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Azole Additions upon Azinium Salts

Rodolfo Lavilla,[a]* Teresa Gotsens,[a] Marta Guerrero,[a] Carme Masdeu,[a] M. Carmen Santano,[b]
Cristina Minguillón,[b] and Joan Bosch[a]

a) Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

b) Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

Abstract: The additions of pyrrole and indole upon *N*-acetyl- and *N*-alkylpyridinium, quinolinium or isoquinolinium salts are reported. The resulting dihydroazines are either isolated or oxidised to the more stable aromatic compounds. The use of a two-phase system was studied and slight enantiomeric excesses were observed when chiral catalysts were used. The separation of enantiomers of some 4-indolyl-1,4-dihydropyridines was achieved by HPLC using chiral stationary phases.
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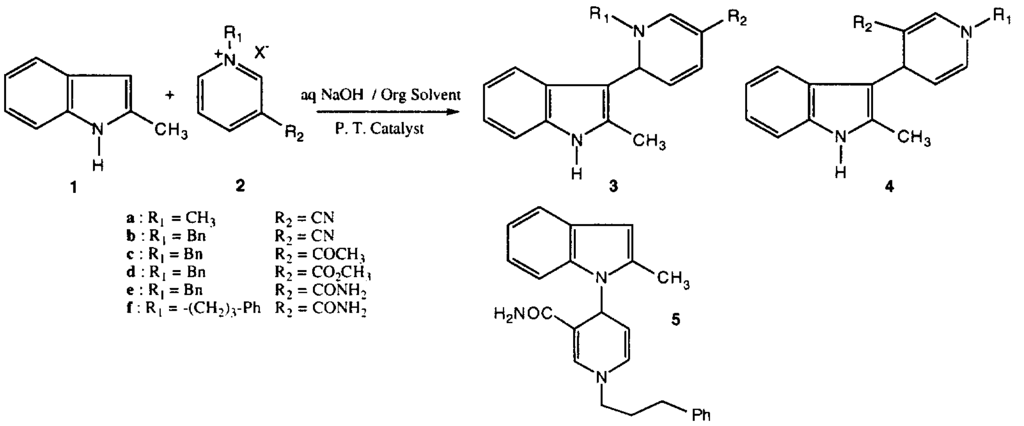
Dihydropyridines are compounds with interesting properties which play important roles in synthetic, therapeutic and bioorganic chemistry.[1] The addition of indoles to *N*-alkyl- and *N*-acetylpyridinium salts has been recently studied in our laboratories and allows the preparation of valuable dihydropyridines. In the course of these experiments, a solvent effect controlling the regioselectivity of the addition was described.[2] Also, access to *N*-unsubstituted dihydropyridines through mild hydrolysis of *N*-acetyl derivatives was developed and the reactivity of these compounds was studied.[3] Intramolecular additions were recently disclosed, thus expanding the scope of this method.[4] In this paper we report the extension of the addition reactions, now involving different conditions (phase-transfer catalysis, including the use of chiral catalysts) and also the combination of different azoles (*e.g.*, pyrrole) with other azinium ions (*e.g.*, quinolinium and isoquinolinium).

The preparation of enantiopure 4-aryl-1,4-dihydropyridines constitutes a synthetic challenge in medicinal chemistry due to the dramatic effect of the stereochemistry on pharmacological activity.[5] To our knowledge, there are no reports dealing with the preparation of chiral dihydropyridines using asymmetric catalysis.[6] With this goal in mind, the addition of indoles to *N*-alkylpyridinium salts **2** was performed under phase-transfer catalysis conditions, in order to determine the scope of the reaction, particularly regarding the regioselectivity. A set of experiments was performed, but the additions of 2-methylindole to salt **2a** (and other 3-substituted *N*-methylpyridinium salts) under a variety of experimental conditions were unsuccessful, no dihydropyridines being detected. Probably the low lipophilicity of these salts precluded the reaction. Therefore, the corresponding *N*-benzyl derivatives **2b-e** were tested next (Scheme 1).



a : $R_1 = CH_3$ $R_2 = CN$
b : $R_1 = Bn$ $R_2 = CN$
c : $R_1 = Bn$ $R_2 = COCH_3$
d : $R_1 = Bn$ $R_2 = CO_2CH_3$
e : $R_1 = Bn$ $R_2 = CONH_2$
f : $R_1 = \text{-}(CH_2)_3\text{-}Ph$ $R_2 = CONH_2$

Scheme 1

These salts were reactive and afforded the corresponding 1,2- and 1,4-dihydropyridines **3** and **4**, respectively. The structure determination of these compounds was based mainly on the ^{13}C-NMR chemical shift of the *sp*^{3} carbon atom of the dihydropyridine ring (≈ 55 ppm for **3** but ≈ 30 ppm for **4**). It is worth mentioning that the previously reported solvent effect for this kind of addition on homogeneous conditions[2] was also a valuable tool for controlling the regiochemistry in the two-phase system. Thus, the interaction of **1** with **2b** in the presence of 50% aqueous NaOH, TBAHS (tetrabutylammonium hydrogen sulfate), and methylene chloride afforded an equimolecular mixture of **3b** and **4b** in 26% overall yield; however, the use of toluene as the organic solvent resulted in the exclusive formation of **4b** (99%). The same trend was observed in the other additions (see Table 1). Although with some exceptions, toluene mainly promotes γ-addition of the nucleophile to the pyridinium salt, leading to 1,4-dihydropyridines, whereas methylene chloride favours the formation of the 1,2 isomers arising from an α addition.

