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Some reactions of 6,8-dimethoxypyrrolo[3,2,1-*hi*]indoles

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ABSTRACT

Two 6,8-dimethoxypyrrolo[3,2,1-*hi*]indole carboxylic esters were hydrolyzed and decarboxylated. In an investigation of their electrophilic substitutions, some pyrroloindoles were formylated using the Vilsmeier reagent, and acylated with oxalyl chloride followed by quenching with dimethylamine to give the glyoxylic amides. The electrophilic substitutions occur at the C2 or C4 position (α to the nitrogen atom) rather than the C1 or C5 position (β to the nitrogen atom). Four of the formyl and acyl products were reduced to the corresponding methanol derivatives. These compounds reacted on treatment with a range of acids, but pure products could not be separated from the complex mixtures.

1. Introduction

The synthesis of pyrrolo[3,2,1-*hi*]indoles has been achieved by the aldol cyclization of 7-formyl-*N*-indolylacetates,[1] the cyclization of *N*-phenacyl-indole-7-carbaldehydes,[1] and by dehydrogenation of a tetrahydropyrroloindole formed from a related indoline.[2] As a result of the different synthetic methods used, a variety of substituents—in addition to the two methoxy groups—appear on the pyrroloindoles. These are typically carboxylic esters, aroyl, or aryl groups. It was of particular interest to investigate the directing influences at work in substitution reaction of the various pyrroloindoles, and this paper described a selection of such reactions.

2. Results and discussion

2.1. Hydrolysis and decarboxylation of pyrroloindole carboxylic esters

It has been reported that dimethyl 4,6-dimethoxyindole-2,3-dicarboxylate undergoes hydrolysis by treatment with ethanolic potassium hydroxide to give an excellent yield of the related dicarboxylic acid.[3] However, when the reaction was conducted using 20% sodium hydroxide for a longer period of time, hydrolysis and single decarboxylation occurred to afford the corresponding 2-carboxylic acid in quantitative yield. The latter finding was in accordance with one reported by Paudler and Shin,[4] who showed that although ethyl pyrrolo[3,2,1-*hi*]indole-2-carboxylate could be hydrolyzed readily with 20% aqueous sodium hydroxide, the decarboxylation of the resulting 2-carboxylic acid to afford the unsubstituted pyrrolo[3,2,1-*hi*]indole required heating in quinoline in the presence of copper(II) oxide.

Treatment of pyrroloindoles **1** and **2** with 10 equiv of 0.5 M ethanolic potassium hydroxide at reflux for 1.5 h followed by acidification with 5% hydrochloric acid gave the related acids **3** and **4**, respectively, in very high yield (Scheme 1). The reaction was efficient and pure products were simply obtained by recrystallization from chloroform/light petroleum. In both cases, the potassium salt intermediates crystallized out on cooling. However, filtration of these salts was not the preferred work-up procedure as better yields of the acids were achieved by removal of the solvent under reduced pressure followed by dilution with water and acidification. The ^{1}H NMR spectra of pyrroloindoles **3** and **4** showed singlets for H7 (6.68 and 6.69 ppm) and H5 (7.45 and 7.73 ppm) and broad singlets for COOH (12.65 and 13.30 ppm). The singlet H2 resonance for pyrroloindole acid **3** appeared at 8.12 ppm. A significant decrease of the carbonyl stretching frequency from 1710 cm^{-1} in the ester precursor **1** to 1670 cm^{-1} in pyrroloindole acid **3** was observed in the infrared spectrum.

The decarboxylation of pyrroloindoles **3** and **4** was achieved by treatment with 4.5 equiv of copper(II) oxide in quinoline at reflux under a nitrogen atmosphere for 30 min to afford pyrroloindoles **5** and **6**, respectively, in high yield (Scheme 1). The reaction was very efficient and only a single product was observed. However, complete removal of the quinoline during work-up was important to avoid difficulties in the chromatographic purification.

The ^{1}H NMR spectra of pyrroloindoles **5** and **6** showed singlets for H7 (6.47–6.48 ppm), doublets for H5 (6.86–6.90 ppm) and doublets for H4 (7.36–7.48 ppm). In the case of pyrroloindole **5**, the

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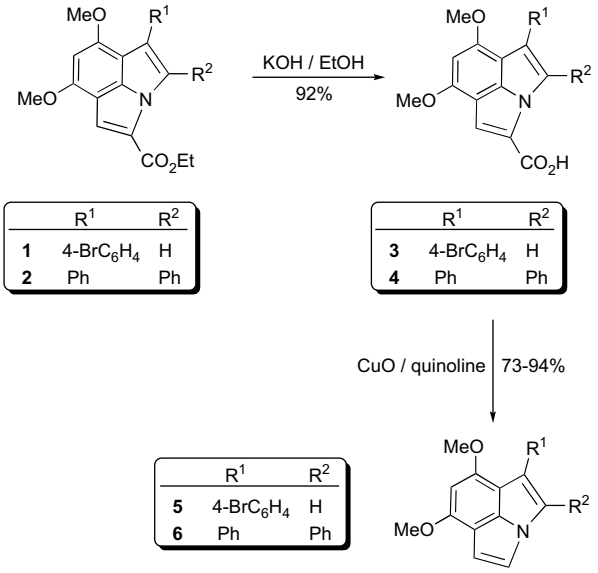
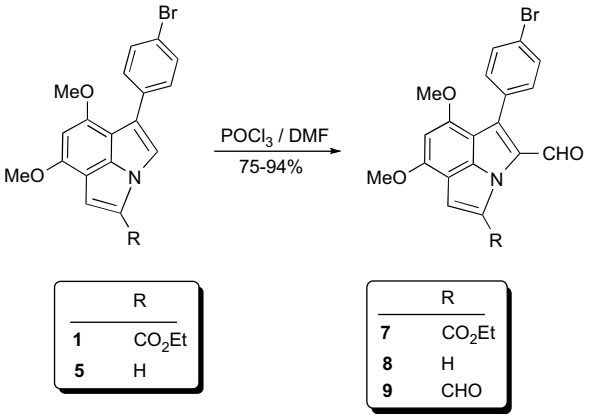


Scheme 1.



Scheme 2.

singlet resonance for H2 appeared at 7.50 ppm. An X-ray crystal structure of pyrroloindole **5** (Fig. 1) showed that the pyrroloindole ring is approximately planar, but the benzene ring of the bromophenyl substituent is twisted out of plane with the pyrroloindole ring by 31.4°. It is also interesting to note that the 8-methoxy group is directed away from the phenyl ring, which indicates that a significant degree of steric hindrance exists between it and the C1 substituent. The crystal data also showed that there is no real difference in the bond lengths of all C–C bonds of the pyrroloindole ring, and in particular there is no difference between the length of the C1–C2 and C4–C5 double bonds. In addition, no prediction about the reactive centres of pyrroloindole **5** could be made as the bond angles of the two pyrrolic rings are also similar.

2.2. Formylation of 6,8-dimethoxypyrroloindoles

Pyrroloindole ester **1** remained intact in the presence of the Vilsmeier reagent at room temperature overnight, presumably deactivated to some extent by the carbethoxy group. However, treatment of pyrroloindole ester **1** with 1.5 equiv of Vilsmeier reagent at 50 °C for 1 h gave the corresponding 2-carbaldehyde **7** in 94% yield (Scheme 2).

