EFFECTIVE STRATEGY FOR THE SYNTHESIS OF PYRIDO[1',2':1,2]IMIDAZO[5,4-c]ISOQUINOLINE SYSTEM

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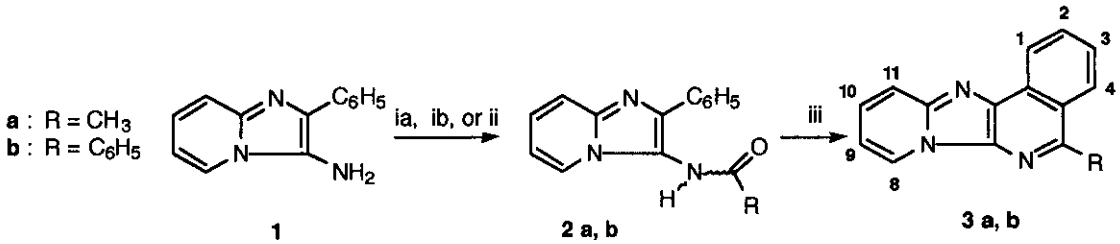
Abstract - Annulation of 3-aceta(benza)mido-2-phenylimidazo[1,2-a]pyridines (**2a,b**) by phosphorus oxychloride results in the formation of pyridoimidazoisoquinolines (**3a,b**) as potent antileukemic structures. An alternative route for obtaining the isoquinoline framework was centered on the aza-Wittig reaction of iminophosphorane (**4**) with different isocyanates.

Complex carboline compounds often show broad and rich physiological activities and these synthons have been developed as potential chemotherapeutic and pharmacologically active agents.[1] Recent works have shown that several structural analogues exhibit various pharmacological properties, such as antitumor activity.[2] In previous papers, we have reported the synthesis and characterization of series of azacarboline alkaloids from iminophosphoranes by tandem aza-Wittig / electrocyclization reaction.[3] In continuing our chemical studies on azacarboline compounds, we examined the isoquinoline annulation from 3-amino-2-phenylimidazo[1,2-a]pyridine (**1**) prepared by a previously reported procedure.[4] The use of acetyl chloride in benzene in presence of pyridine at 10°C gave the amide (**2a**) in a 65 % yield, which was optimized (93 %) by using acetic anhydride at 120°C with (**1**).[5] Interestingly, amide (**2a**) which was identified by mass (m/z : 251, M^+) and nmr spectroscopies occurs as a

mixture of isomers. In fact, in the ^1H and ^{13}C-nmr spectra ($CDCl_3$), the N-acetyl compounds appeared as two rotamers arising from hindered rotation around the amide bond. In contrast, in DMSO-d_6, amide (**2a**) occurs as a sole isomer. These results are in good agreement with investigations given by Petrovic.[6] Thus, the ^{13}C-nmr spectrum (DMSO-d_6) of **2a** showed the presence of five quaternary carbon signals. Peaks at δ : 170.42 and 141.87 are typical of the C=O and C-8a carbons. The distinction between C-2, C-3 and C ipso phenyl is consistent with data reported for imidazoazines[3] and provides further confirmation. In contrast, benzoylation of **1** to the sole product (**2b**) was effected in 85 % yield using benzoyl chloride/nitrobenzene at 200°C for 2 hours. The ^1H-nmr of **2b** in DMSO-d_6 exhibited only one set of resonance peaks.

The cyclization of amide (**2a**) was accomplished by intramolecular Friedel-Crafts type reaction[5] with phosphorus oxychloride in nitrobenzene at 200°C to afford the ring closed derivative (**3a**) in 25 % yield identified by mass (m/z : 233, M^+) and nmr spectroscopies. The ^1H-nmr spectrum confirmed the presence of two characteristic ABXY systems and was a good indication of the C ortho benzenic cyclization.

