Synthesis of Pyrrolopyridines (Azaindoles)

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Improved, convenient, and reliable routes for the synthesis of 4-, 5-, 6-, and 7-azaindole, 7-methyl-4-azaindole, 7-methyl-6-azaindole, and the hitherto unreported 7-amino-4-azaindole are described. The syntheses have been accomplished either by significant modifications to established procedures or by new methods which afford the compounds in improved yields.

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In connection with a continuing study of ambident nucleophile reactivity of nitrogen heterocycles related to purines [1], we needed a series of pyrrolopyridines. With the exception of the 1*H*-pyrrolo[2,3-*c*]pyridine (6-azaindole) nucleus in such alkaloids as yohimbine, harmine, and canthine *etc.*, there are few naturally occurring compounds containing pyrrolopyridine ring systems [2]. These heterocyclic systems are thus almost purely synthetic in origin. Earlier reviews [2-5] indicate that Fischer and particularly Reissert and Madelung syntheses have been the common routes to the pyrrolopyridines, although these routes have problems and many alternatives have been tried. Difficulties in the synthesis of these simple heterocycles, including erratic and sometimes irreproducible yields, have led to their being dubbed "synthetically elusive compounds" [2].

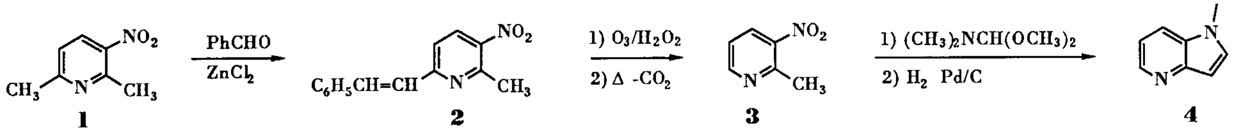
In our preparation of substantive amounts of the parent pyrrolopyridines and some simple methyl and amino substituted systems for our reactivity studies, we have developed modifications of the Madelung and extended Reissert synthetic routes that give enhanced yields and reproducibility.

1H-Pyrrolo[3,2-b]pyridine (4-Azaindole, 4) Systems.

Madelung and modified Madelung routes to unsubstituted 4-azaindole (4) give poor and erratic yields [6-8]. The extended Reissert synthesis developed by Azimov and Yakhontov [9] is simple and gives good yields of 4-azaindole, but suffers from poor availability of the precursor 2-methyl-3-nitropyridine (3) [10]. The latter compound has been made from 2,6-lutidine by nitration to 2,6-dimethyl-3-nitropyridine (1), selective oxidation of the 6-methyl group with permanganate, and then decarboxylation [10,11]. This route has problems in the selective oxidation step, which is low yielding (10-17%), and also in the decarboxylation step, which gives variable yields [11,12]. We have developed an improved synthesis of 3, see Scheme 1, by selectively reacting the 6-methyl group of 1 with benzaldehyde, oxidative ozonolysis of the resulting styryl compound 2, and then mild decarboxylation in hot diphenyl ether. This route gives overall yields of 23% (average) for 4-azaindole (4) from 2,6-lutidine, with improved reliability.

Preparation of the previously unknown 7-amino-4-azaindole (9b) by the extended Reissert route was more complicated, see Scheme 2. 2-Picoline was converted to its *N*-oxide, which on nitration then reduction with iron in acetic acid gave 4-amino-2-methylpyridine (5) [13,14]; we found that the addition of excess sodium citrate to the reduction mixture, prior to basification, greatly facilitated extraction and isolation of the strongly basic

Scheme 1



aminopyridine. Nitration of the aminopyridine **5**, *via* the nitramine, gives the desired 4-amino-2-methyl-3-nitropyridine (**6**) in up to 80% yield [15]. Using the Azimov and Yakhontov [9] approach, **6** was reacted with *N*,*N*-dimethylformamide dimethylacetal, but reaction occurred at the 4-amino rather than at the 2-methyl group, necessitating protection of the amino function. Attempted reaction of the corresponding 4-acetamido-, benzamido-, and phthalimido-derivatives of **6** with *N*,*N*-dimethylformamide dimethylacetal failed, however, to give the desired enamines, probably because the crowded 3-nitro group is unable to achieve coplanarity with the ring necessary for activation of the 2-methyl group. Alternate activation of the 2-methyl group in 4-acetamido-2-methyl-3-nitropyridine, *via* the *N*-oxide **7**, was however successful, allowing condensation with *N*,*N*-dimethylformamide dimethylacetal, to give the red nitroenamine **8** in almost quantitative yield. Raney nickel hydrogenation reduced the activating *N*-oxide and nitro groups giving, after spontaneous cyclisation, 7-acetamido-4-azaindole (**9a**) in 43% yield, see Scheme 2. Hydrolysis of the acetamido group gave the strongly basic, water soluble 7-amino-4-azaindole (**9b**) which proved unexpectedly difficult to isolate.

The hitherto unreported 7-methyl-4-azaindole was made, albeit in small amounts, by reductive cyclisation of 2-(4-methyl-3-nitro-2-pyridyl)-*N*,*N*-dimethylethenamine, a minor by-product in the preparation of 7-methyl-6-azaindole (**23**, see Scheme 5) from 2,4-lutidine.

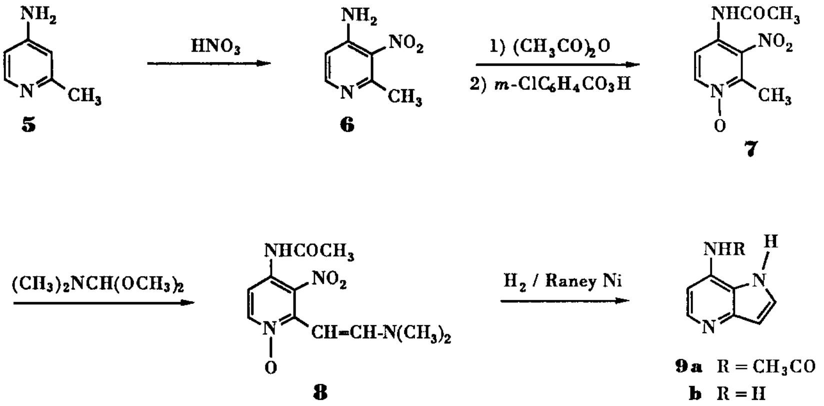
1*H*-Pyrrolo[3,2-*c*]pyridine (5-Azaindole, **13**).

Many reported routes to 5-azaindole also suffer from relative inaccessibility of starting materials [16], long sequences and poor yields [17,18], irreproducibility [19,20], or poor documentation [7,16]. Of the better synthetic routes [8,21], that of Ducrocq *et al.* [21], involving cyclisation of a pyridone ring onto a preformed pyrrole (see Scheme 3), was chosen as it could also give access to 4-amino-5-azaindole. 1-Benzylpyrrole was formylated then condensed with malonic acid giving the acrylic acid **10** [21]. Curtius rearrangement of the corresponding acyl azide gave the pyridone **11**, which was debenzylated then deoxygenated *via* the corresponding chloride **12**. [21] Difficulties in the reported cyclisation and chlorination steps were overcome by using milder conditions. Cyclisation of the acyl azide at the stated 220-240° [22] gave substantial amounts of tar, but by slow inverse addition of the azide to diphenyl ether and triethylamine at 195-200°, an improved yield (59%) of the cyclised pyridone **11** was obtained. Chlorination of the debenzylated pyridone under the reported conditions (phosphorus pentachloride/phosphorus oxychloride) [21] , gave in our hands, a mixture of mono and di-chlorinated products in poor yield. Using excess phosphorus oxychloride at 180° in a sealed tube, however, gave exclusively the monochlorinated product **12** in 77% yield which was converted almost quantitatively to 5-azaindole (**13**), Scheme 3.

