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# Electrochemical Oxidation of 2,5-Dihydro-*1H*-1-Benzazepines : Synthesis of *5H*-1-Benzazepines

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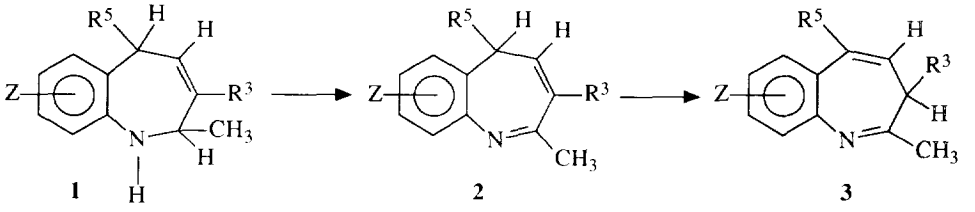
***Key Words*** *: 1-Benzazepines ; electrochemical oxidation ; coupling reaction*

**Abstract** : Formation of *5H*-1-benzazepines was observed after electrochemical oxidation of the title compounds in a flow cell at a graphite felt anode and in acetic buffer. In basic medium, coupling reaction also occurs leading to [2,5-dihydro-*1H*-1-benzazepin-1-yl]-*5H*-1-benzazepines. Oxidation mechanisms are discussed.

## INTRODUCTION

Although many kinds of dihydro-*1H*-1-benzazepines are described in the literature [1], to our knowledge no study has focused on their oxidation to compounds with maximal unsaturation.

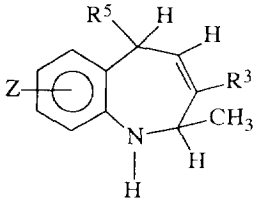
In our previous chemical investigations [2] we observed that oxidation could be performed in refluxing toluene using an iminium ion, resulting from the reaction of boron trifluoride on an enamine and acting as a hydrid anion acceptor [3]. Treatment of 2,5-dihydro-*1H*-1-benzazepines **1**, under the above conditions, led to the formation of an intermediate specie (*5H*-1-benzazepines **2**) which rearranges into *3H*-1-benzazepines **3** (Scheme 1).




Scheme 1

It is possible to carry out electrochemical studies using milder conditions e.g. room temperature or absence of boron trifluoride. It therefore appeared of interest to investigate the anodic behaviour of compounds **1**, although few electrochemical deshydrogenation reactions have been observed. The principal studies in this field concerned reactions of nucleophiles on cationic species, generated at the anode [4,5].

In the present paper, we describe the results obtained with various 2,5-dihydro-*1H*-1-benzazepines (Table 1). Electrochemical oxidations were carried out in either a slightly acidic aqueous medium (acetic buffer, pH = 4.8) or a slightly basic aqueous medium (ammoniacal buffer, pH = 9.2). Investigations using more acidic or more basic mediums were not successful.




| $R^3$ | Me | Me | Me | Me | Me | Me | Et |
|---|---|---|---|---|---|---|---|
| $R^5$ | Me | Me | Me | Me | H | H | H |
| Z | H | Me(6) | Me(9) | F(7) | H | F(7) | H |
| Compounds | **1a** | **1b** | **1c** | **1d** | **1e** | **1f** | **1g** |

Table 1 - Investigated 2,5-dihydro-*1H*-benzazepines

## RESULTS

### *ELECTROANALYTICAL INVESTIGATIONS*

The dihydro-*1H*-1benzazepine **1a** was selected as a model compound.

i) The shape of the voltammogram, obtained in ammoniacal buffer, is shown in figure 1a ; two successive peaks are obtained ($Ep^A$ = + 0.50 and $Ep^B$ = + 0.83 V SCE). The potential of peak A is shifted to more positive values when the scanning rate is increased (0.51 and 0.68 V SCE for scan rates ranging from 0.1 to 1 $V.s^{-1}$) ; the potential value of peak B remains constant (0.83 V) but its relative height decreases at high scan rates.

ii) In acetic buffer (figure 2a), the voltammogram shows a peak located at 0.62 V SCE and a hump around 0.77 V SCE which disappears when the scanning rate is increased ; attribution of the latter will be discussed further.

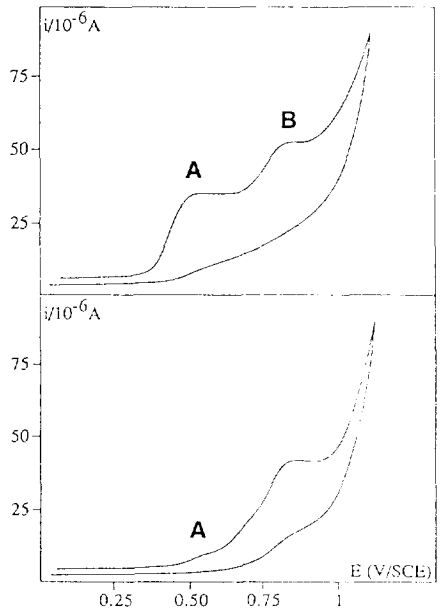



Fig. 1 - Voltammogram of **1a**
in ammoniacal buffer + ethanol (1/1).
Scan rate : 50 mV.s$^{-1}$
a) before electrolysis
b) after a 2e$^-$ oxidation

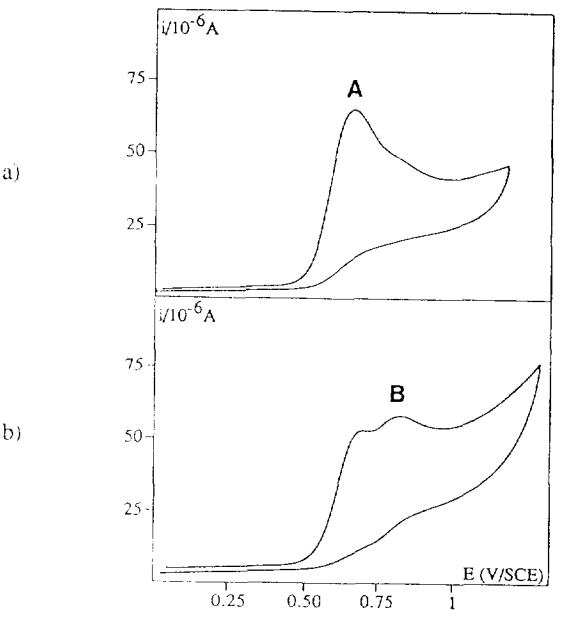
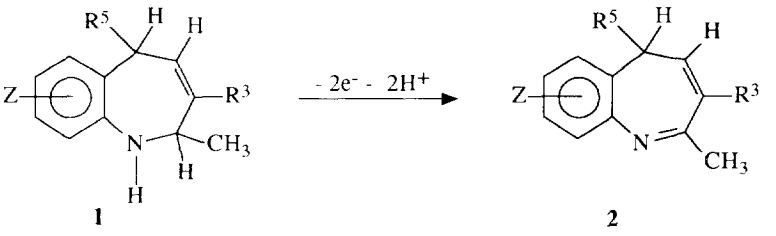



