SYNTHESIS AND REACTIONS OF 1-(4'-BROMOPHENACYL)-3-(4'-BROMO-PHENYL)-4,6-DIMETHOXYINDOLE

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ABSTRACT

*1-Phenacyl-3-aryl-4,6-dimethoxyindoles **2b** and **2c** were obtained in good yields respectively through cyclization of N,N-diphenacylaniline **1b** and **1c** in trifluoroacetic acid. However, instead of giving pyrroloindole **3c**, treatment of phenacylindole **2c** with polyphosphoric acid afforded indolizine **5** in 42% yield. Phenacylindole **2c** reacts with the Vilsmeier aroylation reagent consisted of a mixture of phosphoryl chloride and p-chloro-N,N-dimethylbenzamide to give 2-aroylindole **6** (32%) and pyrroloindole **7** (22%). When treated with sodium borohydride, phenacylindole **2c** gave alcohol **8** in 83% yield. Nonetheless, treatment of alcohol **8** with either p-toluenesulfonic acid in glacial acetic acid or boron trifluoride etherate in benzene did not give the desired dihydropyrroloindole **12**. Instead, the reactions afforded respectively acetyl ester **9** and indole **10** in 56% and 63% yield.*

Keywords: *phenacylindole, aroylindole, pyrroloindole, and indolizine.*

INTRODUCTION

The reaction of *N,N*-diphenacylaniline **1a** with polyphosphoric acid (PPA) has been reported by Bartsch [1,2] to afford either 1-phenacyl-3-phenylindole **2a** or 1,5-diphenylpyrrolo[3,2,1-hi]indole **3a**. When the reaction was carried out at 130^{o}C for 4 hours, 1-phenacyl-3-phenylindole **2a** was the main product. However, when the reaction was performed at the same temperature but in a much longer period of time (50 hours), 1,5-diphenylpyrrolo[3,2,1-*hi*]indole **3a** was obtained in 39%. Clear evidence for this symmetrical pyrroloindole **3** was given by its mass spectrum, which revealed a molecular ion at *m/z* 293, and two fragments at *m/z* 216 and *m/z* 139 originating from the loss of one and two phenyl groups respectively. The elemental analysis and 60 MHz ^{1}H n.m.r. spectrum of this pyrrolindole were consistent with the structure: the latter gave only one multiplet in the aromatic region (7.9-8.1 ppm).

An attempt to develop the Bartsch method has been conducted by Keller [3] who reacted *N,N*-di(4'-bromophenacyl)-3,5-dimethoxyaniline **1c** with PPA under the same conditions as reported by Bartsch. However, instead of the symmetrical pyrroloindole **3c**, the main outcome of this reaction was 3-bromo-5-(4'-bromophenyl)-9,11-dimethoxydibenz[*b,g*]-indolizine **5**. Although this product could not be obtained analytically pure, structural assignment based on its ^{1}H and ^{13}C n.m.r. spectra clearly showed the formation of this compound. Acid-catalyzed rearrangement of the presumed 3-substituted indole **2c** intermediate to afford a 2-substituted indole **4**, which underwent further cyclisation was considered to be the mechanism leading to the formation of the indolizine.

As an attempt to further develops the synthetic route towards pyrroloindole molecules, here the author reports the synthesis and reactions of 1-(4'-bromophenacyl)-3-(4'-bromophenyl)-4,6-dimethoxy-indole. The latter aspect includes reaction of the phenacylindole with PPA and Vilsmeier aroylation agent, as well as reduction of the phenacylindole carbonyl group with $NaBH_4$ followed by treatment of related alcohol with acids. In the case of PPA, a more recent work by Black and coworkers [4] has shown that PPA was a useful medium for the cyclisation of *N*-trifluoroacetyl-*N*-phenacylanilines leading to the generation of 3-aryl-4,6-dimethoxyindoles.

EXPERIMENTAL SECTION

General information

Melting points were measured on a Reichert microscope melting point apparatus and were uncorrected. Microanalyses were performed by Dr. H.P. Pham of the University of New South Wales.