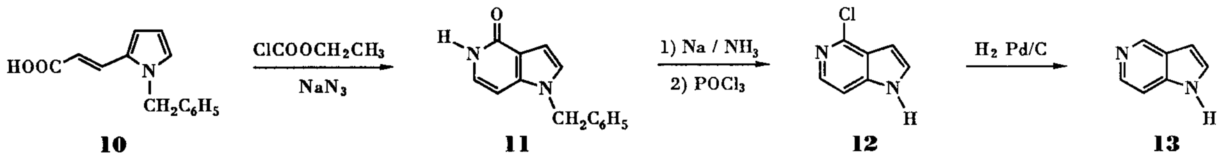
1*H*-Pyrrolo[2,3-*c*]pyridine (6-Azaindole, **19**) Systems.

Of the two reported [7,23] synthetic routes to 6-azaindole, the extended Reissert route of Prokopov and Yakhontov [23] seemed superior but suffered from poor availability of 4-methyl-3-nitropyridine. The latter compound is derived laboriously from the readily available 2-amino-4-methylpyridine (**14**) by nitration to a mixture of the

Scheme 2

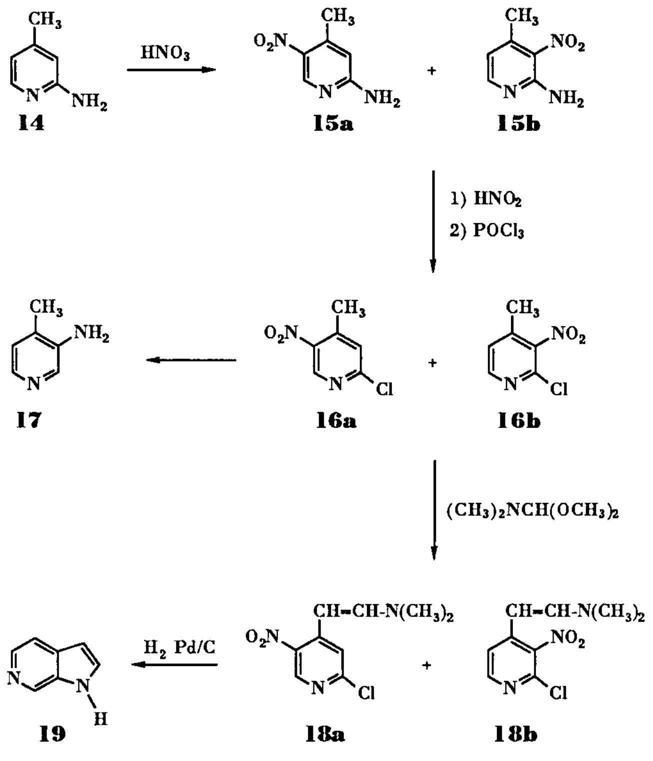


Scheme 3



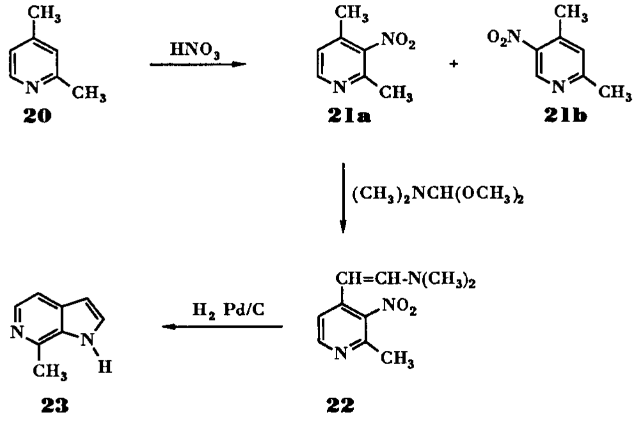
3- and 5-nitropyridines **15a,b**, diazotization to the corresponding 2-pyridones [10], then conversion to the 2-chloropyridines **16a,b** [24], and finally dechlorination with copper powder and acetic [24] or benzoic acid [10,25]. The moderate yields and cumbersome dechlorination step prompted us to attempt modifications. Hydrogenation of the mixture of 2-chloro-4-methyl-3- and -5-nitropyridine (**16a,b**) gave 3-amino-4-methylpyridine (**17**) in excellent yield. But as the attempted ring closure to 6-azaindole by the modified Madelung synthesis (formimidate, formamidine route of Lorentz *et al.* [8]) failed in the last cyclisation step, the extended Reissert synthesis of Yakhontov *et al.* [9,23] was re-examined, see Scheme 4. The mixture of 2-chloro-4-methyl-3- and 5-nitropyridines (**16a,b**) was reacted with *N*,*N*-dimethylformamide dimethylacetal to give the corresponding red nitroenamines **18a,b**, which on hydrogenation underwent, in the one pot, dechlorination, reduction and cyclisation giving crude 6-azaindole (**19**) in 93% yield. This new sequence, Scheme 4, gives an improved, overall yield of 36% 6-azaindole (**19**) in five steps from 2-amino-4-methylpyridine (**14**), without needing to separate the intermediate isomeric mixtures.

Scheme 4



7-Methyl-6-azaindole (**23**, apoharmine [26]) was readily synthesized from 2,4-lutidine in three steps in overall yield of 12.5% using the extended Reissert route, see Scheme 5. Nitration of 2,4-lutidine (**20**) gave the isomeric 3- and 5-nitrated products **21a,b** in almost equal amounts, 16 and 20% respectively [27]; these can be separated by careful fractional distillation. Condensation of 2,4-dimethyl-3-nitropyridine (**21a**) with *N*,*N*-dimethylformamide dimethylacetal gave predominantly 2-(2-methyl-3-nitro-4-pyridyl)-*N*,*N*-dimethylethenamine (**22**, 90-95%) with only a small amount (0-10%) of the 2-vinyl isomer, reflecting the well known enhanced reactivity of 4-methyl over 2-methyl groups in pyridine systems. Hydrogenation of **22** then gave apoharmine (**23**) in 82% yield. Despite the poor first step, this process (12.5%, 3 steps, Scheme 5) represents a substantial improvement on the previous route (4% in two steps from the less readily available 2-pyrrolecarboxaldehyde, [26]).

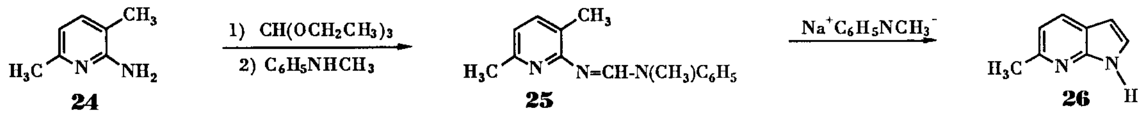
Scheme 5



1*H*-Pyrrolo[2,3-*b*]pyridine (7-Azaindole) Systems.

