Synthesis of *N*-Methyl-4-pyridyl-1,2,3,4-tetrahydroisoquinolines *via* a Pictet-Spengler Cyclisation

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Dedicated to the memory of Professor Raymond N. Castle

The synthesis of *N*-methyl-4-pyridyl-1,2,3,4-tetrahydroisoquinolines (**6a,b,c**) was achieved *via* a Pictet-Spengler cyclization of an activated amino group derivatized in a carbamate form. The obtained compounds have been designed as potential serotonin analogs.

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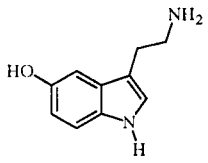
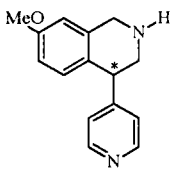
Introduction.

Serotonin (5-hydroxytryptamine, 5-HT) is a neuromodulator and a hormone [1]. In the last decade, research on 5-HT analogues [2] have been accelerated in view of their potential therapeutic effects. During molecular modeling studies, analogies were observed between chemical functions of **5-HT** and 4-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinoline derivatives. Indeed, a 3D comparison of the structure of compound **1** with **5-HT** indicated that the tetrahydroisoquinoline ring may be considered as a bioisoster of the indole ring. In particular, it was noted that the pyridine nitrogen and the oxygen atom of the methoxy group of **1** were placed at the same relative positions as the amine and the hydroxyl in **5-HT**. The three-dimensional structure of **5-HT** was obtained from X-ray crystallographic coordinates, extracted from the Cambridge Structure Data Base [3, 4]. The compound **1** was built and optimized by using the DISCOVER software [5] and the CVFF force field [6].



5-HT



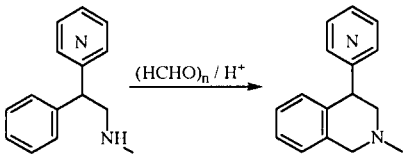
1

A survey of the literature showed that tetrahydroisoquinolines bearing a pyridyl group at the fourth position were unknown. This article describes, for the first time, the synthesis of such compounds unsubstituted on the phenyl ring.

Results.

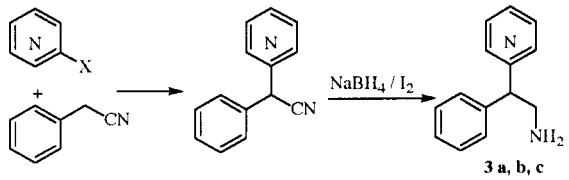
An obvious route to such compounds would hinge on a Pictet-Spengler synthesis [7,8]. This strategy would require access to 2-phenyl-2-pyridylethylamine precursors as well as suitably forcing conditions to bring about ring closure of the unactivated aromatic ring (Scheme 1) [9].

Scheme 1



The precursors to the pyridine series were obtained by reaction of an appropriately substituted pyridine with phenylacetonitrile. Various conditions were reported in the literature. Our guide was the availability of starting materials and the easiness of the experimental conditions.

Scheme 2



2 a, b, c
a : 2-pyridyl
b : 3-pyridyl
c : 4-pyridyl

3 a, b, c

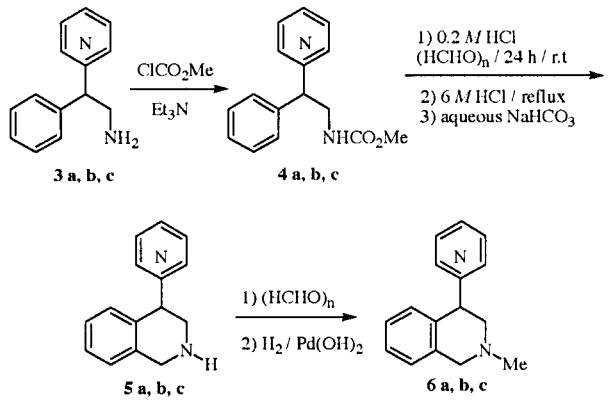
Compound **2a** was obtained in 40% yield by using 2-bromopyridine in the presence of Aliquat 336 and potassium *tert*-butoxide without solvent [10]. Compound **2b** was synthesized by using 3-fluoropyridine, which gave better results than the 3-bromo isomer, in the presence of sodium hydride in tetrahydrofuran [11]. For compound **2c** we tested two methods: 1) condensation of 1-triphenylmethylpyridinium fluoroborate [12] in the presence of lithium diisopropylamide at -78° in