Fig. 2 - Voltammograms in acetic buffer + ethanol (1/1).
Scan rate : 50 mV.s$^{-1}$
a) **1a** alone
b) equimolar mixture of **1a** and **4a**

*MACROSCALE ELECTROLYSES*

These electrolyses were carried out galvanostatically, in a flow cell, fitted with a graphite felt anode [6]. The current was calculated to correspond to a bielectronic oxidation (see experimental section).
i) In acetic buffer, the 5*H*-1-benzazepines **2a-f** were obtained (Scheme 2). Yields ranged from 35% to 45% after elimination of polymers by column chromatography.

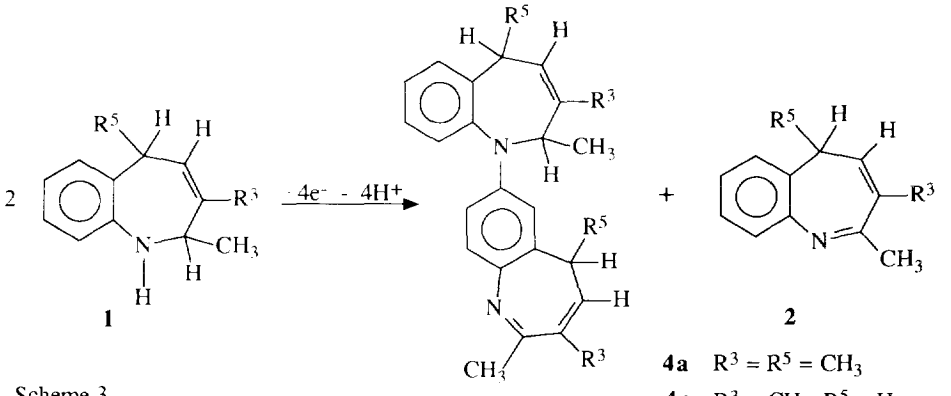
These compounds are not oxidable in the experimental conditions, they are stable in aqueous medium but they rearranged into 3*H*-1-benzazepines **3** when heated in toluene in the presence of boron trifluoride [2].




1 2

Scheme 2

ii) In ammoniacal buffer, oxidation of compounds **1a**, **1e** and **1g** led to a mixture of the corresponding *5H*-1-benzazepines **2a**, **2e** or **2g** and to several coupling products **4a**, **4e** or **4g** [global yield (**2a,e,g** + **4a,e,g**) ≈ 75%] (Scheme 3).




1 4 2

Scheme 3

**4a** $R^3 = R^5 = CH_3$
**4e** $R^3 = CH_3$ $R^5 = H$
**4g** $R^3 = C_2H_5$ $R^5 = H$

For instance, in the case of **1a**, the yields are respectively 25% in **2a** and 50% in **4a**.

A voltammogram registered on the outlet solution shows the quasi complete disappearance of peak A while peak B remains (Figure 1b). The latter has been attributed to **4a** which presents in ammoniacal buffer an oxidation peak located at + 0.80 V SCE (Figure 4).

## STRUCTURAL ELUCIDATION

The detailed spectroscopic data are reported in the Experimental Section but some characteristics which confirm the proposed structures can already be highlighted.

*5H*-1-benzazepines **2**

The oxidation was confirmed in MS by the loss of two hydrogens. The formation of the azomethine bond was attested in IR by the C=N stretching vibration at ≈ 1645 $cm^{-1}$ and in $^{13}C$ NMR by the δ C-2 at ≈

167 ppm. An X-Ray cristallographic study of **2b** (Figure 3) established unambigously the structure of the *5H*-1-benzazepines.

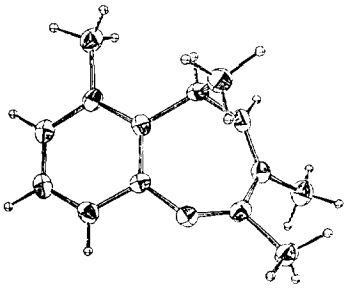


Fig. 3 - Structure of benzazepine **2b**

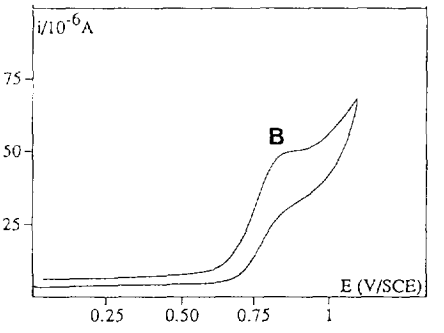



Fig. 4 - Voltammogram of **4a** in ammoniacal buffer + ethanol (1/1) ; scan rate : 50 mV.s$^{-1}$

Coupling products **4**

The coupling reaction was attested in MS by the m/z values of the molecular ions which were twice those of compounds **2**. The $^{1}H$ and $^{13}C$ NMR spectra were analyzed as a juxtaposition of the signals of the 2,5-dihydro-*1H*-1-benzazepine **1** and those of the *5H*-1-benzazepine **2**. The linkage of N'-1 to C-7 (*para*-substitution) was demonstrated (Figure 5) using $^{1}H$ NMR and 2D NMR (COLOC). If $R_3$ = $CH_3$, the compound **4a** appears as a mixture (80/20) of two isomers (**4a**$_1$ and **4a**$_2$), whose configuration has not been attributed.

