SYNTHESIS OF 1,2-DIAZAPHENALENES UNDER MICROWAVE

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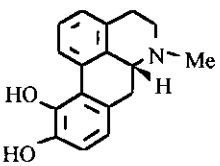
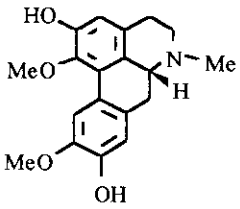
Abstract - 1,2-Diazaphenalenes were prepared by condensation reactions of hydrazine with isophorone derivatives under various conditions: conventional heating in homogeneous solution and microwave activation either in homogeneous solution or in dry media. Microwave irradiation gave the best results with both enhancements in rates and yields. In many cases, decarboxylation of the heterocycles formed took place. When the reactions were carried out in dry media over K10 montmorillonite, dicondensation products were obtained beside the desired heterocycles.

INTRODUCTION

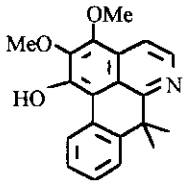
In contrast with the extensive literature on the synthesis of fused heterocycles,[1-3] only few reports dealing with the synthesis of 1,2-diazaphenalene derivatives are available. It has been reported that substituted 1*H*-1,2-diazaphenalenes were obtained by heating 8-hydroxy-1-naphthaldehyde or 8-acetyl-(or benzoyl)-1-naphthol with hydrazine in boiling ethylene glycol.[4,5] Although 1*H*-azaphenalenes decompose rather quickly,[6,7] 1*H*-1,3-diazaphenalenes and 1*H*-1,2-diazaphenalenes are more stable in air.[4,8] The three fused cycles of the monoazaphenalene framework are found in natural and semi-synthetic products such as apomorphine (**1**), boldine (**2**) and melosmine (**3**) (Scheme 1).[9] These aporphinoïds exhibit considerable pharmacological activities.[9] Most of them display promising effects in large clinical trials on animals (NCS antidepressant, dopaminergic agonist and antagonist, antifungus cholagogue ...).[9] Apomorphine is a potential Parkinson's desease therapeutic,[9] and boldine is used to protect biological systems *in vitro* against peroxydation by free radicals.[9] As part of a program devoted to the preparation of fused heterocyclic derivatives and potentially physiologically active compounds using natural substances as starting materials, and on the basis of the structural similarity with the above quoted active compounds, we now describe the synthesis of substituted hexahydro-1,2-diazaphenalenes starting from isophorone derivatives.



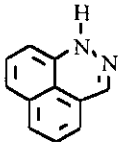
1 apomorphine



2 boldine



3 melosmine



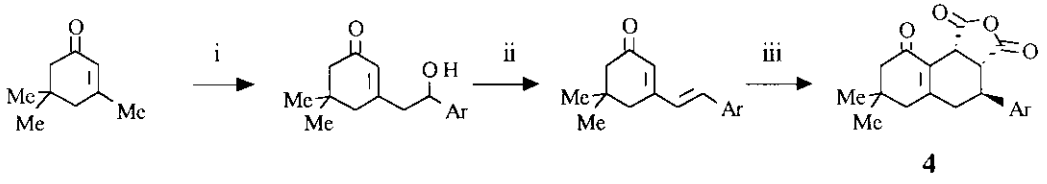
1*H*-1,2-diazaphenalene

Scheme 1

RESULTS AND DISCUSSION

a) Diazaphenalene derivatives synthesis

The condensation of hydrazine with dicarbonyl compounds is certainly the easiest and most studied way to obtain heterocycles with two vicinal nitrogen atoms.[1-3] The synthesis of the skeleton frame of novel compounds of type (**5**) or (**6**) was achieved *via* condensation of 3-aryl-6,6-dimethyl-1,2,3,4,5,6-hexahydro-8-oxo-7*H*-1,2-naphthalenecarboxylic anhydride (**4**) with hydrazine (Schemes 3 and 4). Compounds (**4**) were prepared from isophorone according to a three-steps procedure : alkylation, dehydration and Diels-Alder reaction (Scheme 2). Their stereochemistry was determined.[10]