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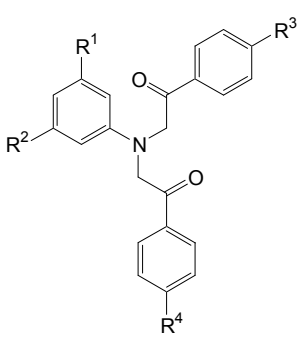

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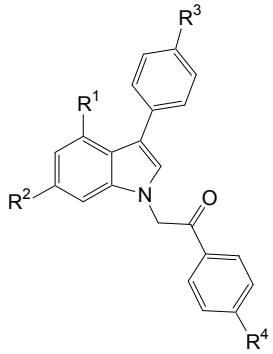
(a) $R^1 = R^2 = R^3 = R^4 = H$
(b) $R^1 = R^2 = OMe$; $R^3 = R^4 = H$
(c) $R^1 = R^2 = OMe$; $R^3 = R^4 = Br$



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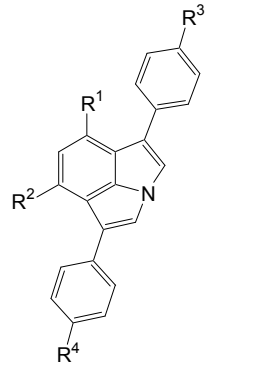
(a) $R^1 = R^2 = R^3 = R^4 = H$
(b) $R^1 = R^2 = OMe$; $R^3 = R^4 = H$
(c) $R^1 = R^2 = OMe$; $R^3 = R^4 = Br$



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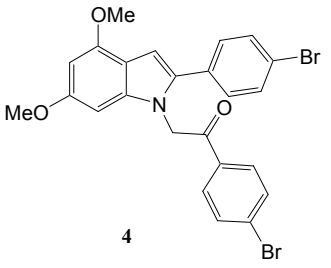
(a) $R^1 = R^2 = R^3 = R^4 = H$
(b) $R^1 = R^2 = OMe$; $R^3 = R^4 = H$
(c) $R^1 = R^2 = OMe$; $R^3 = R^4 = Br$



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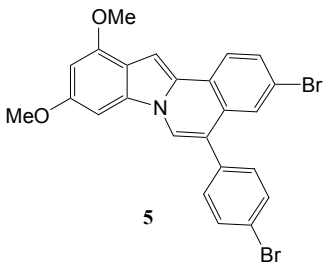

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^{1}H n.m.r. and ^{13}C n.m.r. spectra were recorded in the designated solvents on a Bruker AC300F (300 MHz) or a Bruker AM500 (500MHz) spectrometer. Chemical shifts were determined on the δ scale internally referenced to the solvent peaks: $CDCl_3$ (7.30 ppm, 77.7 ppm) and DMSO-d_6 (2.50 ppm, 39.9 ppm). Ultraviolet spectra were measured on a Hitachi U-3200 spectrometer and refer to solutions in absolute methanol. Infrared spectra were obtained on a Perkin Elmer 298 IR spectrometer and refer to paraffin mulls. The E.I. mass spectra were recorded on a VG Quattro mass spectrometer at 70eV ionisation voltage and 200°C ion source temperature by Dr. Joe Brophy. E.S. mass spectra were recorded on a VG Quattro mass spectrometer at 4000 volts probe voltage, 1000 volts counter electrode, 65 volts cone voltage using a mixture of acetonitrile and water (1:1) containing 1% acetic acid as the solvent and at 5 μL/min flow rate also by Dr. Joe Brophy. High molecular weight compounds were run on matrix assisted laser desorption (MALDI) mass spectrometers Finnigan MAT or lasermat 2000 using a matrix of α-cyano-4-hydroxycinnamic acid by Mr. Ray Lidgard.

Flash column chromatography was carried out using Merck 230-400 mesh silica gel and refers to the technique described by Still [5] using pressure at the top of the column. Suction chromatography was performed using Merck 60H silica gel and refers to the technique of applying suction at the base of the column. Preparative thin layer chromatography was carried out on 20x20x0.1 cm plates using Merck silica gel 7730 $60GF_{254}$. Compounds were detected by short and long wavelength ultraviolet light.