$^{1}H$ NMR

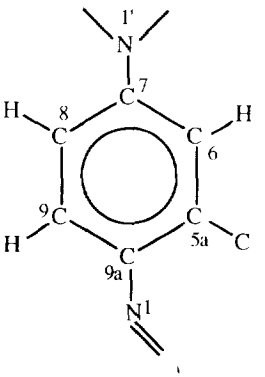
H-6 d ($^{4}J$)

H-8 dd ($^{3}J^{4}J$)

H-9 d ($^{3}J$)

$^{3}J$ = 8.7 Hz

$^{4}J$ = 2.8 Hz




COLOC

$^{3}$JCH correlation between

C-5a H-9

C-7 H-9

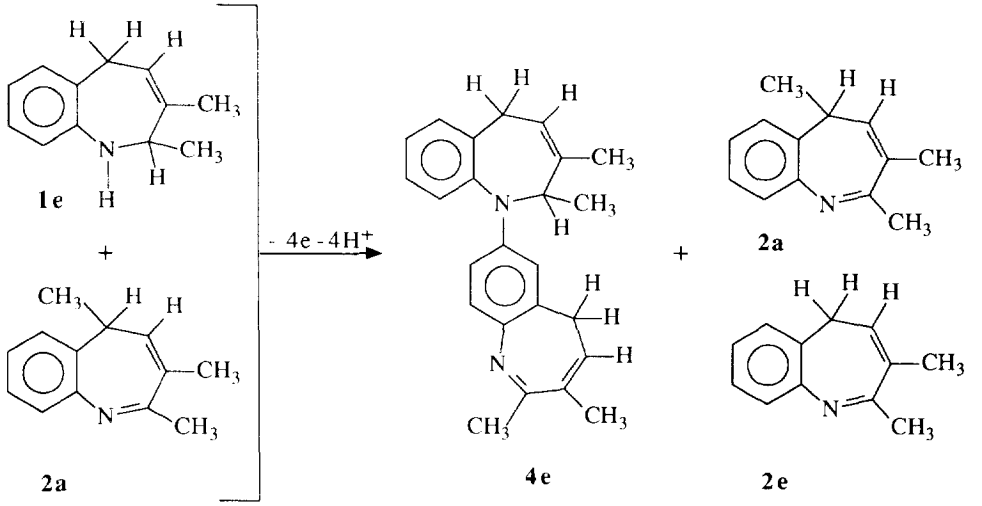
C-9a H-6

Fig. 5 - *para*-substitution

## DISCUSSION

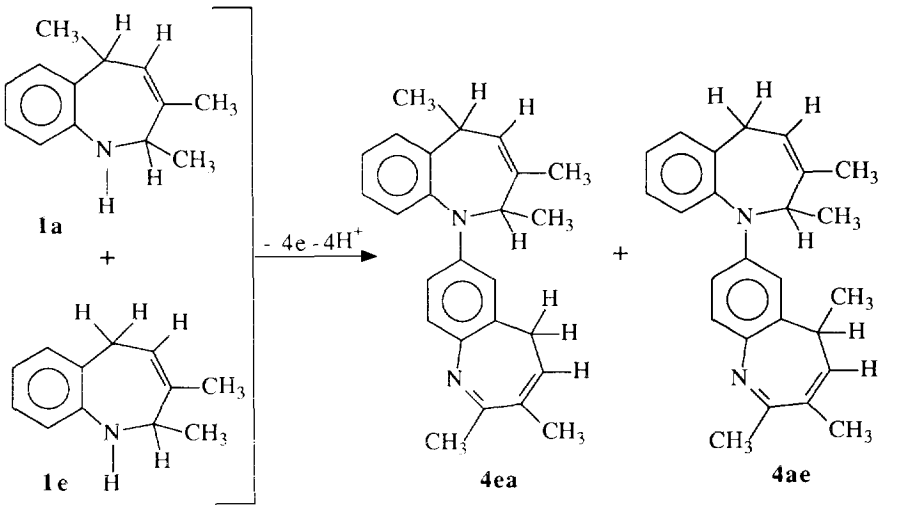
*COUPLING MECHANISM*

i) In order to determine the origin of the coupling products, we have performed complementary cross-coupling experiments : * oxidation of a mixture of **1e** and **2a** (Scheme 4) lead to the formation of the *5H*-1-benzazepine **2e** and to the coupling product **4e**. Absence of cross-coupling products indicates that the oxidation intermediate does not react with *5H*-1-benzazepine **2**.




Scheme 4

* oxidation of a mixture of the two dihydro-*1H*-benzazepines **1a** and **1e** gives, apart from "normal" products **2a**, **2e**, **4a** and **4e**, the cross-coupling compounds **4ae** + **4ea** which were identified by MS.

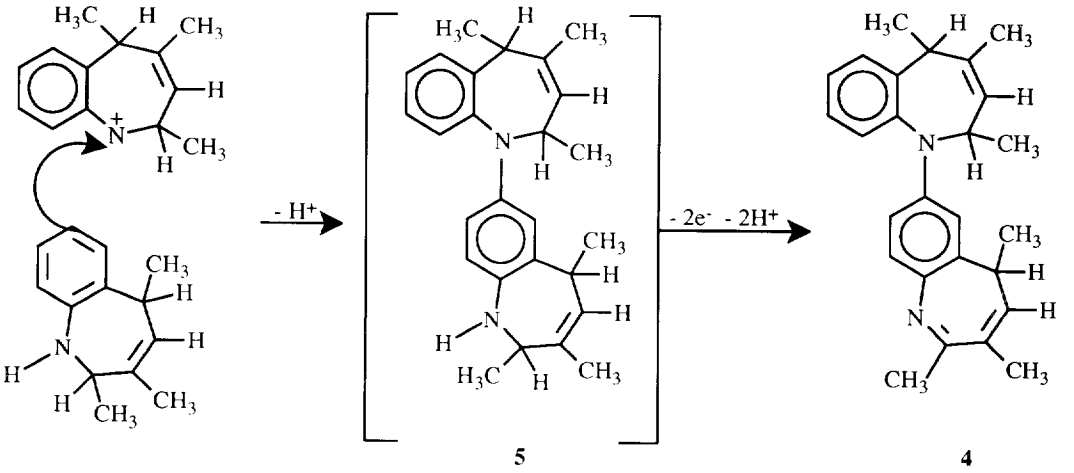



Scheme 5

Following these results, coupling occurs from the reaction of the starting compound **1** with an oxidation intermediate. Two species can be considered for the latter :

- a radical-cation resulting from a monoelectronic transfer ; coupling of such an intermediate with the substrate has been suggested to take place during oxidation of N-alkylanilines [7]. We do not believe that a similar mechanism occurs in our case : first, it would not be regioselective as observed (only *para* to the nitrogen of the starting product) ; secondly, the electrode reaction is a two-electron process (cf. electroanalytical investigations).