Table 1. Phase-Transfer Additions to Pyridinium Salts 2.

Pyridinium Salt	**Products**	
	In CH_2Cl_2	In Toluene
2b	**3b** (13%) + **4b** (13%)	**4b** (99%)
2c	**3c** (20%)	---
2d	**3d** (66%) + **4d** (9%)	**3d** (45%) + **4d** (45%)
2e	**3e** (35%)	**4e** (99%)
2f	**4f** (84%)	**4f** (94%)

In all cases, the (non-optimised) reactions were carried out at room temperature, for 24h, and the products were purified by column chromatography and characterised by spectroscopical means and/or elemental analysis. The most significant chemical shifts of the ^1H- and ^{13}C-NMR spectra of these dihydropyridines are shown in Tables 2 and 3.

Table 2. Significant ^{1}H-NMR Data of Dihydropyridines **3** and **4**.

	H_2	H_3 or H_5	H_4	H_6	N-CH_2	CH_3	R_2
3b	5.50 dd	4.91 dd	5.90 dt	6.98 s	4.01 m	2.35 s	---
3c	5.49 bs	4.93 dd	6.31 m	7.15 s	4.03 m	2.24 s	1.85 d
3d [b]	5.49 bs	4.87 dd	6.42 d	7.22 d	4.10 m	2.16 s	3.75 s
3e [b]	5.92 m	4.90 dd	6.05 d	7.20 s	4.05 m	2.45 s	5.20 bs
4b [a]	7.28 s	4.60 m	4.60 m	6.17 d	4.49 m	2.20 s	---
4d [b]	7.24 s	4.80 m	4.80 m	5.96 d	4.49 s	2.41 s	3.76 s
4e [a]	7.21 s	4.50 m	4.68 d	6.12 d	4.49 s	2.27 s	6.21 bs
4f	7.35 s	4.69 m	4.88 d	5.85 d	3.30 t	2.42 s	5.10 bs

[a] Spectra in DMSO-d_6. [b] Data obtained from a mixture.

Table 3. Significant ^{13}C-NMR Data of Dihydropyridines **3** and **4**.

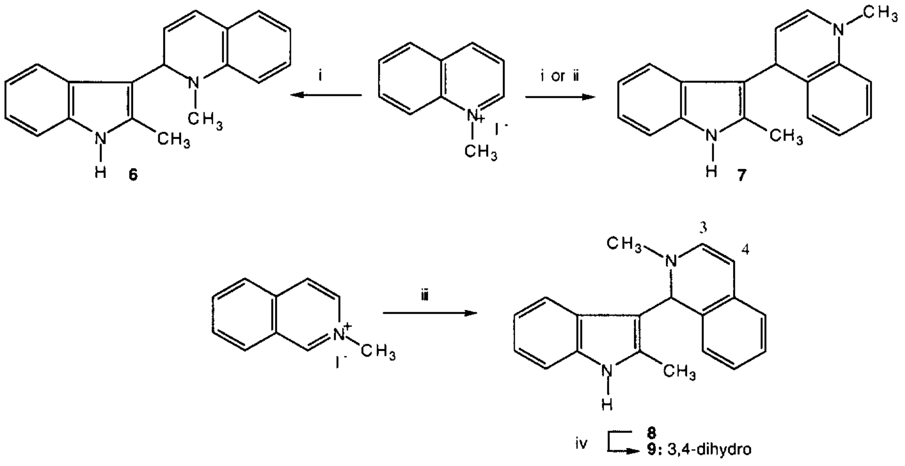
	C2	C3	C4	C5	C6	N-CH_2-	CH_3	R_2
3b	56.8	115.1	119.8	73.9	147.9	52.5	11.3	111.7
3c	53.6	114.9	120.1	109.7	148.5	58.2	10.8	10.7; 149.5
4b [a]	142.2	81.2	29.4	105.3	127.3	56.4	11.3	114.6
4e [a]	136.5	104.2	28.6	105.5	127.6	56.8	11.6	169.8
4f	139.2	100.6	29.0	106.7	128.3	53.7	11.6	171.4

[a] Spectra in DMSO-d_6.

Resolution of the racemic mixtures of **3** and, especially **4**, was possible by HPLC on a chiral stationary phase based on a 3,5-dimethylphenylcarbamate/10-undecenoate of cellulose bonded to the silica matrix.[7] In this way, nice separations were obtained using a 6:4 $CHCl_3$-hexane mixture containing 0.2% DEA as a mobile phase.[8] This analytical tool allowed us to study the asymmetric version of the above reaction.

Interestingly, dihydropyridines **3** and **4** were also produced in the absence of the PTC, although at a lower rate (for instance, **4d** was produced in 17% yield after 1.5 h, whereas with TBAHS the yield after the same time was over 40%). This autocatalytic effect shown by the pyridinium salts **2** limits the experimental conditions that can be used in the asymmetric synthesis. The use of chiral phase-transfer catalysis in asymmetric synthesis has achieved impressive results, particularly regarding the high e.e.'s obtained in the preparation of optically active biomolecules and drugs, and also due to the availability of the catalysts.[9,10] In the event, when performing the addition of **1** to **2b** in a two-phase system (50% aq NaOH / toluene) with 1% mol of *N,O*-dibenzylcinchonidinium bromide,[10] a very low e.e. (<5%) was observed in the production of **4b** (46% yield).[11] Apart from the problems associated with non-productive cycles catalysed by salts **2**, the low stereoselectivity may be attributed to the fact that the process formally involves a double asymmetric induction, in which one stereogenic centre, probably the one with better stereocontrol, is lost in the rearomatisation of the indole nucleus. In an attempt to reduce the autocatalysis, the use of salt **2f** was considered, as increasing the lipophilic chain would decrease the water solubility of the pyridinium salt. As expected, the reactions (addition of **1** in the presence of TBAHS) in the usual two-phase system afforded the corresponding 1,4-dihydropyridine **4f** (94%; traces of **3f** could be detected when dichloromethane was the organic solvent). Interestingly, when no PTC was present in the reaction vessel, the only isolated compound was the labile 1,4-dihydropyridine **5**, resulting from the *N*-addition of the indole at the γ position of the salt.[12] The asymmetric version of this reaction (toluene, *N*-benzylcinchonidinium chloride) afforded **4f** (84%) in 11% e.e. No efforts were made in order to determine the absolute configurations of the enantiomers. Although the results of the attempted chiral catalysis are only modest, it is worth noting that an efficient method for the resolution of racemic 4-indolyl-1,4-dihydropyridines by HPLC has been developed.