3,5-Dimethoxy-N,N-diphenacylaniline *(1b)*

A mixture of 3,5-dimethoxyaniline (3.0 g, 19.59 mmol), α-bromoacetophenone (7.80 g, 39.20 mmol) and sodium carbonate (8.30 g, 78.40 mmol) in 95% ethanol (50 mL) was heated at reflux for 4h. The mixture was allowed to cool, the resulting precipitate was filtered, washed with water and recrystallized from chloroform/light petroleum to give the diphenacylaniline as a brown solid (2.74 g, 36%), m.p. 130-133°C. ^{1}H n.m.r. ($CDCl_3$): δ 3.67, s, OMe; 4.91, s, CH_2; 5.72, d, *J* 2.5Hz, H2,6; 5.92, t, *J* 2.5Hz, H4; 7.51, 7.61 and 8.01, m, ArH. ^{13}C n.m.r. ($CDCl_3$): δ 55.0, OMe; 58.0, CH_2; 89.6, C4; 92.4, C2,6; 127.8, 128,8 and 133.6, ArCH; 135.1, 150.4 and 161.6, ArC; 196.4, CO. Mass spectrum: *m/z* 389(M, 8%), 284(62), 166(22), 122(19), 105(84), 91(100), 84(30), 77(74).

4,6-Dimethoxy-1-phenacyl-3-phenylindole *(2b)*

Diphenacylaniline **1b** (0.20 g, 0.51 mmol) was added into ice-cooled trifluoroacetic acid (4.0 mL), then the mixture was heated at 70°C for 1h. The mixture was allowed to cool, diluted with ice-water (15 mL) and the resulting precipitate was filtered, washed with water and dried. Thin layer chromatography and elution with chloroform afforded the phenacylindole as a brown solid (0.17g, 87%), m.p. 96-98°C. (Found: C, 77.5; H, 6.0; N, 3.6. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%). λ_{max} 210nm (ε 63900), 241(70600), 282(39000). ν_{max} 1700, 1620, 1600, 1220, 1200, 1140 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 3.80 and 3.81, each s, OMe; 5.39, s, CH_2; 6.25, d, *J* 2.3Hz, H5; 6.28, d, *J* 2.3Hz, H7; 6.89, s, H2; 7.36 and 7.51, t, *J* 7.3 Hz, H3',4'; 7.63 and 8.00, d, *J* 7.3Hz, H2'. ^{13}C n.m.r. ($CDCl_3$): δ 52.5, CH_2; 55.1 and 55.7, OMe; 85.3, C5; 92.3, C7; 111.0, 118.8, 134.8, 135.9, 139.2, 155.2 and 157.8, ArC; 125.1, 125.6, 127.5, 128.1, 129.0 and 129.6, ArCH; 134.0, C2; 192.9, CO. Mass spectrum: *m/z* 372(M+1, 13%), 371(M, 53), 267(17), 266(100), 250(21), 105(27), 77(28), 69(30).

1-(4'-Bromophenacyl)-3-(4'-bromophenyl)-4,6-dimethoxyindole (2c)

A mixture of 3,5-dimethoxyaniline (5.0 g, 32.64 mmol), α-bromo-4'-bromoaceto-phenone (18.2 g, 65.30 mmol) and sodium carbonate (13.8 g, 130.41 mmol) in 95% ethanol (80 mL) was heated at reflux for 4 h. The mixture was allowed to cool, and the resulting precipitate was filtered, washed with water and recrystallized from chloroform/light petroleum to give a yellow solid. This diphenacylaniline was reacted with cooled trifluoroacetic acid (15 mL) according to the method of preparation of compound **2b**. The resulting solid was flash chromatographed, and elution with light petroleum in dichloromethane (1:2) afforded the bromophenacylindole as a pale-yellow solid (7.60 g, 44%), m.p. 185-188°C. (Found: C, 54.8; H, 3.8; N, 2.5. $C_{24}H_{19}Br_2NO_3$ requires C, 54.5; H, 3.6, N, 2.7%). λ_{max} 206nm (ε38700), 215(33200), 247(29400), 276(20100), 296(13900). ν_{max} 1710, 1630, 1600, 1560, 1230, 1210, 1150, 1000 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 3.79, s, OMe; 5.35, s, CH_2; 6.19, d, *J* 1.8Hz, H5; 6.27, d, *J* 1.8Hz, H7; 6.85, s, H2; 7.46, s, ArH; 7.65 and 7.84, d, *J* 8.2Hz, ArH. ^{13}C n.m.r. ($CDCl_3$): δ 52.3, CH_2; 55.1 and 55.6, OMe; 85.3, C5; 92.4, C7; 117.7, 119.7, 125.0, 133.3, 134.7, 139.2, 155.0, 158.0 and 192.0, ArC; 125.0, C2; 129.5, 130.6, 131.1 and 132.3, ArCH; 209.6, CO. Mass spectrum: *m/z* 531(M, ^{81}Br, 19%), 530(M+1, $^{79,81}Br$, 18), 529(M, $^{79,81}Br$, 58), 528(M+1, ^{79}Br, 11), 527(M, ^{79}Br, 23), 346(87), 345(42), 344(100), 207(32), 185(37), 185(39), 156(62), 155(65), 76(68), 75(58), 69(53), 43(47).