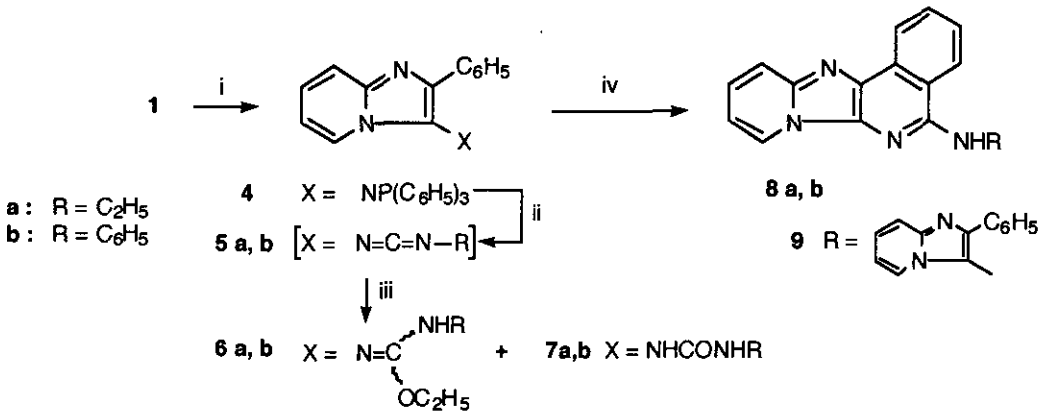


Reagents and conditions : (ia) $(CH_3CO)_2O$, 120°C ; (ib) CH_3COCl, C_6H_6/C_5H_5N, 10°C ; (ii) C_6H_5COCl, $C_6H_5NO_2$, 200°C ; (iii) $POCl_3$, $C_6H_5NO_2$

Proton assignment of **3a** was made on the basis of selective irradiations and by 2D experiments. The COSY spectrum gives H-9 (6.98), H-10 (7.45), H-3 (7.67), H-11 (7.80), H-2 (7.87), H-4 (8.25), H-1 (8.76), H-8 (8.55) connectivities. The observation of long-range $^3J_{CH}$ couplings in ^{13}C-^1H HETCOR experiment was optimized as 8 Hz and allows us to clarify the ambiguity of the isoquinoline system (see experimental section). Similarly, the amide (**2b**) was converted into the tetracyclic structure (**3b**) with 32 % yield, and was characterized by mass [295 (M^+, 100)] and nmr spectroscopies.

An alternative route for obtaining the isoquinoline structure was developed as follows. Our approach is centered on the aza-Wittig reaction of iminophosphorane (**4**) obtained in 75 % yield in a Staudinger reaction of the amine (**1**) under general procedure.[7] On being made to react with ethyl isocyanate in refluxing toluene the iso-urea (**6a**) and urea (**7a**) were obtained after chromatography on neutral alumina with CH_2Cl_2/EtOH (97/3, v/v) as eluents,

supporting the carbodiimide intermediate (**5a**). Unfortunately, direct conversion of the stable products (**6a**, **7a**) to the isoquinoline ring was not possible with a variety of solvents (toluene or 1,2-dichlorobenzene) and conditions (110° - 180°C). Finally, treatment of **4** with EtNCO in hot nitrobenzene gives the desired isoquinoline derivative (**8a**) (38 % yield, m/z : 262, M^+) and a by-product (**9**) (m/z : 426, M^+) with phosphine oxide. The use of C_6H_5NCO in the same conditions parallels the reactivity of iminophosphorane (**4**) with formation of a) : the iso-urea (**6b**) (m/z : 356, M^+) and urea (**7b**) in hot toluene and b) : the isoquinolines (**8b**) (47 % yield, m/z : 310, M^+) and (**9**) with phosphine oxide, respectively.



Reagents and conditions : (i) Triphenylphosphine, CCl_4, $(C_2H_5)_3N$; (ii) Ethyl (or phenyl) isocyanate, toluene, reflux ; (iii) neutral alumina, CH_2Cl_2/C_2H_5OH ; (iv) $C_6H_5NO_2$, reflux.