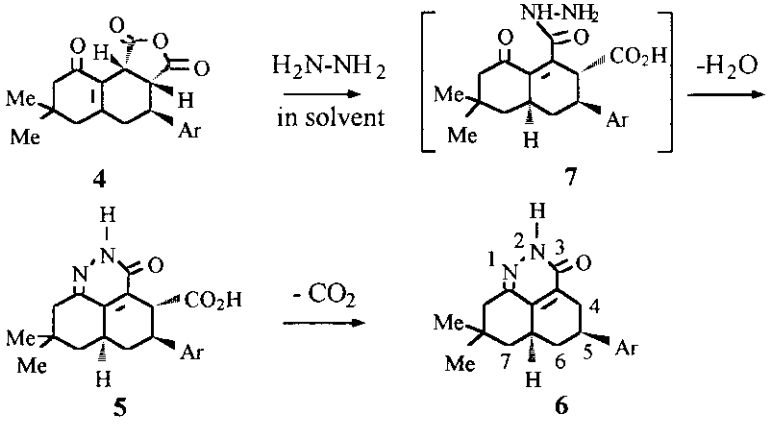


4

i : ArCHO/NaOH/H_2O, ii : *p*-TsOH :Toluene /Δ, iii : Maleic anhydride/ Toluene/Δ

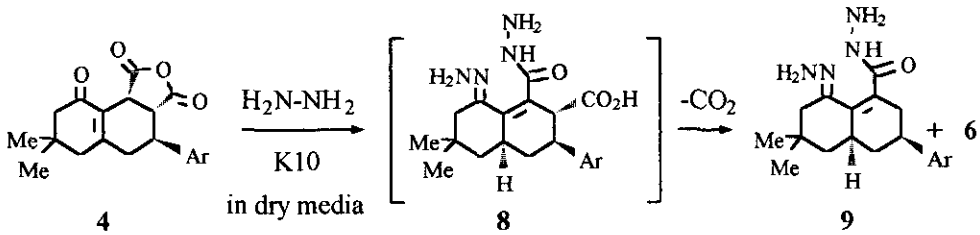
a : C_6H_5, b : *o*-ClC_6H_4, c : *p*-$CH_3C_6H_4$

Scheme 2



4 **7** **5** **6**

Scheme 3



Scheme 4

The preparation of 1,2-diazaphenalene derivatives was an opportunity to look at the reactivity of compounds (**4**) towards hydrazine under different experimental conditions. We choose two activation techniques : the traditional heating in polar and non-polar solvents and the microwave exposure either in homogeneous solution or in « dry media ». The application of microwave activation technique for accelerating organic reactions is a topic of great interest. A number of publications describe its advantages : short reaction times, increase of the purity of the resulting products and enhancement in the chemical yields.[11-17] As a typical example is the addition of amino groups to carbonyl with the lost of a molecule of water which has been carried out in solvent-free conditions by irradiating reactants on acidic supports.[18-24]

In our investigations, we optimized the conditions in order to get better yields in shorter times owing to the ability of microwave to favor water evaporation by shifting equilibrium.[25-27] Two kinds of microwave systems were used for this purpose : a domestic microwave oven (multimode cavity) and a focused microwave reactor (monomode system : Synthewave 402® Prolabo). Under both conditions, reactions were carried out in open vessels for 10 min. Final temperatures (Tf) were measured either by use of a thermometer (domestic oven) or with an infrared detector, which indicates the surface temperature (IR emissivity was calibrated using a thermocouple or an optical fiber introduced in the reaction mixture). The thermal reactions were carried out in refluxing methanol or xylene. Thus, at 120°C, the same reactions were conducted in xylene for 10 min. (Tables 1 and 2).

i) When the reactions were carried out in homogeneous solutions, the final products (**5**) underwent decarboxylation and compounds (**6**) or a mixture of **5** and **6** were obtained. On the other hand, under dry media over acidic clay support (Montmorillonite K10), the irradiation in a focused microwave reactor furnished large amounts of the dicondensation products (**9**) instead of **5**, together with **6**.

ii) In homogeneous phase, under the same conditions (10 min, 120°C), the focused microwave reactor was more efficient than the domestic microwave oven or the conventional heating. This result is due essentially to a better homogeneity of electromagnetic field and a lower emitted power.[29-31]

iii) In any event, microwave irradiation accelerated the reaction sequence. The rate enhancements were about 140 fold under microwave conditions over thermal process. Moreover, when the reactants were heated in xylene in an oil bath at 120°C for 10 min (conditions used for microwave irradiations), no reaction occurred. This fact suggests that a very important specific microwave effect was involved in this reaction.[28-33] In previous investigations, this specific effect of microwaves was evidenced for two examples of reactions performed in xylene.[32,33]

Table 1 : Condensation of hydrazine with **4a-c** using conventional heating in refluxing solvents

	Methanol				Xylene	
Starting material	Conversion[a] or yield (%)	**6** (%)	**5** (%)	time (h)	**6** (%)	time (h)
4a	57	-	57	1	37	4
4b	85[a]	60[a]	40[a]	0.5	40	24
4c	85	-	85	1.5	43	24

[a]Conversion ratios and relative amounts of products were evaluated by ^{1}H NMR on the crude mixture (precision 5%) *versus* remaining starting material.