The synthetic procedure of Lorenz *et al.* [8] represents an efficient and convenient synthesis of the parent 7-azaindole system. Application of the Lorenz modifications, *via* a formimidate and formamidine (**25**), to the synthesis of 6-methyl-7-

Scheme 6



azaindole (**26**) from 2,5-lutidine, see Scheme 6, gave an improved yield (12.5%) with easier purification than reported [28] in the earlier Madelung route (3% yield).

EXPERIMENTAL

Melting points (mp) were determined on a Buchi melting point apparatus and are uncorrected. All boiling points (bp) are uncorrected. Ultraviolet spectra were recorded on a Pye Unicam SP 800 ultraviolet-visible spectrophotometer. Mass spectra (EI) were recorded on a VG micromass 7070 F mass spectrometer at 70 eV, linked on-line to a Finnigan Incos data system. High resolution mass spectra were recorded on an A.E.I. MS 902 spectrometer. Infrared spectra were recorded on a Pye Unicam SP3-100 infrared spectrometer as Nujol mulls, unless otherwise stated. Microanalyses were performed by the Australian National University Microanalytical Services Unit, Canberra.

Unless otherwise stated, ^{1}H nmr spectra were recorded either on a Varian XL 200E (200 MHz) or on a Varian XL 300E (300 MHz) instrument in deuterochloroform solution. The spectra were analysed assuming all couplings to be first order. The ^{13}C spectra were recorded either at 50.30 MHz (Varian XL 200E) or at 75.43 MHz (Varian XL 300E). Samples were run in deuterochloroform using TMS as internal standard. Fully ^{1}H-decoupled with NOE, ^{1}H-coupled with NOE, and selective ^{1}H-decoupled spectra, recorded for each sample using Waltz-16 broadband decoupling, allowed assignments to be made for methine, methylene (none present in the systems analysed) and methyl carbons. One-bond coupling constants were also determined. Assignments for quaternary carbons have not been made.

2-Methyl-3-nitro-6-styrylpyridine (**2**) and 3-Nitro-2,6-distyrylpyridine.

A mixture of 2,6-dimethyl-3-nitropyridine (**1**) (5 g, 32.9 mmoles), benzaldehyde (6 g, 56.5 mmoles), and fused zinc chloride (2 g) in dry *N,N*-dimethylformamide (6 ml) was heated at 100° (bath-temperature) for 24 hours. The crystalline mass obtained on cooling was filtered, and crystallized from methanol to yield pale yellow crystals (4.93 g, 62%) of 2-methyl-3-nitro-6-styrylpyridine (**2**), mp 113-115°, ms: m/z 240 (M$^+$, 49%), 239 (100), 152 (19), 77 (19). ^{1}H nmr: δ 8.34 (d, 1H, $J_{4,5}$ = 8.4 Hz, H-4), 7.84 (d, 1H, J = 16 Hz, C*H*=CHC$_6$H$_5$), 7.68-7.18 (m, 7H, C$_6$H$_5$, H-5, CH=C*H*C$_6$H$_5$), 2.96 (s, 3H, 2-CH$_3$).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7. Found: C, 70.2; H, 5.3; N, 11.6.

The mother liquors from the methanol crystallization were evaporated to dryness, and the residue crystallized from benzene to give deep yellow crystals (2.5 g, 23%) of 3-nitro-2,6-distyrylpyridine, mp 126-128°, ms: m/z 328 (M$^+$, 16%), 223 (22), 194 (33), 167 (35), 91 (55), 78 (100, from solvent C$_6$H$_6$), 77 (40). ^{1}H nmr δ 8.26-7.19 (m, 16H, H-4, H-5, 2 x CH=CHC$_6$H$_5$).

Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.8; H, 4.9; N, 8.5. Found: C, 77.1; H, 4.9; N, 8.4.

2-Methyl-3-nitropyridine (**3**).

Ozonized oxygen was bubbled through a cooled solution of the monostyrylpyridine **2** (2 g, 8.32 mmoles) in chloroform (40 ml) and glacial acetic acid (16 ml) for about 2 hours until it changed from yellow to colourless. Hydrogen peroxide (1.6 ml, 25%) was added and the reaction mixture heated under reflux for 0.5-1 hours. The reaction was monitored by tlc (5% ethanol-chloroform/silica). After evaporating the contents to dryness, the residue (2.02 g) in diphenyl ether (15 ml) was heated over a flame for 0.5 hours (reaction followed by tlc). Diethyl ether was added to the cooled reaction mixture. Extraction with a saturated solution of sodium carbonate (2 x 20 ml) removed benzoic acid. The organic layer was then extracted with concentrated hydrochloric acid (10 ml). The aqueous layer was basified with solid sodium carbonate, and extracted with diethyl ether (4 x 40 ml). The combined ether layers were dried, and solvent removed, to afford 2-methyl-3-nitropyridine (**3**) as a pale brown gum (0.673 g, 68%, mp lit 28.5° [11]); ^{1}H nmr δ (60 MHz) 8.89 (dd, 1H, J = 2.0, 5.0 Hz, H-6), 8.43 (dd, 1H, J = 2.0, 9.0 Hz, H-4), 7.46 (dd, 1H, J = 5.0, 9.0 Hz, H-5), 2.90 (s, 3H, 2-CH$_3$).

1*H*-Pyrrolo[3,2-*b*]pyridine (4-Azaindole, **4**).

2-(3-Nitro-2-pyridinyl)-*N,N*-dimethylethenamine (0.66 g, 3.40 mmoles), derived quantitatively from 2-methyl-3-nitropyridine, was hydrogenated, following the procedure of Azimov and Yakhontov *et al.* [9] until the red colour disappeared. Work-up yielded 4-azaindole (**4**) as pale brown needles (0.38 g, 95%). Vacuum sublimation and recrystallization from benzene gave colourless crystals, mp 124-125°, lit 122-123° [9]. ^{13}C nmr δ 146.04 (C-8), 142.45 (C-5, J = 180.2 Hz), 129.07 (C-9), 128.65 (C-2, J = 191.4 Hz), 118.95 (C-7, J = 162.0 Hz), 116.50 (C-6, J = 163.0 Hz), 102.21 (C-3, J = 183.5 Hz). Other spectral details were identical with that reported [9].

Anal. Calcd. for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.46; H, 4.94; N, 23.72.

N-(2-Methyl-3-nitro-4-pyridyl)acetamide.