The structures of compounds (**8a,b**) were clearly assigned on the basis of nmr data. In particular, analysis of the observed perturbations in the spin-decoupled ^1H spectrum led to the required information regarding these structures. Production of **9** can be rationalized assuming an initial formation of imidazopyridinic isocyanate which reacts with a second molecule of the starting iminophosphorane (**4**) to give **9** as described in quinoxaline series.[8]

EXPERIMENTAL

General. All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. Ir spectra were recorded with a BECKMAN ACCULAB 2 Spectrophotometer. Absorption bands are expressed in centimeters (cm^{-1}), ^1H- and ^{13}C-nmr spectra were recorded on a Bruker AC-400 spectrometer working at 400 MHz (^1H-nmr) and 100 MHz (^{13}C-nmr). Chemical shift data are reported in ppm downfield δ from TMS. Coupling constants, J, are given in Hz ; s, d, t, m, and ps. t indicate singlet, doublet, triplet, multiplet, and pseudo triplet respectively. Mass spectra were performed on HEWLETT PACKARD 5989A and 5985B instruments. Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier.

3-Amino-2-phenylimidazo[1,2-a]pyridine (1) : This compound was prepared according to the literature procedure ; mp 210-212°C, (lit.,[5] mp 210°C).

3-Acetamido-2-phenylimidazo[1,2-a]pyridine (2a) Method A : A mixture of amine (**1**) (0.5 g, 2.4 mmol) and acetic anhydride (1.5 ml, 16 mmol) was stirred at 120°C for 25 min. After cooling, water was added, the solution was made alkaline with 10% aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was purified on neutral alumina column eluting with Hexane-AcOEt (50/50, v/v) to give 0.56 g (93 % yield) of acetamide (**2a**) (recrystallization solvent : diethyl ether) ; mp 225-227°C ; ir (KBr) ν_{max} 3160, 1680, 1500, 1250 ; ^{1}H-nmr (DMSO-d_6) δ 2.25 (s, 3H, CH_3), 6.98 (t, 1H, $J_{5,6}$ = 7 Hz, H-6), 7.35 (ps. t, 1H, H-7), 7.38 (t, 1H, J = 7.5 Hz, Ph), 7.51 (t, 2H, J = 7.5 Hz, Ph), 7.64 (d, 1H, $J_{7,8}$ = 9 Hz, H-8), 8.02 (d, 2H, J = 7.5 Hz, Ph), 8.12 (d, 1H, $J_{5,6}$ = 7 Hz, H-5), 10.22 (s, 1H, NH) ; ^{13}C-nmr (DMSO-d_6) δ 22.69 (CH_3), 112.03 (C-6), 115.65 (C-3), 116.84 (C-8), 123.85 (C-5), 125.08 (C-7), 126.67 (2C-Ph), 127.64 (C-Ph), 128.55 (2C-Ph), 133.54 (C-2), 137.19 (C-Ph), 141.87 (C-8a), 170.42 (CO) ; ms (m/z, relative intensity) 251 (M^+, 25), 209 (30), 181 (80), 78 (100) ; Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.71 ; H, 5.18 ; N, 16.73. Found : C, 71.55 ; H, 5.20 ; N, 16.75.

Method B : To a cooled solution (10°C) of **1** (0.5 g, 2.4 mmol) in benzene (6 ml) were added dry pyridine (0.5 ml) and acetyl chloride (0.5 ml, 7 mmol). After stirring for 4 h, 1.5 ml of cold water was added, the solution was basified with 10% aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and evaporated in vacuo. Chromatography of the residue on neutral alumina with Hexane-AcOEt (50/50, v/v) as eluent gives 0.39 g (65 % yield) of acetamide (**2a**).

