol) was added to a stirred solution of anilide, pyrrolidinone, piperidinone or oxazolidinone (1mmol) and phosphoryl chloride (2mmol) in chloroform (30 ml). After heating under reflux for 5-7h, the mixture was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate and concentrated to a solid, which was recrystallised, or an oil, which was chromatographed to yield the imine, pyrroline, tetrahydropyridine or oxazoline respectively.

### 4,6-Dimethoxy-2,3-diphenyl-7-(phenyliminomethyl)indole (2)

Indole **1** (1.51g, 4.6mmol) and formanilide (0.55g, 4.6mmol) gave the corresponding imine **2** (1.27g, 64%), m.p. 202-204 °C (from dichloromethane/petroleum ether). (Found: C, 80.5; H, 5.5; N, 6.7. $C_{29}H_{24}N_2O_2$ requires C, 80.5; H, 5.6; N, 6.5%). $\nu_{max}$ 3337, 1622, 1605, 1580, 1550, 1282, 1258, 1223, 1159, 993cm$^{-1}$. $^1H$ n.m.r. ($CDCl_3$) $\delta$ 3.80 and 3.98, 2s, OMe; 6.24, s, H5; 7.21-7.44, m, ArH; 9.11, s, imine; 11.54, bs, NH. Mass spectrum: *m/z* 433(M+1, 25%), 432(M, 100), 417(22), 340(19), 57(20).

**4,6-Dimethoxy-2,3-diphenyl-7-(phenylimino-1'-ethyl)indole (3)**

Indole **1** (0.5g, 1.52mmol) and acetanilide (0.21g, 1.52mmol) gave the corresponding imine **3** (0.43g, 63%), mp 190-192 °C (from dichloromethane/petroleum ether). (Found: C, 80.7; H, 5.9; N, 6.1. $C_{30}H_{26}N_2O_2$ requires C, 80.7; H, 5.9; N, 6.3%). $\lambda_{max}$ 252nm($\varepsilon$ 22100), 331(19100). $\nu_{max}$ 3357, 1617, 1588, 1553, 1284, 1243, 1233, 1143, 997, 704 cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$) $\delta$ 2.49, s, Me; 3.82 and 4.02, 2s, OMe; 6.34, s, H5; 7.16-7.50, m, ArH; 11.87, s, NH. $^{13}$C n.m.r. ($CDCl_3$): $\delta$ 22.39, Me; 55.22 and 56.71, OMe; 89.02, C5; 120.74, 123.03, 125.95, 126.76, 127.36, 127.73, 128.43, 129.01 and 131.51, ArCH; 104.76, 113.59, 114.31, 132.67, 133.01, 136.30, 137.04 and 150.94, ArC; 157.25 and 158.75, CO; 168.08, C=N. Mass spectrum: *m/z* 447(M+1, 30%), 446(M, 100), 431(25), 371(30), 354(35), 328(20).

**7-[1'-(3",5"-Dimethoxyphenylimino)-1'-ethyl]-4,6-dimethoxy-2,3-diphenylindole (4)**

Indole **1** (0.5g, 1.52mmol) and 3,5-dimethoxyacetanilide (0.3g, 1.52mmol) gave the corresponding imine **4** (0.54g, 70%), mp 142 °C (from dichloromethane/petroleum ether). (Found: C, 76.1; H, 5.9; N, 5.8. $C_{32}H_{30}N_2O_4$ requires C, 75.9; H, 6.0; N, 5.5%). $\lambda_{max}$ 249nm($\varepsilon$ 19580), 330(16800). $\nu_{max}$ 3336, 1573, 1205, 1147, 1067, 699 cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): $\delta$ 2.44, s, Me; 3.77, s, indole OMe; 3.82, s, phenyl OMe; 3.97, s, indole OMe; 6.07, d, J 2.40Hz, 2H, ArH; 6.25, t, 1H, J 2.40Hz, ArH; 6.28, s, H5; 7.17-7.14, m, 10H, ArH; 11.68, s, NH. $^{13}$C n.m.r. ($CDCl_3$): $\delta$ 22.38, Me; 55.26 and 56.76, indole OMe; 55.39, 2 phenyl OMe; 89.04, C5; 95.17, phenyl CH; 98.66, 2 phenyl CH; 125.97, 126.60, 127.37, 127.76, 128.45 and 131.52, ArCH; 104.62, 113.50, 114.00, 132.71, 132.99, 136.30, 137.01 and 153.14, ArC; 157.35 and 158.84, indole C-OMe; 161.34, phenyl C-OMe; 168.25, C=N. Mass spectrum: *m/z* 507(M+1, 35%), 506(M, 100%), 491(20), 352(38).