- a cationic specie acting as an electrophile towards the substrate. We postulate that the former is a nitrenium cation which reacts on the dihydrobenzazepine leading to compound **5** which is further oxidized in a two electron process into the isolated compound **4** (Scheme 6).




Scheme 6

ii) To prove the intermediate formation of **5a** we have performed the reduction of **4a** (mixture of **4a$_1$** + **4a$_2$**) in methanol by 4 equivalents of sodium borohydride. It leads in a quasi quantitative yield to a mixture of two isomers **5a$_1$** and **5a$_2$** separable by column chromatography. The voltammogram of an equimolar mixture of these two isomers, registered in ammoniacal buffer, is given on figure 6. Oxidation according to peaks C (**5a$_1$**) and C' (**5a$_2$**) leads to compound **4a** as shown by the presence of peak B. Moreover, a preparative electrolysis of an equimolar mixture of **5a$_1$** and **5a$_2$** , performed with a current calculated for a two electron process leads to **4a** in a 80% yield. The easy oxidation of **5a$_1$** and **5a$_2$** ($Ep^c$ = + 0.15 V and $Ep^{c'}$ = + 0.22 V SCE) is in accordance with the phenylenediamine like structure demonstrated in the NMR study.

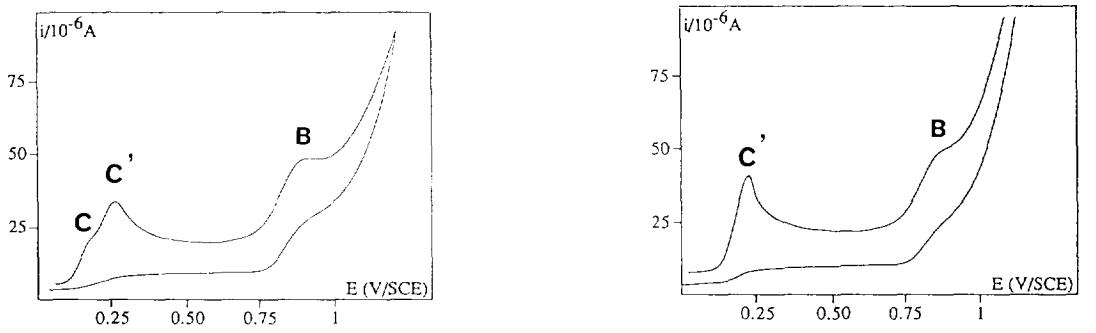
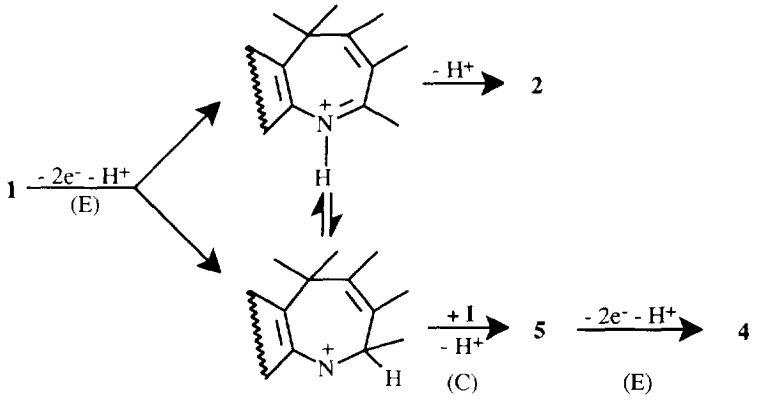



Fig. 6 - Voltammograms in ammoniacal buffer + ethanol (2/3) ; scan rate : 50 mV.s$^{-1}$
a) Equimolar mixture of **5a$_1$** and **5a$_2$**
b) **5a$_2$** alone

*OXIDATION MECHANISM*

In the two investigated medium, the electrode reaction is a two-electron process, leading to a cationic specie. According to the observed results (i.e. imine formation and electrophilic substitution), this intermediate may gave rise to a tautomeric equilibrium between an iminium and α-nitrenium form (Scheme 7).




Scheme 7

i) Without a good nucleophile, formation of the imine **2** takes place, resulting from an α-deprotonation. It is worthnoting than α-deprotonation has been observed during electrooxidation of tertiary amines but only in the presence of a strong nucleophile [7].

ii) If the substrate is nucleophile enough, coupling occurs in competition with the previous pathway leading to **5** immediately oxidized into **4**. Then formation of **4** results from an ECE mechanism (as shown in scheme 7) justifying the modifications of the voltammogram of fig. 1a when the scan rate is changed.

In acetic buffer, the protonation of the substrate **1** ($pK_a$ # 5.8) [9] lowers the formation of **4** as it is classicaly observed in electrophilic substitution with anilinium derivatives. However owing to the limited yield in benzazepine **2** and the absence of recovery of **1**, one cannot exclude that coupling also takes place. Due to the lack of selectivity in the electrolysis (we have verified that the bending observed on the voltammogram in figure 1 corresponded to the oxidation of **4a** as shown on figure 2b) if formed the coupling product would be oxidized leading to polymeric material.

## CONCLUSION

In this study, we demonstrated that an electrochemical oxidation method could be exploited for the unprecedented synthesis of cyclic imines from secondary amines. Application of this strategy to 2,5-dihydro-*1H*-1-benzazepines allowed the preparation of the rarely described 5*H*-1-benzazepines [10,11] although these compounds are isolated in a moderate yield.

Moreover, a coupling reaction occurs in basic medium ; we have shown that this coupling involves a nitrenium cation acting as a nucleophile towards the starting material instead of a radical species (as observed in chemical or photochemical dimerizations [12]).

At last, it must be pointed out that the presence of the double bond between C3 and C4 in the investigated molecules is of importance ; electro-oxidations performed with tetrahydrobenzazepines have been unsuccessful. Further investigations of this study, using other substrates, are now in progress.

**Acknowledgments** : The authors thank Mme Le Roch, Mrs Bourges, Cupif, Ternisien for technical assistance and Mr Guenot and Mr Sinbandhit of the CRMPO (MS and NMR).