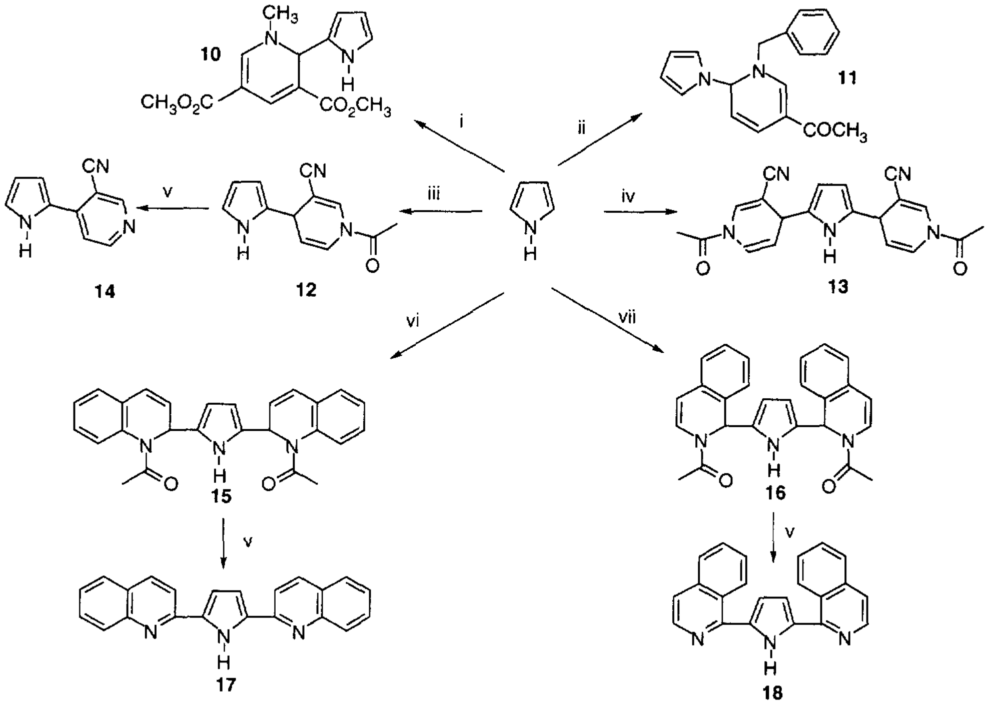
The addition of indoles to *N*-methylquinolinium iodide was studied next. In order to test the extension of the solvent effect described for these processes,[2] several experimental conditions were applied and a certain control of the regioselectivity was achieved again. Thus, carrying out the reaction in DMSO, using NaH as the base, afforded the 1,2-dihydro derivative **6** (34%) together with 1,4-dihydroquinoline **7** (51%), whereas under phase-transfer conditions the 1,4-isomer **7** (84%) was isolated as the only product. On the other hand, indole itself was added in methanol with sodium methoxide as the base to give an equimolecular mixture of 1,2- and 1,4-dihydroquinolines (95 %).[13] The above result allows access to either α- or γ-substituted dihydroquinolines by choice of the reaction conditions.[14] On the other hand, the addition of **1** upon *N*-methylisoquinolinium iodide gave the unstable dihydro derivative **8** (60%), which was reduced with sodium borohydride in methanol to tetrahydroisoquinoline **9** (62%). It is interesting to note that, in the above two indole additions, 1-methyl-2-quinolone and 2-methyl-1-isoquinolone were isolated in low yields.[15]



Scheme 2

Reagents : i) **1**, NaH, DMSO; ii) **1**, 50% aq NaOH, CH_2Cl_2, TBAHS; iii) **1**, NaMeO, MeOH; iv) $NaBH_4$, MeOH.

Little is known about the additions of other azoles to azinium salts.[16] Taking into account the preparative interest of these reactions, the interaction of pyrrole with *N*-alkylpyridinium salts was tested next. Thus, interaction of pyrrole with 3,5-bis(methoxycarbonyl)-1-methylpyridinium iodide gave only traces of the 1,2-dihydropyridine **10**,[17] whereas addition to 3-acetyl-1-benzylpyridinium bromide (**2c**) under phase-transfer conditons (TBAHS-dichloromethane/50% aq NaOH) afforded regioselectively the 1,2-dihydropyridine **11** (17%) (Scheme 3). The addition of pyrrole upon *N*-acetyl-3-cyanopyridinium chloride (generated *in situ*) afforded dihydropyridine **12** (20%), which afforded pyridine **14** in nearly quantitative yield on DDQ oxidation.[18] By changing the stoichiometry of the reactants (a large excess of the *N*-acetylpyridinium salt was empolyed) the unstable 2,5-disubstituted pyrrole **13** [19] was formed in low yield.