Table 2 : Condensation of hydrazine with **4a-c** using microwave irradiation within 10 min in a domestic oven (P = 700W) or in a focused reactor (P = 60W)

	Xylene, domestic oven		Xylene, focused system				K10, focused system			
Starting material	Tf (°C)	**6** (%)	Tf (°C)	Conv[a] (%)	**6**[a] (%)	**5**[a] (%)	Tf (°C)	Conv[a] (%)	**6**[b] (%)	**9**[b] (%)
4a	120	50	122	78	88	12	122	71	33	67
4b	120	43	126	88	92	8	120	73	50	50
4c	114	54	120	90	60	40	106	72	54	46

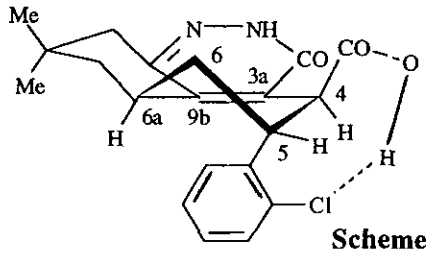
[a]Conversion ratios and relative amounts of products were evaluated by ^{1}H NMR on the crude mixture (precision 5%) *versus* remaining starting material.

Since carbonyl group from ketones is less reactive towards nucleophiles than that of anhydrides, we think that the reaction begins by a monocondensation of hydrazine on the anhydride carbon close to the ketonic group leading to **7** in which the C=C double bond might be either between the two carbonyl groups or at the junction of the two carbocycles. **7** undergoes cyclization before decarboxylation as compound (**5**) is isolated in all cases. If we assume that the cyclisation of **7** needs less energy than its decarboxylation, we can comment Schemes 3 and 4 as follows :

i) In refluxing methanol, the thermal energy involved allows only cyclisation of compounds and is not sufficient for their decarboxylation; therefore heterocycles (**5a**, **5c**) are obtained. The *o*-chlorinated compound (**5b**) seems to be more reactive and partial decarboxylation occurs. This can be explained by the establishment of a hydrogen bond due to the proximity of chlorine to the carboxyl group, weakening the carbone-hydrogen bond, so that decarboxylation is favoured (Scheme 5).

ii) In xylene under thermal conditions or under microwave irradiation, decarboxylation took place, and only compounds (**6**) were formed. In the first case the reflux time is long enough to lead to decarboxylation, as well as under microwave irradiation. In fact, the power applied cannot be known exactly because of the dispersion of microwaves and the heterogenous distribution of the electric field inside the oven. In a focused microwave system, decarboxylation was incomplete and a mixture of **5** and

6 was obtained. In this system, the electromagnetic waves are focused by a well dimensioned wave-guide into a cavity containing the sample, so that no dispersion of microwaves occurs and a low emitted power is sufficient to promote reactions.



5b

Scheme 5

iii) When the reactions are performed in dry media over acidic clay, activation seemed to be greater and each one of the two carbonyl groups (ketone and anhydride) reacted with a molecule of hydrazine to give the dicondensation products (**9**) in addition to **6**. Compound (**9**) was formed by loss of carbon dioxide from **8** and detected by MS from the mixture (**9b** + **6b**): $[M^+]$ at m/z: 404 and $[M - CO_2]^+$ at m/z : 360.

b) Structure assignments

They are based on microanalysis and spectral data : IR, ^1H and ^{13}C NMR.

A clear distinction between **5** and **6** is made from their mass spectral fragmentations. The MS spectra of heterocycles (**5**) exhibit a base peak at m/z 44 $[CO_2]^+$ and a significant peak due to the loss of CO_2 $[M - 44]^+$; the mass of this latter fragment corresponds to that of the molecular peak of **6**. The six membered ring heterocycle in compounds (**5**) and (**6**) may exist either in amidic or iminic forms. The MS fragmentation at m/z [M - ArC_2H_3 - HCO] and the C=O vibration bands in IR spectrum (potassium bromide) of **6a**, **6b** and **6c** at respectively 1650, 1658 and 1644 cm^{-1} might suggest the presence of the amidic form.