## EXPERIMENTAL SECTION

General

Melting points were determined on a Kofler apparatus and were not corrected. Elemental analyses were carried out at the Faculté de Pharmacie (Université de Paris XI). Purifications by column chromatography were done on 70-230 mesh silica gel (Merck). TLC analyses were performed on pre-coated aluminium sheets of silica gel 60 $F_{254}$ (layer thickness : 0.22 mm)(Merck). Indicated Rf values were determined using purification eluent (50:50 petroleum ether-ether). IR spectra were recorded on a Perkin-Elmer 16 PC. NMR spectra[13] were recorded on a Brucker AM 300 FT spectrometer at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO) at 300 MHz ($^1H$) or 75 MHz ($^{13}C$). Chemical shifts were expressed in ppm downfield from TMS and coupling constants (J) in Hertz. The solvent was $CDCl_3$. $^1H$ NMR : AB systems were presented in the following order : H-α (δ : centered) the more deshielded, H-β (δ centered) the more shielded, JH-α H-β. Long-range coupling constants were indicated using Jlr. $^{13}C$ NMR : broad band and gated decoupling spectra were

recorded. The assignments were made using chemical shifts and coupling constants ($^1J$ and long-range coupling). Values with an asterisk * could be interverted. 2D NMR : the sequences were indicated in the text. The high resolution mass spectra were determined on a Varian MAT 311 double-focusing instrument at the CRMPO with a source temperature of 140°C, an ion accelerating potential of 3 kV, and ionizing electrons of 70 eV and 300 mA. Direct Insertion Probe was used.

Electrochemistry

Voltammetric investigations were carried out at a vitreous carbon electrode.

Macroscale electrolyses were performed in a flow cell [6] ; the working anode was a graphite felt cylinder (diameter : 50 mm, thickness : 12 mm) inserted between two planar cathodes. The solutions were prepared by dissolving the substrate (or a mixture of substrates) in a 1/1 mixture of aqueous buffer (0.5 $mol.l^{-1}$) and ethanol. The substrate concentrations were in the range 0.5 to 1 $g.l^{-1}$ ($c = 2.5.10^{-3}$ to $5.10^{-3}$ $mol.l^{-1}$). The flow rate of the solution in the porous anode was regulated at $f = 5$ $ml.mn^{-1}$ and the current calculated according to Faraday's law to correspond to a bielectronic process : $i(oxidation) = 2 \times 96500 \frac{f}{60} (10^{-3}c)$ .

Substrate synthesis

The benzazepines **1** were prepared according to references [14].

Synthesis procedure

After electrolysis, work-up of the solution was made according to the following procedure : Ethanol was evaporated and, after basification, the solution was extracted with ether. The organic layer was dried ($K_2CO_3$) and concentrated. The residue was purified by column chromatography using a 50:50 petroleum ether-ether mixture. A second purification could be performed using a 80:20 $CH_2Cl_2$-ether mixture as solvent. Compounds **2** and **4** showed a characteristic smell. The purity (> 98%) were checked by GC, TLC $^1H$ NMR and MS. The synthetized products had to be stored at - 20°C ; at RT or in $CDCl_3$ degradation occured some days later.

**2,3,5-trimethyl-*5H*-1-benzazepine 2a** (yield 40%)
Rf : 0.6
I.R. ν ($cm^{-1}$) : C=N (1644)
$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.38) ; $CH_3$-3 [(sm:1.82) Jlr (1.3)] ; H-4 (dm:5.55) ; JH-4 H-5 (5) ; $CH_3$-5 (d:1.44), J(7) ; H-5 (m:2.69-2.77) ; Ar (m:7.15-7.31)
$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.37) ; C-2 (168.26) ; $CH_3$-3 [(19.37) $^3J$ (6.2)] ; C-3 (128.75) ; C-4 (139.00) ; $CH_3$-5 (15.77) ; C-5 (33.79) ; C-5a (136.64) ; C-6 (122.34) ; *C-7 (126.11) ; *C-8 (125.20) ; C-9 (125.92) ; C-9a (146.10). For attribution of C-3 and $CH_3$-3 irradiation at 1.826 ppm.
2D NMR : Inadequate
M.S. m/e, rel.intensity % : 185 $[M]^{\cdot+}$ ; 53 ; 184, 17 , 170, 100 ; 157, 12 ; 144, 7 ; 130, 9 ; 129, 20 ; 128, 13.
Exact mass : m/e = 185.1203 (calc. for $C_{13}H_{15}N$ m/e = 185.12044)

**2,3,5,6-tetramethyl-*5H*-1-benzazepine 2b** (yield 45%)
m.p. : 63-65°C
Rf : 0.65
I.R. ν ($cm^{-1}$) : C=N (1650)
$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.36) ; $CH_3$-3 (sd:1.85) ; H-4 (dd:6.09) ; JH-4 H-5 [(9.2) Jlr (1.2)] ; $CH_3$-5 (d:0.97), J(7.3) ; H-5 (m:3.64-3.75) ; $CH_3$-6 (s:2.36) ; H-7 (d:7.04), J(7) ; H-8 (t:7.12), J(7.1) ; H-9 (d:7.18), J(7.9).
$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.76) ; C-2 (167.14) ; $CH_3$-3 [(20.43) $^3J$ (6.6)] ; C-3 (130.09) ; C-4 (137.99) ; $CH_3$-5 (13.13) ; C-5 (31.41) ; C-5a (135.54) ; $CH_3$-6 [(20.26), $^3J$ (4.7)] ; C-6 (133.66) ; C-7 (128.21) ; C-8 (125.91) ; C-9 (125.53) ; C-9a (145.92). For attribution of C-2, C-3, C-6 and C-7 irradiation at 2.38 ppm.
M.S. m/e, rel.intensity % : 199 $[M]^{\cdot+}$ , 62 ; 198, 10 ; 184, 100 ; 144, 8 ; 143, 13 ; 128, 13 ; 115, 9.
Exact mass : m/e = 199.13609 (calc. for $C_{14}H_{17}N$ m/e = 199.1355)