Scheme 3

Reagents : i) 3,5-bis(methoxycarbonyl)-1-pyridinium iodide, NaMeO, MeOH; ii) **2c**, 50% aq NaOH, CH_2Cl_2, TBAHS; iii) 3-cyanopyridine, AcCl, Proton Sponge, dioxane; iv) 3-cyanopyridine (7 eq), AcCl, Proton Sponge, dioxane; v) DDQ, dioxane; vi) quinoline, AcCl, dioxane; vii) isoquinoline, AcCl, dioxane.

On the other hand, addition of pyrrole to *N*-acetylquinolinium and *N*-acetylisoquinolinium chlorides gave the bis adducts **15** (51%) and **16** (13%), respectively, both of them isolated as a single stereoisomer of unknown stereochemistry [20] (Scheme 3). As expected, the reactions took place regioselectively, with bond formation between position 2 of the pyrrole nucleus and the α-carbon of the azinium salt. Oxidation of these dihydro derivatives with DDQ afforded azines **17** and **18**, respectively. These compounds, prepared in a two-step procedure, show an interesting arrangement of π-donor, π-acceptor heterocycles, with potential interest in recognition chemistry.

The reactivity described in this paper, which involves the addition of (benzo)azoles to (benzo)pyridinium salts under different conditions, establishes convenient preparations of a broad variety of interesting polyheterocyclic systems.

EXPERIMENTAL SECTION

General. All solvents were dried by standard methods. All reagents were of commercial quality from freshly opened containers. All reactions were conducted under an atmosphere of dry N_2. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder. Melting points were taken using a Büchi apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba 1106 analyzer by Centro de Investigación y Desarrollo (CSIC), Barcelona. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini-200 instrument (200 and 50.3 MHz, respectively) or on a Varian Gemini-300 (300 and 75.4 MHz, respectively) instrument in $CDCl_3$ with TMS as an internal reference unless otherwise quoted. IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrophotometer. UV spectra were obtained using an Hitachi U-2000 apparatus in MeOH. Low resolution e.i. mass spectra were determined on a Hewlett-Packard 5989A mass spectrometer. The chromatographic experiments were performed on a HPLC system consisting of a Waters model 600E pump, a Waters model 717 autosampler equipped with a Waters model 996 photodiode array detector; column: 250 x 4.6 mm ID; UV detection: 254 nm; flow = 1 ml/ min. Pyridinium salts **2a-e**, 1-methylquinolinium iodide and 2-methylisoquinolinium iodide were prepared by reaction of the corresponding azine with excess alkyl halide.[21]

3-Carbamoyl-1-(3-phenylpropyl)pyridinium Bromide (2f). A solution of 1-bromo-3-phenylpropane (6.3 ml, 41 mmol) in anhydrous MeOH (10 ml) was added dropwise to a solution of nicotinamide (5 g, 41 mmol) in anhydrous MeOH (20 ml), and the mixture was stirred at room temperature for 4 days. The solvent was removed under reduced pressure and the residue was crystallised from MeOH-diethyl ether to yield analytically pure pyridinium salt **2f** (11.2 g, 85%); ^{1}H-NMR (DMSO-d_6) 2.32 (m, 2H, C-CH_2-C); 2.66 (t, J = 6.8 Hz, 2H, CH_2-Ph); 4.71 (t, J = 7.0 Hz, 2H, CH_2-N); 7.22 (m, 5H, ArH); 8.16 (s, 1H, NH); 8.24 (dd, J = 6.6 and 8.0 Hz, 1H, H-5); 8.56 (s, 1H, NH); 8.92 (d, J = 8.0 Hz, 1H, H-4); 9.22 (d, J = 6.6 Hz, 1H, H-6); 9.51 (s, 1H, H-2). ^{13}C-NMR (DMSO-d_6) 31.9; 32.2; 61.3; 126.4; 128.1; 128.5; 128.7; 133.9; 140.6; 143.7; 145.1; 146.7; 163.1. IR (KBr) 3205 (N-H); 1681 (C=O). UV (MeOH) 265 (3.91). Mp 147 - 149°C. Anal. Calcd. for $C_{15}H_{17}BrN_2O{\cdot}H_2O$: C, 53.10; H, 5.60; N, 8.26. Found: C, 52.94; H, 5.60; N, 8.26.

General Procedure for the Phase-Transfer Indole Additions to Pyridinium Salts 2. A solution of sodium hydroxide (30 ml, 50% w/v) was added to a stirred suspension of 2-methylindole (197 mg, 1.5 mmol), the corresponding pyridinium salt **2** (1.8 mmol) and the phase transfer catalyst (TBAHS, benzylcinconinium chloride, benzylcinconidinium chloride, *N,O*-dibenzylcinconinium chloride or *N,O*-dibenzylcinconidinium chloride, 0.1 mmol) in the organic solvent (toluene or CH_2Cl_2, 30 ml), and the mixture was stirred at room temperature for the appropriate time (24 h or 1.5 h). The phases were separated and the organic phase was washed with water, dried, filtered, and evaporated to yield a residue, which was chromatographed over silica-gel. On elution with hexanes-ethyl acetate, pure dihydropyridines **3** and **4** were obtained. In the asymmetric phase-transfer reactions, the purified dihydropyridines were injected to the chiral HPLC column to evaluate the e.e. by relative area integration (the corresponding racemate was used inmediately before as a control).