tetrahydrofuran, but the yields were poor due to the instability of the reagent 2) condensation of 4-methoxypyridine in 70% yield, with phenylacetonitrile in the presence of sodium hydride in tetrahydrofuran over five days (Scheme 2) [13].

The 2-phenyl-2-pyridylacetonitriles **2** were reduced with a mixture of sodium borohydride / iodine (Scheme 2) [14]. The corresponding 2-phenyl-2-pyridylethylamines **3a,b,c** were identified by spectral analysis (see experimental section).

The Pictet-Spengler reactions of amines **3** were tested by condensation of paraformaldehyde and subsequent treatment with acid. Whatever conditions (acetic acid / concentrated sulfuric acid (3/1) at room temperature or at 90-95°, hydrochloric acid at room temperature or at 100°) were employed, we did not obtain the tetrahydroisoquinoline derivatives but only tar like material. It can be postulated that the electrophilic species of the Pictet-Spengler reaction (the aminomethylene cation) may be stabilized by the nitrogen lone pair and become too weak of an electrophile to attack the non-activated phenyl ring. So we decided to enhance the reactivity of the electrophile by diminishing the stabilizing effect of the nitrogen lone pair [15]. To achieve this objective, the amine group was derivatized into the corresponding methylcarbamates **4a,b,c** [16]. Alternatively, treatment with paraformaldehyde and hydrochloric acid (0.2 *M*) yielded the required tetrahydroisoquinoline carbamate derivatives which were *in situ* deprotected (6 *M* hydrochloric acid at reflux) leading to the 4-pyridyl-1,2,3,4-tetrahydroisoquinolines **5a,b,c** (Scheme 3).

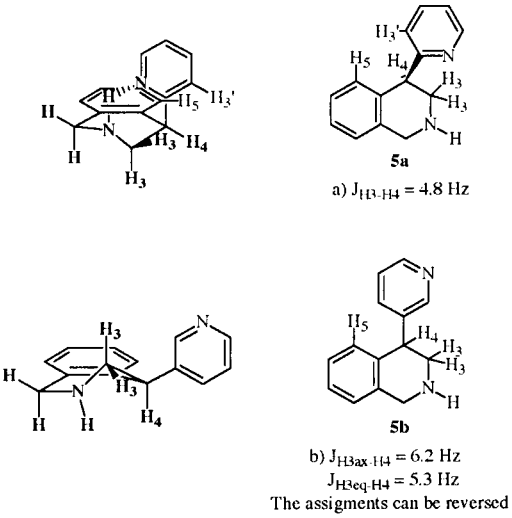
Scheme 3



3 a, b, c **4 a, b, c** **5 a, b, c** **6 a, b, c**

The ^1H nmr spectrum of compound **5a** presents an interesting behaviour compared to **5b** and **5c**. The two protons H3 appear as a doublet with $J_{H3\text{-}H4}$ = 4.8 Hz. On the other hand in **5b** and **5c**, each one of the two protons H3 appears as a doublet of doublet with $J_{H3\text{-}H4}$ = 5.3 and 6.2 Hz. Molecular models clearly show that in the case of **5a**, the two protons H3 are equivalent with respect to H4 when the 2-pyridyl group is axial. This situation is probably a consequence of the occurrence of a hydrogen bond between the amine's proton of the tetrahydroisoquinoline ring and the nitrogen of the axial pyridine ring. With compound **5b** (or **5c**), hydrogen bonding is inhibited and the pyridine ring prefers an equatorial position where the two protons H3 are different with respect to H4 (Scheme 4).