Acetic anhydride (3 ml) was added to 2-methyl-3-nitro-4-pyridinamine (**6**) (1.74 g, 11.36 mmoles) and the mixture heated under reflux for 3 hours. The contents were evaporated to dryness, the resulting brown solid was dissolved in chloroform (30 ml) and extracted with saturated sodium carbonate solution (2 x 20 ml). Evaporation of the dried organic layer gave *N*-(2-methyl-3-nitro-4-pyridyl-)acetamide (1.90 g), as a brown solid. The aqueous layer was evaporated, and the residue obtained shaken with chloroform (6 x 25 ml). The combined chloroform layers were dried, and upon removal of solvent, a further 0.28 g of the desired acetamidopyridine was obtained; total yield, 2.18 g (98%), mp 92-94°. Chromatographic purification of a small sample then recrystallisation from petroleum gave pale buff needles, mp 114-115°; ms: m/z 195 (M^+, 1.4%), 153 (M^+ — CH_2CO, 14), 149 (26), 136 (21), 107 (12), 80 (10), 66 (9), 52 (12), 43 (CH_3CO^+, 100). ^{1}H nmr δ 9.0 (bs, 1H, 4-NH), 8.50 (d, 1H, $J_{6,5}$ = 6.0 Hz, H-6), 8.38 (d, 1H, $J_{5,6}$ = 6.0 Hz, H-5), 2.69 (s, 3H, 2-CH_3), 2.27 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_8H_9N_3O_3$: C, 49.2; H, 4.7; N, 21.5. Found: C, 49.1; H, 4.7; N, 21.5.

N-(2-Methyl-3-nitro-1-oxo-4-pyridyl)acetamide (**7**).

m-Chloroperbenzoic acid (85%, 0.7 g, 3.45 mmoles) was added to a solution of *N*-(2-methyl-3-nitro-4-pyridyl)-acetamide (0.32 g, 1.64 mmoles) in warm chloroform (15 ml), and the solution stirred at room temperature (15 hours). The organic phase was shaken with sodium sulphite solution (10%, 15 ml). After removal of the aqueous phase, the chloroform layer was re-extracted with saturated sodium carbonate solution (3 x 15 ml). The combined aqueous phases were evaporated and the residue shaken with warm chloroform (10 x 50 ml). The combined organic layers were dried and evaporated giving a yellow solid (0.21 g, 61%). Crystallization from chloroform gave yellow crystals of *N*-(2-methyl-3-nitro-1-oxo-4-pyridyl)-acetamide (**7**), mp 195-197°; ms: m/z 211 (M^+, 9.%), 169 (M^+ — CH_2CO, 37), 152 (6), 122 (14), 94 (15), 66 (11), 52 (7), 43 (CH_3CO^+, 100). ^{1}H nmr (DMSO-d$_6$) δ 10.3 (bs, 1H, 4-NH), 8.44 (d, 1H, $J_{6,5}$ = 6.0 Hz, H-6), 7.60 (d, ^{1}H, $J_{5,6}$ = 6.0 Hz, H-5), 2.34 (s, 3H, 2-CH_3), 2.05 (s, 3H, $COCH_3$).

High resolution ms. Calcd. for $C_8H_9N_3O_4$: m/z 211.0593. Found: m/z 211.0594.

N-(2-(2'-Dimethylaminovinyl)-3-nitro-1-oxo-4-pyridyl)acetamide (**8**).

N-(2-Methyl-3-nitro-1-oxo-4-pyridyl)acetamide (**7**, 0.177 g, 0.838 mmoles), *N,N*-dimethylformamide dimethylacetal (0.20 g, 1.68 mmoles) and dry *N,N*-dimethylformamide (2 ml) were heated at 90° (bath temperature) for 12 hours. The *N,N*-dimethylformamide was then removed by codistillation with toluene. The resulting red solid (0.243 g) was dissolved in 20% methanol-chloroform, and a preliminary purification done on a small column of silica. After evaporation of solvent, the residue was purified by radial chromatography (silica, 5% methanol-chloroform). The major red band gave *N*-(2-(2-dimethylaminovinyl)-3-nitro-1-oxo-4-pyridyl)acetamide (**8**, 0.114 g, 51%), as red crystals. ms: m/z 266 (M^+, 100%), 249 (60), 207 (49), 160 (33), 148 (26), 107 (22), 86 (33), 72 (65), 56 (55). ^{1}H nmr δ 9.48 (d, 1H, J = 12.0 Hz, C*H*=CHNMe$_2$), 8.19 (bs, 1H, 4-NH), 8.05 (d, 1H, $J_{6,5}$ = 6.0 Hz, H-6), 7.68 (d, 1H, $J_{5,6}$ = 6.0 Hz, H-5), 5.03 (d, 1H, J = 12.0 Hz, CH=C*H*NMe$_2$), 3.00 (bs, 6H, NMe$_2$), 2.19 (s, 3H, $COCH_3$). This, essentially pure material, was used directly in the next step without further purification.

High resolution ms. Calcd. for $C_{11}H_{14}N_4O_4$: m/z 266.1015. Found: mol wt 266.0998.

N-(7-1*H*-Pyrrolo[3,2-*b*]pyridyl)acetamide (7-Acetamido-4-azaindole, **9a**).

Raney nickel, prepared from 1 g of nickel-aluminium alloy (1:1), was added to a red solution of *N*-(2-(2-dimethylaminovinyl)-3-nitro-1-oxo-4-pyridyl)acetamide (**8**, 0.13 g, 0.488 mmoles) in methanol (20 ml). The mixture was hydrogenated at room temperature (2 hours). The red colour was discharged in about 5 minutes. Tlc of the reaction mixture at this stage showed the absence of starting material and the presence of a new spot (R_f 0.2). This spot decayed with time to produce yet another spot (R_f 0.4) which increased in intensity. At the end of about 2 hours, the lower spot (R_f 0.2) had completely vanished. The reaction mixture was then filtered through Celite and the catalyst washed with warm methanol (3 x 20 ml). Evaporation of the filtrate gave the crude azaindole (75 mg) as a pale yellow oil. Purification by radial chromatography (alumina, 3% methanol-chloroform) gave *N*-(7-1*H*-pyrrolo[3,2-*b*] pyridyl)acetamide (**9a**) as a yellow oil (42 mg, 49%), which on standing gave a solid monohydrate, mp 91-92°; ms: m/z 175 (M^+, 62%), 149 (11), 133 (M^+ — CH_2CO, 100%), 123 (11), 105 (20), 83 (42), 52 (20), 43 (CH_3CO^+, 75); uv, (water): λmax nm 290; (*p*H 2) 250, 288, 320; (*p*H 12) 290. ^{1}H nmr (perdeuteriomethanol): δ 8.0 (d, 1H, $J_{5,6}$ = 5.4 Hz, H-5), 7.36 (d, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 7.12 (d, 1H, $J_{6,5}$ = 5.4 Hz, H-6), 6.41 (d, 1H, $J_{3,2}$ = 3.2 Hz, H-3), 2.09 (s, 3H, $COCH_3$). ^{1}H nmr (deuteriochloroform): δ 11.0 (bs, 1H, H-1), 9.20 (bs, 1H, 7-NH), 8.27 (d, 1H, H-5), 7.43 (d, 1H, H-2), 6.95 (d, 1H, H-6), 6.66 (d, 1H, H-3), 2.23 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_9H_9N_3O.H_2O$: C, 56.0; H, 5.7; N, 21.8; M^+ 175.0746. Found: C, 55.6; H, 5.5; N, 21.4; M^+ 175.0746.

7-Amino-1*H*-pyrrolo[3,2-*b*]pyridine (7-Amino-4-azaindole, **9b**).