1-Benzyl-2-(2-methyl-3-indolyl)-1,2-dihydropyridine-5-carbonitrile (3b). Using CH_2Cl_2 as the organic solvent and TBAHS as PTC, with a reaction time of 24 h, product **3b** (13%) was obtained. IR (KBr) 3339 (N-H), 2189 (C≡N), 1575 and 1459 (C=C). UV (MeOH) 349 (3.84), 279 (4.20). MS (e.i.) 325 (M^+, 78), 324 (25), 310 (44), 234 (100).

5-Acetyl-1-benzyl-2-(2-methyl-3-indolyl)-1,2-dihydropyridine (3c). Using CH_2Cl_2 as the organic solvent and TBAHS as PTC, with a reaction time of 24 h, product **3c** (20%) was obtained. IR (KBr) 3350 (N-H), 1649 (C=O), 1610 (C=C).

1-Benzyl-4-(2-methyl-3-indolyl)-1,4-dihydropyridine-3-carbonitrile (4b). Using toluene as the organic solvent and TBAHS as PTC, with a reaction time of 24 h, product **4b** (99 %) was obtained. IR (KBr) 3388 (N-H), 2195 (C≡N), 1592 (C=C). UV (MeOH) 331 (3.66), 283 (3.92). MS (e.i.) 325 (M^+, 9), 234 (19), 130 (6). Mp 197-199°C (MeOH-CH_2Cl_2). Anal. Calcd. for $C_{22}H_{19}N_3$: C, 81.20; H, 5.88; N, 12.91. Found: C, 81.15; H, 5.96: N, 12.93.

1-Benzyl-4-(2-methyl-3-indolyl)-1,4-dihydropyridine-3-carboxamide (4e). Using toluene as the organic solvent and TBAHS as PTC, with a reaction time of 24 h, product **4e** (99 %) was obtained. IR (KBr) 3476, 3227, 3155 (N-H), 1679 (C=O), 1552 (C=C). MS (e.i.) 343 (M^+, 12), 328 (10), 91 (100). Mp 193-195°C (MeOH-CH_2Cl_2). Anal. Calcd. for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.20; N, 12.24. Found: C, 76.89; H, 6.35: N, 12.13.

4-(2-Methyl-3-indolyl)-1-(3-phenylpropyl)-1,4-dihydropyridine-3-carboxamide (4f). Using toluene as the organic solvent and TBAHS as PTC, with a reaction time of 24 h, product **4f** (94 %) was obtained. IR (KBr) 3475, 3231, 3155 (N-H), 1681 (C=O), 1551 (C=C). MS (e.i.) 371 (M^+, 7), 356 (10), 241(17), 130 (100). UV (MeOH) 347 (4.01); 282 (4.17). Mp 192-194°C (MeOH-CH_2Cl_2). Anal. Calcd. for $C_{24}H_{25}N_3O$: C, 77.62; H, 6.74; N, 11.32. Found: C, 77.44; H, 6.78: N, 11.35.

4-(2-Methyl-1-indolyl)-1-(3-phenylpropyl)-1,4-dihydropyridine-3-carboxamide (5). Using toluene or CH_2Cl_2 as the organic solvent without PTC, with a reaction time of 24 h, unstable dihydropyridine **5** (91% in CH_2Cl_2 and 25% in toluene) was obtained. ^{1}H-NMR 1.98 (m, 2H, C-CH_2-); 2.43 (s, 3H, CH_3); 2.58 (m, 2H, CH_2-Ph); 3.10 (m, 2H, CH_2-N); 4.82 (dd, *J* = 7.6 and 4.0 Hz, 1H, H-5 pyr); 5.80 (m, 1H, H-4 pyr); 6.02 (d, *J* = 7.6 Hz, 1H, H-6 pyr); 6.23 (s, 1H, H-3 indole); 6.98 - 7.26 (m, 11H, NH_2, H-2 pyr and ArH); 8.05 (bs, 1H, NH indole). ^{13}C-NMR 13.8; 31.9; 32.3; 38.9; 54.3; 100.1; 102.6; 102.8; 110.2; 119.4; 119.5; 120.7; 126.0; 128.3; 128.5; 129.5; 132.4; 135.1; 136.0; 138.4; 140.8; 165.4. IR (KBr) 3400, 3281 (N-H), 1672 (C=O), 1565 (C=C). MS (chemical ionization, CH_4) 372 (M+1, 7). UV (MeOH) 353 (3.86); 265 (3.99).

1-Methyl-2-(2-methyl-3-indolyl)-1,2-dihydroquinoline (6). A suspension of sodium hydride (100 mg, 60% in oil, w/w, 2.5 mmol) in dimethyl sulfoxide (20 ml) was stirred at 80°C under nitrogen atmosphere for 30 min. The flask was cooled to room temperature, and 2-methylindole (131 mg, 1 mmol) was added. The solution was stirred at room temperature for 10 min, and 1-methylquinolinium iodide (326 mg, 1.2 mmol) was added in one portion. Stirring was continued for 24 h, and the solvent was removed under reduced pressure. The residue was taken up in water and extracted with ethyl acetate. The organic extracts were washed with water and dried. The solvent was evaporated and the residue was chromatographed over silica gel (hexanes/ethyl acetate) to yield **6** (94 mg, 34%).^{1}H-NMR 8.90 (bs, 1H, NH indole), 7.42 (d, *J*= 8 Hz, 1H, H-4 indole), 7.26 (d, *J*=8 Hz,1H, H-7 indole), 7.13 - 6.60 (m, 6H, ArH), 6.37 (dd, *J*=8.0 and 1.1 Hz, 1H, H-4 quin), 5.67 (d, *J*=3.5 Hz,1H, H-2 quin), 5.53 (dd,*J*=8.0 and 3.6 Hz, 1H, H-3 quin), 2.61 (s, 3H, NCH_3), 2.39 (s, 3H, CH_3). ^{13}C-NMR 142.5, 133.7, 129.8, 129.4, 127.7, 126.8, 126.4, 124.6, 123.0, 121.2, 119.6, 119.2, 116.2, 115.8, 110.2, 108.9, 57.0, 35.2, 12.0. IR (KBr) 3392 (N-H), 1613 and 1459 (C=C). UV (MeOH) 429 (3.45), 270 (4.08), 215 (4.45). MS (e.i.) 274 (M^+, 19), 273 (31), 257 (100), 130 (59). Further elution gave **7** (140 mg, 51%).