**2,3,5,9-tetramethyl-5*H*-1-benzazepine 2c** (yield 45%)
Rf : 0.88
I.R. ν ($cm^{-1}$) : C=N (1646)
$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.38) ; $CH_3$-3 [(sm:1.80) Jlr (1.4)] ; H-4 (dm:5.51) ; $CH_3$-5 (d:1.42) ; H-5 (m:2.66) ; H-6 and H-8 (d:7.09 and d:7:00), J(6.2) ; H-7 (t:7.11), J(7.2) ; $CH_3$-9 (s:2.38).
$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.17) ; C-2 (166.72) ; $CH_3$-3 [(19.21) $^3J$ (5.7)] ; C-3 (128.61) ; C-4 (138.93) ; $CH_3$-5 (15.99) ; C-5 (33.71) ; C-5a (137.03) ; C-6 (127.78) ; C-7 (125.59) ; C-8 (119.80) ; $CH_3$-9 [(18.59) $^3J$ (4.3)] ; C-9 (132.88) ; C-9a (144.52). For attribution of C-2, C-3 and C-4 irradiation at 1.844 ppm.
For attribution of C-6 irradiation at 2.42 ppm.
M.S. m/e, rel.intensity % : 199 $[M]^{\cdot+}$, 100 ; 198, 7 ; 184, 81 ; 171, 10 ; 143, 7 ; 141, 6 ; 129, 19 ; 115, 1.
Exact mass : m/e = 199.13609 (calc. for $C_{14}H_{17}N$ m/e = 199.1362)

**2,3,5-trimethyl-7-fluoro-5*H*-1-benzazepine 2d** (yield 35%)
Rf : 0.6
I.R. ν ($cm^{-1}$) : C=N (1644)
$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.36) ; $CH_3$-3 (sm:1.82) : H-4 (d:5.51) ; JH-4 H-5 (5.5) ; $CH_3$-5 (d:1.41), J(7) ; H-5 (m:2.66-2.75) ; H-6 (dd:6.85) ), J(9.7x2.7) ; H-8 (td:6.93) ), J(8.5x2.8) ; H-9 (dd:7.25), J(8.5x3).
$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.31) ; C-2 (168.06) ; $CH_3$-3 [(19.36) $^3J$ (6.2)] ; C-3 (129.14) ; C-4 (138.01) ; $CH_3$-5 (15.71) ; C-5 (33.64) ; C-5a [(138.35) $^3JCF$ (6.7)] ; C-6 [(109.11), $^2JCF$ (22.9)] ; C-7 [(161.75), $^1JCF$ (243.8) ; C-8 [(112.87) $^2JCF$ (22.4)] ; C-9 [(126.60) $^3JCF$ (8.6)] ; C-9a [(142.44) $^4JCF$ (2.3)]).
For attribution of C-2, C-3 and C-4 irradiation at 1.844 ppm.
For attribution of C-6 irradiation at 2.42 ppm.
M.S. m/e, rel.intensity % : 203 $[M]^{\cdot+}$, 56 ; 202, 14 ; 188, 100 ; 175, 12 ; 162, 10 ; 148, 14 ; 147, 24 ; 146, 15.
Exact mass : m/e = 203.11102 (calc. for $C_{13}H_{14}NF$ m/e = 203.1121)

**2,3-dimethyl-5*H*-1-benzazepine 2e** (yield 42%)
Rf : 0.52
I.R. ν ($cm^{-1}$) : C=N (1644)
$^1H$ NMR($CDCl_3$) : $CH_3$-2 [(s:2.37), Jlr (1.3)] ; $CH_3$-3 (sm:1.84) ; H-4 (tq:5.88) ), J(8.3x1.3) ; 2 H-5 (d:2.83) ; JH-4 H-5 (7) ; H-6 (d:7.07) ), J(7.3) ; H-7 (t:7.13) ), J(7.5) ; H-8 (t:7.24) ), J(7.8) ; H-9 (d:7.28) ), J(8).
$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.64) ; C-2 (168.45) ; $CH_3$-3 [(19.61) $^3J$ (6)] ; C-3 (131.01) ; C-4 (131.91) ; C-5 (31.74) ; C-5a (132.92) ; C-6 (126.64) ; C-7 (125.77) ; C-8 (126.59) ; C-9 (125.26) ; C-9a (146.50)
For attribution of C-3 and C-5a irradiation at 7.10 ppm.
2D NMR : Cosy and correlation $^{13}C$ $^1H$
M.S. m/e, rel.intensity % : 171 $[M]^{\cdot+}$, 100 ; 170, 42 ; 156, 39 ; 143, 12 ; 130, 20 ; 129, 24 ; 128, 19 ; 115, 16.
Exact mass : m/e = 171.10479 (calc. for $C_{12}H_{13}N$ m/e = 171.1049)

**2,3-dimethyl-7-fluoro-5*H*-1-benzazepine 2f** (yield 38%)
Rf : 0.56
I.R. ν ($cm^{-1}$) : C=N (1646)
$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.36) ; $CH_3$-3 (sm:1.85) ; H-4 (tm:5.85) ; JH-4 H-5 (7) Jlr (1.4) ; 2 H-5 (d:2.81), J(8) ; H-6 (dd:6.77), J(8.9x2.8) ; H-8 (td:6.93), J(8.5x2.8) ; H-9 (dd:7.25), J(8.5x2.8).
$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.61) ; C-2 (168.23) ; $CH_3$-3 [(19.65) $^3J$ (6.4)] ; C-3 (131.42) ; C-4 (131.01) ; C-5 (31.65) ; C-5a [(134.31) $^3JCF$ (7.5)] ; *C-6 [(112.92) $^2JCF$ (22.6)] ; C-7 [(161.18) $^1JCF$ (244)] ; *C-8 [(113.40) $^2JCF$ (22.6)] ; C-9 [(126.72) $^3JCF$ (8.7)] ; C-9a [(142.97) $^4JCF$ (2.8)]
M.S. m/e, rel.intensity % : 189 $[M]^{\cdot+}$, 100 ; 188, 46 ; 174, 39 ; 162, 14 ; 161, 13 ; 149, 28 ; 147, 17 ; 146, 19 ; 133, 15.
Exact mass : m/e = 189.09537 (calc. for $C_{12}H_{12}NF$ m/e = 189.0953)

**2,3,5-trimethyl-7-[2,3,5-trimethyl-2,5-dihydro-*1H*-1-benzazepin-1-yl]-*5H*-1-benzazepine 4a** (mixture of two isomers **$4a_1$ + $4a_2$** not separated (Rf 0.3) (80/20)) (yield 50%)

**$4a_1$** (major isomer)
Rf : 0.3

I.R. ν ($cm^{-1}$) : C=N (1648) (weak)

$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.32) ; $CH_3$-3 (sm:1.81) ; H-4 (d:5.50) ; JH-4 H-5 (6) ; $CH_3$-5 (d:1.29), J(7.4) ; H-5 (m:2.70) ; H-6 (sd:6.42) ; H-8 (dd:6.52) ; H-9 (d:7.10) ; $CH_3$-2' (d:1.09) ; H-2' (m:4.48) ; $CH_3$-3' (sm:1.72) ; H-4' (sm:5.19) ; $CH_3$-5' (d:1.32), J(7.4) ; H-5'(m:3.53-3.62) ; Ar (m:7.13-7.28).