3-Benzamido-2-phenylimidazo[1,2-a]pyridine (2b) : To a solution of amine (**1**) (0.5 g, 2.4 mmol) in nitrobenzene (5 ml) at 200°C was added benzoyl chloride (0.42 g, 3 mmol). After stirring for 2 h the resulting precipitate was filtered, washed with cold water and then poured into 10 % aqueous Na_2CO_3. The solution was extracted with CH_2Cl_2, dried (Na_2SO_4) and the solvent was removed under reduced pressure to give 0.64 g (85 %) of **2b** (recrystallization solvent : ethanol) ; mp 240-242°C ; ir (KBr) ν_{max} 3090, 2610, 1670, 1265 ; ^{1}H-nmr (DMSO-d_6) δ 7.51 (t, 1H, $J_{5,6}$ = 7 Hz, H-6), 7.56 (ps. t, 1H, H-7), 7.65 (m, 4H, Ph), 7.75 (t, 1H, J = 7 Hz, Ph), 8.00 (m, 3H, Ph), 8.07 (d, 1H, $J_{7,8}$ = 9 Hz, H-8), 8.20 (d, 2H, J = 7 Hz, Ph), 8.72 (d, 1H, $J_{5,6}$ = 7 Hz, H-5), 11.40 (s, 1H, NH) ; ^{13}C-nmr (DMSO-d_6) δ 113.13 (C-6), 116.72 (C-8), 117.07 (C-3), 125.82 (C-7), 127.17 (C-Ph), 127.36 (2C-Ph), 128.45 (2C-Ph), 128.81 (2C-Ph), 129.36 (2C-Ph), 130.16 (C-Ph), 131.09 (C-2 or C-Ph), 132.17 (C-Ph or C-2), 132.83 (C-5), 132.98 (C-Ph), 138.52 (C-8a), 167.33 (CO) ; ms (m/z, relative intensity) 313 (M^+, 58), 208 (67), 181 (65), 105 (33), 78 (100), 51 (34) ; Anal. Calcd for $C_{20}H_{15}N_3O$:

C, 76.68 ; H, 4.79 ; N, 13.42. Found : C, 76.75 ; H, 4.78 ; N, 13.45.

Cyclization procedure for amides (2a,b). A mixture of amide (3.2 mmol), phosphorus oxychloride (10 ml, 0.11 mol) and nitrobenzene (20 ml) was heated at 200°C for 4 h. After cooling, the solvent was removed. The residue was poured into water, basified with 10% aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on neutral alumina to give the corresponding pyrido[1', 2': 1, 2]imidazo[5,4-c]isoquinoline (**3a**, **b**).

3a : (eluent : CH_2Cl_2) 0.19 g (25 % yield) (recrystallization solvent : hexane) ; mp 140-142°C ; ir (KBr) ν_{max} 1615, 1365, 1345 ; ^{1}H-nmr ($CDCl_3$) δ 3.10 (s, 3H, CH_3), 6.98 (t, 1H, $J_{8,9}$ = 7 Hz, H-9), 7.45 (ps. t, 1H, H-10), 7.67 (t, 1H, $J_{2,3} = J_{3,4}$ = 7.5 Hz, H-3), 7.80 (d, 1H, $J_{10,11}$ = 9 Hz, H-11), 7.87 (t, 1H, $J_{1,2} = J_{2,3}$ = 7.5 Hz, H-2), 8.25 (d, 1H, $J_{3,4}$ = 7.5 Hz, H-4), 8.76 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 8.85 (d, 1H, $J_{8,9}$ = 7 Hz, H-8) ; ^{13}C-nmr ($CDCl_3$) δ 22.29 (CH_3), 110.80 (C-9), 117.29 (C-11), 122.18 (C-1) , 123.28 (C-8), 125.80 (C-3), 126.30 (C-4), 126.39 (C-4a), 127.76 (C-10), 129.27 (C-12b), 129.71 (C-2), 130.80 (C-12a), 134.23 (C-6a), 145.51 (C-11a), 152.09 (C-5) ; ms (m/z, relative intensity) 233 (M^+, 100), 78 (50), 51 (34) ; Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.25 ; H, 4.72 ; N, 18.03. Found : C, 77.29 ; H, 4.71 ; N, 18.00.