3-Bromo-5-(4'-bromophenyl)-9,11-dimethoxy-dibenz[b,g]indolizine (5)

Polyphosphoric acid (4.0 g) was heated at 130°C, then indole **2c** (0.15 g, 0.28 mmol) was added and the mixture stirred for 1h. The mixture was allowed to cool, diluted with water (30 mL) and basified with 20% sodium hydroxide. The resulting suspension was extracted with dichloromethane (3x60 mL), and the combined organic layers were washed with water, dried over magnesium sulfate and evaporated to leave a brown solid. Thin layer chromatography and elution with light petroleum in dichloromethane (1:4) gave the title compound as a yellow solid (60 mg, 42%), m.p. 86-88°C. ^1H n.m.r. ($CDCl_3$) δ 3.90 and 4.00, each s, OMe; 6.43, d, *J* 1.8Hz, H5; 6.77, d, *J* 1.8 Hz, H7; 7.37-8.01, m, H3 and ArH. Mass spectrum: *m/z* 513(M, ^{81}Br, 28%), 511(M, $^{79,81}Br$, 56), 509(M, ^{79}Br, 28), 498(22), 49(41), 49(24), 313(26), 26 (50), 236(43), 97(100), 83(84).

Reaction of indole 2c with 4-chloro-N,N-dimethylbenzamide and $POCl_3$

Indole **2c** (0.15 g, 0.28 mmol) was added in portions into a solution of *p*-chloro-*N,N*-dimethylbenzamide (0.10 g, 0.55 mmol) in phosphoryl chloride (1.0 mL) at 80°C. The mixture was stirred for 3h, then cooled in an ice-bath, diluted cautiously with cold water (20 mL) and basified with 2 N sodium hydroxide. The resulting suspension was extracted with dichloromethane (3x60 mL), and the combined organic layers were washed with water, dried over magnesium sulfate and evaporated to leave a brown solid. Thin layer chromatography and elution with light petroleum in dichloromethane (1:4) gave two products.

i. 1-(4'-Bromophenacyl)-3-(4'-bromophenyl)-2-(4'-chlorobenzoyl)-4,6-dimethoxyindole ***(6)***

The title compound was obtained as a pale yellow solid (60 mg, 32%). ^1H n.m.r. ($CDCl_3$): δ 3.69 and 3.84, each s, OMe; 5.86, s, CH_2; 6.21, d, *J* 1.8Hz, H5; 6.24, d, *J* 1.8 Hz, H7; 6.98-7.82, m, ArH.

ii. 1,5-Di-(4'-bromophenyl)-2-(4'-chlorobenzoyl)-6,8-dimethoxypyrrolo[3,2,1-hi]indole ***(7)***

This compound was isolated as a yellow solid (40 mg, 22%), m.p. 173-175°C. ^1H n.m.r. ($CDCl_3$): δ

3.91 and 4.05, each s, OMe; 6.42, s, H7; 7.06-7.78, m, ArH; 7.98, s, H4. Mass spectrum: *m/z* 655(M+2, ^{81}Br, ^{37}Cl, 10%), 653(M, ^{81}Br, ^{37}Cl, 14), 651(M, ^{79,81}Br, ^{37}Cl, 12), 471(9), 185(97), 183(100), 157(69), 155(76), 139(30), 75(26).