The reaction was clean and the crude product was sufficiently pure for further reaction. The mass spectrum of pyrroloindole carbaldehyde **7** revealed a molecular ion at 457 (^{81}Br, 17%), while the ^{1}H NMR spectrum showed the presence of three singlets at 6.37, 7.61 and 10.57 ppm corresponding to H7, H5 and CHO, respectively. Evidence for substitution at C2 rather than at C5 was obtained via an NOE experiment in which irradiation of the formyl proton gave positive NOE for the bromophenyl protons (7.53–7.62 ppm) and vice versa.

Moreover, the X-ray crystal structure of pyrroloindole carbaldehyde **7** (Fig. 2) confirmed that the formyl group is at the 2-position. It is also interesting to note that the orientation of all substituents in the crystal structure of aldehyde **7** is similar to those of the starting pyrroloindole **1**, except for the phenyl ring, which is twisted out of plane with the pyrroloindole ring by 41.8°.

The more reactive pyrroloindole **5** underwent reaction with 1.5 equiv of the Vilsmeier reagent at room temperature in 1 h to afford the corresponding 2-carbaldehyde **8** and 2,4-dicarbaldehyde **9** in 75 and 17% yields, respectively (Scheme 2). The reaction was very clean and the crude product contained only those two compounds. The mass spectrum of aldehyde **8** revealed a molecular ion at 385 (^{81}Br, 96%) and the infrared spectrum showed the presence of a carbonyl stretching frequency at 1650 cm^{-1}. The ^{1}H NMR spectrum gave clear evidence for formylation at C2 as the two typical doublets for H5 (6.85 ppm) and H4 (7.90 ppm) were still present. The resonances for H7 and the formyl proton appeared as singlets at 6.35 and 9.76 ppm, respectively. The mass spectrum of

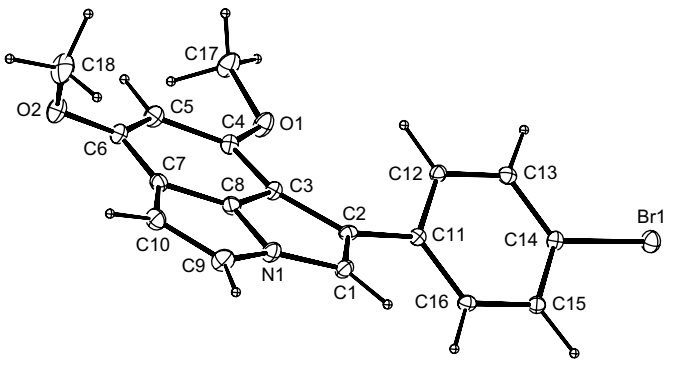


Figure 1. ORTEP diagram derived from the single-crystal X-ray analysis of compound **5**.

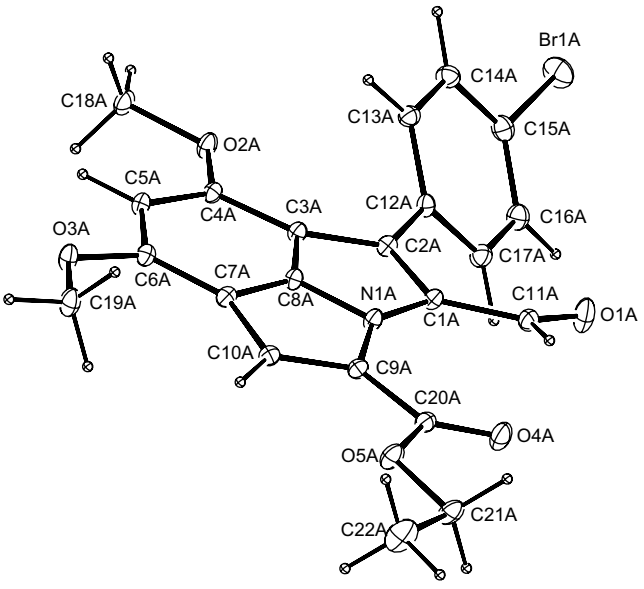
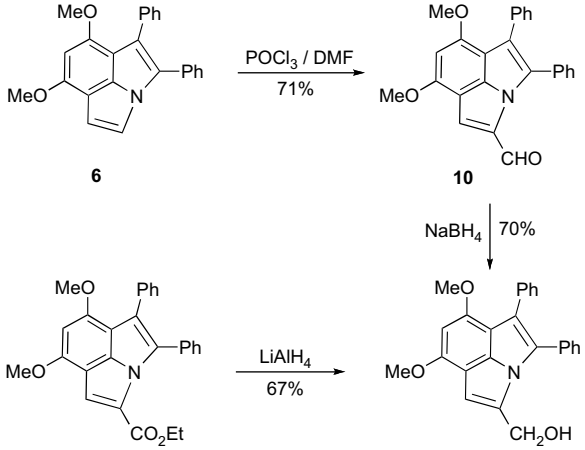


Figure 2. ORTEP diagram derived from the single-crystal X-ray analysis of compound **7**.

dialdehyde **9** revealed a molecular ion at 413 (^{81}Br, 16%), whereas the ^{1}H NMR spectrum showed four singlets at 6.45, 7.76, 9.80 and 10.92 ppm corresponding to H7, H5 and the two formyl protons, respectively.

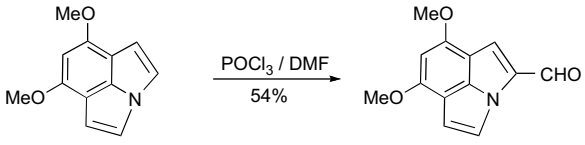
Treatment of diphenylpyrroloindole **6** with 1.5 equiv of the Vilsmeier reagent at 60 °C for 2 h gave the corresponding 4-carbaldehyde **10** in 71% yield (Scheme 3). The ^{1}H NMR spectrum showed three singlets at 6.50, 7.68 and 9.69 ppm corresponding to H7, H5 and the formyl proton, respectively. Conclusive evidence for the structure of compound **10** was obtained by its reduction to the related alcohol **11**, which was identical to the product of reduction of pyrroloindole ester **2** with lithium aluminium hydride (Scheme 3).



6 **10** **2** **11**

Scheme 3.

Treatment of the parent 6,8-dimethoxypyrroloindole **12** with 1.5 equiv of the Vilsmeier reagent at 0 °C for 1 h afforded the related 2-carbaldehyde **13** in 54% yield (Scheme 4).



12 **13**

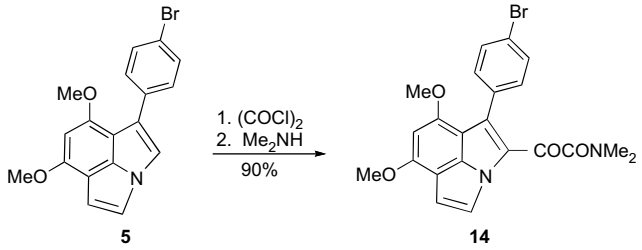
Scheme 4.

Only a moderate yield could be obtained as the reaction also produced two other products, which seemed to be the related 2,4-dialdehyde (21%) and 7-carbaldehyde (13%) on the basis of the ^{1}H NMR spectra. However, both by-products could not be well characterized and the mass spectra indicated that the compounds were contaminated with other substances having higher molecular ions. The mass spectrum of aldehyde **13** showed a molecular ion at 229 (100%) and the ^{1}H NMR spectrum showed two singlets at 6.40 and 9.83 ppm corresponding to H7 and the formyl proton, respectively. Evidence for formylation at C2 rather than at C1 was given by the NOESY ^{1}H NMR spectrum, which showed correlation between H1 and the protons of the 8-methoxy group. The resonances for H1 and H4 appeared as doublets at 7.51 and 7.82 ppm, respectively, since these were coupled to H5 arising as a doublet of doublets at 6.86 ppm. This latter proton gave two correlations in the NOESY spectrum, resulting from its interaction with H4 and the protons of the 6-methoxy group. The NOESY spectrum also displayed a single correlation for H4 originating from its interaction with H5. The presence of a long range coupling between H1 and H5, which involves seven atoms, was interesting. Furthermore, it is worth mentioning that the NOESY spectrum of pyrroloindole **13** provides a useful basis for the assignment of the resonances for H2, H4 and H5 of related pyrroloindoles.