$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.26) ; C-2 (165.12) ; $CH_3$-3 (19.74) ; C-3 (129.10) ; C-4 (137.49) ; $CH_3$-5 (15.69) ; C-5 (34.44) ; C-6 (106.75) ; C-7 (147.77) ; C-8 (111.97) ; C-9 (126.81) ; $CH_3$-2' (18.87) ; C-2' (54.55) ; $CH_3$-3' (22.88) ; C-4' (128.28) ; $CH_3$-5' (19.06) ; C-5' (31.80) ; *C-3'-*C-5a-*C-9a (136.86-136.86-137.86) ; C-5'a (145.81) ; C-6' (124.85) ; C-7' (126.82) ; C-8' (126.40) ; C-9' (131.42) ; C-9'a (142.43).

2D NMR : $^{13}C$ $^1H$ correlation

M.S. m/e, rel.intensity % : 370 $[M]^{\cdot+}$, 100 ; 355, 27 ; 341, 26 ; 315, 21 ; 199, 18.
Exact mass : m/e = 370.24089 (calc. for $C_{26}H_{30}N_2$ m/e = 370.2391)

| | | | | |
|---|---|---|---|---|
| Analysis : | Calc.% | C : 84.27 ; | H : 8.16 ; | N : 7.56 |
| | Found % | C : 84.39 ; | H : 8.14 ; | N : 7.34 |

**$4a_2$** (minor isomer)

$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.32) ; $CH_3$-3 (sm:1.81) ; H-4 (d:5.50) ; $CH_3$-5 (d:1.29), J(7.3) ; H-5 (m:2.70) ; H-6 (sd:6.39) ; H-8 (dd:6.55) ; H-9 (d:7.11) ; $CH_3$-2' (d:1.10) ; H-2' (m:4.48) ; $CH_3$-3' (sm:1.72) ; H-4' (sm:5.19) ; $CH_3$-5' (d:1.32) ; H-5'(m:3.57) ; Ar (m:7.13-7.28).

$^{13}C$ NMR ($CDCl_3$) non attributed :15.69 ; 18.59 ; 19.00 ; 19.74 ; 22.91 ; 26.25 ; 31.65 ; 34.42 ; 54.61 ; 107.15 ; 112.04 ; 124.84 ; 126.40 ; 126.67 ; 128.47 ; 129.05 ; 131.39 ; 136.83 ; 137.44 ; 137.84 ; 142.48 ; 145.89 ; 147.88 ; 165.08.

**2,3-dimethyl-7-[2,3-dimethyl-2,5-dihydro-*1H*-1-benzazepin-1-yl]-*5H*-1-benzazepine 4e** (yield 25%)
Rf : 0.28

I.R. ν ($cm^{-1}$) : C=N (1644) (weak)

$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.31) ; $CH_3$-3 (sm:1.82) ; H-4 (td:5.78), J(7x1.4) ; 2 H-5 (d:2.75) ; JH-4 H-5 (7) ; H-6 (sd:6.23) ; H-8 (dd:6.52), J(8.7x2.8) ; H-9 (d:7.11), J(8.7) ; $CH_3$-2' (d:1.09), J(6.9) ; H-2' (m:4.38) ; $CH_3$-3' (sm:1.76) ; H-4' (dm:5.42) ; H-5'α(dm:3.22) ; JH-5'α H-4'(2.5) ; JH-5'α H-5'β(17) ; H-5'β(dd:2.82) ; JH-5'β(17) H-4' (8.4) ; Ar (m:7.16-7.29).

$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.30) ; C-2 (165.67) ; $CH_3$-3 (19.85) ; C-3 (131.19) ; C-4 (130.98) ; C-5 (32.49) ; C-5a (133.22) ; C-6 (111.02) ; C-7 (147.54) ; C-8 (112.11) ; C-9 (126.58) ; C-9a (137.94) ; $CH_3$-2' (19.52) ; C-2' (55.07) ; $CH_3$-3' (23.13) ; C-3' (137.98) ; C-4' (119.90) ; C-5' (32.69) ; C-5'a (141.76) ; C-6' (129.59) ; C-7' (127.03) ; C-8' (126.95) ; C-9' (131.83) ; C-9'a (142.92).

M.S. m/e, rel.intensity % : 340 $[M]^{\cdot+}$, 100 ; 327, 29 ; 313, 7 ; 287, 43 ; 273, 8 ; 185, 22.
Exact mass : m/e = 342.20959 (calc. for $C_{24}H_{26}N_2$ m/e = 342.2094)

**3-ethyl-2-methyl-7-[3-ethyl-2-methyl-2,5-dihydro-*1H*-1-benzazepin-1-yl]-*5H*-1-benzazepine 4g** (yield 28%)
Rf : 0.3

I.R. ν ($cm^{-1}$) : C=N (1645) (weak)

$^1H$ NMR ($CDCl_3$) : $CH_3$-2 (s:2.31) ; $CH_2$-$CH_3$ (q:2.20, t:0.92) ; H-4 (d:5.41), JH-4 H-5 (7.1) ; 2H-5 (d:2.72), J(7) ; H-6 (d:6.26), J(2.8) ; H-8 (dd:6.53), J(8.8x2.8) ; H-9 (d:7.13) ; H-2' (m:4.47) ; $CH_3$-2' (d:1.08) ; H-2' (m:4.38) ; $CH_2$-$CH_3$-3' (q:2.06, t:1.13) ; H-4' (tm:5.77) ; H-5'α(dm:3.32) ; H-5'β (dd:2.87) ; JH-5'α H-5'β (17) ; JH-4 H-5'β (8.4) ; Ar (m:7.10-7.30).

2D NMR : Correlation $^{13}C$ $^1H$ and COLOC

$^{13}C$ NMR ($CDCl_3$) : $CH_3$-2 (26.22) ; C-2 (165.67) ; $CH_2$-$CH_3$-3 (26.22-12.97) ; C-3 (137.11) ; C-4 (128.98) ; C-5 (32.42) ; C-5a (133.51) ; C-6 (110.86) ; C-7 (147.36) ; C-8 (111.94) ; C-9 (126.55) ; C-9a (138.00) ; $CH_3$-2' (20.10) ; C-2' (53.89) ; $CH_2$-$CH_3$-3' (28.97-12.91) ; C-3' (143.59) ; C-4' (118.22) ; C-5' (32.72) ; C-5'a (141.82) ; C-6' (129.65) ; C-7' (127.08) ; C-8' (126.98) ; C-9' (131.88) ; C-9'a (143.01).

