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Electrochemical Behaviour of an Unsymmetrical 4-(o-Nitrophenyl)-1,4-Dihydropyridine in Protic Medium.

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***Key Words** : 1-,4-dihydropyridine - electrochemical oxidation*

Abstract : The electrochemical behaviour of 3-cyano-5-methoxycarbonyl-2,6-dimethyl-4(o-nitrophenyl)-1,4-dihydropyridine and the corresponding N-methyl derivative have been investigated in hydroalcoolic medium. The 4 electron reduction leads to an amino-benzonaphtyridine N-oxide (cyclization from the reaction of the hydroxylamino group with the cyano substituent) when performed in acidic medium ; in basic medium, the same reduction leads to a cyclic hydroxamic acid resulting from the condensation of the hydroxylamino group with the ester substituent. Anodic oxidations give the corresponding pyridine or pyridinium derivatives ; subsequent reductions of the latter always lead to cyclic hydroxamic acids.

INTRODUCTION

The study of the electrochemical behaviour of Nifedipine [3,5-dimethoxycarbonyl-2,6-dimethyl-4(o-nitrophenyl)-1,4-dihydropyridine] has shown that none of the products issued from the nitro group reduction (nitroso, hydroxylamine, amine) were stable in protic medium [1]. Surprisingly, despite the steric proximity between this nitro group and the ester substituents at 3 and 5 position, no cyclization of the corresponding phenylhydroxylamine was observed. However, such a cyclization occurs in the pyridine or pyridinium serie, leading to the expected hydroxamic acid [2] (Scheme 1).

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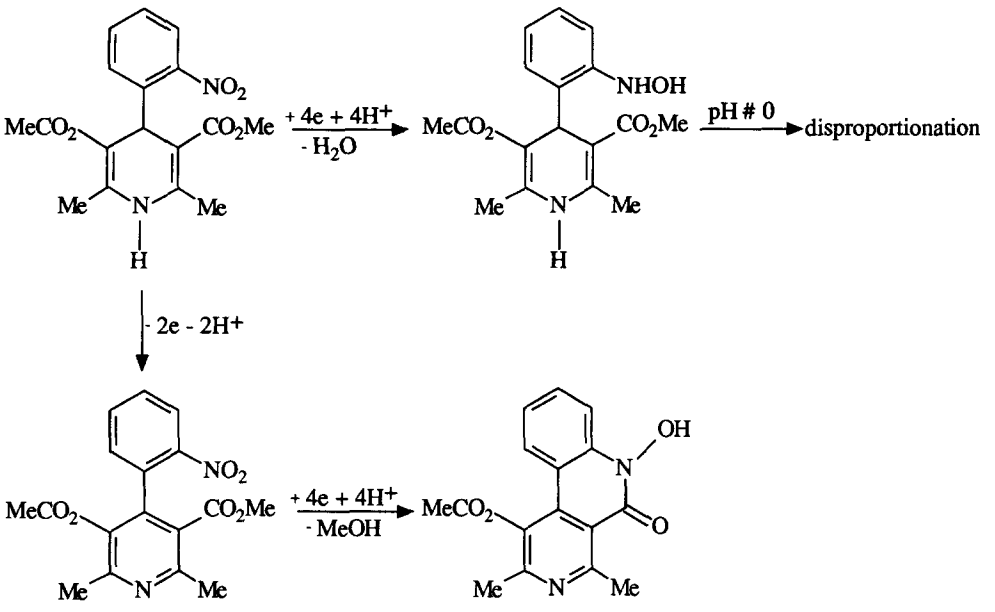
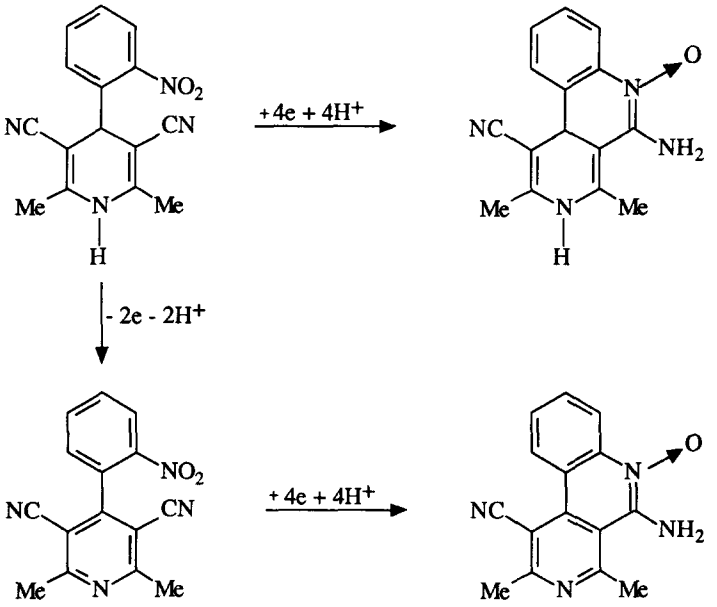