2.3. Acylation of 6,8-dimethoxypyrroloindoles with oxalyl chloride

The reactions of activated indoles give rise to useful products and also involve subtle regiochemistry, controlled to some extent by solvent.[5–7] It was therefore of interest to investigate the reaction of pyrroloindoles with oxalyl chloride, with the aim of determining the reactive centres of these molecules.

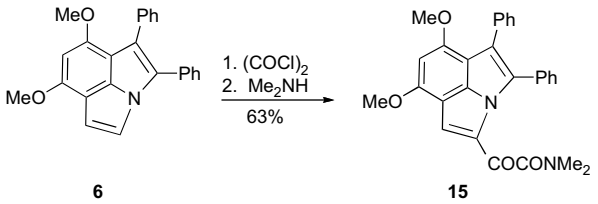
Treatment of pyrroloindole **5** with 2 equiv of oxalyl chloride in benzene at room temperature for 1.5 h followed by addition of excess dimethylamine gave the related 2-glyoxylamide **14** in 90% yield: no other by-product was detected (Scheme 5).



5 **14**

Scheme 5.

This is interesting as the related formylation also yielded 2,4-dialdehyde **9** in addition to 2-aldehyde **8**. Presumably this reflects the stronger electron withdrawing capacity of the glyoxyloyl group compared to the iminium ion functionality, as well as a greater steric footprint. The ^{1}H NMR spectrum shows the two typical doublets for H4 and H5 at 7.95 and 6.85 ppm, respectively, and the singlet resonance for H7 at 6.30 ppm. The ^{13}C NMR spectrum showed signals at 166.1 and 183.4 ppm corresponding to the two glyoxylamide carbonyl carbons, and the mass spectrum revealed a molecular ion at 456 (^{81}Br, 25%). More vigorous conditions were required for the less reactive diphenylpyrroloindole **6**, and treatment of this compound with 2 equiv of oxalyl chloride in benzene at reflux for 3 h, followed by addition of excess dimethylamine afforded the related 4-glyoxylamide **15** in 63% yield (Scheme 6).



6 **15**

Scheme 6.

Pyrroloindole **15** revealed a molecular ion at 453 (100%) in its mass spectrum and the infrared spectrum confirmed the presence of carbonyl groups. The ^{1}H NMR spectrum of glyoxylamide **15** showed singlets at 7.55 and 6.37 ppm for H5 and H7, respectively. An X-ray crystal structure of pyrroloindole **15** (Fig. 3) established that the glyoxylamide group is at the 4-position. Again, the crystal data showed that the pyrroloindole ring is approximately planar and that the 1- and 2-phenyl rings are out of plane with the pyrroloindole ring by 41.2° and 55.8°, respectively.

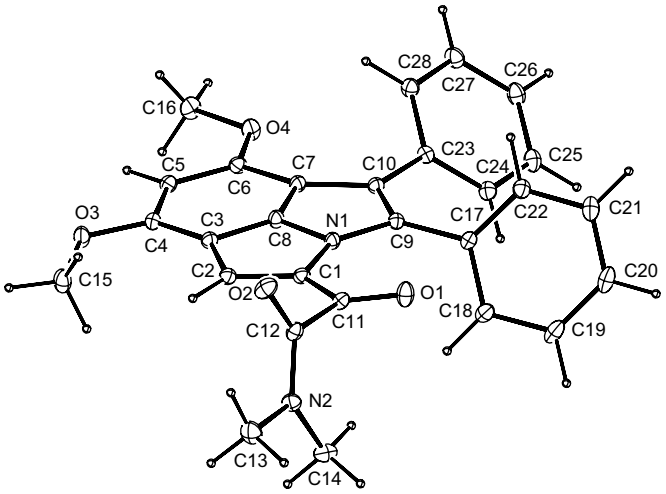
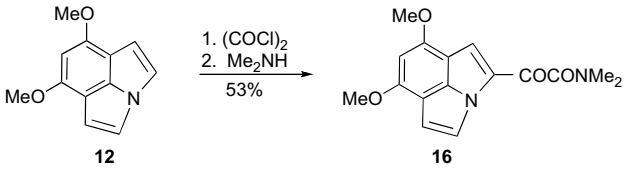


Figure 3. ORTEP diagram derived from the single-crystal X-ray analysis of compound **15**.

Pyrroloindole **12** also underwent substitution with oxalyl chloride and dimethylamine under similar conditions to afford 2-glyoxylamide **16** in 53% yield (Scheme 7).



Scheme 7.

Only a moderate yield was obtained as the reaction also formed some minor products, which were not isolated. The ^{1}H NMR spectrum of glyoxylamide **16** showed a singlet at 6.39 ppm corresponding to H7, and doublet resonances for H1 and H4 at 7.61 ppm and 7.88 ppm, respectively, resulting from coupling with H5, which appeared as a doublet of doublets at 6.88 ppm. Again, the unusual coupling between H1 and H5, which involves seven atoms, as previously seen in the related 2-formyl compound was observed in the ^{1}H NMR spectrum of glyoxylamide **16**. An X-ray crystal structure of pyrroloindole **16** (Fig. 4) confirmed that the glyoxylamide group is at the 2-position. It was also interesting to note that the two carbonyl groups of the glyoxylamide substituent of pyrroloindole **16** are oriented at 125.2° to each other, as compared to an orientation of 93.7° for those in glyoxylamide **15**.

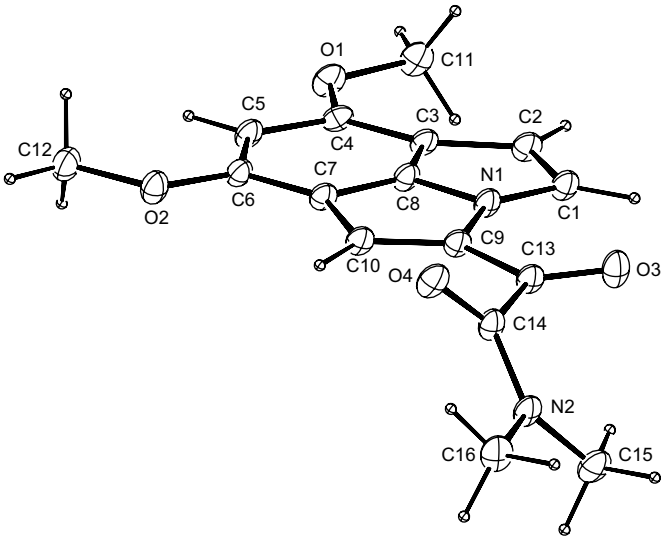
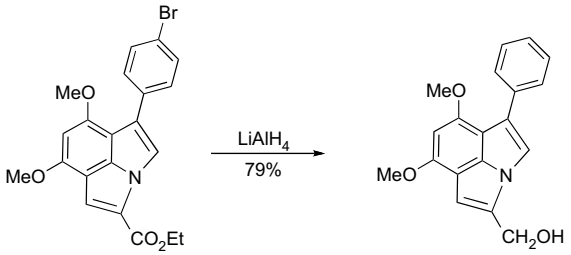


Figure 4. ORTEP diagram derived from the single-crystal X-ray analysis of compound **16**.

