

REACTIVITY OF AMINOETHYLIMIDAZO[1,2-*a*]PYRIDINE : ACCESS TO AZA- γ -CARBOLINE SERIES

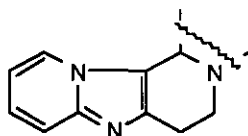
Anne Jouanisson,¹ Olivier Chavignon,¹ Jacques Couquelet,¹ Jean-Claude Teulade,^{1*} Jean-Louis Chabard,¹ and Gérard Dauphin²

¹ Département d'Analyse Structurale et de Pharmacologie, Faculté de Pharmacie
B P 38, 28 P. H. Dunant, 63001 Clermont-Ferrand CEDEX 1, France

² Laboratoire de Chimie Organique Biologique, URA-CNRS 485, 63170 Aubière,
France

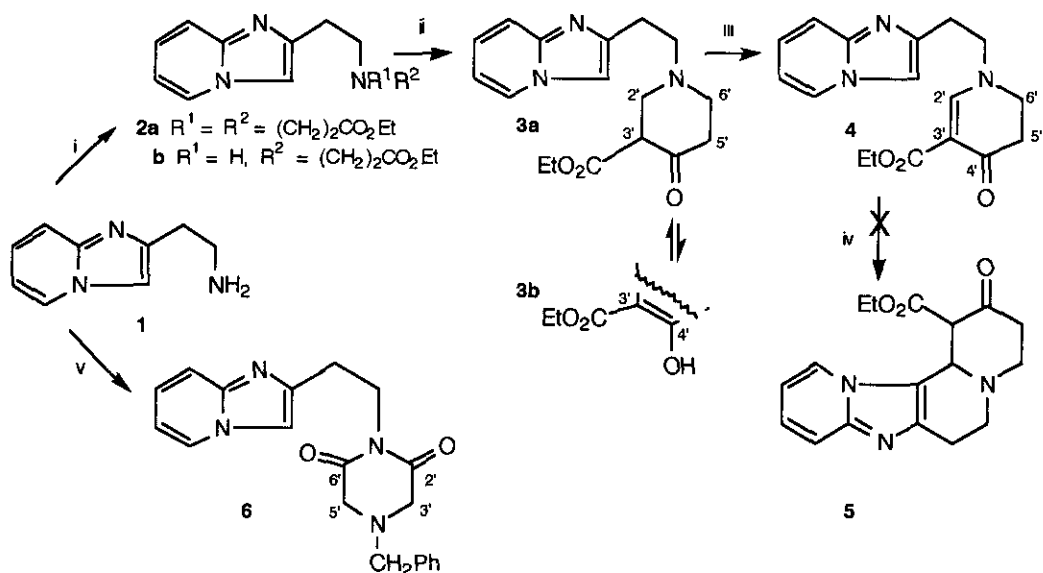
Abstract - From 2-(2-aminoethyl)imidazo[1,2-*a*]pyridine (**1**), the synthesis of compounds possessing the azatetrahydrocarboline moiety was described. The Fujii procedure did not afford the expected tetracyclic compound (**5**). However, the Pictet-Spengler reaction led to tricyclic aza- γ -carbolinic type compounds (**8a-c**).

The access to polycyclic indole alkaloids has been a widespread area of interest during last decades. In particular, the synthesis of pentacyclic indole derivatives related to yohimbine¹ and reserpine due to their potential pharmaceutical importance, has been intensively investigated.² Furthermore, it was noted that the addition of a nitrogen atom in an alkaloidic structure generally increased its activity and-or generated modifications of the pharmacological profile.³ In the course of our search on biologically active alkaloids, we decided to synthesize by different routes polycyclic compounds possessing the imidazo[1,2-*a*]pyridine moiety.⁴