**7-[1'-(3",5"-Dimethoxyphenylimino)-2'-phenyl-1'-ethyl]-4,6-dimethoxy-2,3-diphenylindole (5)**

Indole **1** (0.5g, 1.52mmol) and N-(3,5-dimethoxyphenyl)-phenylacetamide (0.41g, 1.52mmol) gave the corresponding imine **5** (0.58g, 65%), mp 189-192 °C (from dichloromethane/petroleum ether). (Found: C, 76.4; H, 5.8; N, 4.4. $C_{38}H_{34}N_2O_4$ requires C, 76.0; H, 6.0; N, 4.7%). $\lambda_{max}$ 256nm($\varepsilon$ 19770), 324(14965). $\nu_{max}$ 3338, 3282, 1682, 1595, 1568, 1550, 1293, 1207, 1156, 1055, 702 cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): $\delta$ 3.63, s, indole OMe; 3.68, s, phenyl OMe; 3.72, s, indole OMe; 4.35, s, $CH_2$; 6.03, d, J 2.29Hz, 2H, ArH; 6.13, s, H5; 6.19, t, J 2.28Hz, 1H, ArH; 7.09-7.42, m, 15H, ArH; 11.84, s, NH. Mass spectrum: *m/z* 583(M+1, 25%), 582(M, 60%), 492(38), 491(100).

**4,6-Dimethoxy-2,3-diphenyl-7-(phenyliminobenzyl)indole (6)**

Indole **1** (0.83g, 2.5mmol) and benzanilide (0.50g, 2.5mmol) gave the corresponding imine **6** (1.20g, 92%), m.p. 194-195 °C (from dichloromethane/petroleum ether). (Found: C, 82.2; H, 5.3; N, 5.3. $C_{35}H_{28}N_2O_2$ requires C, 82.6; H, 5.3; N, 5.5%). $\nu_{max}$ 3391, 1604, 1380, 1350, 1282, 1219, 1172, 993cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): $\delta$ 3,32 and 3.80, 2s, OMe; 3.62 and 3.75, 2s, OMe; 6.20, s, H5; 6.70-7.90, m, ArH; 7.62, bs, NH; 11.15, bs, NH. Mass spectrum: *m/z* 509(M+1, 37%), 508(M, 100), 254(20), 104(31), 77(59), 56(52).

**4,6-Dimethoxy-2,3-diphenyl-7-(1-pyrrolin-2-yl)indole (7)**

Indole **1** (1.0g, 3.04mmol) and 2-pyrrolidinone (0.26g, 3.04mmol) gave the corresponding pyrroline **7** (0.99g, 82%), m.p. 254-255 °C (from ethyl acetate). (Found: C, 78.7; H, 5.9; N, 7.1. $C_{26}H_{24}N_2O_2$ requires C, 78.7; H, 6.1; N, 7.1%). $\nu_{max}$ 3230, 1615, 1610, 1598, 1582, 1564, 1545, 1470, 1380, 1362, 1320, 1305, 1244, 1230, 1160, 1140cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): $\delta$ 1.94, m, $CH_2$; 3.20, m, $CH_2$; 4.03, m, $CH_2$; 3.76 and 3.94, 2s, OMe; 6.23, s, H5; 7.17-7.43, m, ArH; 12.12, bs, NH. Mass spectrum: *m/z* 396(M, 100%), 381(42).