1-Methyl-4-(2-methyl-3-indolyl)-1,4-dihydroquinoline (7). A solution of 1-methylquinolinium iodide (298 mg, 1.1 mmol) in aqueous sodium hydroxide (50%, 20 ml) was added to a solution of 2-methylindole (131 mg, 1 mmol) and TBAHS (32 mg, 0.1 mmol) in CH_2Cl_2 (20 ml) and stirring was continued for 24 h at room temperature under inert atmosphere. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were washed with water, dried, and evaporated to dryness to yield **7** (230 mg, 84%). ^{1}H-NMR (DMSO-d_6) 10.70 (bs, 1H, NH indole), 7.32 (d, *J*= 8 Hz, 1H, H-4 indole), 7.20 (d, *J*=8 Hz,1H, H-7 indole), 7.03 - 6.60 (m, 6H, ArH), 6.20 (dd, *J*=7.8 and 1.1 Hz, 1H, H-2quin), 5.07 (d, *J*=3.6 Hz,1H, H-4 quin), 4.40 (dd, *J*=7.8 and 3.6 Hz, 1H, H-3 quin), 3.16 (s, 3H, NCH_3), 2.36 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) 140.9, 135.5, 132.0, 130.7, 129.7, 127.7, 126.9, 124.8, 120.4, 120.0, 118.7, 118.2, 117.8, 111.3, 110.5, 100.0, 38.0, 33.0, 11.7. IR (KBr) 3375 (N-H), 1603 and 1492 (C=C). UV (MeOH) 291 (4.35), 284 (4.34), 224 (4.85). MS (e.i.) 274 (M^+, 70), 273 (100), 144 (31). Mp 150-152°C. Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.21; H, 6.57; N, 10.22. Found: C, 83.30; H, 6.54; N, 10.20.

2-Methyl-1-(2-methyl-3-indolyl)-1,2-dihydroisoquinoline (8). 2-Methylindole (131 mg, 1 mmol) was added to a solution of sodium methoxide (1.2 mmol) in anhydrous MeOH (25 ml) and stirred at room temperature for 10 min. Then, 2-methylisoquinolinium iodide (325 mg, 1.2 mmol) was added in one portion, and the mixture stirred at room temperature for 4 h. The solvent was removed under reduced pressure, and the residue was taken up in water and extracted with ethyl acetate to give dihydroisoquinoline **8** (164 mg, 60%).

^{1}H-NMR 2.44 (s, 3H, CH$_3$); 2.53 (s, 3H, NCH$_3$); 5.28 (d, *J* = 8.0 Hz, 1H, H-4 quin); 5.82 (s, 1H, H-1 quin); 6.16 (d, *J* = 8.0 Hz, 1H, H-3 quin); 6.80 - 7.50 (m, 8H, ArH); 8.10 (bs, 1H, NH). MS (e.i) 274 (M$^+$, 22); 273 (27), 130 (100).

2-Methyl-1-(2-methyl-3-indolyl)-1,2,3,4-tetrahydroisoquinoline (9). A solution of crude dihydroisoquinoline **8** (110 mg, 0.40 mmol) in MeOH (10 ml) was added to a solution of sodium borohydride (15 mg, 0.40 mmol) in MeOH (20 ml), and the mixture stirred at room temperature for 30 min. The solvent was removed, and the residue taken up in water and extracted in ethyl acetate. The organic extracts were dried and concentrated to give a residue, which was chromatographed over silica gel (ethyl acetate) to give pure **9** (69 mg, 62%). ^{1}H-NMR 2.25 (s, 2H, CH$_3$), 2.35 (s, 3H, NCH$_3$); 2.58 - 2.90 (m, 2H, H-4 quin); 3.06 -3.19 (m, 2H, H-3 quin); 4.57 (s, 1H, H-1 quin); 6.80 - 7.28 (m, 8H, ArH); 7.80 (bs, 1H, NH). ^{13}C-NMR 12.1, 29.8, 44.4, 53.2, 62.6, 109.8, 113.2, 119.2, 119.4, 120.8, 125.6, 125.7, 127.6, 128.0, 128.6, 133.3, 134.4, 135.2, 139.7. IR (KBr) 3469 (N-H), 1461 (C=C). UV (MeOH) 277 (3.53), 215 (4.41). MS (e.i.) 276 (M$^+$, 100), 232 (26), 218 (84). The picrate showed a mp 181-183°C (acetone-MeOH). Anal. Calcd. for $C_{25}H_{23}N_5O_7$: C, 59.41; H, 4.55; N, 13.86. Found: C, 59.48; H, 4.70; N, 13.60.