Scheme 4



5a

a) $J_{H3\text{-}H4}$ = 4.8 Hz

5b

b) $J_{H3ax\text{-}H4}$ = 6.2 Hz
$J_{H3eq\text{-}H4}$ = 5.3 Hz
The assigments can be reversed

In agreement with the 3D-structure model, the NOESY spectra of **5a** confirms that the two protons H3 are equivalent with respect to H4. Moreover, nOes were observed between the H4 atom and the protons H5 and H3' (Scheme 4).

Finally secondary amines **5a,b,c** were converted into the *N*-methyl derivatives **6a,b,c** through reductive amination in the presence of palladium hydroxide (Scheme 3). The racemic compounds obtained will be submitted to deracemization prior to biological testing.

EXPERIMENTAL

The following compounds were prepared by literature methods: 2-(pyrid-2-yl)phenylacetonitrile (**2a**) [10], 2-(pyrid-3-yl)phenylacetonitrile (**2b**) [11], 2-(pyrid-4-yl)phenylacetonitrile (**2c**) [13]. Commercially available reagents were used as received unless otherwise stated. Tetrahydrofuran was distilled from sodium / benzophenone ketyl prior to use. ^1H and ^{13}C nmr spectra were recorded on Bruker AC 200 or Avance 300 spectrometers, in deuteriochloroform with tetramethy lsilane (TMS) as an internal standard. The infrared spectra were recorded on a Perkin Elmer FT-IR 1650 spectrometer. Elemental analyses were performed on a CE Instruments EA-1110 CHNS-O apparatus. The high resolution mass spectra (hrms) were obtained on a JEOL JMS-AX500 instrument.

General Procedure for the Synthesis of Amines **3a,b,c**.

A solution of the appropriate nitrile **2** (2.00 g, 10 mmoles) and sodium borohydride (0.90 g, 23 mmoles) in dry tetrahydrofuran

(100 ml) was cooled at 0°. A solution of iodine (2.61 g, 10 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise under nitrogen. The resulting mixture was then stirred at reflux for three hours. Methanol (50 ml) was added drop by drop at room temperature and the solution was stirred for one hour. The solvents were removed *in vacuo*, a 20% aqueous solution of potassium hydroxide (100 ml) was added to the residue and the mixture was then stirred overnight. The aqueous solution was extracted several times with dichloromethane and the organic phase was finally dried (magnesium sulfate), filtered and evaporated. The oily residue obtained was purified as follows: the crude product was transformed into a hydrochloride salt by trituration with a solution of hydrochloric acid in methanol, and washed with diethylether. The aqueous solution was basified with sodium hydrogenocarbonate, extracted with dichloromethane and the organic phase was finally dried, filtered and evaporated to give 2-phenyl-2-pyridylethylamine (**3**). Due to somewhat instability, only hrms were performed for amines **3a,b,c**.

2-Phenyl-2-(pyrid-2-yl)ethylamine (**3a**).

This compound was obtained as a yellow oil, in 60% yield. ir: ν 3358 (NH_2), 1591 (C=N) cm^{-1}; ^1H nmr: δ 8.54 (d, J = 4.7 Hz, 1H, aromatic H), 7.51 (td, J = 7.7, 1.7 Hz, 1H, aromatic H), 7.41-7.03 (m, 7H, aromatic H), 4.10 (t, J = 7.3 Hz, 1H, CH), 3.50 (dd, J = 12.7, 7.8 Hz, 1H, CH_2), 3.24 (dd, J = 12.7, 6.8 Hz, 1H, CH_2), 2.39 (s, 2H, NH_2); ^{13}C nmr: δ 162.3, 149.5, 142.1, 137.0, 129.1, 128.7, 127.2, 124.2, 122.0 (aromatic carbons), 56.6 (CH), 46.7 (CH_2) ppm; hrms required for $C_{13}H_{14}N_2$ (MH^+): m/z 199.1235. Found: m/z 199.1226.