### 4,6-Dimethoxy-7-(5-methyl-1-pyrrolin-2-yl)-2,3-diphenylindole (8)

Indole **1** (1.0g, 3.04mmol) and 5-methyl-2-pyrrolidinone (0.30g, 3.04mmol) gave the corresponding pyrroline **8** (0.97g, 78%), m.p. 195-196 °C (from dichloromethane/light petroleum). (Found: C, 78.9; H, 6.1; N, 6.7. $C_{27}H_{26}N_2O_2$ requires C, 79.0; H, 6.4; N, 6.8%). $\nu_{max}$ 3228, 1610, 1598, 1585, 1560 1541, 1468, 1396, 1386, 1358, 1308, 1238, 1155, 1138, 1080cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): $\delta$ 1.39, d, J 6.7Hz, Me; 1.45-1.59, m, $CH_2$; 2.13-2.24, m, $CH_2$; 3.76 and 3.94, 2s, OMe; 4.28, bq, CH; 6.24, s, H5; 7.18-7.44, m, ArH; 12.28, bs, NH. Mass spectrum: *m/z* 410(M, 71%), 395(47).

### 7-(3',4',5',6'-Tetrahydro-2'-pyridyl)-4,6-dimethoxy-2,3-diphenylindole (9)

Indole **1** (2.0g, 6.08mmol) and 2-piperidinone (0.61g, 6.1mmol) gave the corresponding tetrahydropyridine **9** as a pale yellow solid (2.14g, 86%), m.p. 200-202 °C (from chloroform). (Found: C, 78.7; H, 6.5; N, 6.8. $C_{27}H_{26}N_2O_2$ requires C, 79.0; H, 6.4; N, 6.8%). $\lambda_{max}$ 328nm($\varepsilon$ 40200), 254(43700). 215(41300). $\nu_{max}$ 3180, 1600, 1580, 1340, 1225, 1155, 1135, 993, 695cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): $\delta$ 1.69, m, H4', H5'; 2.82, m, H3'; 3.72 and 3.92, 2s, OMe; 3.91, m, H6'; 6.21, s, H5; 7.13-7.38, m, ArH; 11.80, bs, NH. $^{13}$C n.m.r. ($CDCl_3$) $\delta$ 20.13 and 22.21, C4', C5'; 31.45, C3'; 49.32, C6'; 55.22 and 57.07, OMe; 89.47, 125.77, 126.64, 127.91, 128.33 and 131.55, ArCH; 105.33, 113.57, 114.00, 132.61, 133.38, 136.44, 137.06, 155.90 and 157.04, ArC; 168.84, C=N. Mass spectrum: *m/z* 411(M+1, 28%), 410(M, 100), 395(30), 340(15), 254(7), 197(10), 139(10), 84(30), 77(15), 70(15), 49(27), 41(30).

### 3-(4''-Bromophenyl)-7-(3',4',5',6'-tetrahydro-2'-pyridyl)-4,6-dimethoxyindole (11)

Indole **10** (2.0g, 5.6mmol) and 2-piperidinone (0.6g, 6mmol) gave the corresponding tetrahydropyridine **11** as a yellow solid (1.5g, 65%), m.p. 190-192 °C. (Found: C, 60.7; H, 5.4; N, 6.6. $C_{21}H_{21}BrN_2O_2$ requires C, 61.0; H, 5.1; N, 6.8%). $\lambda_{max}$ 310nm($\varepsilon$ 28500), 247(28700). 214(26700). $\nu_{max}$ 3125, 1610, 1580, 1325, 1210, 1150cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): $\delta$ 1.73, m, H4', H5'; 2.86, m, H3'; 3.88, m, H6'; 3.83 and 3.90, 2s, OMe; 6.25, s, H5; 7.05,s, H2; 7.44, s, ArH. $^{13}$C n.m.r. ($CDCl_3$) $\delta$ 20.04, C4'; 22.13, C5'; 31.44, C3'; 49.21, C6'; 55.08 and 57.04, OMe; 89.27, C5; 121.56, C2; 130.54 and 131.10, ArCH; 105.56, 110.65, 116.79, 119.36, 135.45, 138.07, 155.56 and 157.08, ArC; 169.05, C=N. Mass spectrum: *m/z* 415(M+1, $^{81}$Br, 20%), 414(M, $^{81}$Br, 95), 413(M+1, $^{79}$Br, 25), 412(M, $^{79}$Br, 100), 397(35), 262(20), 167(60), 137(50), 109(40), 95(50).