The first route that was investigated for the synthesis of tetracyclic compounds is depicted in Scheme 1. The condensation of **1** obtained from 2-(2-aminoethyl)imidazo[1,2-*a*]pyridine dihydrochloride derivative,⁵ with ethyl

acrylate at 0°C resulted in the formation of two compounds (**2a**) and (**2b**), which were identified by mass [m/z : 361 (M^+); 261 (M^+) respectively] and by nmr spectroscopy. The same condensation at room temperature afforded only the diester (**2a**) in 59 % yield. Compound (**2a**) was dissolved in toluene and caused to undergo a Dieckmann reaction using an excess of potassium *ter*-butoxide as a condensing agent.⁶ The reaction was performed at 0°C for four hours with stirring at room temperature to yield compound (**3a,b**), which was identified in mass spectroscopy [m/z : 315 (M^+)]. The ¹³C-nmr spectrum showed a ketonic form (**3a**) (C-3' : 56.42 ; C-4' : 203.46) and an enolic form (**3b**) (C-3' : 96.74 ; C-4' : 171.03). In order to obtain tetracyclic compound (**5**), oxidation of the crude piperidine derivative (**3a,b**) followed by cyclisation in one step was foreseen.⁷ With Fujii⁸ procedure, **3a,b** was oxidized to the 2-[2-(2,3-dehydro-3-ethoxycarbonyl-4-oxopiperidino)ethyl]imidazo[1,2-*a*]pyridine (**4**), which was identified by mass [m/z : 313 (M^+)] and nmr spectroscopy. The ¹H-nmr spectrum presented a singlet at δ 7.38 for the olefinic proton, and four triplets at δ 2.37, 3.03, 3.48, and 3.79 due to the methylene protons. In the ¹³C-nmr spectrum, signals at δ 100.14 and 159.57 assigned to C-3' and C-2' confirmed the presence of the unsaturated structure.



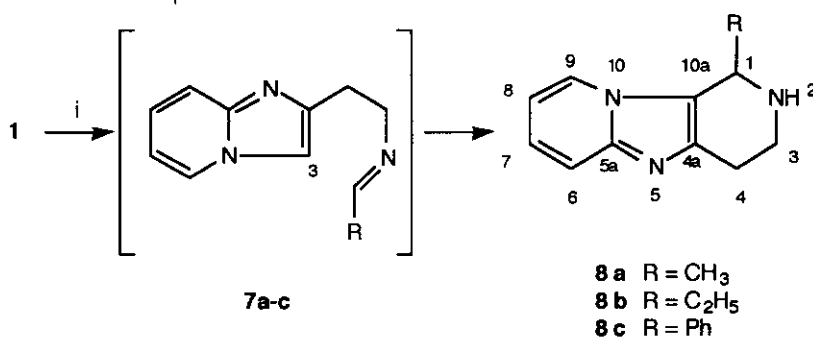
Reagents and conditions : (i) ethyl acrylate, triethylamine, H₂O, MeOH, 0°C ; (ii) toluene, potassium *t*-butoxide 1.5 mol, 4 h, room temperature ; (iii) 33 % aq. EtOH, 3 eq. Hg(OAc)₂, 3 eq. disodium edetate (EDTA-2Na), reflux 3 h ; (iv) H₂SO₄ 10 %, room temperature or reflux ; (v) *N*-benzyliminodiacetic acid, 250°C, 5 min.

Scheme 1

The pyridine annelation of compound (4) by aqueous sulfuric acid⁹ did not afford the expected quinolizidine compound (5). It may be postulated that both conjugated carbonyl and ester functions stabilize the double bond,¹⁰ avoiding thus cyclisation into tetracyclic quinolizidine derivative.

Another route of access to tetracyclic structures was attempted according to literature data from indolopiperazinedione.¹¹ Piperazinedione (6) was prepared in 7 % yield by heating at 250°C for 5 min *N*-benzyliminodiacetic acid with the ethyl amine (1). The structure of compound (6) [m/z : 348 (M^+)] was established by ¹H and ¹³C-nmr spectral data. Due to the very poor yield, this route was discarded.