3b : (eluent : Hexane-AcOEt 70/30, v/v) 0.30 g (32 % yield) (recrystallization solvent : diethyl ether) ; mp 259-260°C ; ir (KBr) ν_{max} 1640, 1345, 1280 ; ^{1}H-mnr ($CDCl_3$) δ 7.22 (t, 1H, $J_{8,9}$ = 7 Hz, H-9), 7.60 (m, 3H, Ph, H-10), 7.72 (m, 2H, H-7, H-3), 7.79 (d, 2H, J = 7 Hz, Ph), 7.98 (ps. t, 1H, H-2), 8.12 (d, 1H, $J_{10,11}$ = 9 Hz, H-11), 8.30 (d, 1H, $J_{3,4}$ = 8.5 Hz, H-4), 9.02 (d, 1H, $J_{1,2}$ = 8 Hz, H-1), 9.07 (d, 1H, $J_{8,9}$ = 7 Hz, H-8) ; ^{13}C-nmr ($CDCl_3$) δ 111.68 (C-9), 117.86 (C-11), 122.64 (C-1), 124.29 (C-8), 126.38 (C-4a), 126.54 (C-3), 128.49 (C-4 or C-10), 128.68 (C-10 or C-4), 129.03 (2C-Ph), 129.20 (C-2), 130.39 (2C-Ph), 131.62 (C-12a), 135.23 (C-6a), 139.77 (C-Ph), 146.81 (C-11a), 154.77 (C-5), (C-12b : not observed) ; ms (m/z, relative intensity) 295 (M^+, 100), 190 (13), 147 (20), 78 (25), 51 (15) ; Anal. Calcd for $C_{20}H_{13}N_3$: C, 81.35 ; H, 4.41 ; N, 14.24. Found : C, 81.31 ; H, 4.40 ; N, 14.29.

Iminophosphorane (4) : To a solution of amine (**1**) (4.18 g, 20 mmol) in dry acetonitrile (50 ml), were added triphenylphosphine (10.5 g, 40 mmol), triethylamine (30 ml) and carbon tetrachloride (20 ml). The resulting mixture was stirred at room temperature for 6 h. Triethylammonium chloride was separated by filtration and the filtrate was concentrated to dryness to give 7.03 g (75 % yield) of **4** (recrystallization solvent : acetonitrile) ; mp 165-167°C ; ir (KBr) ν_{max} 1595, 1535, 1230, 740 ; ^{1}H-nmr ($CDCl_3$) δ 6.38 (t, 1H, $J_{5,6}$ = 7 Hz, H-6), 6.83 (ps. t, 1H, H-7), 7.04 (ps. t, 1H, Ph), 7.09 (m, 2H, Ph), 7.36 (m, 7H, H-8, Ph), 7.48 (m, 3H, Ph), 7.56 (m, 6H, Ph), 7.73 (d, 1H, $J_{5,6}$ = 7 Hz, H-5), 7.87 (d, 2H, J = 7.5 Hz, Ph) ; ^{13}C nmr ($CDCl_3$) δ 110.08 (C-6), 116.97

(C-8), 121.31 (C-7), 122.7 (C-5), 125.61 (C-Ph), 127.63 (4C-Ph), 128.08 (C-2), 128.65 (6C, J = 12 Hz, C-Ph), 130.78 (3C, J = 99 Hz, C-Ph), 131.49 (1C, J = 8 Hz, C-3), 131.98 (3C-Ph), 132.45 (6C, J = 10 Hz, C-Ph), 135.99 (C-Ph), 139.95 (C-8a), ms (m/z, relative intensity) 469 (M^+, 45), 262 (100), 183 (70), 108 (46), 78 (20) ; Anal. Calcd for $C_{31}H_{24}N_3P$: C, 79.32 ; H, 5.12 ; N, 8.96. Found : C, 79.34 ; H, 5.11 ; N, 8.95.

Iso-ureas (6a,b) and ureas (7a,b) : To a solution of **4** (1.5 g, 3.2 mmol) in toluene (100 ml) was added dropwise at 0°C ethyl or phenyl isocyanate (3.2 mmol) in toluene (10 ml). The mixture was stirred at room temperature for 3 h and then at reflux for 4 h. After removal of the solvent, the crude product was purified by chromatography on alumina eluting with CH_2Cl_2-EtOH (97/3, v/v) to give iso-ureas (**6a,b**) then ureas (**7a,b**).