2-Phenyl-2-(pyrid-3-yl)ethylamine (**3b**).

This compound was obtained as a yellow oil, in 55% yield. ir: ν 3368 (NH_2), 1575 (C=N) cm^{-1}; ^1H nmr: δ 8.55 (d, J = 2.2 Hz, 1H, aromatic H), 8.45 (dd, J = 4.7, 1.5 Hz, 1H, aromatic H), 7.55 (d, J = 7.6 Hz, 1H, aromatic H), 7.34-7.20 (m, 6H, aromatic H), 4.06 (t, J = 7.6 Hz, 1H, CH), 3.37 (dd, J = 7.6, 2.7 Hz, 2H, CH_2), 2.23 (s, 2H, NH_2); ^{13}C nmr: δ 150.1, 148.3, 141.8, 138.7, 135.7, 129.3, 128.9, 128.4, 127.3, 123.9 (aromatic carbons), 53.0 (CH), 47.1 (CH_2); hrms required for $C_{13}H_{14}N_2$ (MH^+): m/z 199.1235. Found: m/z 199.1236.

2-Phenyl-2-(pyrid-4-yl)ethylamine (**3c**).

This compound was obtained as a yellow oil, in 60% yield. ir: ν 3360 (NH_2), 1598 (C=N) cm^{-1}; ^1H nmr: δ 8.48 (d, J = 6.1 Hz, 2H, aromatic H), 7.34-7.17 (m, 7H, aromatic H), 4.05 (t, J = 7.7 Hz, 1H, CH), 3.36 (d, J = 7.6 Hz, 2H, CH_2), 2.28 (s, 2H, NH_2); ^{13}C nmr: δ 151.7, 149.9, 140.8, 128.8, 128.1, 127.1, 123.3 (aromatic carbons), 54.3 (CH), 46.3 (CH_2); hrms required for $C_{13}H_{14}N_2$ (MH^+): m/z 199.1235. Found: m/z 199.1240.

General Procedure for Conversion of the Primary Amines into Methyl Carbamate Derivatives.

The amine **3** (1.00 g, 5 mmoles) was dissolved in dichloromethane (25 ml) under a nitrogen atmosphere and freshly distilled triethylamine (2.11 ml, 15 mmoles) was added dropwise. Then, methyl chloroformate or methyl cyanoformate was added dropwise and the resulting solution was stirred for 24 hours at room temperature. Water was added, the layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried (magnesium sulfate), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on neutral alumina (Prolabo, medium screen: 0.05-0.16 mm) with dichloromethane as eluent.

Methyl Carbamate of 2-Phenyl-2-(pyrid-2-yl)ethylamine (**4a**).

According to the general procedure, amine **3a** (1.00 g, 5 mmoles) was converted into methyl carbamate **4a** in 65% yield, by using methyl chloroformate (0.78 ml, 10 mmoles). Yellow oil. R_f = 0.6 (dichloromethane). ir: ν 3334 (NH), 1718 (C=O) cm^{-1}; ^1H nmr: δ 8.58 (d, J = 4.9 Hz, 1H, aromatic H), 7.57 (td, J = 7.6, 1.8 Hz, 1H, aromatic H), 7.34-7.05 (m, 7H, aromatic H), 5.40 (s, 1H, NH), 4.34 (t, J = 7.2 Hz, 1H, CH), 4.05-3.70 (m, 2H, CH_2), 3.62 (s, 3H, OCH_3); ^{13}C nmr: δ 161.9 (CO), 157.4, 149.4, 141.8, 137.0, 129.1, 128.7, 127.4, 124.7, 122.1 (aromatic carbons), 53.1 (CH), 52.4 (OCH_3), 45.4 (CH_2).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$ (256.3): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.20; H, 6.22; N, 10.80.

Methyl Carbamate of 2-Phenyl-2-(pyrid-3-yl)ethylamine (**4b**).