The stereochemistry of **5** and **6** is determined by considering the vicinal coupling constants of their related protons. These constants are given in Tables 3 and 4. Compounds (**5**) show J_{H4H5} 2 5Hz. These values are compatible with a trans pseudoequatorial position of the two protons H_4, H5. On the other hand, the vicinal coupling constants, J_{H5H6ax}=4Hz, J_{H5H6eq}=5Hz, $J_{H7eqH6a}$=5Hz and $J_{H7axH6a}$=13Hz for compounds (**6**) are favourable to a trans configuration of H_5, H_{6a} with H_{6a} in a pseudoaxial position.

Compounds (**9a** - **c**) were not isolated but were identified by GCMS and ^1H NMR from the spectrum of the mixtures (**9** + **6**). Their MS spectra exhibit significant peaks corresponding to their molecular ions at m/z = 326, 360 and 340 respectively, and caracteristic peaks due to the loss of N_2H_3 at m/z = 295, 329, 309 , N_2H_2 at m/z = 296, 330, 310 and H_2O at m/z = 308, 342, 322. ^1H NMR spectrum of the mixtures show broad signals between 2.30 and 3.30 ppm assigned to NH and NH_2 of compounds (**9**). In contrast, in compounds (**6**) the NH signals appear as sharp singlets downfield (11.9, 12.9 ppm). On addition of trifluoroacetic acid to the mixtures, the intensity of the broad signals dicreases while the sharp signals disappear. Otherwise NMR spectra of **9** and **6** exhibit similar pattern with slight differences in CH_3, H_7 and H_9 chemical shifts.

Table 3 : ^1H NMR assignments of compounds (**5**) ($CDCl_3$)

	NH	H_4	H_{6ax}	H_{6eq}	H_5	H_{6a}	H_{7ax}	H_{7eq}	H_{9ax}	H_{9eq}	H_{ar}	CH_3	H_{11}	H_{12}
5a	-	4.19 d J=4	1.70 m 1.80	2.80 ———	br s	3.00	1.26 lt* J=13	1.77 dd J=12, J=5	2.44 d J=15	2.60 d J=15	7.10 - 7.30	-	0.90 s	1.15 s
5b	8.50 - 9.50	4.28 d J=5	1.55 m 1.80	2.00 m 2.20	2.85 br s 2.95		1.28 lt J=13	1.50 m	2.40 d J=16	2.61 d J=16	7.00 - 7.40 m	-	0.90 s	1.14 s
5c	10.80	4.20 d J=4	1.40 m 1.90	2.95 ———	br s	3.05	1.29 lt J=13	1.82 dd J=13, J=6	2.47 d J=15	2.63 d J=15	7.14 d, J=8 7.26 d, J=8	2.33 s	0.98 s	1.20 s

* like triplet

Table 4 : ^1H NMR assignments of compounds (**6**) ($CDCl_3$)

	NH	H_4	H_5	H_{6ax}	H_{6eq}	H_{6a}	H_{7ax}	H_{7eq}	H_{9ax}	H_{9eq}	H_{11}	H_{12}	H_{ar}	CH_3
6a	12.90	3.03 m	3.38 m	1.77 ddd J=13 J=4 J=10	2.02 dt* J=13 J=5	2.40 br s 2.50	1.23 t J=13	1.54 dd J=13 J=5	2.41 d J=16	2.55 d J=16	0.92 s	0.97 s	7.10 m 7.30	-
6b	-	2.80 m 3.20	3.78 m	1.72 ddd J=4 J=10 J=13	2.11 dt J=13 J=5	2.30 br s 2.50	1.26 t J=13	1.57 ddd J=10 J=5 J=13	2.41 d J=16	2.55 d J=16	0.94 s	0.99 s	6.93 7.17 7.38	-
6c	11.90	2.90 m 3.10	3.30 m 3.40	1.74 ddd J=13 J=10 J=4	2.20 ddd J=13 J=5 J=5	2.30 br s 2.50	1.22 t J=13	1.58 dd J=13 J=5	2.40 d J=16	2.54 d J=16	0.94 s	0.98 s	7.10 d, J=8 7.00 d, J=8	2.30 s

*Doublet of like triplet

CONCLUSION

The condensation of hydrazine with compounds (**4**) was carried out under different conditions. In most cases,the hexahydro-1,2-diazaphenalene derivatives were obtained. Microwave irradiation using focused

microwave reactor and homogeneous solution in xylene gave better results when compared with traditional reflux or irradiation in a domestic microwave oven. The use of K10, as acidic clay support, under microwave irradiation was not suitable for our samples, since it leads to non desired dicondensation products (**9**).