Scheme 1

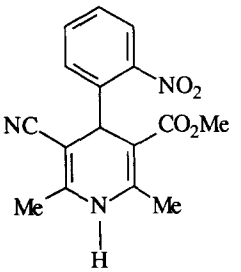
In contrast, cyclization of the hydroxylamine issued from the 3,5-dicyano analog is observed either in the dihydropyridine or the pyridine series [3], giving an amino-naphtyridine N-oxide derivative (Scheme 2).



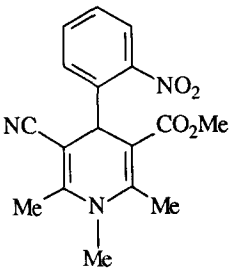
Scheme 2

This difference of behaviour can be understood by a configurational change between the diester and the dicyano compound. X-ray diffraction studies have shown that the dihydropyridine ring in Nifedipine is boat-shaped [4], while it is planar in the dicyano derivative [3].

In order to complete this work, it seems interesting to investigate the electrochemical behaviour of the unsymmetrical 1,4-dihydropyridine **1a**, substituted by an ester group and a cyano group at positions 3 and 5, and the corresponding N-methyl derivative **1b**.



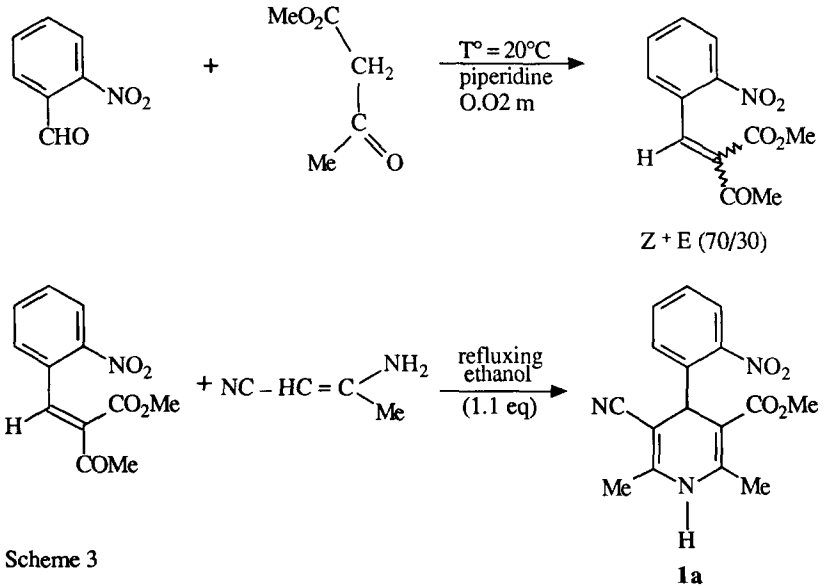
1a



1b

The first synthesis of **1a** – a one-pot reaction between o-nitrobenzaldehyde, β-amino crotononitrile and ethyl-β-aminocrotonate [5] – leads only to a 22% yield. Further, it was reported that unsymmetrical dihydropyridines can be synthesized from the reaction of (2-nitrobenzylidene)acetoacetate with isobutyl-aminocrotonate [6]. Therefore, we selected this method for the preparation of **1a** (Scheme 3) :