A solution of the acetamidoazaindole **9a** (47 mg) in aqueous sodium hydroxide (0.5 *M*, 2.5 ml) was heated under reflux for 2 hours. The cooled reaction mixture [uv, (water): λ max nm: 280] was acidified with hydrochloric acid (2 *M*) to *p*H 2 [uv, (water, *p*H 2): λ max nm: 240, 275, 290; (*p*H 12) 280]. This solution showed a single component on tlc with R_f 0.2 (20% methanol-chloroform). It was then basified to *p*H 10 with sodium carbonate and evaporated to dryness. The residue was shaken with chloroform (2 x 10 ml), but this failed to extract the product. The residue was then treated with an ethanol-chloroform (1:1) mixture. A pale yellow solution was obtained, and its tlc showed the presence of a species with an R_f value 0.2. It was evaporated to dryness, treated with water (2 ml) and basified with sodium hydroxide to *p*H 13-14. The contents (R_f 0.02, 20% methanol-chloroform) were again evaporated to dryness and the residue shaken with an ethanol-chloroform mixture as before; uv (water): λ max nm: 276; (*p*H 2) 240, 275, 292; (*p*H 12) 278. Removal of solvent gave 7-amino-4-azaindole (**9b**, 24 mg), as a pale yellow solid residue; uv (water): λ max nm: 275, 290; (*p*H 2) 240, 275, 292; (*p*H 12) 281; (R_f 0.02, 20% methanol-chloroform). ms: m/z 133 (M^+, 100%), 105 (23), 93 (11), 79 (14), 53 (19), 52 (19). ^1H nmr (perdeteriomethanol): δ 7.87 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-5), 7.38 (d, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 6.43 (d, 1H, $J_{3,2}$ = 3.2 Hz, H-3), 6.40 (d, 1H, $J_{6,5}$ = 5.6 Hz, H-6).

To determine the nature of the species with R_f 0.2, the above residue (**9b**, 24 mg), was treated with water (3 ml), the solution acidified with hydrochloric acid (2 *M*) to a *p*H of 2-3, evaporated to dryness and worked up as above. Evaporation of the ethanol-chloroform solvent mixture afforded a residue with a R_f value of 0.2 (20% methanol-chloroform); uv (water): λ max nm: 240, 275, 292; (*p*H 2) 240, 275, 292; (*p*H 12) 282; ^1H nmr (perdeteriomethanol) δ 7.92 (d, 1H, $J_{5,6}$ = 6.8 Hz, H-5), 7.68 (d, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 6.63 (d, 1H, $J_{6,5}$ = 6.8 Hz, H-6), 6.54 (d, 1H, $J_{3,2}$ = 3.1 Hz, H-3). On treatment with silver nitrate solution, a white precipitate was obtained which turned dark on exposure to light, confirming the presence of chloride. The R_f 0.2 compound was apparently the hydrochloride salt of 7-amino-4-azaindole (**9b**), which moved on tlc as an ion pair.

In another attempt, the acetamidoazaindole **9a** (47 mg), in aqueous sodium hydroxide (0.5 *M*, 2.5 ml) was heated under reflux for 3 hours. Hydrochloric acid (2 *M*) was added in drops until the spot with an R_f 0.2 appeared. Sodium hydroxide (2 *M*) was then added until this spot collapsed to yield the species with an R_f of 0.02. The solution was then evaporated to dryness, and shaken with an ethanol-chloroform mixture (1:1). The uv and ^1H nmr spectra of the residue were in agreement with those obtained previously for the species with an R_f 0.02. Purification by radial chromatography (silica, 50% methanol-chloroform), followed by vacuum sublimation gave 7-amino-4-azaindole (**9b**) as a colourless solid (9 mg, 25%), mp 210° (softens, darkens 200°); uv, λ max (water) nm: 275, 290; (*p*H 2) 240, 275, 293; (*p*H 12) 282. ^1H nmr (perdeteriomethanol): δ 7.89 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-5), 7.40 (d, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 6.45 (d, 1H, $J_{3,2}$ = 3.2 Hz, H-3), 6.43 (d, 1H, $J_{6,5}$ = 5.6 Hz, H-6).

Anal. Calcd. for $C_7H_7N_3$: C, 63.1; H, 5.3; N, 31.6; M^+ 133.0640. Found: C, 63.2; H, 5.4; N, 31.3; M^+ 133.0640.

1-Benzyl-4,5-dihydro-4-oxopyrrolo[3,2-*c*]pyridine (**11**).

Following the procedure of Eloy and Deryckere [22], the acrylic acid **10** (3.64 g, 16.0 mmoles), triethylamine (1.9 g, 18.8 mmoles), ethyl chloroformate (2.25 g, 20.7 mmoles) and sodium azide (1.6 g, 24.6 mmoles) were reacted to form the benzylpyridone **11**, obtained as a brown gum (2.5 g). Purification on alumina using chloroform as eluent gave the pure benzylpyridone **11** (0.78 g, 22%).

Better results were obtained with the following modifications. Two (instead of 1.3) equivalents of ethyl chloroformate were added and stirring continued for 1.5 hours (instead of 0.5 hours) at 0°; The temperature was maintained between 195-210° (*cf.* 220-240°) during the addition of the azide solution and the reaction mixture then allowed to cool to ambient temperature. The solution was concentrated to half its volume, diethyl ether added (equivalent amount), and left for about 12 hours. Pale brown crystals of 1-benzyl-4,5-dihydro-4-oxopyrrolo[3,2-*c*]pyridine (**11**) were collected, washed with diethyl ether and dried (8.0 g, 59%, lit 48% [22]), mp 194-195° (dec.); lit 202° [22] . ^1H nmr (60 MHz) δ 12.41 (bs, 1H, H-5), 7.89-7.66 (m, 8H, C_6H_5, H-2, H-3, H-7), 6.46 (d, 1H, J = 8.0 Hz, H-6), 5.30 (s, 2H, N-CH_2).

4,5-Dihydro-4-oxo-1*H*-pyrrolo[3,2-*c*]pyridine.

The benzylpyridone **11** (4 g, 17.8 mmoles) was debenzylated using sodium and liquid ammonia by adopting the procedure of Ducrocq *et al.* [21] to give 4,5-dihydro-4-oxo-1*H*-pyrrolo[3,2-*c*]pyridine (2.4 g, 79%), as very pale brown needles (tlc pure), mp 236° dec, lit 243° [21]; ms: m/z 134 (M^+, 100%), 107 (17), 79 (73); ^1H nmr (60 MHz, DMSO-d_6) δ 11.69, 10.86 (bs, 2H, 2 x NH), 7.17 (d, 1H, J = 3.5 Hz, H-2), 7.10 (d, 1H, J = 7.50 Hz, H-6), 6.59 (d, 1H, J = 3.0 Hz, H-3), 6.46 (d, 1H, J = 7.5 Hz, H-7). The proton chemical shifts were consistent with those reported in the literature [21]. Yields ranged from 60-83% in the subsequent four repeats.

4-Chloro-1*H*-pyrrolo[3,2-*c*]pyridine (4-Chloro-5-azaindole, **12**).