5-Acetyl-1-benzyl-2-(1-pyrrolyl)-1,2-dihydropyridine (11). Following the general method for indole additions to pyridinium salts in phase-transfer conditions, using CH$_2$Cl$_2$ as the organic solvent and TBAHS as the catalyst, dihydropyridine **11** (17%) was obtained. ^{1}H-NMR 2.24 (s, 3H, CH$_3$); 4.30 (m, 2H, CH$_2$); 5.35 (dd, *J* = 9.7 and 4.4 Hz, 1H, H-3 pyr); 5.90 (d, *J* = 4.4 Hz, 1H, H-2 pyr); 6.20 (t, *J*= 2.3 Hz, 2H, H-3 and H-4 pyrrole); 6.67 (t, *J* = 2.3 Hz, 2H, H-2 and H-5 pyrrole); 7.02 (d, *J* = 9.7 Hz, 1H, H-4 pyr); 7.21 - 7.43 (m, 5H, ArH); 7.50 (s, 1H, H-6 pyr). ^{13}C-NMR 24.5, 56.9, 68.0, 107.5, 109.3, 111.1, 119.3, 123.2, 127.8, 128.9, 129.2, 134.3, 145.0, 192.1. IR (KBr) 1647 (C=O); 1455 (C=C). UV (MeOH) 327 (4.17); 269 (4.26). MS (e.i) 278 (M$^+$, 2); 213 (15), 91 (100).

1-Acetyl-4-(2-pyrrolyl)-1,4-dihydropyridine-3-carbonitrile (12). Acetyl chloride (660 µl, 8.19 mmol) was added to a solution of 3-cyanopyridine (850 mg, 8.19 mmol) in dioxane (20 ml), and the mixture was stirred at room temperature for 10 min. A solution of Proton Sponge® (1.75 g, 8.19 mmol) in dioxane (10 ml) was then added and, after 5 min, a solution of pyrrole (500 mg, 7.45 mmol) in dioxane (10 ml) was added. Stirring was continued for 12 h. The resulting precipitate was removed by filtration, and the filtrate was poured into a solution of saturated aqueous sodium carbonate (100 ml) and extracted with ethyl acetate (4 x 25 ml). The organic extract, once dried and evaporated, was crystallised from MeOH-CH$_2$Cl$_2$ to yield pure **12** (318 mg, 20%): ^{1}H-NMR (DMSO-*d*$_6$) 10.78 (s, 1H, NH pyrrole), 7.79 (s, 1H, H-2 pyr), 7.00 (bs, 1H, H-6 pyr), 6.69 (m, 1H, H-5 pyrrole), 5.95 (m, 1H, H-4 pyrrole), 5.86 (m, 1H, H-3 pyrrole), 5.15 (bs, 1H, H-3 pyr), 4.33 (d, *J*=2.6Hz, 1H, H-4 pyr), 2.31 (s, 3H, CH$_3$). IR (KBr) 3282 (N-H), 2206 (C≡N), 1672 (C=O), 1603 (C=C). UV (MeOH) 287 (3.91), 243 (4.03), 205 (4.05). MS (e.i.) 213 (M$^+$, 21), 171 (30), 170 (100). Mp 174-176°C. Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.71; H, 5.18: N, 19.64.

4-(2-Pyrrolyl)pyridine-3-carbonitrile (14). DDQ (107 mg, 0.47 mmol) was added to a solution of dihydropyridine **12** (100 mg, 0.47 mmol) in dioxane (15 ml), and the mixture was stirred at r.t. for 5 h. The resulting suspension was poured into a solution of aqueous sodium hydroxide (1M, 100 ml) and extracted with ethyl acetate (4 x 10 ml). The organic extract, once dried and evaporated, yielded pure **14** (76 mg, 96%). ^{1}H-NMR (DMSO-*d*$_6$) 11.90 (s, 1H, NH pyrrole), 8.88 (s, 1H, H-2 pyr), 8.70 (d, *J*=5.5 Hz, 1H, H-6 pyr), 7.74 (d, *J*=5.5 Hz, 1H, H-5 pyr), 7.20 (m, 2H, H-4 and H-5 pyrrole), 6.33 (m, 1H, H-3 pyrrole). MS (e.i.) 169 (M$^+$, 13), 142 (11), 130 (21). HRMS calcd for $C_{10}H_7N_3$ 169.0640, found 169.0638.

2,5-Bis(1-acetyl-1,2-dihydro-2-quinolyl)pyrrole (15). Acetyl chloride (5.30 ml, 74.5 mmol) was added to a solution of quinoline (9.62 g, 74.5 mmol) in dioxane (50 ml), and the mixture was stirred at r.t. for 10 min. A solution of pyrrole (1 g, 15 mmol) in dioxane (10 ml) was added and stirring was continued for 12 h. The resulting suspension was poured into a solution of saturated aqueous sodium carbonate (100 ml) and extracted with ethyl acetate (4 x 30 ml). The organic extract, once dried and evaporated, was chromatographed over silica gel (hexane/EtOAc) to afford pure **15** (3 g, 50%). ^{1}H-NMR 8.65 (bs, 1H, NH pyrrole), 7.13 - 6.82 (m, 8H, H-2 quin, ArH), 6.62 (d, *J*=9.6 Hz, 2H, H-4 quin), 6.38 (bs, 2H, H-2 quin), 6.13 (m, 2H, H-3 quin), 5.69 (bs, 2H, H-3 and H-4 pyrrole), 2.28 (s, 6H, CH$_3$). ^{13}C-NMR 170.6, 134.5, 129.0, 127.4, 127.2, 127.1, 126.4, 125.5, 125.2, 123.9, 107.3, 48.2, 22.9. IR (KBr) 3191 (N-H), 1658 and 1642 (C=O), 1486 (C=C). UV (MeOH) 272 (4.01), 232 (4.62). MS (e.i.) 409 (M^+, 3), 366 (12), 237 (10), 130 (100). An analytical sample was recrystallised from CH_2Cl_2-MeOH and showed a mp 224-226°C (lit.[20] 204-205°C). Anal. Calcd. for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.56; N, 10.26. Found: C, 76.12; H, 5.69; N, 10.22.