2.4. Formation of hydroxymethyl-6,8-dimethoxypyrroloindoles and their treatment with acid

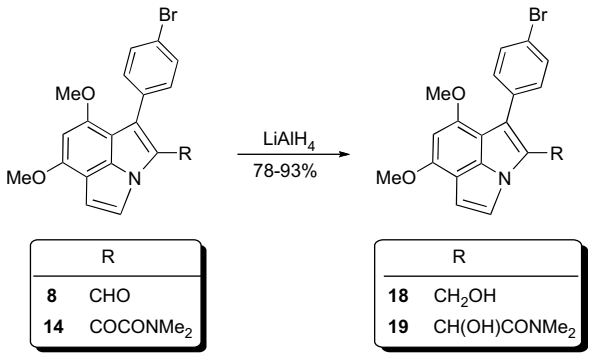
It has been shown that 2- and 7-hydroxymethyl-4,6-dimethoxyindoles undergo reaction under a variety of acidic conditions to give interesting macrocyclic structures such as calixindoles.[8,9] It was therefore of interest to obtain similar hydroxymethylpyrroloindoles and investigate their behaviour with acids.

Four representative examples were chosen. Reduction of diphenylpyrroloindole-4-carbaldehyde **10** with sodium borohydride in a mixture of absolute ethanol and tetrahydrofuran, or reduction of the related carboxylic ester **2** with lithium aluminium hydride gave 4-methanol **11** in approximately 70% yield (Scheme 3). Similar lithium aluminium hydride reduction of pyrroloindole ester **1** resulted in debromination, and thus the formation of 1-phenylpyrroloindole-4-methanol **17** in 79% yield (Scheme 8).



Scheme 8.

Treatment of pyrroloindole-2-carbaldehyde **8** and the corresponding glyoxylamide **14** with sodium borohydride gave the corresponding pyrroloindole-2-methanols **18** and **19** in 93 and 78% yields, respectively (Scheme 9).



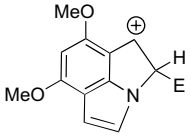
Scheme 9.

These four pyrroloindole methanols were submitted to a wide range of acidic conditions suitable for the formation of structures similar to the calixindoles. While there were some spectroscopic indications of the formation of interesting, possibly macrocyclic structures, pure compounds could not be obtained from the complex reaction mixtures.

3. Conclusions

The main conclusion that can be drawn from the formylation and acylation reactions of a range of pyrrolo[3,2,1-*hi*]indoles is that

the most reactive centre is at C2 or at C4, rather than at C1 or C5. Thus the pyrroloindoles behave like pyrroles, which undergo 2-substitution, rather than indoles, which undergo 3-substitution. Electrophilic attack α to the nitrogen atom would generate cation **20**, which would show greater resonance stability than cation **21**, which would be formed from electrophilic attack β to the nitrogen atom. Cation **20** is benzylic, and in the case of a 1-arylpyrroloindole even doubly benzylic, whereas cation **21** resembles an anti-aromatic cyclopentadienyl cation.



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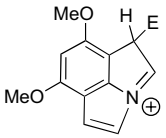

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4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed by Dr. H. P. Pham at UNSW. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC300F (300 MHz) or a Bruker AM500 (500 MHz) spectrometer. Mass spectra were recorded on either a VG Quattro MS (EI) or a Finnegan MAT (MALDI). Infrared spectra were recorded with a Perkin Elmer 298 IR spectrometer. Ultraviolet–visible spectra were recorded using a Hitachi U-3200 spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 $60GF_{254}$.

4.2. 1-(4′-Bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-*hi*]indole-4-carboxylic acid (3)

A mixture of pyrroloindole **1** (0.40 g, 0.93 mmol) in 0.5 M ethanolic potassium hydroxide (20 mL, 10 mmol) was heated at reflux for 1.5 h. The mixture was allowed to cool, then the solvent removed under reduced pressure. The residue was diluted with water (30 mL), then acidified with 5% hydrochloric acid. The resulting precipitate was filtered, washed with water and dried to afford pyrroloindole carboxylic acid **3** as a yellow solid (0.34 g, 92%), mp 265–267 °C (from chloroform/light petroleum). Found: C, 56.7; H, 3.8; N, 3.4. $C_{19}H_{14}BrNO_4$ requires C, 57.0; H, 3.8; N, 3.4%. λ_{max} 210 nm (ε 29,700 cm^{-1} M^{-1}), 244 (21,500), 277 (19,600), 328 (30,700). ν_{max} 1670, 1645, 1580, 1505, 1345, 1300, 1210, 1010, 745 cm^{-1}. ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 4.09 and 4.27 (6H, 2s, OMe), 6.69 (1H, s, H7), 7.67 and 7.98 (4H, 2d, *J* 7.9 Hz, ArH), 7.73 (1H, s, H5), 8.12 (1H, s, H2), 12.81–14.10 (1H, br s, COOH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 56.6 and 58.1 (OMe), 95.8 (C7), 115.9 (C5), 119.3 (C2), 129.7 and 131.4 (ArCH), 101.6, 101.9, 119.7, 125.0, 126.2, 133.6, 140.4, 157.8 and 158.1 (ArC), 162.2 (COOH). Mass spectrum: *m*/*z* 402 (M+1, ^{81}Br, 18%), 401 (M, ^{81}Br, 98), 399 (M, ^{79}Br, 100), 357 (35), 355 (37), 305 (42), 261 (21), 201 (22), 190 (27), 95 (28), 43 (33).

4.3. 6,8-Dimethoxy-1,2-diphenylpyrrolo[3,2,1-*hi*]indole-4-carboxylic acid (4)

A mixture of pyrroloindole **2** (0.50 g, 1.18 mmol) in 0.5 M ethanolic potassium hydroxide (23.5 mL, 11.76 mmol) was heated at reflux for 1 h. Further treatment was according to the method of preparation of compound **1** to give pyrroloindole carboxylic acid **4** as a yellow solid (0.43 g, 92%), mp 217–219 °C (from chloroform/light petroleum). Found: C, 73.6; H, 5.1; N, 3.2. $C_{25}H_{19}NO_4 \cdot 0.6H_2O$ requires C, 73.6; H, 5.0; N, 3.4%. λ_{max} 212 nm (ε 13,900 cm^{-1} M^{-1}), 247 (14,300), 327 (17,600). ν_{max} 3370, 1680, 1660, 1330, 1260, 1215, 1000, 720 cm^{-1}. ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 3.95 and 4.27 (6H, 2s, OMe), 6.68 (1H, s, H7), 7.23–7.39 (10H, m, ArH), 7.45 (1H, s, H5), 12.65 (1H, br s, COOH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 56.6 and 58.2 (OMe), 95.7 (C7), 117.3 (C5), 126.6, 127.6, 127.7, 128.0, 130.7 and 131.5 (ArCH), 101.6, 103.3, 123.0, 128.3, 132.4, 133.4, 134.6, 140.0, 157.5 and 157.8 (ArC), 161.4 (COOH). Mass spectrum: *m*/*z* 398 (M+1, 24%), 397 (M, 100), 353 (33), 105 (24), 69 (25).