**Cross coupling experiment**
M.S. m/e, rel.intensity % : 370, 42 ; 356, 100 ; 342, 46 ; 341, 49.
370 and 342 : normal coupling products **4a** and **4e** ; 356 cross coupling products **4ae** and **4ea**.
Exact mass (**4ae** ; **4ea**).: m/e = 356.2255 (calc. for $C_{25}H_{28}N_2$ m/e = 356.22524)
Exact mass (**4a**) : m/e = 370.2427 (calc. for $C_{26}H_{30}N_2$ m/e = 370.2489)
Exact mass (**4e**) : m/e = 342.2094 (calc. for $C_{24}H_{26}N_2$ m/e = 342.20959)

**2,3,5-trimethyl-7-[2,3,5-trimethyl-2,5-dihydro-1H-1-benzazepin-yl]-2,5-dihydro *1H*-1 benzazepin 5a$_1$** (major isomer - 80%) **+ 5a$_2$** (minor isomer - 20%)

The reduction of **4a** (mixture of two isomers 80/20) leads to **5a$_1$** (major isomer 80%) and **5a$_2$** (minor isomer 20%) which are separable by column chromatography ; they appear themselves as a mixture of two isomers (50/50) observable either in $^1H$ NMR by the splitting of some signals (cf. experimental) or in $^{13}C$ NMR by the broadening or the splitting of all the signals. The reduction of the imine unit is attested :

- in mass spectra by a molecular ion at 372 a.m.u.
- in $^{13}C$ NMR by the dissapearance of the signal for C-2 at δ : 170 which is transformed into a doublet ($^1J$ = 135 Hz) located at δ : 70
- in $^1H$ NMR by the transformation of $CH_3$-2 (s: δ 2.32) into a doublet (J = 7 Hz ; δ : 1.25).

**5a$_1$**
Rf : 0.38
I.R. ν ($cm^{-1}$) : N-H (3300)
$^1H$ NMR ($CDCl_3$) : H-1 (s:2.5; broad) ; $CH_3$-2 (d:1.25), J(7) ; H-2 (q:3.52), J(7) ; $CH_3$-3 (s:1.57) ; H-4 (s:5.30) ; H-5 (m:3.77) ; $CH_3$-5 (d:1.25 and 1.27) ; H-6 and H-8 (m:6.35-6.64) ; H-9 (d:6.68 and 6.67) ; H-2' (q:4.42) ; $CH_3$-2' (d:1.08 and 1.09) ; $CH_3$-3' (s:1.69) ; H-4' (s:5.19) ; H-5' (m:3.65) ; $CH_3$-5' (d:1.33) ; Ar (m(4H)7.12-7.25).
$^{13}C$ NMR ($CDCl_3$) only $sp^3$ carbons : 6 methyl groups : 18.44 and 18.53 ; 19.07 and 19.06 ; 23.14 and 22.93 ; 21.48 ; 22.93 ; 23.14 ; C-2 (57.05 and 57.07) ; C-2' (54.67 and 54.75) ; C-5 (34.82 and 34.96) ; C-5' (31.68 and 31.76).
M.S. m/e, rel.intensity % : 372 $[M]^{\cdot+}$ , 75 ; 370 $[M\text{-}2H]^{\cdot+}$, 36 ; 357, 33 ; 172, 100 ; 157, 55.
Exact mass : m/e = 372.2578 (calc. for $C_{26}H_{32}N_2$ m/e = 372.25653)

**5a$_2$**
Rf : 0.34
I.R. ν ($cm^{-1}$) : N-H (3300)
$^1H$ NMR ($CDCl_3$) : H-1 (s:2.6) ; $CH_3$-2 (d:1.18), J(8.3) ; H-2 (m:3.65) ; $CH_3$-3 (s:1.59) ; H-4 (s:5.42) ; H-5 (m:3.59) ; $CH_3$-5 (d:1.34), J(7.1) ; H-6 (d:6.45), J(2.7) ; H-8 (dd:6.37) ; H-9 (d:6.63) ; H-2' (q:4.42) ; $CH_3$-2' (d:1.08 and 1.09) ; $CH_3$-3' (s:1.69) ; H-4' (s:5.19) ; H-5' (m:3.65) ; $CH_3$-5' (d:1.33) ; Ar (m(4H)7.12-7.24).
$^{13}C$ NMR ($CDCl_3$) only $sp^3$ carbons : 6 methyl groups : 18.64 and 18.57 ; 19.18 ; 20.23 and 20.17 ; 21.79 ; 23.04 ; 23.30.
M.S. m/e, rel.intensity % : 372 $[M]^{\cdot+}$ , 100 ; 370 $[M\text{-}2H]^{\cdot+}$, 36 ; 357, 52 ; 317 , 26.
Exact mass : m/e = 372.2578 (calc. for $C_{26}H_{32}N_2$ m/e = 372.25653)

**Crystal data for 2b**

$C_{14}H_{17}N$ : Mr = 199.30, orthorhombique, Pbca, a = 11.116 (6), b = 13.138 (9), c = 15.754 (4) $Å^{-3}$, Z = 8, Dx = 1.15, $Mg.m^{-3}$, λ (Mo-Kα) = 0.70926 Å, μ = 0.62 $cm^{-1}$, F(000) = 864, T = 120 K, crystal size 0.20 x 0.40 x 0.50 mm). The data collection (2 θmax = 50°, scan ω/2θ = 1, $t_{max}$ = 60 s, range hkl : h 0.12, k 0.15, l 0.18) gave 2070 reflections from which 1311 were independent with I > 36 (I).
The structure was solved using direct methods. After isotropic refinement (R = 0.12) followed by anisotropic refinement (R = 0.092), all the hydrogen atoms could be located by a Fourier difference map. The whole structure was refined by full-matrix least-square technique (use of F magnitude ; x, y, z, βij for C and N ; x, y, z for H, $\omega = 1/\sigma (Fo)^2 = [\sigma^2 (I) + (0.04\ Fo^2)2]^{-1/2}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1974). All calculations were performed on a Digital Micro VAX 3100 computer with the MOLEN (FAIR, 1990) package [15,16].

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