### 4,6-Dimethoxy-7-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)-2,3-diphenylindole (14)

***Method (a).*** Indole **1** (2.0g, 6.08mmol), 4,4-dimethyl-2-oxazolidinone (2.8g, 24mmol) and phosphoryl chloride (4.0ml, 43mmol) gave the corresponding oxazoline **14** as a white solid (1.35g, 52%), m.p. 232-234 °C. (Found: C, 76.0; H, 6.3; N, 6.6. $C_{27}H_{26}N_2O_3$ requires C, 76.0; H, 6.1; N, 6.6%). $\lambda_{max}$ 333nm($\varepsilon$ 35700), 248(38600). 214(37600). $\nu_{max}$ 3290, 1620, 1600, 1340, 1295, 1165, 1150cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): $\delta$ 1.44, s, Me; 3.78 and 4.00, 2s, OMe; 4.19, s, H5'; 6.27, s, H5; 7.21-7.42, m, ArH; 11.50, bs, NH. $^{13}$C n.m.r. ($CDCl_3$) $\delta$ 28.90, Me; 55.26 and 57.66, OMe; 65.73, C4'; 78.60, C5'; 89.17, 125.00, 126.87, 127.40, 127.87, 128.46 and 131.49, ArCH; 113.06, 114.58, 132.62, 133.08, 136.04, 137.54 and 157.69, ArC; 162.06, C2'. Mass spectrum: *m/z* 428(M+2, 5%), 427(M+1, 23), 426(M, 85), 354(100), 339(60), 296(15), 267(20), 83(60), 69(45), 55(35), 43(45).

**Method (b).** To an ice-cold solution of 4,6-dimethoxy-2,3-diphenylindole-7-carboxylic acid **17** (0.2g, 0.5mmol) in tetrahydrofuran was added phosphoryl chloride (0.25ml, 2.7mmol) and the resulting solution stirred at 0 °C for 1h. 2-Amino-2-methyl-1-propanol (0.5ml, 5mmol) was then added to the solution and stirring continued for a further 30 min. The resulting mixture was then filtered to give a white solid which was purified by column chromatography (ethyl acetate/petroleum ether) to yield the product **14** (0.03g,15%), m.p. 231-233 °C, identical to that described above.

**4,6-Dimethoxy-7-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)-3-(4''-bromophenyl)indole (15)**

Indole **10** (0.5g, 1.4mmol), 4,4-dimethyl-2-oxazolidinone (0.5g, 4.3mmol) and phosphoryl chloride (0.5ml, 5.4mmol) gave the corresponding oxazoline **15** as a white solid after chromatography (chloroform/methanol 90:10) (0.30g, 50%), m.p. 152-154 °C. (Found: C, 57.5; H, 5.0; N, 6.4. $C_{21}H_{21}Br.N_2O_3.0.5H_2O$ requires C, 57.6; H, 5.0; N, 6.1%). $\lambda_{max}$ 295nm(ε 33700), 247(34900). 216(33000). $\nu_{max}$ 3300, 1620, 1600, 1590, 1340, 1295, 1210, 1145, 795cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): δ 1.40, s, Me; 3.87 and 3.98, 2s, OMe; 4.15, s, H5'; 6.28, s, H5; 7.11, d, H2;7.45, s, ArH; 11.31, bs, NH. $^{13}$C n.m.r. ($CDCl_3$) δ 28.83, Me; 55.18 and 57.72, OMe; 65.70, C4'; 78.62, C5'; 89.15, 121.49, 130.65 and 131.09, ArCH; 93.07, 110.23, 117.51, 119.66, 135.05, 138.55, 157.39 and 157.93, ArC; 162.08, C=N. Mass spectrum: *m/z* 431(M+1, $^{81}$Br, 20%), 430(M, $^{81}$Br, 75), 429(M+1, $^{79}$Br, 20), 428(M, $^{79}$Br, 75), 358(95), 356(100), 341(20), 262(55), 247(20), 164(35).