A mixture of 4,5-dihydro-4-oxo-1*H*-pyrrolo[3,2-*c*]pyridine (1.24 g, 9.24 mmoles) and phosphorus oxychloride (10 ml) was heated in a sealed tube at 180° (bath temperature) for 5 hours. Excess phosphorus oxychloride was evaporated, the residue treated with cold water (25 ml), basified with bicarbonate and extracted with ether (4 x 30 ml). Evaporation of the dried organic phase gave 4-chloro-5-azaindole (**12**) as a white residue (1.1 g, 78%), pure by tlc, mp 195-197°, lit 190-193° [21]; ms: m/z 154 (M^++2, 32.6%), 152 (M^+, 100), 117 (M^+ — Cl, 93), 90 (16), 63 (16); ^1H nmr (100 MHz, DMSO-d_6): δ 12.00 (bs, 1H, H-1), 8.04 (d, 1H, $J_{6,7}$ = 5.8 Hz, H-6), 7.58 (d, 1H, H-2), 7.48 (d, 1H, $J_{7,6}$ = 5.4 Hz, H-7), 6.60 (d, 1H, $J_{3,2}$ = 2 Hz, H-3). The proton chemical shifts were consistent with those reported in the literature [21].

1*H*-Pyrrolo[3,2-*c*]pyridine (5-Azaindole, **13**).

As described in the literature [21], the chloropyridine **12** (0.79 g, 5.18 mmoles) in alkaline ethanol (80 ml) was hydrogenated (8 hours) over palladium-carbon catalyst (10%, 0.3 g) and the reaction was followed by tlc (10% ethanol-chloroform). The catalyst was removed by filtration and washed well with alkaline ethanol. After removal of the solvent, the residue was taken in water and extracted with chloroform. The dried organic phase was evaporated to give 5-azaindole (**13**) as colourless needles (0.59 g, 96%; lit 83% after crystallization [21]). Crystallization from benzene-cyclohexane (1:1), followed by vacuum sublimation yielded the pure compound, mp 109-

110°, lit 111° [21]; uv, (water): λ max nm: 264, 275 (sh); (*p*H 2) 270, 291; (pH 12) 264, 275 (sh); [lit [21] (water): 265; (*p*H 6) 268, 293 nm)]; ^{1}H nmr: δ 11.10 (bs, 1H, H-1), 9.03 (s,1H, H-4), 8.32 (d, 1H, $J_{6,7}$ = 5.8 Hz, H-6), 7.38 (d,1H, $J_{7,6}$ = 5.8 Hz, H-7), 7.31 (d, 1H, $J_{2,3}$ = 3.4 Hz, H-2), 6.70 (d, 1H, $J_{3,2}$ = 3.4 Hz, H-3). ^{13}C nmr: δ 142.63 (C-4, 176.2 Hz), 140.20 (C-8 or C-9), 139.14 (C-6, 177 Hz), 126.61 (C-2, 183.0 Hz), 125.19 (C-9 or C-8), 107.32 (C-7, 163.1 Hz), 101.02 (C-3, 174.6 Hz).

Anal. Calcd. for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.4; H, 5.4; N, 24.0.

4-Methyl-3-pyridinamine (**17**) and 6-Ethoxy-4-methyl-3-pyridinamine.

A mixture of isomeric 2-chloro-4-methyl-3- and 5-nitropyridines (**16a,b**) was prepared from 2-amino-4-methylpyridine (**14**) according to the procedures of Baumgarten and coworkers [10,24]. The mixed chloromethyl-nitropyridines (**16a,b**, 3 g, 17.4 mmoles) were dissolved in absolute ethanol (200 ml) containing sodium hydroxide (0.8 g, 20 mmoles) and hydrogenated (10 hours) over palladium-carbon catalyst (0.6 g, 10%). The catalyst was removed by filtration and washed well with alkaline ethanol. The residue, after evaporation, was treated with saturated potassium carbonate solution (15 ml), extracted with ether (4 x 25 ml), and the combined ether extracts dried. Removal of solvent afforded a residue (1.5 g) which was purified by chromatography on alumina using chloroform as eluent. An red-orange compound which eluted first (0.94 g, 36%) was identified as 6-ethoxy-4-methyl-3-pyridinamine. It was recrystallized twice from petroleum spirit (60-90°) as colourless needles and then sublimed, mp 63-66°. The crystals turned red after a few days; ^{1}H nmr: δ 7.59 (s, 1H, H-2), 6.50 (s, 1H, H-5), 4.43 (q, 2H, CH_2CH$_3$), 3.36 (bs, 2H, NH$_2$), 2.16 (s, 3H, 4-CH$_3$), 1.50 (t, 3H, CH$_2$CH_3).

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.1; H, 8.0; N, 18.4. Found: C, 63.3; H, 8.3; N, 18.4.

The colourless compound (0.36 g, 19%) which eluted second was 4-methyl-3-pyridinamine (**17**); mp lit 106° [29]. Its identity was established by ^{1}H nmr spectroscopy; ^{1}H nmr: (100 MHz) δ 8.08 (s, 1H, H-2), 8.00 (d, 1H, $J_{6,5}$ = 4.0 Hz, H-6), 7.00 (d, 1H, $J_{5,6}$ = 4.0 Hz, H-5), 3.84 (bs, 2H, NH2), 2.08 (s, 3H, 4-CH$_3$).

In subsequent hydrogenations, sodium hydroxide was excluded, and the reactions were carried out in solutions containing a drop of concentrated hydrochloric acid. The aminopyridine (**17**) was then obtained in 89% average yield without contamination by the ethoxy derivative.

2-(2-Chloro-3-nitro-4-pyridyl)-*N,N*-dimethylethenamine (**18b**) and 2-(2-Chloro-5-nitro-4-pyridyl)-*N,N*-dimethylethenamine (**18a**).

The mixture of the isomeric 2-chloro-4-methyl-3- and 5-nitropyridines (**16a,b**, 5.0 g, 29.0 mmoles [10,24]) and *N,N*-dimethylformamide dimethylacetal (7.5 g, 62.9 mmoles) were dissolved in anhydrous *N,N*-dimethylformamide (40 ml) and heated at 90° (bath temperature) for 8 hours (reaction followed by tlc). Dimethylformamide was removed by codistillation with toluene and the deep red solid residue was crystallized from benzene to give a 3:1 mixture of 2-(2-chloro-3-nitro-4-pyridyl)-*N,N*-dimethylethenamine (**18b**) and 2-(2-chloro-5-nitro-4-pyridyl)-*N,N*-dimethylethenamine (**18a**) as deep red crystals (4.5 g, 68%); ^{1}H nmr δ 8.80 (s, 1H, H-6, **18a**), 7.99 (d, 1H, $J_{6,5}$ = 5.6 Hz, H-6, **18b**), 7.35 (d, 1H, J = 13.2 Hz, C*H*=CHNMe$_2$, **18a**), 7.28 (s, 1H, H-3, **18a**), 7.20 (d, 1H, J = 13 Hz, C*H*=CHNMe$_2$, **18b**), 7.13 (d, 1H, $J_{5,6}$ = 5.4 Hz, H-5, **18b**), 5.96 (d, 1H, J = 13.2 Hz, CH=C*H*NMe$_2$, **18a**), 4.71 (d, 1H, J = 13 Hz, CH=C*H*NMe$_2$, **18b**), 3.07(s, 6H, N-Me$_2$, **18a**), 2.99 (s, 6H, N-Me$_2$, **18b**). This mixture was used directly for the next step.

1*H*-Pyrrolo[2,3-*c*]pyridine (6-Azaindole, **19**).