According to the general procedure, amine **3b** (1.00 g, 5 mmoles) was converted into methyl carbamate **4b** in 50% yield, by using methyl cyanoformate (1 ml, 13 mmoles). R_f = 0.25 (dichloromethane). ir: ν 3322 (NH), 1715 (C=O) cm^{-1}; ^1H nmr: δ 8.67 (d, J = 2.0 Hz, 1H, aromatic H), 8.43 (dd, J = 4.8, 1.7 Hz, 1H, aromatic H), 7.53 (d, J = 7.9 Hz, 1H, aromatic H), 7.36-7.14 (m, 6H, aromatic H), 5.10 (s, 1H, NH), 4.24-4.16 (m, 1H, CH), 3.85-3.77 (m, 2H, CH_2), 3.61 (s, 3H, OCH_3); ^{13}C nmr: δ 157.1 (CO), 149.7, 148.2, 140.7, 137.5, 135.5, 129.0, 128.1, 127.3, 123.6 (aromatic carbons), 52.2 (OCH_3), 48.8 (CH), 45.2 (CH_2).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$ (256.3): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.24; H, 6.23; N, 10.82.

Methyl Carbamate of 2-Phenyl-2-(pyrid-4-yl)ethylamine (**4c**).

According to the general procedure, amine **3c** (1.00 g, 5 mmoles) was converted into methyl carbamate **4c** in 70% yield, by using methyl cyanoformate (2.4 ml, 30 mmoles). R_f = 0.25 (dichloromethane). ir: ν 3326 (NH), 1714 (C=O) cm^{-1}; ^1H nmr: δ 8.47 (d, J = 6.5 Hz, 2H, aromatic H), 7.42-7.15 (m, 7H, aromatic H), 4.88 (s, 1H, NH), 4.33 (t, J = 7.6 Hz, 1H, CH), 3.99-3.68 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3); ^{13}C nmr: δ 156.8 (CO), 154.9, 147.4, 138.5, 129.3, 128.0, 124.8, 123.3 (aromatic carbons), 52.3 (OCH_3), 50.4 (CH), 44.5 (CH_2).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$ (256.3): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.22; H, 6.24; N, 10.84.

General Procedure for Synthesis of the Tetrahydroisoquinoline Structure *via* Pictet-Spengler Cyclization.

To methyl carbamate **4** (1.80 g, 7 mmoles) in concentrated hydrochloric acid (35 ml), paraformaldehyde (0.42 g, 14 mmoles) was added. The resulting mixture was stirred for 24 hours at room temperature. Water was then added, the solution was neutralized with sodium hydrogencarbonate and then extracted with dichloromethane. The combined organic phases were dried (magnesium sulfate), filtered and evaporated *in vacuo*. The residue was dissolved in hydrochloric acid 6 *N* (35 ml) and the mixture was warmed to reflux for 24 hours. Then the mixture was cooled, washed with diethylether, neutralized with sodium hydrogencarbonate and extracted with diethylether. The combined organic phases were dried (magnesium sulfate), filtered and evaporated under reduced pressure to give 4-pyridyl-1,2,3,4-tetrahydroisoquinoline **5** as an oil.

The freshly obtained compounds **5** were analysed and stored as hydrochloride salts (by trituration with a solution of gaseous hydrochloric acid in methanol), or directly submitted to the *N*-methylation.

4-(Pyrid-2-yl)-1,2,3,4-tetrahydroisoquinoline (**5a**).