4.4. 1-(4′-Bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-*hi*]indole (5)

Copper(II) oxide (0.30 g, 3.83 mmol) was suspended in a solution of pyrroloindole **3** (0.34 g, 0.85 mmol) in quinoline (10 mL) under nitrogen. The mixture was heated at reflux for 30 min, then allowed to cool and diluted with chloroform (70 mL). The resulting mixture was washed with 5% hydrochloric acid (3×40 mL) followed by water, dried over magnesium sulfate and evaporated to leave a brown oil. Flash chromatography and elution with dichloromethane/light petroleum (2:3) afforded pyrroloindole **5** as a white solid (0.22 g, 73%), mp 126–128 °C. Found: C, 60.9; H, 4.1; N, 3.8. $C_{18}H_{14}BrNO_2$ requires C, 60.7; H, 4.0; N, 3.9%. λ_{max} 213 nm (ε 9100 cm^{-1} M^{-1}), 248 (9100), 280 (9900), 309 (10,500). ν_{max} 1660, 1595, 1520, 1340, 1230, 1180, 1090, 725 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 3.96 and 4.20 (6H, 2s, OMe), 6.47 (1H, s, H7), 6.86 (1H, d, *J* 3.1 Hz, H5), 7.36 (1H, d, *J* 3.1 Hz, H4), 7.50 (1H, s, H2), 7.52 and 7.76 (4H, 2d, *J* 8.5 Hz, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 56.2 and 57.7 (OMe), 95.1 (C7), 109.1 (C5), 117.4 (C2), 121.4, 129.4 and 131.4 (ArCH), 102.0, 102.5, 120.2, 125.8, 134.1, 140.7, 155.7 and 155.9 (ArC). Mass spectrum: *m*/*z* 358 (M+1, ^{81}Br, 19%), 357 (M, ^{81}Br, 98), 355 (M, ^{79}Br, 100), 261 (57), 246 (24), 190 (28), 101 (28), 95 (31). Crystals for X-ray determination were obtained by recrystallization from chloroform/ethanol.

4.5. 4,6-Dimethoxy-1,2-diphenylpyrrolo[3,2,1-*hi*]indole (6)

A mixture of copper(II) oxide (0.35 g, 4.31 mmol), pyrroloindole **4** (0.38 g, 0.96 mmol) and quinoline (20 mL) was heated at reflux under nitrogen for 30 min, and further treatment was in accordance with the method of preparation of compound **5**. Flash chromatography and elution with light petroleum/dichloromethane (1:1) afforded pyrroloindole **6** as a white solid (0.32 g, 94%), mp 162–164 °C. Found: C, 81.7; H, 5.6; N, 3.8. $C_{24}H_{19}NO_2$ requires C, 81.6; H, 5.4; N, 4.0%. λ_{max} 209 nm (ε 13,200 cm^{-1} M^{-1}), 246 (7900), 316 (8100). ν_{max} 1650, 1590, 1505, 1345, 1325, 1230, 1210, 1180, 1130, 700 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 3.89 and 4.23 (6H, 2s, OMe), 6.48 (1H, s, H7), 6.90 (1H, d, *J* 3.1 Hz, H5), 7.48 (1H, d, *J* 3.1 Hz, H4), 7.26–7.58 (10H, m, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 56.4 and 57.7 (OMe), 95.4 (C7), 108.7 (C5), 121.2 (C4), 126.4, 127.5, 127.9, 128.6, 129.4 and 130.8 (ArCH), 102.6, 104.6, 121.8, 131.0, 132.1, 135.1, 139.4, 155.5 and 155.9 (ArC). Mass spectrum: *m*/*z* 354 (M+1, 24%), 353 (M, 100), 338 (21), 84(22).

4.6. Ethyl 1-(4′-bromophenyl)-6,8-dimethoxy-2-formylpyrrolo[3,2,1-*hi*]indole-4-carboxylate (7)

A cooled solution of phosphoryl chloride (0.06 mL, 0.63 mmol) in dry dimethylformamide (0.5 mL) was added dropwise into a cooled solution of pyrroloindole **1** (0.18 g, 0.42 mmol) in dry dimethylformamide (3 mL). The mixture was stirred at 0 °C for 15 min, then at 50 °C for 1 h, cold water (10 mL) was added, followed by 2 M sodium hydroxide until the mixture was strongly basic. The resulting suspension was stirred at room temperature overnight, and the precipitate filtered, washed with water and

dried. The solid was recrystallized from dichloromethane/light petroleum to give formylpyrroloindole **7** as a yellow solid (0.18 g, 94%), mp 207–210 °C. Found: C, 52.7; H, 4.2; N, 2.6. $C_{22}H_{18}BrNO_5 \cdot 2.4H_2O$ requires C, 52.9; H, 4.6; N, 2.8%. λ_{max} 209 nm (ε 16,600 $cm^{-1}\,M^{-1}$), 226 (15,400), 247 (14,800), 269 (12,600), 363 (17,500). ν_{max} 1710, 1660, 1590, 1440, 1335, 1265, 1220, 1190, 1135, 750 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.43 (3H, t, *J* 7.2 Hz, Me), 3.85 and 4.23 (6H, 2s, OMe), 4.44 (2H, q, *J* 7.2 Hz, CH_2), 6.37 (1H, s, H7), 7.53–7.62 (4H, m, ArH), 7.61 (1H, s, H5), 10.57 (1H, s, CHO). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.3 (Me), 56.2 and 58.3 (OMe), 61.4 (CH_2), 96.4 (C7), 117.7 (C5), 130.6 and 132.8 (ArCH), 101.1, 103.7, 122.7, 128.4, 130.1, 131.4, 133.5, 160.5, 161.2 and 161.4 (ArC), 183.6 (CO), 196.2 (CHO). Mass spectrum: *m*/*z* 457 (M, ^{81}Br, 17%), 455 (M, ^{79}Br, 17), 428 (15), 426 (15), 376 (16), 331 (22), 330 (100), 230 (19), 202 (22), 201 (30), 188 (43), 174 (32). Crystals for X-ray determination were obtained from chloroform/ethanol.

4.7. Formylation of 1-(4′-bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-*hi*]indole (5)

A cooled solution of phosphoryl chloride (0.06 mL, 0.63 mmol) in dry dimethylformamide (0.50 mL) was added dropwise into an ice-cooled solution of pyrroloindole **5** (0.15 g, 0.42 mmol) in dry dimethylformamide (5.0 mL). The mixture was stirred at 0 °C for 1 h, then at room temperature for another 1 h and further treatment was in accordance with the method of preparation of compound **7**. Thin layer chromatography and elution with dichloromethane gave two products.

*4.7.1. 1-(4′-Bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-hi]indole-2-carbaldehyde (**8**)*

Monoaldehyde **8** was isolated as a bright yellow solid (0.12 g, 75%), mp 209–212 °C. Found: C, 59.6; H, 3.9; N, 3.5. $C_{19}H_{14}BrNO_3$ requires C, 59.4; H, 3.8; N, 3.7%. λ_{max} 211 nm (ε 5700 $cm^{-1}\,M^{-1}$), 253 (4400), 362 (5400). ν_{max} 1650, 1590, 1320, 1235, 1210, 1135, 800 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.88 and 4.23 (6H, 2s, OMe), 6.35 (1H, s, H7), 6.85 (1H, d, *J* 3.1 Hz, H5), 7.58 and 7.61 (4H, 2d, *J* 8.8 Hz, ArH), 7.90 (1H, d, *J* 3.1 Hz, H4), 9.76 (1H, s, CHO). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 56.1 and 58.2 (OMe), 96.4 (C7), 101.5, 103.5, 122.9, 129.1, 131.4, 136.4, 140.7, 158.6 and 160.2 (ArC), 109.5 (C5), 124.1 (C4), 131.2 and 132.4 (ArCH), 181.5 (CHO). Mass spectrum: *m*/*z* 386 (M+1, ^{81}Br, 18%), 385 (M, ^{81}Br, 96), 384 (M+1, ^{79}Br, 52), 383 (M, ^{79}Br, 100), 382 (36), 289 (38), 246 (27), 190 (49), 152 (52), 69 (66).