- a Knovelagen condensation between o-nitrobenzaldehyde and methylacetoacetate, in the presence of a catalytic amount of piperidine, leads to a mixture of Z and E o-nitrobenzylidene.
- reaction of the Z isomer with 3-aminocrotononitrile gives **1a**, in a 70% yield.



Scheme 3

1a

N-methylation of **1a** has been achieved by reaction of dimethylsulfate, using a phase transfer catalytic procedure [7].

RESULTS AND DISCUSSION

1 - ANALYTICAL BEHAVIOUR

The two investigated compounds display the same behaviour in cyclic voltammetry.

For instance, voltammograms registered at a glassy carbon electrode on a solution of **1a** in an acetic buffer are reported on fig. 1 :

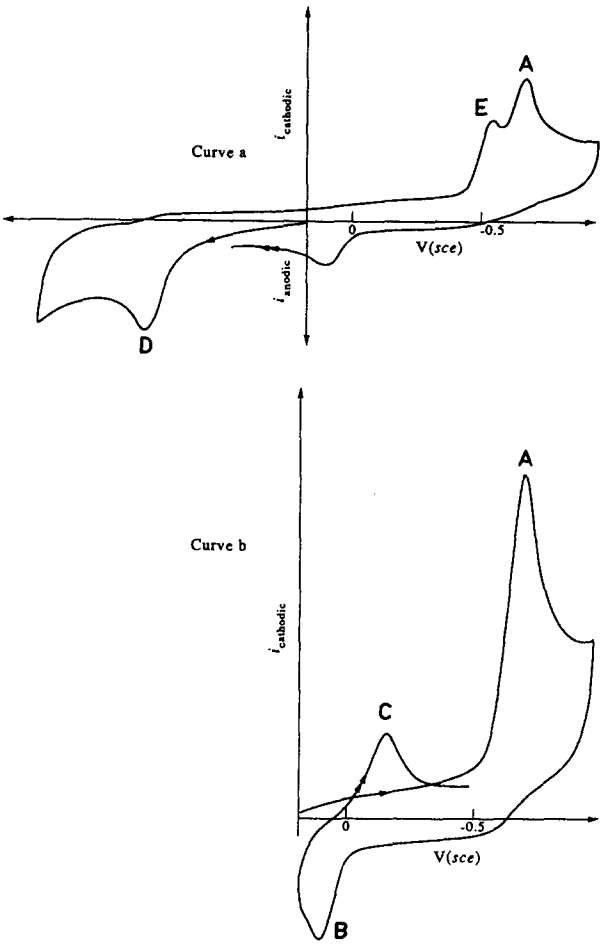


Fig. 1 - Voltammograms of dihydropyridine **1a** in a mixture of aqueous acetic buffer 0.5 mol.l^{-1} and ethanol (1/1). Electrode : vitreous carbon ; sweep rate : 0.1 V.s^{-1}. Curve (a) : first scan in the anodic way. Curve (b) : first scan in the cathodic way.

i) when the first scan is performed in the cathodic way (curve b), reduction of the nitro group into hydroxylamine appears (peak A) ; on the reverse scan, oxidation of hydroxylamine into the nitroso derivative is observed (peak B), the latter being reduced into hydroxylamine (peak C) on the second cathodic scan.