A new synthetic pathway was then worked up. The Pictet-Spengler reaction has been developed for the synthesis of carbolines and has often been applied to the synthesis of indole alkaloids.¹² The condensation of an aldehyde R-CHO (R = CH₃, C₂H₅, Ph) with compound (1) at room temperature gave, through the formation of a Schiff base in an aprotic solvent, tetrahydrocarbolines (8a-c) in 20 %, 22 %, and 25 % yields, respectively (Scheme 2). They were identified by nmr spectroscopy ; the ¹H-nmr spectrum of 8a exhibited a quartet at δ 4.36 due to H-1. The ¹³C-nmr spectrum showed the presence of three quaternary carbons at δ 122.16, 140.73, 144.45 corresponding to C-10a, C-4a, and C-5a respectively. In compound (8b) the two methylenic protons on α position of the asymmetric center C-1 were in enantiotopic relationships. We noted in ¹H-nmr spectrum of 8c the shielding of the signal corresponding to H-9, due to the effect of the phenyl nucleus. All these structures were also confirmed by mass spectroscopy [m/z : 187 (8a), 201 (8b), 249 (8c)].



Reagents and conditions : (i) Acetaldehyde, propionaldehyde or benzaldehyde 1.2 mol, methanol, room temperature, 8 h.

Scheme 2

In the Pictet-Spengler reaction, the use of various electrophilic reagents as Me₃SiCl, which could activate the C=N double bond did not enhance the reaction rate contrary to the work of Hino in the indole serie.¹³

EXPERIMENTAL

General. Ir spectra were recorded with a BECKMAN ACCULAB 2 spectrophotometer. Absorption bands are expressed in 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) and on a Bruker MSL-300 working at 300 MHz (^1H -nmr) and 75 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, q, m, ps. t and br s indicate singlet, doublet, triplet, quartet, multiplet, pseudo triplet and broad singlet respectively ; Im indicates imidazo[1,2-a]pyridine. Mass spectra were performed on HEWLETT PACKARD 5989A and 5985B instruments.

2-(2-Aminoethyl)imidazo[1,2-a]pyridine (1) : The treatment of 2-(2-aminoethyl)imidazo[1,2-a]pyridine dihydrochloride (8.72 g, 38 mmol)⁵ with aqueous ammonia (20 %, 50 ml) at room temperature for 30 min afforded after filtration pure compound (1) (6 g, 38 mmol) ; mp 240-242°C ; ir (KBr) ν_{max} 3100, 1550, 1400, 760 ; ^1H -nmr (300 MHz, DMSO-d_6) δ 3.14 (m, 4H, CH_2), 4.14 (br s, 2H, NH_2), 6.96 (t, 1H, $J = 7$ Hz, H-6), 7.34 (ps. t, 1H, H-7), 7.54 (d, 1H, $J = 9$ Hz, H-8), 7.92 (s, 1H, H-3), 8.59 (d, 1H, $J = 7$ Hz, H-5) ; ^{13}C -nmr (75 MHz, DMSO-d_6) δ 25.43 (Im- CH_2), 38.45 (Im- CH_2CH_2), 111.41 (C-6), 113.33 (C-3), 115.14 (C-8), 126.99 (C-7), 127.39 (C-5), 139.98 (C-2), 143.23 (C-8a) ; ms (m/z, relative intensity) 161 (M^+ , 22), 143 (14), 132 (100), 131 (28), 78 (18) ; Anal. Calcd for $\text{C}_9\text{H}_{11}\text{N}_3$: C, 67.08 ; H, 6.83 ; N, 26.09. Found : C, 67.05 ; H, 6.85 ; N, 26.10.