*4.7.2. 1-(4′-Bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-hi]indole-2,4-dicarbaldehyde (**9**)*

Dialdehyde **9** was obtained as a pale yellow solid (30 mg, 17%), mp 296–298 °C. Found: C, 58.0; H, 3.7; N, 3.1. $C_{20}H_{14}BrNO_4$ requires C, 58.3; H, 3.4; N, 3.4%. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.93 and 4.29 (6H, 2s, OMe), 6.45 (1H, s, H7), 7.56 and 7.63 (4H, d, *J* 8.5 Hz, ArH), 7.76 (1H, s, H5), 9.80 and 10.92 (2H, 2s, CHO). Mass spectrum: *m*/*z* 413 (M, ^{81}Br, 16%), 411 (M, ^{79}Br, 15), 333 (20), 332 (100), 289 (47), 274 (22), 246 (28), 201 (23), 190 (41), 166 (41), 123 (22), 69 (28).

4.8. 6,8-Dimethoxy-1,2-diphenylpyrrolo[3,2,1-*hi*]indole-4-carbaldehyde (10)

A cooled solution of phosphoryl chloride (0.14 mL, 1.49 mmol) in dry dimethylformamide (0.5 mL) was added dropwise into an ice-cooled solution of pyrroloindole **6** (0.35 g, 0.99 mmol) in dry dimethylformamide (5.0 mL). The mixture was stirred at 0 °C for 15 min, then warmed at 60 °C for 2 h and further treatment was according to the method of preparation of compound **7**. Flash chromatography and elution with dichloromethane afforded formylpyrroloindole **10** as a yellow solid (0.27 g, 71%), mp 189–191 °C. Found: C, 78.5; H, 5.3; N, 3.4. $C_{25}H_{19}NO_3$ requires C, 78.7; H, 5.0; N, 3.7%. λ_{max} 213 nm (ε 12,700 $cm^{-1}\,M^{-1}$), 258 (13,600), 294 (12,600), 340 (16,200), 359 (16,700). ν_{max} 1680, 1650, 1585, 1340, 1210, 1070, 1130, 725, 700 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.92 and 4.21 (6H, 2s, OMe), 6.50 (1H, s, H7), 7.22–7.48 (10H, m, ArH), 7.68 (1H, s, H5), 9.69 (1H, s, CHO). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 56.3 and 57.8 (OMe), 95.5 (C7), 118.3 (C5), 126.4, 127.6, 128.3, 128.5, 130.5 and 131.1 (ArCH), 102.8, 104.0, 123.4, 132.1, 132.7, 134.1, 135.7, 141.0, 158.4 and 159.2 (ArC), 180.5 (CHO). Mass spectrum: *m*/*z* 382 (M+1, 27%), 381 (M, 100), 105 (62), 77 (33), 57 (27).

4.9. 6,8-Dimethoxypyrrolo[3,2,1-*hi*]indole-2-carbaldehyde (13)

Pyrroloindole **12** (0.21 g, 1.05 mmol) was dissolved in dry dimethylformamide (4.0 mL), then reacted with phosphoryl chloride (0.15 mL, 1.57 mmol) in dry dimethylformamide (0.5 mL) at 0 °C according to the method of preparation of compound **7**. The resulting solid was purified by means of thin layer chromatography, and elution with ethyl acetate in dichloromethane (1:9) gave formylpyrroloindole **13** as a yellow solid (0.13 g, 54%), mp 135–138 °C. Found: C, 67.8; H, 5.2; N, 5.8. $C_{13}H_{11}NO_3$ requires C, 68.1; H, 4.8; N, 6.1%. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 4.09 and 4.19 (6H, 2s, OMe), 6.40 (1H, s, H7), 6.86 (1H, dd, *J* 3.1 and 1.3 Hz, H5), 7.51 (1H, d, *J* 1.3 Hz, H1), 7.82 (1H, d, *J* 3.1 Hz, H4), 9.83 (1H, s, CHO). Mass spectrum: *m*/*z* 229 (M, 100%), 214 (22), 186 (30), 171 (23).

4.10. *N,N*-Dimethyl{1-(4′-bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-*hi*]indol-2-yl}glyoxylamide (14)

Oxalyl chloride (0.06 mL, 0.67 mmol) was added dropwise into a solution of pyrroloindole **5** (0.12 g, 0.34 mmol) in dry benzene (7.0 mL) under nitrogen. The mixture was stirred at room temperature for 1 h, then aqueous dimethylamine (40%, 0.51 mL, 4.02 mmol) was added and the stirring continued for 30 min. The mixture was diluted with chloroform (70 mL), then washed with water, dried over magnesium sulfate and evaporated to leave a sticky yellow oil. Preparative thin layer chromatography and elution with dichloromethane in ethyl acetate (1:3) afforded glyoxylamide **14** as a yellow solid (0.14 g, 90%), mp 89–91 °C. Found: C, 52.9; H, 4.4; N, 5.3. $C_{22}H_{19}BrN_2O_4 \cdot 2.5H_2O$ requires C, 52.8; H, 4.8; N, 5.6%. λ_{max} 213 nm (ε 7300 $cm^{-1}\,M^{-1}$), 257 (7900), 340 (9400), 386 (10,600), 391 (10,600). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.50 and 2.76 (6H, 2s, NMe_2), 3.78 and 4.23 (6H, 2s, OMe), 6.30 (1H, s, H7), 6.85 (1H, d, *J* 3.1 Hz, H5), 7.42 and 7.55 (4H, 2d, *J* 8.2 Hz, ArH), 7.95 (1H, d, *J* 3.1 Hz, H4). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 33.4 and 36.8 (NMe_2), 56.1 and 58.3 (OMe), 96.6 (C7), 109.4 (C5), 124.8 (C4), 130.4 and 132.2 (ArCH), 101.3, 122.7, 126.4, 131.6, 132.1, 134.2, 140.6, 158.9 and 160.6 (ArC), 166.1 (*C*OCONMe$_2$), 183.4 (*C*OCONMe$_2$). Mass spectrum: *m*/*z* 456 (M, ^{81}Br, 25%), 454 (M, ^{79}Br, 25), 385 (22), 383 (82), 382 (86), 304 (38), 303 (100), 288 (39), 260 (31), 202 (30), 188 (28), 72 (84).