3-(4'-Bromophenyl)-1-{2-(4'-bromophenyl)-2-hydroxyethyl}-4,6-dimethoxyindole (8)

Sodium borohydride (86 mg, 2.28 mmol) was added into a cooled solution of indole **2c** (0.30 g, 0.57 mmol) in a mixture of absolute ethanol and tetrahydrofuran (1:1, 10 mL). The mixture was stirred at 0 °C for 45 min, then at room temperature for another 30 min. The solvent was removed under reduced pressure and the residue was diluted with water (40 mL). The resulting precipitate was filtered, washed with water and dried to give the hydroxyindole as a white solid (0.25 g, 83%), m.p. 97-99 °C (from dichloromethane/light petroleum). (Found: C, 53.9; H, 4.2; N, 2.3. $C_{24}H_{21}Br_2NO_3$ requires C, 54.3; H, 4.0; N, 2.6%). λ_{max} 214nm (ε4700), 315(5600). ν_{max} 3200, 1620, 1590, 1545, 1340, 1205, 1165, 1060, 1010, 800 cm^{-1}. ^{1}H n.m.r ($CDCl_3$): δ 2.06, s (br), OH; 3.78 and 3.85, each s, OMe; 4.16, d, *J* 6.2Hz, CH_2; 4.98, d, *J* 6.2Hz, CH; 6.26, s, H5; 6.35, s, H7; 6.82, s, H2; 7.17-7.51, m, ArH. ^{13}C n.m.r. ($CDCl_3$): δ 54.0, CH_2; 55.1 and 55.7, OMe; 72.8, CH; 85.6, C5; 92.1, C7; 110.6, 117.0, 119.6, 122.2, 134.7, 138.7, 140.0, 155.0 and 157.7, ArC; 125.0, C2; 127.6, 130.6, 131.0 and 131.8, ArCH. Mass spectrum: *m/z* 533(M, ^{81}Br, 21%), 531(M, ^{79,81}Br, 42), 529(M, ^{79}Br, 21), 347(20), 346(97), 344(100), 265 (18), 77 (28).

1-(4'-Bromophenyl)-2-{3'-(4''-bromophenyl)-4',6'-dimethoxyindol-1-yl}acetate (9)

A mixture of indole **8** (0.15 g, 0.28 mmol), *p*-toluenesulfonic acid monohydrate (53 mg, 0.28 mmol) and glacial acetic acid (8 mL) was heated at reflux for 2 h. The mixture was allowed to cool, then diluted with water (40 mL), cooled in an ice-bath, and basified by adding sodium hydroxide pellets slowly. The resulting suspension was extracted with ether (3x70 mL), the combined ethereal layers were washed with water, dried over magnesium sulfate and evaporated to leave a brown solid. Thin layer chromatography and elution with dichloromethane gave the acetoxyindole as a white solid (90 mg, 56%), m.p 80-82°C. (Found: C, 55.8; H, 4.7; N, 2.0. $C_{26}H_{23}Br_2NO_4$ requires C, 54.5; H, 4.0; N, 2.4%). λ_{max} 213nm (ε18000), 233(18200), 288(13200), 298(12200). ν_{max} 1745, 1625, 1590, 1230, 1170, 1055, 800 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 2.07, CH_3; 3.79 and 3.86, each s, OMe; 4.22 and 4.45, each q, *Jgem* 14.6Hz, *Jvic* 6.4 and 6.2Hz, CH_2; 6.00, t, *J* 6.2Hz, CH; 6.24, d, *J* 1.8Hz, H5; 6.40, d, *J* 1.8Hz, H7; 6.58, s, H2; 7.07-7.47, m, ArH. Mass spectrum: *m/z* 575 (M, ^{81}Br, 37%), 573(M, ^{79,81}Br, 73), 571(M, ^{79}Br, 35), 346(100), 344(97), 330(22), 328(16), 265(15), 77(19), 43(76).

3-(4'-Bromophenyl)-4,6-dimethoxy-1-(1-phenyl-4'-bromophenethyl)indole (10)

Boron trifluoride etherate (4 drops) was added into a cooled solution of indole **8** (0.20 g, 0.35 mmol) in dry benzene (10 mL). The mixture was heated at reflux for 2h, then allowed to cool, diluted with chloroform (80 mL), washed with water, dried over magnesium sulfate and evaporated to leave a brown oil. Thin layer chromatography and elution with light petroleum in dichloromethane (1:4) afforded the phenethylindole as a yellow solid (0.13 g, 63%), m.p. 87-89 °C. (Found: C, 61.7; H, 4.9; N, 2.0. $C_{30}H_{25}Br_2NO_2$ requires C, 60.9; H, 4.2; N, 2.4%). ^{1}H n.m.r. ($CDCl_3$) δ 3.80 and 3.82, each s, OMe; 4.45, t, *J* 7.4Hz, CH; 4.60 and 4.63, each d, *J* 7.4Hz, CH_2; 6.25, d, *J* 1.8Hz, H5; 6.27, d, *J* 1.8Hz, H7; 6.40, s, H2; 6.99-7.43, m, ArH. Mass spectrum (MALDI): *m/z* 590(M+1, ^{79}Br, 47%), 400(32), 379(46), 190(95), 172(95), 146(52).