Preparation of 2-[2-bis(2-ethoxycarbonylethyl)aminoethyl]imidazo[1,2-a]pyridine (2a) and of 2-[(2-ethoxycarbonylethyl)aminoethyl]imidazo[1,2-a]pyridine (2b) : Method A : A mixture of compound (1) (6 g, 38 mmol), water (44 ml), methanol (60 ml) and triethylamine (18 ml) was stirred and cooled to 0°C. Ethyl acrylate (10.6 ml, 98 mmol) was then added dropwise over 15 min. The solution was stirred at 0°C for 6 h. After solvent removal in vacuo, the residue was chromatographed on neutral alumina with CH_2Cl_2 -EtOH (98 : 2, v/v) to yield **2a** (4.7 g, 35 %) as an oil ; ir (NaCl) ν_{max} 1720, 1630, 1170, 750 ; ^1H -nmr (400 MHz, CDCl_3) δ 1.11 (t, 6H, $J = 7$ Hz, CH_3), 2.35 (t, 4H, $J = 7$ Hz, CH_2CO), 2.76 (m, 8H, Im- CH_2 , Im- CH_2CH_2 , $2\text{CH}_2\text{CH}_2\text{CO}$), 3.98 (q, 4H, $J = 7$ Hz, OCH_2), 6.61 (t, 1H, $J = 7$ Hz, H-6), 7.00 (ps. t, 1H, H-7), 7.30 (s, 1H, H-3), 7.40 (d, 1H, $J = 9$ Hz, H-8), 7.95 (d, 1H, $J = 7$ Hz, H-5) ; ^{13}C -nmr (100 MHz, CDCl_3) δ 13.98 (CH_3), 26.64 (Im- CH_2), 32.53 (CH_2CO), 49.03 ($\text{CH}_2\text{CH}_2\text{CO}$), 53.27 (Im- CH_2CH_2), 60.06 (OCH_2), 109.48 (C-6), 111.74 (C-3), 116.52 (C-

8), 124.00 (C-7), 125.21 (C-5), 144.52 (C-8a or C-2), 145.20 (C-2 or C-8a), 172.31 (CO) ; ms (m/z, relative intensity) 361 (M⁺, 25), 274 (20), 260 (20), 230 (100), 216 (75), 145 (50), 131 (20), 78 (20) ; Anal. Calcd for C₁₉H₂₇N₃O₄ : C, 63.16 ; H, 7.48 ; N, 11.63. Found C, 63.18 ; H, 7.47 ; N, 11.64. Further elution gave compound (**2b**) (0.30 g, 3 %) as an oil ; ir (NaCl) ν_{\max} 1720, 1180, 750 ; ¹H-nmr (400 MHz, CDCl₃) δ 1.21 (m, 3H, CH₃), 2.08 (br s, 1H, NH), 2.52 (t, 2H, J = 6.5 Hz, CH₂CO), 2.96 (m, 4H, CH₂), 3.05 (m, 2H, CH₂), 4.10 (q, 2H, J = 7 Hz, OCH₂), 6.73 (t, 1H, J = 7 Hz, H-6), 7.13 (ps. t, 1H, H-7), 7.40 (s, 1H, H-3), 7.52 (d, 1H, J = 9 Hz, H-8), 8.04 (d, 1H, J = 7 Hz, H-5) ; ¹³C-nmr (100 MHz, CDCl₃) δ 14.19 (CH₃), 29.25 (Im-CH₂), 34.77 (CH₂CO), 44.97 (CH₂CH₂CO), 48.98 (Im-CH₂CH₂), 60.39 (OCH₂), 109.64 (C-6), 111.92 (C-3), 117.12 (C-8), 124.12 (C-7), 125.35 (C-5), 145.23 (C-8a or C-2), 145.65 (C-2 or C-8a), 172.69 (CO) ; ms (m/z, relative intensity) 261 (M⁺, 2), 174 (13), 160 (10), 145 (10), 132 (100), 78 (10) ; Anal. Calcd for C₁₄H₁₉N₃O₂ : C, 64.37 ; H, 7.28 ; N, 16.09. Found : C, 64.35 ; H, 7.30 ; N, 16.08.

Method B : According to the above procedure at room temperature, compound (**2a**) was obtained as a sole product in 59 % yield.