2,5-Bis(2-acetyl-1,2-dihydro-1-isoquinolyl)pyrrole (16). Using the same procedure, from acetyl chloride (5.32 ml, 74.5 mmol), isoquinoline (9.62 g, 74.5 mmol) and pyrrole (1 g, 15.0 mmol), compound **16** (800 mg, 13%) was obtained after chromatography (silica gel, hexane-EtOAc). ^{1}H-NMR 9.20 (bs, 1H, NH pyrrole), 7.27 - 7.10 (m, 8H, ArH), 6.75 (s, 2H, H-1 isoquin), 6.49 (dd, *J*=9.6 Hz and 0.7 Hz, 2H, H-4 isoquin), 5.92 (d, *J*=9.6 Hz, 2H, H-3 isoquin), 5.15 (d, *J*= 1.8 Hz, 2H, H-3 and H-4 pyrrole), 2.27 (s, 6H, CH_3). ^{13}C-NMR 169.5, 132.3, 130.2, 129.9, 127.9, 127.4, 127.3, 124.6, 124.3, 109.8, 109.9, 50.3, 21.4. IR (KBr) 3348 (N-H), 1661 and 1625 (C=O), 1378 (C=C). UV (MeOH) 294 (4.56), 225 (4.74). MS (e.i.) 409 (M^+, 4), 308 (16), 237 (49), 130 (100). An analytical sample was recrystallised from MeOH and showed a mp 159-161°C (lit.[20] 263-264°C). Anal. Calcd. for $C_{26}H_{23}N_3O_2 \cdot 1/2\ H_2O$: C, 74.64; H, 5.74; N, 10.05. Found: C, 74.92; H, 5.96; N, 9.69.

2,5-Bis(2-quinolyl)pyrrole (17). DDQ (166 mg, 0.72 mmol) was added to a solution of dihydroquinoline **15** (150 mg, 0.36 mmol) in dioxane (30 ml), and the mixture was stirred at r.t. for 24 h. The resulting suspension was poured into a solution of aqueous sodium hydroxide (1M, 50 ml) and extracted with ethyl acetate (4 x 10 ml). The organic extract, once dried and evaporated, was chromatographed over silica gel (hexanes-EtOAc) to yield pure **17** (40 mg, 35%). ^{1}H-NMR 10.99 (bs, 1H, NH pyrrole), 8.11 (d, *J*=8.5 Hz, 2H, H-4 quin), 8.05 (d, *J*=5.3 Hz, 2H, H-8 quin), 7.72 - 7.67 (m, 6H, ArH), 7.45 (t, *J*=5.5 Hz, 2H, H-6 quin), 6.83 (s, 2H, H-3 and H-4 pyrrole). ^{13}C-NMR 149.5, 148.0, 136.2, 134.3, 129.7, 128.8, 127.5, 126.9, 125.5, 117.7, 110.7. IR (KBr) 3340 (N-H), 1596 (C=C). UV (MeOH) 405 (3.62), 285 (3.41), 210 (3.76). MS (e.i.) 321 (M^+, 100), 320 (18), 160 (19), 128 (16). The dipicrate was recrystallised from MeOH and showed a mp 259-260°C. Anal. Calcd. for $C_{34}H_{21}N_9O_{14}$: C, 52.38; H, 2.71; N, 16.13. Found: C, 52.36; H, 2.75; N, 16.02.

2,5-Bis(1-isoquinolyl)pyrrole (18). Using the above procedure, from dihydroisoquinoline **16** (150 mg, 0.36 mmol) and DDQ (166 mg, 0.72 mmol) in dioxane (30 ml), compound **18** (50 mg, 43%) was obtained after chromtography (silica gel, hexane-EtOAc) and was crystallised from CH_2Cl_2-MeOH. ^{1}H-NMR 10.90 (bs, 1H, NH pyrrole), 8.73 (d, *J*=8.5 Hz, 2H, H-8 isoquin), 8.52 (d, *J*=5.5 Hz, 2H, H-3 isoquin), 7.83 (d, *J*=7.8 Hz, 2H, H-5 isoquin), 7.71 - 7.60 (m, 4H, H-6 and H-7 isoquin), 7.50 (d, *J*=5.5 Hz, 2H, H-4 isoquin), 7.13 (s, 2H, H-3 and H-4 pyrrole). ^{13}C-NMR 150.2, 141.9, 137.1, 132.1, 129.9, 127.5, 127.2, 126.4, 125.5, 119.0, 113.6. IR (KBr) 3439 (N-H), 1552 (C=C). UV (MeOH) 381 (4.58), 219 (4.94). MS (e.i.) 321 (M^+, 98), 320 (46), 193 (100). Mp 159-161°C. Anal. Calcd. for $C_{22}H_{15}N_3 \cdot 1/3\ CH_2Cl_2$: C, 76.64; H, 4.48; N, 12.01. Found: C, 77.02; H, 4.53; N, 11.84.

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