6a : 0.54 g (55 % yield) (recrystallization solvent : diethyl ether) ; mp 178-180°C ; ir (KBr) ν_{max} 3080, 1620, 1110, 740 ; ^{1}H-nmr ($CDCl_3$) δ 0.85 (t, 3H, J = 7.5 Hz, CH_3), 1.45 (t, 3H, J = 7.5 Hz, CH_3), 3.05 (m, 2H, CH_2), 4.55 (m, 3H, NH, OCH_2), 6.65 (t, 1H, $J_{5,6}$ = 7 Hz, H-6), 6.98 (ps. t, 1H, H-7), 7.20 (t, 1H, J = 7.5 Hz, Ph), 7.39 (t, 2H, J = 7.5 Hz, Ph), 7.40 (d, 1H, $J_{7,8}$ = 9 Hz, H-8), 7.84 (d, 1H, $J_{5,6}$ = 7 Hz, H-5), 7.91 (d, 2H, J = 7.5 Hz, Ph) ; ^{13}C-nmr ($CDCl_3$) δ 14.72 (CH_3), 15.39 (CH_3), 36.18 (CH_2), 62.99 (OCH_2), 111.04 (C-6), 116.92 (C-8), 122.20 (C-5), 123.07 (C-7), 126.17 (2C-Ph), 126.56 (C-Ph), 128.26 (2C-Ph), 129.82 (C-2), 134.66 (C-Ph), 141.42 (C-8a), 155.15 (N=C), (C-3 : not observed) ; ms (m/z, relative intensity) 308 (M^+, 83), 208 (63), 181 (90), 78 (100), 51 (19) ; Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.13 ; H, 6.49 ; N, 18.18. Found : C, 70.25 ; H, 6.50 ; N, 18.15.

6b : 0.71 g (62 % yield) (recrystallization solvent : diethyl ether) ; mp 243-245°C ; ir (KBr) ν_{max} 1620, 1590, 1320, 1050 ; ^{1}H-nmr ($CDCl_3$) δ 1.51 (t, 3H, J = 8.0 Hz, CH_3), 4.53 (m, 2H, CH_2), 6.55 (s, 1H, NH), 6.81 (m, 3H, H-6, Ph), 7.00 (t, 1H, J = 7.5 Hz, Ph), 7.15 (m, 3H, H-7, Ph), 7.27 (ps. t, 1H, Ph), 7.38 (t, 2H, J = 7.5 Hz, Ph), 7.57 (d, 1H, $J_{8,9}$ = 9 Hz, H-8), 7.96 (d, 2H, J = 7.5 Hz, Ph), 8.02 (d, 1H, $J_{5,6}$ = 7.0 Hz, H-5) ; ^{13}C-nmr ($CDCl_3$) δ 14.62 (CH_3), 63.88 (CH_2), 111.65 (C-6), 117.05 (C-8), 121.53 (2C-Ph), 122.49 (C-5), 124.04 (C-7, C-Ph), 125.27 (C-Ph), 126.56 (2C-Ph), 127.31 (C-Ph), 128.72 (2C-Ph), 128.79 (2C-Ph), 129.64 (C-3), 134.04 (C-2), 137.11 (C-Ph), 141.76 (C-8a), 152.23 (N=C) ; ms (m/z, relative intensity) 356 (M^+, 100), 208 (73), 181 (93), 120 (23), 78 (98), 51 (24) ; Anal. Calcd for $C_{22}H_{20}N_4O$: C, 74.16 ; H, 5.62 ; N, 15.73. Found : C, 74.30 ; H, 5.68 ; N, 15.51.

7a : 0.52 g (58 %) (recrystallization solvent : dichloromethane) ; mp 256-258°C ; ir (KBr) ν_{max} 3150, 1650, 1530, 1290 ; ^{1}H-nmr (DMSO-d_6) δ 1.07 (t, 3H, J = 7.5 Hz, CH_3), 3.14 (m, 2H, CH_2), 6.65 (m, 1H, NH), 6.98 (t, 1H, $J_{5,6}$ = 7 Hz, H-6), 7.34 (ps. t, 1H, H-7), 7.36 (t, 1H, J = 7.5 Hz, Ph), 7.49 (t, 2H, J = 7.5 Hz, Ph), 7.61 (d, 1H, $J_{7,8}$ = 9 Hz, H-8), 8.03 (m, 3H, Ph, H-5), 8.31 (s, 1H, NH) ; ^{13}C-nmr (DMSO-d_6) δ 15.51