4.11. *N,N*-Dimethyl(6,8-dimethoxy-1,2-diphenylpyrrolo[3,2,1-*hi*]indol-4-yl)glyoxylamide (15)

Oxalyl chloride (0.05 mL, 0.56 mmol) was added dropwise into a solution of pyrroloindole **6** (0.10 g, 0.28 mmol) in dry benzene (8 mL) under nitrogen. The mixture was heated at reflux for 3 h, then allowed to cool, aqueous dimethylamine (40%, 0.43 mL, 3.36 mmol) was added and further treatment was according to the method of preparation of compound **14**. Thin layer chromatography and elution with ethyl acetate in dichloromethane (1:9) afforded glyoxylamidopyrroloindole **15** as a yellow solid (80 mg, 63%), mp

181–183 °C. Found: C, 74.3; H, 5.5; N, 6.0. $C_{28}H_{24}N_2O_4$ requires C, 74.3; H, 5.4; N, 6.2%. λ_{max} 212 nm (ε 7600 $cm^{-1}\,M^{-1}$), 227 (7300), 256 (7300), 279 (6600), 363 (9400). ν_{max} 1645, 1580, 1340, 1220, 1180, 1130, 1035, 855, 740 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.84 and 2.94 (6H, 2s, NMe_2), 3.81 and 4.09 (6H, 2s, OMe), 6.37 (1H, s, H7), 7.11–7.27 (10H, m, ArH), 7.55 (1H, s, H5). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 34.4 and 37.4 (NMe_2), 56.4 and 57.8 (OMe), 95.2 (C7), 122.8 (C5), 126.3, 127.5, 127.6, 128.1, 130.7 and 131.4 (ArCH), 102.9, 103.9, 123.6, 132.3, 132.7, 134.2, 134.3, 141.5, 158.6 and 159.7 (ArC), 166.8 (*C*OCONMe$_2$), 180.4 (*C*OCONMe$_2$). Mass spectrum (ES): 475 (M+Na^+, 27%), 453 (M, 100), 380 (23). Crystals for X-ray determination were obtained from chloroform/ethanol.

4.12. *N,N*-Dimethyl(6,8-dimethoxypyrrolo[3,2,1-*hi*]indol-2-yl)glyoxylamide (16)

Pyrroloindole **12** (100 mg, 0.50 mmol) in dry benzene (6 mL) was reacted with oxalyl chloride (0.08 mL, 0.94 mmol) and aqueous dimethylamine (40%, 0.64 mL, 5.01 mmol) according to the method of preparation of compound **14**. Thin layer chromatography and elution with ethyl acetate in dichloromethane (1:4) afforded glyoxylamide **16** as a yellow solid (80 mg, 53%), mp 148–150 °C. Found: C, 64.0; H, 5.6; N, 9.0. $C_{16}H_{16}N_2O_4$ requires C, 64.0; H, 5.4; N, 9.3%. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.09 and 3.13 (6H, 2s, NMe_2), 4.09 and 4.20 (6H, 2s, OMe), 6.39 (1H, s, H7), 6.88 (1H, dd, *J* 1.0 and 3.1 Hz, H5), 7.61 (1H, d, *J* 1.0 Hz, H1), 7.88 (1H, d, *J* 3.1 Hz, H4). Mass spectrum: *m*/*z* 300 (M, 24%), 229 (20), 228 (100), 200 (22), 72 (37). Crystals for X-ray determination were obtained from chloroform/ethanol.

4.13. 6,8-Dimethoxy-4-hydroxymethyl-1-phenylpyrrolo[3,2,1-*hi*]indole (17)

Bromophenylpyrroloindole **1** (0.14 g, 0.33 mmol) was added into an ice-cooled suspension of lithium aluminium hydride (0.13 g, 3.30 mmol) in dry tetrahydrofuran under nitrogen. The mixture was stirred at 0 °C for 1 h, then at room temperature for another 2 h and then excess hydride was destroyed by cautiously adding cold water (5 mL). The solvent was removed under reduced pressure, and the residue extracted with dichloromethane (3×60 mL). The combined organic layers were washed with water, dried over magnesium sulfate, evaporated and recrystallized from dichloromethane/light petroleum to afford the hydroxymethylpyrroloindole **17** as white needles (0.08 g, 79%), mp 167–170 °C. Found: C, 74.4; H, 5.8; N, 4.4. $C_{19}H_{17}NO_3$ requires C, 74.3; H, 5.6; N, 4.6%. λ_{max} 212 nm (ε 16,000 $cm^{-1}\,M^{-1}$), 241 (12,900), 267 (11,400), 309 (15,500). ν_{max} 3355, 1660, 1610, 1515, 1360, 1340, 1230, 1160, 1010, 740 cm^{-1}. ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 4.04 and 4.21 (6H, 2s, OMe), 4.88 (2H, d, *J* 5.6 Hz, CH_2), 5.59 (1H, t, *J* 5.6 Hz, OH), 6.59 (1H, s, H7), 6.91 (1H, s, H5), 7.35 (1H, t, *J* 7.4 Hz, H4′), 7.51 (2H, t, *J* 7.4 Hz, H3′, H5′), 8.01 (2H, d, *J* 7.4 Hz, H2′, H6′), 8.03 (1H, s, H2). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 56.0 and 56.4 (OMe), 58.0 (CH_2), 95.1 (C7), 106.2 (C5), 118.0 (C2), 126.3, 127.4 and 128.5 (ArCH), 102.1, 125.3, 132.3, 135.0, 137.3, 140.3, 155.0 and 155.3 (ArC). Mass spectrum: *m*/*z* 308 (M+1, 20%), 307 (M, 100), 290 (60), 69 (22), 43 (23).

4.14. 4,6-Dimethoxy-1,2-diphenyl-4-hydroxymethyl-pyrrolo[3,2,1-*hi*]indole (11)

4.14.1. Method A

Pyrroloindole **2** (0.20 g, 0.47 mmol) was added into a cooled suspension of lithium aluminium hydride (90 mg, 2.35 mmol) in dry tetrahydrofuran (8.0 mL) under nitrogen. The mixture was stirred at 0 °C for 1.5 h, and further treatment was according to method A for the preparation of compound **17** to give hydroxymethylpyrroloindole **11** as a white solid (0.12 g, 67%), mp 158–160 °C. Found: C, 77.7; H, 5.6; N, 3.6. $C_{25}H_{21}NO_3\cdot 0.1H_2O$ requires C, 77.9; H, 5.6; N, 3.6%. λ_{max} 212 nm (ε 1600 $cm^{-1}\,M^{-1}$), 244 (1400), 311 (1500). ν_{max} 3290, 1655, 1600, 1505, 1335, 1210, 1120, 700 cm^{-1}. ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 3.93 and 4.23 (6H, 2s, OMe), 4.45 (2H, d, *J* 5.6 Hz, CH_2), 5.22 (1H, t, *J* 5.6 Hz, OH), 6.59 (1H, s, H7), 6.96 (1H, s, H5), 7.24–7.58 (10H, m, ArH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 56.1 (CH_2), 56.3 and 57.8 (OMe), 95.1 (C7), 107.4 (C5), 126.3, 127.8, 128.4, 128.5, 130.4 and 130.9 (ArCH), 101.9, 103.5, 121.8, 128.4, 131.8, 134.7, 138.7, 139.2, 154.9 and 155.1 (ArC). Mass spectrum: *m*/*z* 384 (M, 34%), 383 (100), 366 (27), 139 (27).

4.14.2. Method B

Sodium borohydride (4 0 mg, 1.05 mmol) was added into a cooled solution of pyrroloindole **10** (0.10 g, 0.26 mmol) in a mixture of absolute ethanol and tetrahydrofuran (1:1, 8 mL). The mixture was stirred at 0 °C for 30 min, then at room temperature for another 15 min. The solvent was removed and the residue diluted with water to give hydroxymethylpyrroloindole **11** as a white solid (70 mg, 70%).