The compound **5a** was obtained in 35% yield. Yellow oil. ir: ν 3290 (NH), 1589 (C=N) cm^{-1} ; ^1H nmr: δ 8.46 (d, J = 4.4 Hz, 1H, aromatic H), 7.49 (td, J = 7.7, 1.8 Hz, 1H, aromatic H), 7.33-7.00 (m, 4H, aromatic H), 6.95 (d, J = 7.7Hz, 1H, aromatic H), 6.87 (d, J = 7.3 Hz, 1H, aromatic H), 4.12 (t, J = 4.8 Hz, 1H, C_4H), 4.08 (d, J = 16.8 Hz, 1H, C_1H_2), 4.00 (d, J = 16.8 Hz, 1H, C_1H_2), 3.38 (s, 1H, NH), 3.32 (d, J = 4.8 Hz, 2H, C_3H_2); ^{13}C nmr: δ 164.7, 149.9, 136.9, 136.3, 130.5, 127.0, 126.8, 126.6, 123.5, 121.9 (aromatic carbons), 50.5 (C_3H_2), 48.6 (C_1H_2), 46.3 (C_4H); hrms required for $C_{14}H_{14}N$ (MH^+): m/z 211.1235. Found: m/z 211.1237.

4-(Pyrid-3-yl)-1,2,3,4-tetrahydroisoquinoline (**5b**).

The compound **5b** was obtained in 50% yield. Yellow oil. ir: ν 3293 (NH), 1585 (C=N) cm^{-1}. ^1H nmr: δ 8.36 (dd, J = 4.8, 1.5 Hz, 2H, aromatic H), 7.28 (dt, J = 7.7, 2.0 Hz, 1H, aromatic H), 7.15-6.96 (m, 4H, aromatic H), 6.75 (d, J = 7.9 Hz, 1H, aromatic H), 4.06 (d, J = 15.9 Hz, 1H, C_1H_2), 4.02 (s_{app}, 1H, C_4H), 3.98 (d, J = 15.9 Hz, 1H, C_1H_2), 3.31 (dd, J = 13.0, 5.3 Hz, 1H, C_3H_2), 2.96 (dd, J = 13.0, 6.2 Hz, 1H, C_3H_2), 2.21 (s, 1H, NH); ^{13}C nmr: δ 150.6, 148.3, 140.8, 136.6, 136.5, 130.5, 127.0, 127.0, 126.5, 123.8 (aromatic carbons), 52.4 (C_3H_2), 48.8 (C_1H_2), 42.8 (C_4H).

4-(Pyrid-4-yl)-1,2,3,4-tetrahydroisoquinoline (**5c**).

The compound **5c** was obtained in 50% yield. Yellow oil. ir: ν 3296 (NH), 1597 (C=N) cm^{-1} ; ^1H nmr: δ 8.48 (dd, J = 4.5, 1.6 Hz, 2H, aromatic H), 7.33-6.98 (m, 5H, aromatic H), 6.84 (d, J = 5.5 Hz, 1H, aromatic H), 4.10-4.01 (m, 3H, C_4H, C_1H_2), 3.41 (dd, J = 12.9, 5.3 Hz, 1H, C_3H_2), 3.07 (dd, J = 12.9, 6.2 Hz, 1H, C_3H_2), 2.35 (s, 1H, NH); ^{13}C nmr: δ 154.2, 150.0, 136.3, 135.7, 130.3, 127.2, 127.2, 126.6, 124.5 (aromatic carbons), 51.7 (C_3H_2), 48.5 (C_1H_2), 44.5 (C_4H).

General Procedure for Synthesis of *N*-methyl-4-pyridyl-1,2,3,4-tetrahydroisoquinoline Derivatives.

To a stirred solution of 4-pyridyl-1,2,3,4-tetrahydroisoquinoline (0.700 g, 3.33 mmoles) in methanol (25 ml) was added paraformaldehyde (0.120 g, 3.99 mmoles). The mixture was stirred at reflux for 45 minutes and then allowed to reach room temperature. After addition of palladium hydroxide (0.3 g), the solution was stirred under a hydrogen atmosphere for 24 hours. After removal of the catalyst by filtration through Celite and washing with methanol, the filtrate was evaporated under reduced pressure to give *N*-methyl-4-pyridyl-1,2,3,4-tetrahydroisoquinoline **6** as an oil. The residue was purified by flash chromatography on silica gel (Merck Geduran SI 60, medium screen: 0.063-0.200 mm) with toluene/ethanol/aqueous ammonia (90/9/1) as eluent. Due to a relative unstability, only hrms will be given.