EXPERIMENTAL

Melting points were determined with a Büchi 510 melting point apparatus and were uncorrected. Those of compounds (**5**) could not be determined because decarboxylation occurring before melting.The purity of samples was determined by means of TLC performed using Merck silica gel 60 F_{254} precoated on aluminum sheets, or by GC on an FID Carlo Erba CG 6000 apparatus fitted with a capillary column OV_1, 15 m. The IR spectra were recorded with potassium bromide disks using a Perkin Elmer 1600 spectrophotometer. The NMR spectra were recorded on a Gemini 200 BB "Gem 2000" spectrometer using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. MS spectra were run on a Ner Mag R 10-10 spectrometer at 70eV coupled to a gas chromatograph Girdel 31. Microanalyses were performed by the CNRS of Vernaison (France). The microwave apparatus used in this work was either a domestic oven Samsung® RE-995 CG operating at a power level of 700 watts, or a focused microwave reactor (Synthewave 402® Prolabo), where temperature, time and power applied were programmed using a software. In the first case open Erlenmeyer flasks and in the second one special open Pyrex tubes (matras) of 2.0 cm diameter and 15 cm length were used. Conversion rates and relative amounts of products were evaluated by ^1H NMR on the crude mixture *versus* remaining starting material .

General procedure :

Each experiment was carried out with the same amount of reagents under different conditions : 1 mmol of **4**, 10 equivalents of 85% hydrazine; 40 mL, 20 mL and 5 mL of solvent were used respectively in classical reflux, microwave oven and focused microwave systems. Powers of 700 and 60 watts were applied when using respectively the domestic oven and the focused reactor. Final temperatures were measured at the end of the reaction (reaction time = 10 min) with a thermometer in the case of the domestic oven and all along the reaction in the monomode reactor using IR detection.

In dry media, montmorillonite K10 (K10 : **4** = 4 : 1 w/w) was added to 20 mL of an ethereal solution of **4**. The mixture was stirred at rt for 5 min. After evaporation of the solvent under reduced pressure at rt, the impregnated powder was introduced into the pyrex tube. 10 mmol of hydrazine were added and the mixture was stirred with a thin glass rod. The mixture was exposed to the focused microwave irradiation under continuous stirring. Products were extracted from the clay by washing with methanol and ethyl acetate, the combined solvents were evaporated.

The products cristallized from acetone and the remaining starting materials were recovered by adding cold acetone to the crude mixture. White solids were then isolated and recrystallised from acetone. Compound (**5b**) was separated from the mixture (**5b**+**6b**) by liquid chromatography on silica gel (hexane : ethyl acetate = 6 : 4 v/v). Melting points of compounds (**5**) could not be measured because decarboxylation happened before melting.

9*H*-5-Aryl-4-carboxy-4,5,6,6a,7,8-hexahydro-1,2-diazaphenalen-3-one

5a : Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 71.00; H, 6.50; N, 8.28. Found : C, 71.20; H, 6.40; N, 8.14; MS : m/z= 294 (64%) $[M - CO_2]^+$, 44 (100%) $[CO_2]^+$; IR : 3500-2500 cm^{-1} (ν OH and ν NH), 1667 (νC=O); ^{13}C NMR : δ 171.9 (CO_2H), 162.2 (C_3), 148.8 (C_{3a}), 140.9 (C_{3b}), 145.0 (C_{9a}), 132.5, 128.0,128.3 (C_{ar}), 44.9 (C_4), 38.9 (C_5), 42.1 (C_6), 31.5 (C_{6a}), 28.6 (C_7), 30.1 (C_8), 43.6 (C_9), 30.5, 30.7 (C_{11},C_{12}).

5b : MS : m/z = 328 (22%) $[M - CO_2]^+$, 44 (100%) $[CO_2]^+$; IR : 3500-2600 cm^{-1} (ν OH and ν NH), 1668 (ν C=O); ^{13}C NMR : δ 172.9 (CO_2H), 162.4 (C_3), 148.4 (C_{3a}), 140.5 (C_{3b}), 144.3 (C_{9a}), 134.0, 138.4, 125.2, 127.4, 128.2 (C_{ar}), 44.2 (C_4), 37.1 (C_5), 41.9 (C_6), 28.4 (C_7), 30.1 (C_8), 43.5 (C_9), 30.4, 30.7 (C_{11}, C_{12}).