The mixture of nitro-enamines **18a,b** (0.2 g, 0.88 mmoles) was hydrogenated over palladium-carbon catalyst (10%, 0.06 g), in absolute ethanol (11 ml) containing 0.5 drop of concentrated hydrochloric acid, until the red colour was discharged. The catalyst was removed by filtration and washed well with warm ethanol. Removal of the solvent afforded the crude azaindole **19** (0.077 g, 75%), as colourless needles. Two repeat hydrogenations yielded 84 and 93% of the desired compound. Crystallization from benzene, followed by vacuum sublimation gave 6-azaindole (**19**) as a colourless sublimate, mp 131-132°, lit 133-135° [23]; uv, (water): λ max nm 260, 293, 320 (sh); (*p*H 2) 261, 267, 318; (*p*H 12) 260, 291 (lit [5] (water); (*p*H 6) 261, 319; (*p*H 10) 260, 291 nm); ^{1}H nmr δ 11.85 (bs, 1H, H-1) 8.85 (s, 1H, H-7), 8.26 (d, 1H, $J_{5,4}$ = 6.0 Hz, H-5), 7.61 (d, 1H, $J_{4,5}$ = 6.0 Hz, H-4), 7.48 (d, 1H, $J_{2,3}$ = 2.6 Hz, H-2), 6.58 (d, 1H, $J_{3,2}$ = 2.6 Hz, H-3); ^{13}C nmr δ 137.34 (C-5, 176.0 Hz), 133.72 (C-7, 177.5 Hz), 133.59 (C-8 or C-9), 132.95 (C-8 or C-9), 129.24 (C-2, 182.6 Hz), 115.40 (C-4, 162.9 Hz), 101.32 (C-3, 174.4 Hz).

Anal. Calcd. for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.3; H, 5.2; N, 23.7.

2,4-Dimethyl-3-nitropyridine (**21a**) and 2,4-Dimethyl-5-nitropyridine (**21b**).

2,4-Dimethylpyridine (**20**, 10 g, 93.3 mmoles, crude commercial fraction), was slowly dissolved in cold fuming sulphuric acid (30%, 50 ml), finely powdered potassium nitrate (16.5 g, 0.163 mole) was then added in portions to the cooled reaction mixture, and the contents gradually heated in an oil-bath [27]. When the bath temperature reached 120°, a vigorous reaction occurred with the internal temperature rising above 200°. After the reaction had subsided, heating was continued for 8 hours (bath temperature 130-140°). The cooled reaction mixture was then poured onto ice, neutralised with excess concentrated aqueous ammonia, and extracted with dichloromethane. After evaporation of the dichloromethane, the crude products from two reaction runs were combined and distilled to recover 7.7 g (38% based) of starting material, bp 55-60°/15 mm. The dark residue from distillation was chromatographed on silica (150 g) using 40% ethyl acetate-hexane as eluent. The ^{1}H nmr spectrum of the yellow oil (5.4 g) indicated it to be an approximately 1:1 mixture of the 3-nitro and 5-nitropyridines **21a,b** which were separated using a spinning band distillation column. 2,4-Dimethyl-3-nitropyridine (**21a**, 1.95 g, 16%) had bp 74-80°/1.5 mm, lit 118-123°/12 mm [27]; ^{1}H nmr: δ 8.47 (d, 1H, $J_{6,5}$ = 5.0 Hz, H-6), 7.13 (d, 1H, $J_{5,6}$ = 5.0 Hz, H-5), 2.57 (s, 3H, 2-CH_3), 2.36 (s, 3H, 4-CH_3). 2,4-Dimethyl-5-nitropyridine (**21b**, 1.5 g): bp 81-95°/1.5 mm, lit 135-140°/12 mm [27]; ^{1}H nmr: δ 9.11 (s, 1H, H-6), 7.17 (s, 1H, H-3), 2.65-2.63 (2 s, 6H, 2-CH_3, 4-CH_3). This fraction contained traces of the 3-nitropyridine and 2,5-dimethyl-3-nitropyridine [^{1}H nmr: δ 8.60 (s, 1H, H-6), 8.13 (s, 1H, H-4), 2.82 (s, 3H, 2-CH_3), 2.43 (s, 3H, 5-CH_3)]. The pot residue (0.9 g) was almost pure 2,4-dimethyl-5-nitropyridine (**21b**) giving a total yield of 2.4 g (20%) for this isomer.

2-(2-Methyl-3-nitro-4-pyridyl)-*N*,*N*-dimethylethenamine (22) and 2-(4-methyl-3-nitro-2-pyridyl)-*N*,*N*-dimethylethenamine.

A mixture of 2,4-dimethyl-3-nitropyridine (**21a**, 0.31 g, 2.04 mmoles) and *N*,*N*-dimethylformamide dimethylacetal (0.5 g, 4.20 mmoles) in dry *N*,*N*-dimethylformamide (1 ml) was heated at 100° (bath temperature) for 16 hours. The resulting deep red solution was codistilled with toluene to remove *N*,*N*-dimethylformamide. The red residue (0.51 g) was purified by radial chromatography (silica, 40% ethyl acetate-hexane). Band 1 (0.098 g) was mainly starting material (sm) with about 5% of 2-(4-methyl-3-nitro-2-pyridyl)-*N*,*N*-dimethylethenamine (mpi), a minor isomer of the main product; ^{1}H nmr: δ 8.48 (d, 1H, $J_{6,5}$ = 5.0 Hz, H-6, sm), 8.21 (d, 1H, $J_{6,5}$ = 5.0 Hz, H-6, mpi), 7.77 (d, 1H, J = 12.4 Hz, C*H*=CHNMe$_2$, mpi), 7.13 (d, 1H, $J_{5,6}$ = 5.0 Hz, H-5, sm), 6.68 (d, 1H, $J_{5,6}$ = 5.0 Hz, H-5, mpi), 5.00 (d, 1H, J = 12.4 Hz, CH=C*H*NMe$_2$, mpi), 2.93 (s, 6H, N-Me$_2$, mpi), 2.57 (s, 3H, 2-CH_3, sm), 2.35 (s, 3H, 4-CH_3, sm), 2.23 (s, 3H, 4-CH_3, sm). Band 2, obtained as a red oil, solidified on standing, and was 2-(2-methyl-3-nitro-4-pyridyl)-*N*,*N*-dimethylethenamine (**22**, 0.277 g, 90%). Recrystallization from *n*-heptane gave deep red crystals, mp 88-90°; ms: m/z 207 (M$^+$, 30%), 190 (17), 145 (14), 93 (100), 86 (53), 65 (44), 58 (61). ^{1}H nmr:δ 8.12 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-6), 7.14 (d, 1H, J = 13.2 Hz, C*H*=CHNMe$_2$), 7.07 (d, 1H, $J_{5,6}$ = 5.6 Hz, H-5), 4.80 (d, 1H, J = 13.2 Hz, CH=C*H*NMe$_2$), 2.92 (s, 6H, N-Me$_2$), 2.44 (s, 3H, 2-CH_3).

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.3; N, 20.3; M$^+$ 207.1008. Found: C, 57.8; H, 6.4; N, 20.1; M$^+$ 207.1009.

7-Methyl-1*H*-pyrrolo[2,3-*c*]pyridine (Apoharmine, **23**).