Preparation of 2-[2-(3-ethoxycarbonyl-4-oxopiperidino)ethyl]imidazo[1,2-a]pyridine (**3a**) : To a cooled (0°C) solution of **2a** (3 g, 8.3 mmol) in toluene (15 ml) was added dropwise a solution of tBuOK (1.2 g, 10.7 mmol) in toluene (15 ml). After stirring 4 h at room temperature, water (15 ml) was added and the mixture was extracted with dichloromethane. After solvent removal in vacuo, the crude residue (**3a**) was directly used in the subsequent reaction without further purification ; ir (KBr) ν_{\max} 3400, 1730, 1650, 1500, 1240, 760 ; ¹H-nmr (400 MHz, CDCl₃) δ 1.23 (m, 3H, CH₃), 2.40–3.70 (m, 11H), 4.10 (m, 2H, OCH₂), 6.70 (m, 1H, H-6), 7.10 (m, 1H, H-7), 7.40 (s, 1H, H-3), 7.50 (d, 1H, J = 9 Hz, H-8), 8.00 (d, 1H, J = 7 Hz, H-5) ; ¹³C-nmr (100 MHz, CDCl₃) ketonic form (**3a**) δ 14.25 (CH₃), 27.05 (Im-CH₂), 40.65 (CH₂), 53.16 (CH₂), 55.14 (CH₂), 56.42 (C-3'), 56.47 (Im-CH₂CH₂), 60.28 (OCH₂), 109.43 (C-6), 111.88 (C-3), 116.93 (C-8), 124.17 (C-7), 125.33 (C-5), 144.99 (C-8a or C-2), 145.55 (C-2 or C-8a), 170.12 (CO), 203.46 (C-4') ; enolic form (**3b**) δ 14.25 (CH₃), 27.05 (Im-CH₂), 29.36 (CH₂), 49.33 (2CH₂), 57.33 (Im-CH₂CH₂), 60.28 (OCH₂), 96.74 (C-3'), 109.43 (C-6), 111.88 (C-3), 116.93 (C-8), 124.17 (C-7), 125.33 (C-5), 144.99 (C-8a or C-2), 145.55 (C-2 or C-8a), 170.12 (CO), 171.03 (C-4') ; ms (m/z, relative intensity) 315 (M⁺, 10), 242 (20), 230 (25), 216 (20), 184 (40), 146 (100), 145 (90), 138 (60), 132 (70), 78 (25).

Preparation of 2-[2-(2,3-dehydro-3-ethoxycarbonyl-4-oxopiperidino)ethyl]imidazo[1,2-a]pyridine (**4**) : To a solution of **3** (0.315 g, 1 mmol) in ethanol (15 ml) was added a solution of EDTA disodium salt dihydrate (1.1 g,

3 mmol) and mercuric acetate (0.96 g, 3 mmol) in water (30 ml). The resulting mixture was heated under reflux for 3 h. After cooling, the reaction mixture was poured into saturated aqueous ammonia (20 %, 20 ml) and extracted with dichloromethane (30 ml). The combined extracts were dried with K_2CO_3 , filtered and evaporated; the residue was purified by chromatography on silica gel with CH_2Cl_2 -EtOH (90 : 10, v/v) to yield **4** (0.081 g, 26 %) as a viscous oil; ir (KBr) ν_{max} 1710, 1680, 1600, 1500, 1240, 750; 1H -nmr (400 MHz, $CDCl_3$) δ 1.10 (t, 3H, $J = 7$ Hz, CH_3), 2.37 (t, 2H, $J = 8$ Hz, CH_2-5'), 3.03 (t, 2H, $J = 7$ Hz, Im- CH_2), 3.48 (t, 2H, $J = 8$ Hz, CH_2-6'), 3.79 (t, 2H, $J = 7$ Hz, Im- CH_2CH_2), 4.01 (q, 2H, $J = 7$ Hz, OCH_2), 6.69 (t, 1H, $J = 7$ Hz, H-6), 7.09 (ps. t, 1H, H-7), 7.38 (s, 1H, H-2'), 7.43 (d, 1H, $J = 9$ Hz, H-8), 7.92 (s, 1H, H-3), 8.02 (d, 1H, $J = 7$ Hz, H-5); ^{13}C -nmr (100 MHz, $CDCl_3$) δ 14.51 (CH_3), 28.22 (Im- CH_2), 35.95 (C-5'), 46.79 (Im- CH_2CH_2), 56.65 (C-6'), 59.65 (OCH_2), 100.14 (C-3'), 110.55 (C-6), 112.62 (C-3), 117.00 (C-8), 125.28 (C-7), 125.77 (C-5), 141.99 (C-2), 145.51 (C-8a), 159.57 (C-2'), 165.00 (CO), 186.85 (CO); ms (m/z, relative intensity) 313 (M^+ , 2), 284 (33), 266 (20), 240 (10), 182 (10), 145 (100), 132 (65), 78 (20); Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.18; H, 6.07; N, 13.42. Found: C, 65.15; H, 6.06; N, 13.44.