**4,6-Dimethoxy-2,3-diphenyl-7-(2'-pyridyl)-indole (12)**

To a solution of indole **9** (0.5g, 1.2mmol) in dry xylene (30ml) was added palladium-charcoal catalyst (0.2g of 10%) and the mixture was refluxed for 96h with a nitrogen sweep. The mixture was filtered hot and the solvent removed to yield compound **12** as a white solid (0.3g, 60%), m.p. 220-222 °C (from chloroform). (Found: C, 77.9; H, 5.6; N, 6.7. $C_{27}H_{22}N_2O_2.0.5H_2O$ requires C, 78.0; H, 5.5; N, 6.5%). $\lambda_{max}$ 328nm(ε 23000), 250(29500). 210(35700). $\nu_{max}$ 3320, 1590, 1425, 1260, 1135, 795, 755, 690cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): δ 3.75 and 3.99, 2s, OMe; 6.35, s, H5; 7.10-7.42, m, ArH; 7.72, t, J 7.8Hz, H5'; 8.36, d, J 8.0Hz, H3'; 8.67, d, J 4.9Hz, H6'; 11.69, bs, NH. $^{13}$C n.m.r. ($CDCl_3$) 55.34 and 57.24, OMe; 89.96, 120.10, 124.81, 125.83, 126.78, 127.31, 128.03, 128.38, 131.59, 136.16 and 147.89, ArCH; 103.61. 114.20, 132.82, 133.39, 136.40, 137.16, 155.61, 155.96 and 156.43, ArC . Mass spectrum: *m/z* 408(M+2, 5%), 407(M+1, 25), 406(M, 100), 391(60), 376(20), 348(20), 319(20), 104(15), 95(27), 84(50), 81(50), 78(30), 77(25), 69(65).

**4,6-Dimethoxy-3-(4''-bromophenyl)-7-(2'-pyridyl)indole (13)**

To a solution of indole **11** (0.5g, 1.2mmol) in dry xylene (30ml) was added palladium-charcoal catalyst (0.2g of 10%) and the mixture was refluxed for 120h with a nitrogen sweep. The mixture was filtered hot and the solvent removed to yield compound **13** as a yellow solid after chromatography (chloroform) (0.05g, 10%), m.p. 189-191 °C. (Found: C, 60.5; H, 4.3; N, 6.4. $C_{21}H_{17}BrN_2O_2.0.5H_20$ requires C, 60.3; H, 4.3; N, 6.7%). $\lambda_{max}$ 338nm(ε 49100), 294(48400). 238(82300)., 208(92700). $\nu_{max}$ 3380, 1580, 1535, 1430, 1205, 1140, 1115, 980,795cm$^{-1}$. $^1$H n.m.r. ($CDCl_3$): δ 3.87 and 3.96, 2s, OMe; 6.37, s, H5; 7.11, d, J 2.3Hz. H2; 7.12, dt, J 1.2 and4.9Hz, H5'; 7.45, s, ArH; 7.78, dt, J 8.2 and 2.0Hz, H4'; 8.32, d, J 8.2Hz, H3'; 8.60, dd, J 4.9 and 1.2Hz, H6'; 11.55, bs, NH. Mass spectrum: *m/z* 411(M+1, $^{81}$Br, 20%), 410(M, $^{81}$Br, 100), 409(M+1, $^{79}$Br, 20), 408(M, $^{79}$Br, 100), 395(40), 393(40), 330(15), 314(45), 242(50), 205(50), 136(80), 107(65), 78(90), 69(95), 57(85).