DISCUSSION

A classical problem arising frequently in the Bischler indole synthesis is migration of the related alkyl or aryl substituents which leads to the formation of either the isomeric 2- or 3-substituted indoles. An example of such migration was observed by Crowther and coworkers [6] in which secondary phenacylanilines underwent rapid cyclisation in the presence of a trace of aniline hydrobromide to form 2-phenylindoles. A similar phenomenon was seen by Black and coworkers [4] who found that secondary α-arylaminoketones derived from 3,5-dimethoxyaniline and phenacyl bromides cyclised to afford 2-arylindoles rather than 3-arylindoles.

A different situation, indeed, has also been reported by Crowther and coworkers [6] for the cyclization of tertiary phenacylanilines such as *N*-phenylphenacylaniline. Instead of the 1,2-diphenyl-indole, treatment of *N*-phenylphenacyl-aniline with zinc chloride formed the 1,3-diphenylindole.

Black and co-workers [7] have shown that *N*-trifluoroacetyl-*N*-phenacylanilines underwent cyclization leading to a series of 3-arylindoles. Two cyclising media used were a slurry of polyphosphoric

acid at 110°C and trifluoroacetic acid. Although good yields of the indoles were obtained in both media, easy isolation of the product and cleaner reactions were generally found when the cyclisations were conducted in trifluoroacetic acid. It was envisaged that cyclisation of *N,N*-diphenacylanilines with trifluoroacetic acid would lead to the generation of 1-phenacyl-3-arylindoles rather than 1-phenacyl-2-arylindoles.

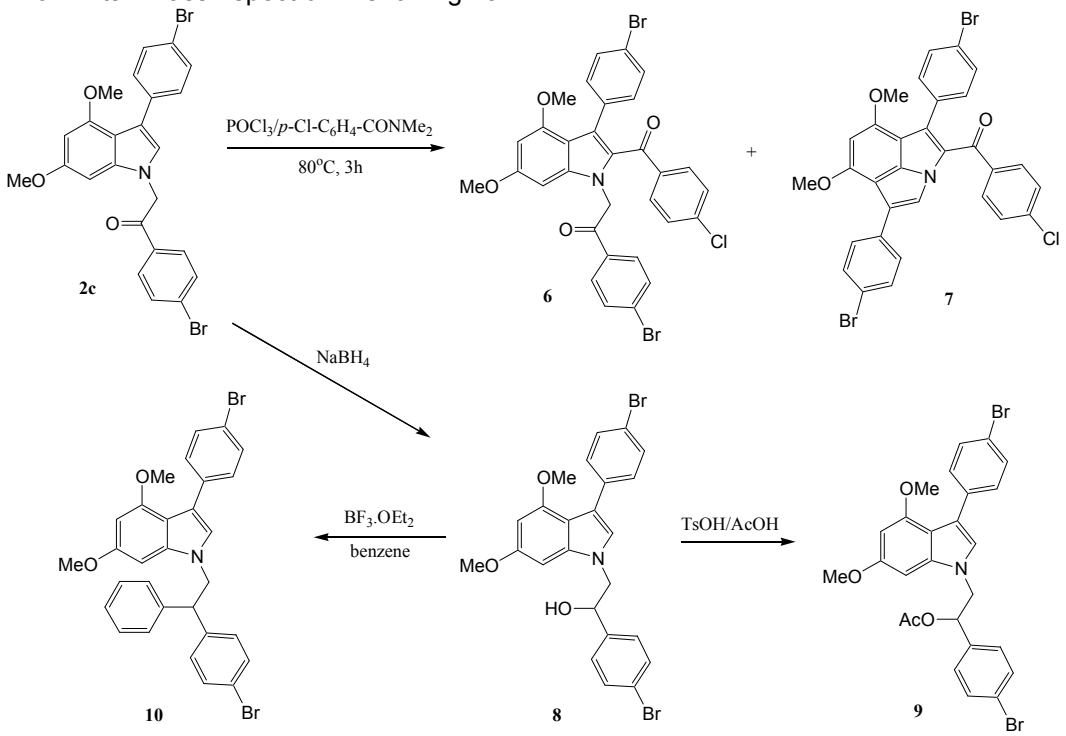
Treatment of diphenacylanilines **1b** and **1c** with trifluoroacetic acid at 70°C for 1.5h gave respectively indoles **2b** and **2c** in high yields. There was no further cyclisation observed when the reaction was further heated at reflux for 5 hours. On the other hand, the majority of starting material was still present when the reaction was conducted at room temperature.