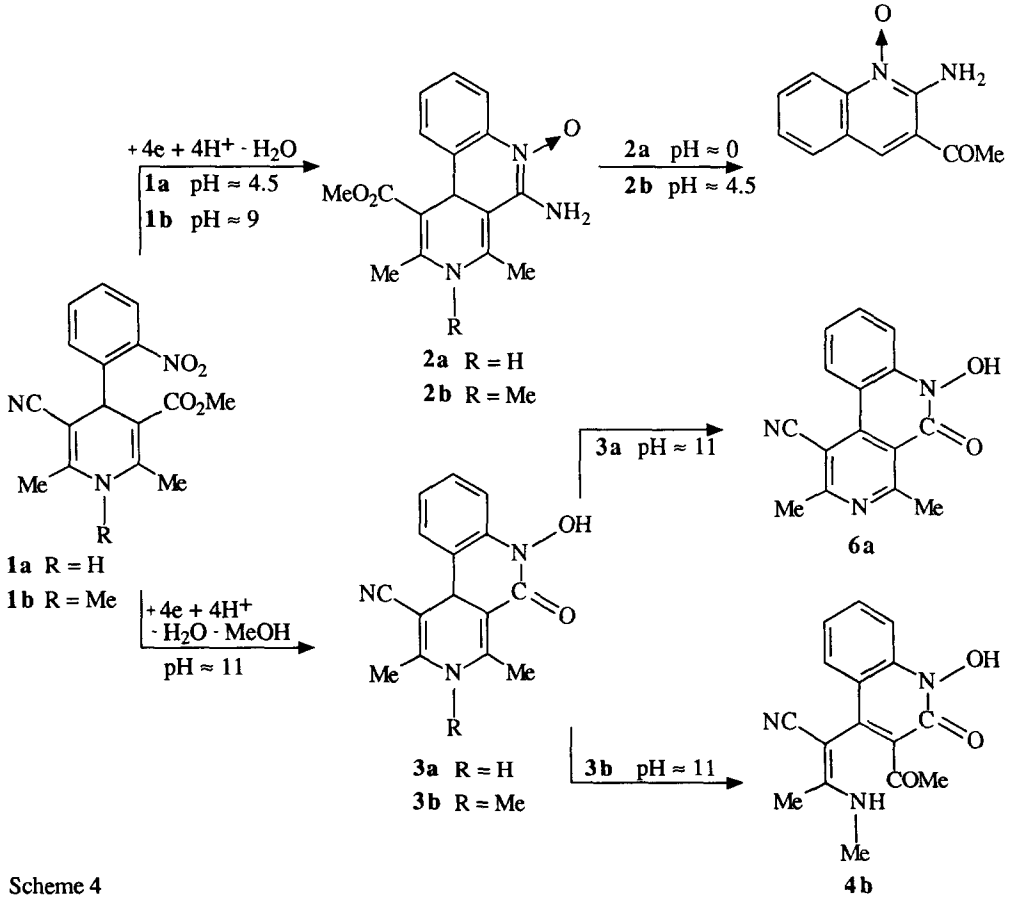
ii) when the first scan is performed in the anodic way (curve a), oxidation of the dihydro pyridine ring takes place (peak D) ; on the reverse cathodic scan, two reduction peaks are observed : peak A again corresponds to the reduction of the nitro group of the dihydropyridine compound ; peak E can then be assigned to the nitro group reduction of the pyridine derivative (formed by oxidation at peak D).

2 - MACROSCALE CATHODIC REDUCTIONS

i) The reduction of **1a** and **1b** were first performed in a batch cell at a mercury pool electrode, in an acetic buffer (pH ≈ 4.5) for **1a** and in an ammonium acetate solution (pH ≈ 9) for **1b** (vide infra).

While the corresponding phenylhydroxylamines are stable at the time scale of cyclic voltammetry (fig. 1, curve b), they do not accumulate during macroscale electrolyses, as shown by the disappearance of their oxidation wave ($E_{1/2}$ = - 0.02 V SCE) and the appearance of a new cathodic wave ($E_{1/2}$ = - 1.35 V SCE). After consumption of 4 electron moles per mole of substrate, the cyclized amino N-oxide derivatives **2a** and **2b** are isolated (Scheme 4), in a nearly quantitative yield for **2a** and a 70% yield (after purification) for **2b**.