**4,6-Dimethoxy-2,3-diphenylindole-7-carbonitrile (17)**

To a suspension of oxazoline **14** (0.2g, 0.5mmol) in pyridine (20ml) was added phosphoryl chloride (0.4ml, 4mmol) and the resulting yellow solution warmed to 80 °C for 48h. The solution was diluted with chloroform and washed with a saturated solution of ammonium chloride (3 x 50ml). The organic layer was dried over magnesium sulfate and the solvent removed under reduced pressure to yield nitrile **17** as a white solid (0.1g, 62%), m.p. 240-242 °C (from dichloromethane/methanol). (Found: C, 70.6; H, 5.1; N, 6.8. $C_{23}H_{18}N_2O_2.2H_2O$ requires C, 70.8; H, 5.6: N, 7.1%). $\lambda_{max}$ 331nm(ε 42800), 309(35800). 258(43800), 216(40500). $\nu_{max}$ 3235, 2200, 1595, 1215, 1155, 1120, 980, 790, 690cm$^{-1}$. $^1$H n.m.r. (CDCl$_3$): $\delta$ 3.72 and 3.95, 2s, OMe; 6.44, s, H5; 7.18-7.28, m, ArH. $^{13}$C n.m.r. (CDCl$_3$) $\delta$ 55.09 and 56.43, OMe; 87.78, C5; 116.23, CN; 125.87, 126.98, 127.06, 127.84, 128.32 and 131.00, ArCH; 127.92, 131.66, 133.89, 135.00, 137.22, 158.89 and 160.56, ArC. Mass spectrum: *m/z* 355(M+1, 25%), 354(M, 100), 339(50), 324(15), 296(20), 104(12), 77(30), 69(25).

**6-Hydroxy-4-methoxy-7-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)-2,3-diphenylindole (19)**

To a solution of phenylmagnesium bromide (0.32g, 1.8mmol) in tetrahydrofuran (5ml) was added a solution of oxazoline **14** (0.25g, 0.6mmol) in tetrahydrofuran (5ml). The resulting yellow solution was refluxed for 120h then diluted with dichloromethane and washed with ammonium chloride (3 x 50ml) and water (2 x 50ml). The organic layer was dried over magnesium sulfate and the solvent removed under reduced pressure. Purification of the crude product by column chromatography (dichloromethane) gave the product **19** as a white solid, (0.15g, 62%), m.p. 161-163 °C. (Found: C, 74.0; H, 6.1; N, 6.5. $C_{26}H_{24}N_2O_3.0.5H_2O$ requires C, 74.0; H, 6.0; N, 6.6%). $\lambda_{max}$ 333nm($\varepsilon$ 69000), 306(78200), 246(98600). 211(114300). $\nu_{max}$ 3480, 1640, 1620, 1600, 1300, 1205, 1170, 1070, 1025, 955, 810, 695cm$^{-1}$. $^1$H n.m.r. (CDCl$_3$): $\delta$ 1.45, s, Me; 3.79, s, OMe; 4.27, s, H5'; 6.34, s, H5; 7.21-7.38, m, ArH; 9.17, bs, NH, 12.20, bs, OH. $^{13}$C n.m.r. (CDCl$_3$) $\delta$ 28.59, Me; 55.28, OMe; 65.96, C4'; 78.77, C5'; 92.20, 126.04, 126.94, 127.32, 127.88, 128.46 and 131.44, ArCH; 88.17, 111.89, 115.21, 132.91, 134.86, 135.73, 158.80 and 160.10, ArC; 163.54, C2'. Mass spectrum: *m/z* 413(M+1, 10%), 412(M, 30), 81(30), 69(100), 57(75), 55(75), 43(75).