N-Methyl-4-(pyrid-2-yl)-1,2,3,4-tetrahydroisoquinoline (**6a**).

This compound was obtained in 65% yield. Yellow oil. R_f = 0.05. ^1H nmr: δ 8.56 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H, aromatic H), 7.54 (td, J = 7.7, 1.8 Hz, 1H, aromatic H), 7.27-7.04 (m, 5H, aromatic H), 6.94 (d, J = 7.2 Hz, 1H, aromatic H), 4.46 (t, J = 5.8 Hz, 1H, C_4H), 3.76 (d, J = 14.9 Hz, 1H, C_1H_2), 3.61 (d, J = 14.9 Hz, 1H, C_1H_2), 2.96 (sept., J = 5.8 Hz, 2H, C_3H_2), 2.41 (s, 3H, NCH_3); ^{13}C nmr: δ 164.4, 148.9, 136.2, 135.3, 129.3, 126.4, 126.3, 126.2, 125.2, 123.5, 121.3 (aromatic carbons), 59.5 (CH_2), 58.2 (CH_2), 47.7 (NCH_3), 45.9 (CH). hrms required for $C_{15}H_{16}N_2$ (MH^+): m/z 225.1392. Found: m/z 225.1395.

N-Methyl-4-(pyrid-3-yl)-1,2,3,4-tetrahydroisoquinoline (**6b**).

This compound was obtained in 76% yield. Yellow oil. R_f = 0.05. ^1H nmr: δ 8.53 (s, 1H, aromatic H), 8.47 (d, J = 4.7 Hz, 1H, aromatic H), 7.48 (dt, J = 8.0, 1.9 Hz, 1H, aromatic H), 7.30-7.05 (m, 4H, aromatic H), 6.85 (d, J = 7.1 Hz, 1H, aromatic H), 4.26 (t, J = 6.2 Hz, 1H, C_4H), 3.77 (d, J = 15.5 Hz, 1H, C_1H_2), 3.61 (d, J = 15.5 Hz, 1H, C_1H_2), 2.98 (dd, J = 11.5, 5.3 Hz, 1H, C_3H_2), 2.62 (dd, J = 11.5, 7.1 Hz, 1H, C_3H_2), 2.42 (s, 3H, NCH_3); ^{13}C nmr: δ 150.6, 148.3, 141.0, 136.8, 136.2, 135.7, 129.7, 126.9, 126.8, 126.8, 123.7 (aromatic carbons), 61.5 (CH_2), 58.6 (CH_2), 46.4 (NCH_3), 43.6 (CH). hrms required for $C_{15}H_{16}N_2$ ($M^{+\bullet}$): m/z 224.1313. Found: m/z 224.1308.

N-Methyl-4-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinoline (**6c**).

This compound was obtained in 86% yield. Yellow oil. R_f = 0.2. ^1H nmr: δ 8.55 (dd, J = 4.4, 1.6 Hz, 2H, aromatic H), 7.31-6.98 (m, 5H, aromatic H), 6.76 (d, J = 7.2 Hz, 1H, aromatic H), 4.13 (t, J = 5.9 Hz, 1H, C_4H), 3.65 (d, J = 15.2 Hz, 1H, C_1H_2), 3.55 (d, J = 15.2 Hz, 1H, C_1H_2), 2.88 (dd, J = 11.5, 5.4 Hz, 1H, C_3H_2), 2.55 (dd, J = 11.5, 6.9 Hz, 1H, C_3H_2), 2.32 (s, 3H, NCH_3); ^{13}C nmr: δ 153.8, 149.5, 135.2, 134.8, 129.1, 128.5, 126.4, 126.3, 124.1 (aromatic carbons), 60.4 (CH_2), 58.0 (CH_2), 45.8 (NCH_3), 45.0 (CH). hrms required for $C_{15}H_{16}N_2$ ($M^{+\bullet}$): m/z 224.1313. Found: m/z 224.1321.

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