Then, in these experimental conditions, regioselective cyclization occurs from the reaction between the hydroxylamino group and the cyano substituent.



Scheme 4

Remarks : - the cathodic wave at - 1.35 V corresponds to the reduction of the N-oxide group of **2a** and **2b**.

- compounds **2a** and **2b** are hydrolyzed into 3-acetyl-2-amino-quinoline N-oxide [9] in acidic medium, at pH ≈ 0 for **1a** but at pH ≈ 4.5 for **2b** ; this fact explains the choice of the medium for the electrolyses.

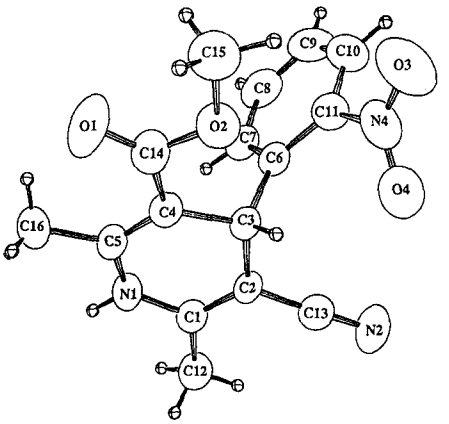
ii) Fine examination of the crude product resulting from **1b** reduction shows that a cyano streching band still remains in IR spectra, even after complete reduction of the nitro group and total disappearance of the hydroxylamine. Then a lack of regioselectivity in the cyclization can be expected in basic medium. In order to confirm this idea, electrolysis of **1a** and **1b** were performed in a more basic medium (NaOH 2.5 mol.l^{-1}), in a flow cell in order to neutralize sodium hydroxide immediately after reduction with addition of pure acetic acid (vide infra). The resulting solutions do not show oxidation nor reduction waves. Removal of the solvent under nitrogen atmosphere leads to white precipitates of cyclic hydroxamic acids **3a** and **3b** (Scheme 4). Then, in basic medium, cyclization occurs only from the reaction of the hydroxylamino group with the ester substituent.

Compounds **3a** and **3b** are easily oxidized by oxigen under basic conditions leading respectively to the pyridine derivative **6a** and the ring-open compound **4b** mixed with some polymeric products ; such ring-opening reactions by nucleophilic attack of the medium are classicaly observed for cationic species [8]. These side reactions occur very slowly in acidic medium, explaining the selection of our experimental conditions.

Following the finding that cyclization between the hydroxylamine and the ester groups can take place in basic medium, we carried out the same reduction on Nifedipine and again obtained the cyclic hydroxamic acid. Remembering that the latter cannot be obtained under acidic conditions [1] unambigously proves a basic catalysis of the intramolecular condensation between hydroxylamine and ester groups.

iii) To conclude, a high regioselectivity of the cyclization is observed under acidic or mild basic conditions ; it probably takes its origin in structural considerations. X-ray study of **1a** shows that the side of the dihydropyridine ring which supports the cyano substituent is flatter than the side linked to the ester group ; hence, the distance of interaction between the hydroxylamino group and the cyano substituent is shorter and reaction between these groups occurs. However, in basic medium, the regioselectivity is reversed ; may be it is then an anionic form of the hydroxylamine function which reacts with the ester substituent in an intramolecular nucleophilic substitution.