Clear evidence for indoles **2b** and **2c** was obtained from the ^{1}H n.m.r. spectra which show typical doublets for H5 and H7 (6.19-6.28 ppm), more downfield singlets for H2 (6.85-6.89 ppm) and intense singlets of the acetyl CH_2 (5.35-5.39 ppm). In addition, the infrared spectra proved the absence of NH groups and the existence of carbonyl stretching frequencies (1700-1710 cm^{-1}).

Treatment of *N*-phenacylindole **2c** with PPA at 130°C gave a mixture of products with indolizine **5** being isolated as the major component (42%). Evidence for the indolizine structure **5** was obtained from its mass spectrum showing a molecular ion at 513 (^{81}Br, 28%) and the ^{1}H n.m.r. spectrum demonstrating the existence of two doublets at 6.43 and 6.77 ppm respectively. The same compound, indeed, was obtained by Keller [4] from the reaction of diphenacylaniline **1c** with PPA. Hence, the mechanism as proposed by Keller is consistent with this result.

Treatment of indole **2c** with 2 equivalents of phosphoryl chloride and *p*-chloro-*N,N*-dimethylbenzamide at 70°C for 2h gave only starting materials. When the reaction was conducted in more vigorous conditions using the same amount of the benzamide and a large excess of phosphoryl chloride at 100°C for 3h, the product was 2-aroylindole **6** and pyrroloindole **7** in 32 and 22% yield respectively (Scheme 1).

It was quite surprising that indole **2c** underwent benzoylation at C2, as the analogous formylation gave a good yield of the 7-carbaldehyde. Perhaps these phenomena indicated that greater steric hindrance for substitution at C7 should be encountered for the benzoylation rather than formylation. This is understandable as the chloromethyleniminium salt involved in the benzoylation should be more bulky than the intermediate participating in the formylation. The formation of pyrroloindole **7** itself presumably was assisted by the buttressing effect originating from the 2-aroyl substituent.



Scheme 1

Evidence for aroylindole **6** was given by its ^{1}H n.m.r. spectrum showing the disappearance of a singlet at 6.85 ppm corresponding to H2 of the starting indole **2c** and the presence of an additional four protons in the aromatic region. The resonances for CH_2, H5 and H7 appeared as a singlet and doublets at 5.86, 6.21 and 6.24 ppm (*J* 1.8Hz) respectively. However, aroylindole **6** could not be well characterized, and the mass spectrum showed that the compound was still contaminated with other materials having higher molecular ions.

Pyrroloindole **7** revealed a molecular ion peak at *m/z* 653 (^{81}Br, ^{37}Cl, 14%) in its mass spectrum. The ^{1}H n.m.r. spectrum showed the existence of two singlets at 6.42 and 7.98 ppm originating from H7 and H4 respectively, typical singlets for the protons of the methoxy groups (3.91 and 4.05 ppm), and multiplets between 7.06-7.78 ppm of the aromatic protons.

Attempts to generate the pyrroloindole **3c** via direct cyclisation of *N*-phenacylindole **2c**, were so far unsuccessful. It was of interest to reduce phenacylindole **2c** to the corresponding benzylic alcohol, which could be expected to generate a stabilized carbocation **11** on treatment with acid. It was hoped that this carbocation would be sufficiently reactive to react with the indole C7 to give the dihydro-pyrroloindole **12**.

Reduction of *N*-phenacylindole **2c** with sodium borohydride in a mixture of ethanol and tetrahydrofuran (1:1) at room temperature for 45 min afforded alcohol **6** in 83% yield. The reaction was simple and the crude product was pure enough for spectroscopic measurements and further reaction. The reduction could be seen to be complete when the initial yellow colour turned colourless. Evidence for alcohol **8** was given by its elemental analysis, mass and ^{1}H n.m.r. spectra.