## ACKNOWLEDGEMENTS

We thank the Australian Research Council for financial support.

## REFERENCES

1. Black, D.StC.; Craig, D.C.; Kumar, N.; Wong, L.C.H.*J. Chem. Soc., Chem. Commun.* **1985**, 1172-1173.
2. Black, D.StC.; Kumar, N.; Wong, L.C.H. *Synthesis* **1986,** 474-476.
3. Black, D.StC.; Deb-Das, R.B.; Kumar, N. *Aust. J. Chem.*. **1992,** 44, 1051-1056.
4. Black, D.StC.; Bowyer, M.C.; Catalano, M.M.; Ivory, A.J.; Keller, P.A.; Kumar, N.; Nugent, S.J. *Tetrahedron* **1994**, 50, 10497-10508 .
5. A preliminary report of some of these results has appeared: Black, D.StC.; Bowyer, M.C.; Choy, A.; Craig, D.C.; Kumar, N. *J. Chem. Soc., Perkin Trans. 1* **1989**, 200-201.
6. Black, D.StC.; Bowyer, M.C.; Bowyer, P.K.; Ivory, A.J.; Kim, M.; Kumar, N.; McConnell, D.B.; Popiolek, M. *Aust. J. Chem.* **1994,** 47, 1741-1750.
7. Rapoport, H.; Castagnoli, N. *J. Am. Chem. Soc.* **1962**, 84, 2178-2181.
8. Rapoport, H.; Castagnoli, N.; Holden, K. G. *J. Org. Chem.*, **1964,** 29, 883-885.
9. Black, D.StC.; Deacon, G.B.; Edwards, G.L. *Aust. J. Chem.* **1991,** 44, 1771-1781.
10. Meyers, A.I.; Temple, D.L. *J. Am. Chem. Soc.* **1970**, 92, 6644-6646.
11. Meyers, A.I.; Collington, E.W. *J. Am. Chem. Soc.* **1970**, 92, 6676-6677.
12. Reuman, M.; Meyers, A.I. *Tetrahedron* **1985**, 41, 837-860.
13. Close, W.J. *J. Am. Chem. Soc.* **1951**, 73, 95-98.

14. Dordor, I.M.; Mellor, J.M.; Kennewell, P.D. *J. Chem. Soc., Perkin Trans. 1* **1984**, 6, 1253-1258.
15. Black, D.StC.; Wade, M.J. *Aust. J. Chem.* **1972**, 25, 1797-1810.
16. Bolm, C.; Schlingloff,G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1848-1849.
17. Lowenthal, R.E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990,** 31, 6005-6008.
18. Lowenthal, R.E.; Masamune, S. *Tetrahedron Lett.* **1991,** 32, 7373-7376.
19. Pfaltz, A. *Acc. Chem. Res.* **1993**, 26, 339-345.
20. Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1991**, 30, 542-543.
21. Corey, E.J.; Ishihara, K. *Tetrahedron Lett.* **1992**, 33, 6807-6810.
22. Evans, D.A.; Miller, S.J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, 115, 6460-6461.
23. Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* 1991, 257-259.
24. Denmark, S.E.; Nakajima, N.; Nicaise, O.J.-C.; Faucher, A.-M.; Edwards, J.P. *J. Org. Chem.* **1995** 60, 4884-4892.
25. Meyers, A.I.; Mihelich, E.D. *J. Am. Chem. Soc.* **1975**, 97, 7383-7385.
26. Meyers, A.I.; Gabel, R.; Mihelich, E.D. *J. Org. Chem.* **1978,** 43, 1372-1379.
27. Gant, T.G.; Meyers, A.I. *J. Am. Chem. Soc.* **1992**, 114, 1010-1015.
28. Gant, T.G.; Meyers, A.I. *Tetrahedron* **1994**, 50, 2297-2360.

(*Received in UK* 17 *November* 1995; *accepted* 1 *February* 1996)