Crystal structure of **1a**



3 - MACROSCALE ANODIC OXIDATIONS

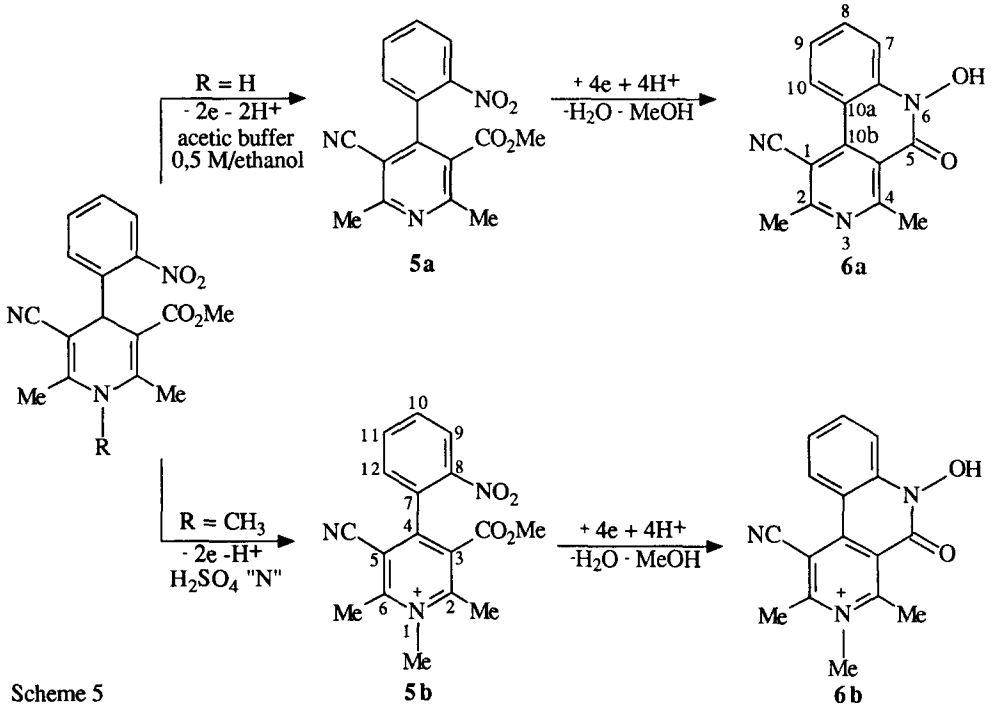
i) According to the analytical study the dihydropyridines **1a** and **1b** can be oxidized, in acetic buffer for **1a** and more efficiently in sulphuric acid medium (pH ≈ 0) for **1b**, into the pyridine **5a** and the pyridinium cation **5b** (Scheme 5) isolated as its hexafluorophosphate salt.

ii) Due to the electron-donor effect of the dihydropyridine nucleus, transformation of dihydropyridine into pyridine or pyridinium structure induces an easier reductibility of the nitro group. Macroscale reductions of compounds **5a** and **5b** were performed under the following conditions :

- in acetic buffer and in a batch cell for **5a** ; the tricyclic hydroxamic acid **6a** precipitates in a quasi quantitative yield.

- in a 0.5 M sulphuric acid medium and in a flow cell for **5b** leading after treatment to the hexafluorophosphate of pyridinium **6b**.

As previously observed [2], cyclization on the ester group takes place selectively in the pyridine serie, due to the planarity of the substrates.



Scheme 5

4 - ELECTROCHEMICAL BEHAVIOUR OF THE NAPHTYRIDINE N-OXIDE 2a

i) Cathodic reduction : we noticed above that compound **2a** displays in polarography a bielectronic reduction wave ($E_{1/2}$ = - 1.35 V SCE in acetic buffer). In contrast to the results obtained in the dicyano serie [3], we did not succeed in the selective reduction of the N-oxide group. After controlled potential electrolysis at

- 1.4 V SCE, we only isolated 5% of the amino-naphtyridine **7a** (cf. Scheme 6) ; the latter probably results from an air oxidation of the corresponding dihydro compound during treatment of the solution.

ii) Anodic oxidation : the voltammogram of **2a**, registered in acetic buffer, shows two oxidation peaks (fig. 2, curve a) : the first (Ep = 0.78 V SCE) is a bielectronic oxidation of the dihydropyridine nucleus ; the second (Ep = 0.98 V SCE) corresponds to further oxidation of the amino group. Using a flow cell, by a precise control of the intensity and the flow rate of the solution, it is possible to oxidize selectively at peak A ; on the voltammogram of the outlet solution (fig. 2, curve b) peak A has totaly vanished while peak B remains unchanged. After distillation of the solvent, the amino-naphtyridine N-oxide **8a** is obtained in a 65% yield.