Preparation of 2-[2-(4-benzyl-2, 6-dioxopiperazino)ethyl]imidazo[1,2-a]pyridine (**6**): Compound (**1**) (0.1 g, 0.6 mmol) and *N*-benzyliminodiacetic acid (0.14 g, 0.6 mmol) were mixed and heated to 250°C for 5 min under a nitrogen atmosphere. The residue was purified by column chromatography on neutral alumina with CH_2Cl_2 -EtOH (98 : 2, v/v) to give **6** as an oil (0.015 g, 7%); ir (KBr) ν_{max} 2920, 1670, 750; 1H -nmr (400 MHz, $CDCl_3$) δ 3.05 (t, 2H, $J = 7.5$ Hz, Im- CH_2), 3.40 (s, 4H, CH_2-3' , CH_2-5'), 3.60 (s, 2H, CH_2Ph), 4.15 (t, 2H, $J = 7.5$ Hz, Im- CH_2CH_2), 6.74 (t, 1H, $J = 7$ Hz, H-6), 7.13 (ps. t, 1H, H-7), 7.30 (m, 5H, Ph), 7.42 (s, 1H, H-3), 7.55 (d, 1H, $J = 9$ Hz, H-8), 8.03 (d, 1H, $J = 7$ Hz, H-5); ^{13}C -nmr (100 MHz, $CDCl_3$) δ 27.00 (CH_2), 29.78 (CH_2), 38.70 (CH_2), 56.39 (CH_2), 60.76 (CH_2), 109.82 (C-6), 112.42 (C-3), 117.03 (C-8), 124.81 (C-7), 125.53 (C-5), 128.22 (C-Ph), 128.75 (C-Ph), 129.19 (C-Ph), 135.50 (C-*ipso*), 143.63 (C-8a or C-2), 144.79 (C-2 or C-8a), 169.93 (CO); ms (m/z, relative intensity) 348 (M^+ , 10), 257 (100), 145 (35), 132 (10), 91 (35); Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.97; H, 5.75; N, 16.09. Found: C, 68.95; H, 5.76; N, 16.07.

General procedure for the preparation of the 1,2,3,4-tetrahydroimidazo[1,2-a : 5,4-c']dipyridine (**8a-c**): To a solution of **1** (0.2 g, 1.2 mmol) in methanol (15 ml) was added 1.2 mmol of aldehyde. The mixture was stirred for 4 h at room temperature. After addition of $MgSO_4$ (2 g) and stirring for additional 4 h, the mixture was filtered off and was washed with dichloromethane. Solvent was removed in vacuo, and the residue was chromatographed on neutral alumina with CH_2Cl_2 -EtOH (98 : 2, v/v) to give compounds (**8a-c**) as oils.