4.15. 1-(4′-Bromophenyl)-6,8-dimethoxy-2-hydroxy-methylpyrrolo[3,2,1-*hi*]indole (18)

A solution of formylpyrroloindole **8** (0.15 g, 0.39 mmol) in a mixture of absolute ethanol and tetrahydrofuran (1:1, 8 mL) was reacted with sodium borohydride (0.06 g, 1.58 mmol) according to the method of preparation of compound **11**. Recrystallization from dichloromethane/light petroleum afforded the hydroxy-methylpyrroloindole as a white solid (0.14 g, 93%), mp 168–171 °C. Found: C, 59.2; H, 4.5; N, 3.3. $C_{19}H_{16}BrNO_3$ requires C, 59.1; H, 4.2; N, 3.6%. λ_{max} 210 nm (ε 50,600 $cm^{-1}\,M^{-1}$), 244 (36,600), 276 (31,100), 308 (44,800). ν_{max} 3260, 1590, 1330, 1220, 1170, 1130 cm^{-1}. ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 3.95 and 4.22 (6H, 2s, OMe), 4.83 (2H, d, *J* 5.4 Hz, CH_2), 5.65 (1H, t, *J* 5.4 Hz, OH), 6.58 (1H, s, H7), 7.06 (1H, d, *J* 2.8 Hz, H5), 7.67 and 7.73 (4H, d, *J* 8.5 Hz, ArH), 7.81 (1H, d, *J* 2.8 Hz, H4). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 54.3 (CH_2), 56.2 and 57.6 (OMe), 94.9 (C7), 96.1, 102.3, 119.8, 120.5, 132.1, 133.8, 138.5, 155.2 and 155.4 (ArC), 108.8 (C5), 122.2 (C4), 130.9 and 131.8 (ArCH). Mass spectrum: *m*/*z* 388 (M+1, ^{81}Br, 21%), 387 (M, ^{81}Br, 100), 386 (M+1, ^{79}Br, 27), 385 (M, ^{79}Br, 98), 370 (53), 368 (53), 289 (35), 274 (33), 259 (27), 196 (52), 157 (44), 139 (62), 107 (44), 43 (70).

4.16. *N,N*-Dimethyl 2-{1-(4′-bromophenyl)-6,8-dimethoxy-pyrrolo[3,2,1-*hi*]indol-2-yl}-2-hydroxyacetamide (19)

Pyrroloindole **14** (100 mg, 0.22 mmol) in a mixture of absolute ethanol and tetrahydrofuran (1:1, 8.0 mL) was reacted with sodium borohydride (40 mg, 1.06 mmol) according to the method of preparation of compound **11** to give hydroxyacetamidopyrroloindole **19** as a white solid (80 mg, 78%), mp 110–113 °C (from dichloromethane/light petroleum). Found: C, 53.3; H, 4.7; N, 5.1. $C_{22}H_{21}BrN_2O_4\cdot 0.67CH_2Cl_2$ requires C, 53.0; H, 4.4; N, 5.4%. λ_{max} 213 nm (ε 12,400 $cm^{-1}\,M^{-1}$), 246 (11,900), 269 (9700), 310 (13,900). ν_{max} 3400, 1655, 1590, 1510, 1330, 1210, 1130, 1060, 1015, 720 cm^{-1}. ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 3.0 and 3.3 (6H, 2s, NMe_2), 4.35 and 4.63 (6H, 2s, OMe), 5.95 (1H, s, C*H*OH), 6.46 (1H, s, CHO*H*), 6.99 (1H, s, H7), 7.44 (1H, d, *J* 3.1 Hz, H5), 8.0 (1H, d, *J* 3.1 Hz, H4), 8.07 and 8.20 (4H, 2d, *J* 8.2 Hz, ArH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 35.2 (NMe_2), 55.7 and 57.2 (OMe), 63.0 (*C*HOH), 94.5 (C7), 108.5 (C5), 122.4 (C4), 130.8 and 131.3 (ArCH), 101.4, 120.0, 121.3, 128.6, 132.8, 138.2, 155.0, 155.5 and 169.5 (ArC), 176.0 (*C*ONMe$_2$). Mass spectrum: *m*/*z* 458 (M, ^{81}Br, 8%), 456 (M, ^{79}Br,

8), 387 (27), 386 (93), 385 (36), 384 (100), 305 (24), 262 (28), 190 (26), 72 (82).

4.17. Crystallographic studies

4.17.1. Crystal data for compound ***5***

$C_{18}H_{14}BrNO_2$, *M* 356.2, orthorhombic, space group *Pbcm*, *a* 20.985(4), *b* 9.719(2), *c* 7.438(2) Å, *V* 1517.0(5) Å^3, D_c 1.56 g cm^{-3}, *Z* 4, μ_{Mo} 26.90 cm^{-1}, $2\theta_{max}$ 50°. The number of reflections was 818 considered observed out of 1455 unique data. The molecule lies across the mirror plane at $z=1/4$, and hence is disordered. Final residuals *R*, R_w were 0.037, 0.041 for the observed data.

4.17.2. Crystal data for compound ***7***

$(C_{22}H_{18}BrNO_5)_2\cdot CHCl_3$, *M* 1032.0, triclinic, space group *P*-1, *a* 7.677(2), *b* 10.657(5), *c* 28.673(11) Å, *α* 81.63(2), *β* 85.59(2)°, *γ* 68.83(3)°, *V* 2164(1) Å^3, D_c 1.58 g cm^{-3}, *Z* 2, μ_{Cu} 46.86 cm^{-1}, $2\theta_{max}$ 140°. The number of reflections was 5645 considered observed out of 7346 unique data. Final residuals *R*, R_w were 0.058, 0.103 for the observed data. The chloroform was disordered over two sites with occupancies of 0.52, 0.48.

4.17.3. Crystal data for compound ***15***

$C_{28}H_{24}N_2O_4$, *M* 452.5, orthorhombic, space group $P2_12_12_1$, *a* 9.082(1), *b* 9.214(2), *c* 27.052(5) Å, *V* 2263.8(7) Å^3, D_c 1.33 g cm^{-3}, *Z* 4, μ_{Cu} 7.22 cm^{-1}, $2\theta_{max}$ 140°. The number of reflections was 2183 considered observed out of 2462 unique data. Final residuals *R*, R_w were 0.033, 0.050 for the observed data.

4.17.4. Crystal data for compound ***16***

$C_{16}H_{16}N_2O_4$, *M* 300.3, monoclinic, space group $P2_1/c$, *a* 9.576(6), *b* 7.784(2), *c* 19.918(9) Å, *β* 102.65(2)°, *V* 1449(1) Å^3, D_c 1.38 g cm^{-3}, *Z* 4, μ_{Cu} 8.29 cm^{-1}, $2\theta_{max}$ 140°. The number of reflections was 1501 considered observed out of 2742 unique data. Final residuals *R*, R_w were 0.078, 0.096 for the observed data.

4.17.5. Structure determination

Reflection data were measured with an Enraf-Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode using graphite monochromatized copper (λ 1.5418 Å) or molybdenum radiation (λ 0.7107) Å. Reflections with $I>2\sigma(I)$ were considered observed. The structures were determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions and were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full matrix least squares.

Reflection weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o)=[\sigma^2(I_o)+(0.04I_o)^2]^{1/2}$. The weighted residual is defined as $R_w=(\Sigma w\Delta^2/\Sigma wF_o^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography.[10] Structure solutions were by SIR92[11] and refinement used RAELS.[12] ORTEP-II[13] running on an eMac was used for the structural diagrams, and the eMac was also used for calculations.

Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 694315 for structure **5**, CCDC 694316 for structure **7**, CCDC 694317 for structure **15**, CCDC 694318 for structure **16**). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Rd, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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