(CH_3), 34.42 (CH_2), 111.98 (C-6), 116.58 (C-3), 116.80 (C-8), 123.32 (C-5), 124.90 (C-7), 126.63 (2C-Ph), 127.47 (C-Ph), 128.40 (2C-Ph), 133.84 (C-2), 137.62 (C-Ph), 141.68 (C-8a), 155.93 (CO) ; ms (m/z, relative intensity) 280 (M^+, 6), 209 (36), 181 (17), 78 (100), 51 (53) ; Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.57 ; H, 5.71 ; N, 20.00. Found : C, 68.50 ; H, 5.70 ; N, 20.05.

7b : 0.69 g (66 %) (recrystallization solvent : dichloromethane) ; mp 250-252°C ; ir (KBr) ν_{max} 3150, 1650, 1530, 1290 ; ^{1}H-nmr (DMSO-d_6) δ 7.02 (m, 2H, H-6, Ph), 7.34 (m, 4H, H-7, Ph), 7.53 (m, 4H, Ph), 7.65 (d, 1H, $J_{7,8}$ = 9 Hz, H-8), 8.08 (m, 2H, Ph), 8.18 (d, 1H, $J_{5,6}$ = 7 Hz, H-5), 8.52 (s, 1H, NH), 9.30 (s, 1H, NH) ; ^{13}C-nmr (DMSO-d_6) δ 112.11 (C-6), 115.93 (C-3), 116.83 (C-8), 118.53 (2C-Ph), 122.14 (C-Ph), 123.62 (C-5), 125.10 (C-7), 126.66 (2C-Ph), 127.61 (C-Ph), 128.54 (2C-Ph), 128.72 (2C-Ph), 133.74 (C-Ph), 137.94 (C-2), 139.65 (C-Ph), 141.82 (C-8a), 153.61 (CO) ; ms (m/z, relative intensity) 328 (M^+, 21), 209 (75), 181 (34), 78 (100), 51 (44) ; Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.17 ; H, 4.88 ; N, 17.07. Found : C, 72.96 ; H, 4.89 ; N, 17.11.

5-Aminoethylpyrido[1',2':1,2]imidazo[5,4-c]isoquinoline (8a) and (**9**) : To a solution of **4** (1.5 g, 3.2 mmol) in dry nitrobenzene (50 ml) at 0°C was added dropwise a solution of ethyl isocyanate (0.23 g, 3.2 mmol) in nitrobenzene (5 ml). The solution was allowed to stand at room temperature for 1 h and then at 170°C for 4 h. The solvent was removed in vacuo to dryness, and the residue was washed with cold ethanol to remove phosphine oxide. The resulting residue was chromatographed on neutral alumina eluting with Hexane-AcOEt (50/50, v/v) to give 0.32 g (38 % yield) of **8a** (recrystallization solvent : diethyl ether) ; mp 226-228°C ; ir (KBr) ν_{max} 3270, 1620, 1575, 1535 ; ^{1}H-nmr ($CDCl_3$) δ 1.42 (t, 3H, J = 7.5 Hz, CH_3), 3.55 (m, 2H, CH_2), 5.43 (s, 1H, NH), 6.85 (t, 1H, $J_{8,9}$ = 7 Hz, H-9), 7.26 (ps. t, 1H, H-10), 7.52 (t, 1H, $J_{2,3} = J_{3,4}$ = 7.5 Hz, H-3), 7.69 (d, 1H, $J_{10,11}$ = 9 Hz, H-11), 7.77 (t, 1H, $J_{1,2} = J_{2,3}$ = 7.5 Hz, H-2), 7.90 (d, 1H, $J_{3,4}$ = 7.5 Hz, H-4), 8.60 (d, 1H, $J_{8,9}$ = 7 Hz, H-8), 8.63 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1) ; ^{13}C-nmr ($CDCl_3$) δ 14.81 (CH_3), 36.93 (CH_2), 111.01 (C-9), 117.33 (C-11), 118.60 (C-4a), 122.74 (C-1), 122.99 (C-8), 123.24 (C-3), 124.60 (C-12b), 125.68 (C-4), 126.13 (C-10), 130.33 (C-2), 131.00 (C-12a), 134.82 (C-6a), 143.54 (C-11a), 152.14 (C-5) ; ms (m/z, relative intensity) 262 (M^+, 27), 123 (14), 78 (100), 51 (38) ; Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.28 ; H, 5.34 ; N, 21.37. Found : C, 73.36 ; H, 5.32 ; N, 21.32. Further elution yielded 0.52 g of **9** (admixed with Ph_3PO). Due to the complexity of the product mixture, nmr data are listed without assignment ; ^{1}H-nmr ($CDCl_3$) δ 6.71 (2H), 7.24, 7.65, 7.80 (d, 1H, J = 7 Hz), 7.89 (t, 1H, J = 7.5 Hz), 7.97 (d, 2H, J = 7 Hz), 8.08 (d, 1H, J = 7 Hz), 8.18 (s, 1H, NH), 8.53 (d, 1H, J = 8 Hz), 8.77 (d, 1H, J = 8 Hz) ; ^{13}C-nmr ($CDCl_3$) δ 110.92, 111.55, 117.48 (2C), 117.91, 118.49, 123.15, 123.59, 123.91, 124.69, 126.33, 126.80, 127.16, 127.49,