5c : Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.59; H, 6.81; N, 7.95. Found : C, 71.63; H, 6.78; N, 7.97; MS : m/z = 308 (36%) $[M - CO_2]^+$, 44 (100%) $[CO_2]^+$; IR : 3500-2400 cm^{-1} (ν OH et ν NH), 1674 (ν C=O); ^{13}C NMR : δ 172.9 (CO_2H), 163.1 (C_3), 148.5 (C_{3a}), 139.6 (C_{3b}), 144.7 (C_{9a}), 132.8, 129.6, 128.3, 129.2 (C_{ar}), 43.0 (C_4), 38.3 (C_5), 38.6 (C_6), 30.7 (C_{6a}), 30.1 (C_7), 30.2 (C_8), 41.3 (C_9), 30.0, 27.9 (C_{11}, C_{12}), 21.0 (CH_3).

9*H*-5-Aryl-4,5,6,6a,7,8-hexahydro-1,2-diazaphenalen-3-one

6a : mp = 201-203°C; Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.55; H, 7.48; N, 9.52. Found : C, 77.62; H, 7.53; N, 9.45; MS : m/z = 294 (100%) $[M]^+$, 104 (91%) $[ArC_2H_3]^+$, 91 (58%) $[ArCH_2]^+$, 190 (95%) $[M - ArC_2H_3]^+$, 161 (20%) $[M - ArC_2H_3 - CHO]^+$; IR : 3575-3375 cm^{-1} (ν NH), 1650 (ν C=O), 1637 (νC=N); ^{13}C NMR : δ 162.6 (C_3), 141.8 (C_{3a}), 135.4 (C_{3b}), 146.1 (C_{9a}), 145.1, 127.0, 128.5, 126.4 (C_{ar}), 42.3 (C_4), 35.7 (C_5), 35.4 (C_6), 31.7 (C_{6a}), 27.3 (C_7), 30.2 (C_8), 42.7 (C_9), 27.5, 27.6 (C_{11},C_{12}).

6b : mp = 240-242°C; Anal. Calcd for $C_{19}H_{21}N_2OCl$: C, 69.50; H, 6.40; N, 8.53. Found : C, 69.78 ; H, 6.35 ; N, 8.59; MS: m/z = 328 (93.5%) $[M]^+$, 138 (30%) $[ArC_2H_3]^+$, 125 (50%) $[ArCH_2]^+$, 190 (100%) $[M - ArC_2H_3]^+$, 161 (50%) $[M - ArC_2H_3 - CHO]^+$; IR : 3554-3312 cm^{-1} (ν NH), 1658 (ν C=O), 1646 (ν C=N); ^{13}C NMR : δ 162.3 (C_3), 141.7 (C_{3a}), 135.5 (C_{3b}), 146.1 (C_{9a}), 142.1, 133.5, 127.0, 127.6, 127.9 (C_{ar}), 42.0 (C_4), 32.8 (C_5), 32.4 (C_6), 31.7 (C_{6a}), 27.3 (C_7), 30.2 (C_8), 42.8 (C_9), 27.5, 27.7 (C_{11}, C_{12}).

6c : mp = 255-257°C; Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.92 ; H, 7.79 ; N, 9.09. Found : C, 78.08 ; H, 7.74 ; N, 8.98; MS : m/z = 308 (55%) $[M]^+$, 118 (100%) $[ArC_2H_3]^+$, 105 (69%) $[ArCH_2]^+$, 190 (24%) $[M - ArC_2H_3]^+$, 161 (16%) $[M - ArC_2H_3 - CHO]^+$; IR : 3554-3414 cm^{-1} (ν NH), 1644(ν C=O), 1639 (νC=N); ^{13}C NMR : δ 162.4 (C_3), 141.9 (C_{3a}), 135.9 (C_{3b}), 146.2 (C_{9a}), 142.0, 135.6, 126.8, 129.2 (C_{ar}), 42.3 (C_4), 35.5 (C_5), 35.4 (C_6), 31.7 (C_{6a}), 27.4 (C_7), 30.3 (C_8), 42.7 (C_9), 27.5, 27.7 (C_{11}, C_{12}), 20.9 (CH_{3ar}).

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