Evidence for aroylindole **6** was given by its ^{1}H n.m.r. spectrum showing the disappearance of a singlet at 6.85 ppm corresponding to H2 of the starting indole **2c** and the presence of an additional four protons in the aromatic region. The resonances for CH_2, H5 and H7 appeared as a singlet and doublets at 5.86, 6.21 and 6.24 ppm (*J* 1.8Hz) respectively. However, aroylindole **6** could not be well characterized, and the mass spectrum showed that the compound was still contaminated with other materials having higher molecular ions.

Pyrroloindole **7** revealed a molecular ion peak at *m/z* 653 (^{81}Br, ^{37}Cl, 14%) in its mass spectrum. The ^{1}H n.m.r. spectrum showed the existence of two singlets at 6.42 and 7.98 ppm originating from H7 and H4 respectively, typical singlets for the protons of the methoxy groups (3.91 and 4.05 ppm), and multiplets between 7.06-7.78 ppm of the aromatic protons.

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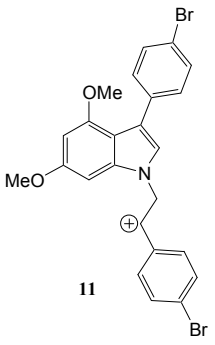

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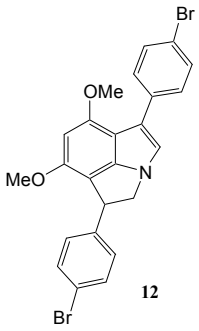

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The cyclisation of alcohol 8 to the related dihydropyrroloindole has been tried using several acids. A complex reaction mixture was the sole product when the reaction was carried out utilizing PPA. Likewise, only the corresponding ester 9 in 56% yield was obtained when alcohol 8 was heated in refluxing acetic acid in the presence of p-toluenesulfonic acid. The similar ester formation was seen when the reaction was conducted in refluxing trifluoroacetic acid.

While the two diastereotopic methylene protons of alcohol **8** appeared in the ^{1}H n.m.r. spectrum only as a doublet at 4.16 ppm (*J* 6.2Hz), those of ester **9** resonated individually and appeared as two quartets at 4.22 ppm and 4.45 ppm (*J*gem 14.6Hz, *J*vic 6.4Hz and 6.2Hz). Probably, the presence of the bulkier acetyl group retards the rotation of the ethyl C-C bond to such a rate that enables separate detection on the n.m.r. time scale.

The use of a Lewis acid such as $BF_3.OEt_2$ was also tried. Surprisingly, treatment of either alcohol **8** or ester **9** with this acid in refluxing benzene

afforded indole **10** as a result of electrophilic substitution of benzene. Indole **10** was obtained in 63% yield and its mass spectrum revealed a molecular ion at 590 (^{79}Br, 47%). Although the compound could not be obtained analytically pure, clear evidence was given by the ^{1}H n.m.r spectrum showing the presence of two doublets at 6.25 and 6.27 ppm (*J* 1.8Hz) which are typical for indole H5 and H7. In addition, the spectrum also demonstrated the existence of two doublets at 4.60 and 4.63 ppm (*J* 7.4Hz), and a triplet at 4.45 ppm (*J* 7.4Hz) corresponding to CH_2 and CH respectively.

Both alcohol **8** and ester **9** remained intact when these were treated with $BF_3.OEt_2$ in refluxing dichloromethane, chloroform or acetonitrile. Similarly, no reaction was observed when K10-clay or *p*-toluenesulfonic acid in various solvents were utilized.

CONCLUSIONS

Cyclization of *N,N*-diphenacylaniline **1b** and **1c** in trifluoroacetic acid afforded respectively phenacylindole **2b** and **2c** in high yields. Treatment of phenacylindole **2c** with polyphosphoric acid gave indolizine **5** in 42% yield. Phenacylindole **2c** reacts with the Vilsmeier aroylation reagent consisted of a mixture of phosphoryl chloride and *p*-chloro-*N,N*-dimethylbenzamide to give 2-aroylindole **6** (32%) and pyrroloindole **7** (22%). Treatment of phenacylindole **2c** with sodium borohydride gave alcohol **8** in 83% yield. Alcohol **8** reacts with *p*-toluenesulfonic acid in glacial acetic acid to give acetyl ester **9** in 56% yield. On the other hand, treatment of alcohol **8** with boron trifluoride etherate in benzene afforded indole **10** in 63% yield.

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