127.68, 128.48 (2C), 130.86, 131.68, 132.13 (2C), 133.77, 134.12, 138.60, 142.93, 144.78, 149.16 ; ms (m/z, relative intensity) 426 (M^+, 47), 245 (7), 181 (27), 78 (100).

5-Aminophenylpyrido[1',2':1,2]imidazo[5,4-c]isoquinoline (8b) : Reaction of **4** (1.5 g, 3.2 mmol) in dry nitrobenzene (50 ml) with phenyl isocyanate (0.4 g, 3.4 mmol) in nitrobenzene (10 ml) gave after identical workup 0.47 g (47 % yield) of **8b** (recrystallization solvent : diethyl ether) ; mp 212-214°C ; ir (KBr) ν_{max} 3320, 1620, 1590, 1485, 1305 ; ^{1}H-nmr ($CDCl_3$) δ 6.91 (t, 1H, $J_{8,9}$ = 7 Hz, H-9), 7.12 (t, 1H, J = 7.5 Hz, Ph), 7.34 (ps. t, 1H, H-10), 7.39 (s, 1H, NH), 7.43 (t, 2H, J = 7.5 Hz, Ph), 7.63 (t, 1H, $J_{2,3} = J_{3,4}$ = 8.5 Hz, H-3), 7.73 (d, 1H, $J_{10,11}$ = 9 Hz, H-11), 7.81 (ps. t, 1H, H-2), 7.85 (d, 2H, J = 7.5 Hz, Ph), 8.09 (d, 1H, $J_{3,4}$ = 8.5 Hz, H-4), 8.63 (d, 1H, $J_{8,9}$ = 7 Hz, H-8), 8.73 (d, 1H, $J_{1,2}$ = 8 Hz, H-1) ; ^{13}C-nmr ($CDCl_3$) δ 111.32 (C-9), 117.52 (C-11), 119.36 (C-4a), 119.69 (2C-Ph), 122.61 (C-1), 122.82 (C-8), 123.26 (C-3), 123.49 (C-4), 126.31 (C-10), 126.76 (C-12b), 127.07 (C-Ph), 129.03 (2C-Ph), 130.70 (C-2), 131.18 (C-12a), 133.43 (C-6a), 140.49 (C-Ph), 144.48 (C-11a), 148.01 (C-5) ; ms (m/z, relative intensity) 310 (M^+, 100), 205 (10), 155 (12), 78 (41), 51 (21) ; Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.43 ; H, 4.51 ; N, 18.06. Found : C, 77.56 ; H, 4.32 ; N, 18.12. Further elution yielded 0.6 g of **9** admixed with Ph_3PO.

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