The 4-vinylpyridine **22** (0.7 g, 3.38 mmoles) in absolute ethanol (50 ml) was hydrogenated using palladium-carbon catalyst (10%, 0.23 g) until the red colour was discharged (4 hours). The catalyst was removed by filtration and the solvent evaporated to give a brown oil (0.564 g) which was purified by radial chromatography (silica, 20% methanol-chloroform). The major band gave apoharmine (**23**, 0.36 g, 82%), as deep brown crystals which were sublimed twice (0.1 mm/120-130°), and recrystallized from benzene to afford colourless crystals, mp 184-85°, lit 184-185° [30]; ms: m/z 132 (M$^+$, 100%), 104 (29), 77 (7), 66 (9), 51 (7); uv (water): λ max nm 263, 292, 320 (sh); (*p*H 2) 264, 268, 315; (pH 12) 260, 290; ^{1}H nmr:δ 8.16 (d, 1H, $J_{5,4}$ = 5.6 Hz, H-5), 7.48 (d, 1H, $J_{4,5}$ = 5.6 Hz, H-4), 7.42 (d, 1H, $J_{2,3}$ = 3.0 Hz, H-2), 6.60 (d, 1H, $J_{3,2}$ = 3.0 Hz, H-3), 2.79 (s, 3H, 7-CH_3); ^{13}C nmr:δ 142.39, 132.57, 132.27 (C-7 or C-8 or C-9), 137.11 (C-5, 175.8 Hz), 128.36 (C-2, 182.6 Hz), 113.64 (C-4, 162.7 Hz), 101.92 (C-3, 172.6 Hz), 20.0 (7-CH_3).

Anal. Calcd. for $C_8H_8N_2$: C, 72.7; H, 6.1; N, 21.2. Found: C, 72.6; H, 6.1; N, 21.2.

7-Methyl-1*H*-pyrrolo[3,2-*b*]pyridine (7-Methyl-4-azaindole).

The mixture (0.4 g) of 2-(4-methyl-3-nitro-2-pyridyl)-*N*,*N*-dimethylethenamine and 2,4-dimethyl-3-nitropyridine (**21a**) (chromatography Band 1 from the preparation of **22** above) was hydrogenated (4 hours) over palladium-carbon catalyst (10%, 0.1 g) in absolute ethanol (25 ml). Filtration of catalyst and evaporation of the solvent yielded a deep brown residue (0.28 g) of the desired azaindole and 2,4-dimethyl-3-pyridinamine. Purification by radial chromatography (alumina, chloroform) gave 2,4-dimethyl-3-pyridinamine (0.175 g) as the first band; ^{1}H nmr: δ 7.82 (d, 1H, $J_{6,5}$ = 4.8 Hz, H-6), 6.83 (d, 1H, $J_{5,6}$ = 4.8 Hz, H-5), 3.67 (bs, 1H, 3-NH_2), 2.39 (s, 3H, 2-CH_3), 2.13 (s, 3H, 4-CH_3). The second band was 7-methyl-4-azaindole (33 mg), mp 165-168°; ms: m/z 132 (M$^+$, 100%), 117 (M$^+$ - 15, 8), 104 (15), 52 (14); uv (water): λ max nm 285; (*p*H 2) 279, 318; (*p*H 12) 287; ^{1}H nmr:δ 9.90 (bs, 1H, H-1), 8.38 (d, 1H, $J_{5,6}$ = 4.8 Hz, H-5), 7.48 (d, 1H, $J_{2,3}$ = 3.0 Hz, H-2), 6.96 (d, 1H, $J_{6,5}$ = 4.8 Hz, H-6), 6.73 (d, 1H, $J_{3,2}$ = 3.0 Hz, H-3), 2.54 (s, 3H, 7-CH_3). ^{13}C nmr:δ 145.55, 129.51, 129.11 (C-7 or C-8 or C-9), 143.13 (C-5, 176.3 Hz), 127.59 (C-2,184.4 Hz), 117.76 (C-6, 160.1 Hz), 103.13 (C-3, 174.5 Hz), 16.58 (7-CH_3).

Anal. Calcd. for $C_8H_8N_2$: C, 72.7; H, 6.1; N, 21.2; M$^+$ 132.0687. Found: C, 72.8; H, 6.2; N, 21.0; M$^+$ 132.0688.

6-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine (6-methyl-7-azaindole, **26**).

3,6-Dimethyl-2-pyridinamine (**24**, 11 g, 0.090 mole [28]), triethyl orthoformate (30 g, 0.202 mole) and alcoholic hydrogen chloride (2.5 ml) were heated under an air cooled distillation column for 5 hours, during which time ethanol distilled out and the pot temperature rose to 145°. Vacuum distillation of the pot residue gave ethyl *N*-(3,6-dimethyl-2-pyridyl)formamidate as a colourless liquid (7.8 g, 50%), bp 120-126°/15 mm; ^{1}H nmr: δ 8.12 (s, 1H, =CH-O), 7.28 (d, 1H, J = 7.6 Hz, H-4), 6.78 (d, 1H, J = 7.6 Hz, H-5), 4.36 (q, 2H, J = 7.6 Hz, CH_2), 2.40 (s, 3H, C6-CH_3), 2.18 (s, 3H, C3-CH_3), 1.36 (t, 3H, J = 7.6 Hz, -CH_2-C*H*$_3$).

The crude formimidate (7.8 g, 43.8 mmoles) and *N*-methylaniline (12 g, 0.112 mole) were heated over 2 hours, during which time ethanol slowly distiled out and the pot temperature climbed to 185°. Excess *N*-methylaniline was removed by vacuum distillation (bp 82-84°/15 mm) leaving a pot residue of almost pure *N*-(3,6-dimethyl-2-pyridyl)-*N*-methyl-*N*-phenylformamidine (**25**, 10.34 g, 99%); ^{1}H nmr: δ 8.78 (s, 1H, =CH-N), 7.0-7.44 (m, 6H,

C_6H_5, H-4), 6.62 (d of d, 1H, J = 8.16 Hz, H-5), 3.5 (s, 3H, N-CH_3), 2.4 (s, 3H, C6-CH_3), 2.30 (s, 3H, C3-CH_3). This was used without further purification.

Sodium hydride (3 g, 50% in oil, 62.5 mmoles) and *N*-methylaniline (14 ml) were heated under reflux and nitrogen for 0.5 hours. To this was added a warm solution of **25** (8.5 g, 35.5 mmoles) in *N*-methylaniline (10 ml) over 15 minutes and then reflux was continued for 3-4 hours until reaction was complete by tlc. The cooled reaction mixture was poured into water and extracted with ether (4 x 40 ml). The dried ethereal extract was distiled to remove ether and excess *N*-methylaniline (bp 82-84°/15 mm). The dark pot residue was then chromatographed over silica gel (300 g). Acetone/benzene (1:9) eluted crude 6-methyl-7-azaindole (**26**, 2.17 g, 45%) which was recrystallized from isopropyl acetate. Vacuum sublimation produced colourless crystals, mp 137-138°, lit 136-138° [28]; ^{1}H nmr: (100 MHz) δ 7.78 (d, 1H, J = 8 Hz, H-4), 7.24 (d, 1H, J = 4 Hz, H-2), 6.88 (d, 1H, J = 8 Hz, H-5), 6.38 (d, 1H, J = 4 Hz, H-3), 2.68 (s, 3H, C6-CH_3).

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