1-Methyl-1,2,3,4-tetrahydroimidazo[1,2-a : 5,4-c']dipyridine (8a) : Yield : 20 % ; ir (KBr) ν_{\max} 3400, 2920, 1500, 760 ; $^1\text{H-nmr}$ (400 MHz, CDCl_3) δ 1.52 (d, 3H, $J = 6.5$ Hz, CH_3), 2.10 (br s, 1H, NH), 2.87 (m, 2H, H-4,4'), 3.15 (m, 1H, H-3), 3.31 (m, 1H, H-3'), 4.36 (q, 1H, $J = 6.5$ Hz, H-1), 6.78 (t, 1H, $J = 7$ Hz, H-8), 7.13 (ps. t, 1H, H-7), 7.55 (d, 1H, $J = 9$ Hz, H-6), 7.85 (d, 1H, $J = 7$ Hz, H-9) ; $^{13}\text{C-nmr}$ (100 MHz, CDCl_3) δ 18.96 (CH_3), 27.02 (C-4), 40.58 (C-3), 46.22 (C-1), 111.71 (C-8), 117.36 (C-6), 122.16 (C-10a), 123.07 (C-7 or C-9), 123.14 (C-9 or C-7), 140.73 (C-4a), 144.45 (C-5a) ; ms (m/z, relative intensity) 187 (M^+ , 20), 172 (100), 157 (15), 145 (18), 78 (22) ; Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3$: C, 70.59 ; H, 6.95 ; N, 22.46. Found C, 70.55 ; H, 6.97 ; N, 22.48.

1-Ethyl-1,2,3,4-tetrahydroimidazo[1,2-a : 5,4-c']dipyridine (8b) : Yield : 22 % ; ir (KBr) ν_{\max} 3400, 2940, 1500, 750 ; $^1\text{H-nmr}$ (400 MHz, CDCl_3) δ 1.07 (t, 3H, $J = 7.5$ Hz, CH_3), 1.77 (m, 1H, CH_2CH_3), 1.94 (m, 1H, CH_2CH_3), 2.30 (br s, 1H, NH), 2.86 (m, 2H, H-4,4'), 3.13 (m, 1H, H-3), 3.27 (m, 1H, H-3'), 4.12 (m, 1H, H-1), 6.77 (t, 1H, $J = 7$ Hz, H-8), 7.12 (ps. t, 1H, H-7), 7.55 (d, 1H, $J = 9$ Hz, H-6), 7.84 (d, 1H, $J = 7$ Hz, H-9) ; $^{13}\text{C-nmr}$ (100 MHz, CDCl_3) δ 10.62 (CH_3), 25.14 (CH_2), 26.96 (C-4), 40.33 (C-3), 52.25 (C-1), 111.75 (C-8), 117.35 (C-6), 121.35 (C-10a), 123.09 (C-7 or C-9), 123.20 (C-9 or C-7), 141.10 (C-4a), 144.49 (C-5a) ; ms (m/z, relative intensity) 201 (M^+ , 5), 172 (100), 155 (5), 145 (10), 78 (20) ; Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3$: C, 71.64 ; H, 7.46 ; N, 20.90. Found : C, 71.63 ; H, 7.47 ; N, 20.88.

1-Phenyl-1,2,3,4-tetrahydroimidazo[1,2-a : 5,4-c']dipyridine (8c) : Yield : 25 % ; ir (KBr) ν_{\max} 3400, 2920, 1490, 740, 690 ; $^1\text{H-nmr}$ (400 MHz, CDCl_3) δ 2.17 (br s, 1H, NH), 2.99 (m, 2H, H-4,4'), 3.14 (m, 1H, H-3), 3.31 (m, 1H, H-3'), 5.36 (s, 1H, H-1), 6.54 (t, 1H, $J = 7$ Hz, H-8), 7.09 (ps. t, 1H, H-7), 7.20-7.33 (m, 6H, Ph, H-9), 7.57 (d, 1H, $J = 9$ Hz, H-6) ; $^{13}\text{C-nmr}$ (100 MHz, CDCl_3) δ 26.92 (C-4), 41.89 (C-3), 56.27 (C-1), 111.61 (C-8), 117.04 (C-6), 118.91 (C-10a), 123.52 (C-7 or C-9), 123.66 (C-9 or C-7), 128.09 (C-Ph), 128.45 (C-Ph), 129.18 (C-Ph), 139.88 (C-ipso), 142.70 (C-4a), 144.80 (C-5a) ; ms (m/z, relative intensity) 249 (M^+ , 20), 248 (M^+-1 , 22), 219 (25), 172 (100), 145 (10), 78 (20) ; Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3$: C, 77.11 ; H, 6.02 ; N, 16.87. Found C, 77.13 ; H, 6.03 ; N, 16.84.

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