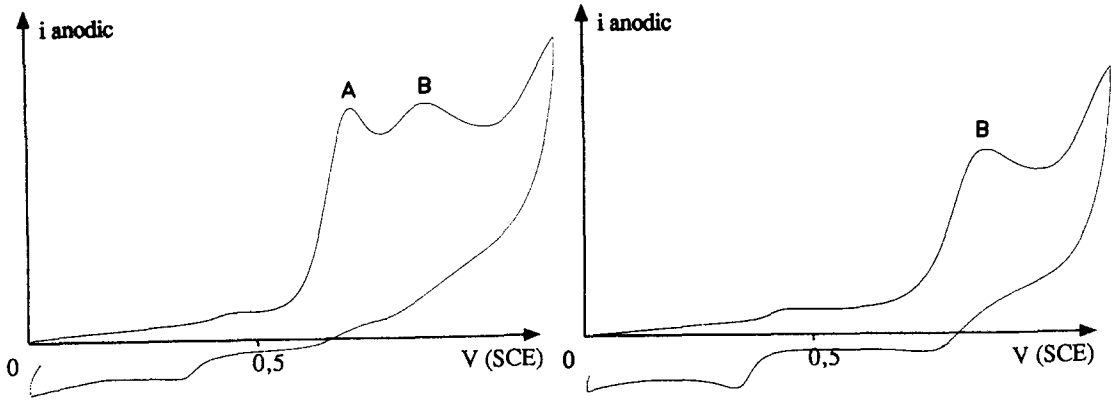


Fig. 2 - Voltammograms of dihydro benzo(c)-[2,7]naphtyridine
Curve a : voltammogram of **2a** registered at a vitreous carbon electrode ; sweep rate 0.1 $V.s^{-1}$, acetic buffer 0.5 M/ethanol 1/1
Curve b : voltammogram of **8a** (same conditions).

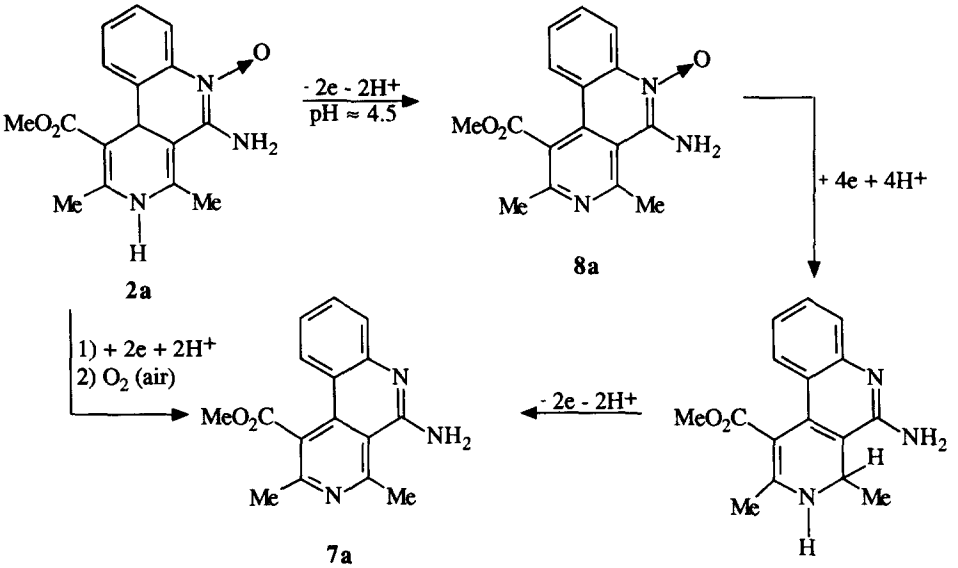
iii) Another way to amino-naphtyridine **7a**

The polarographic behaviour of the N-oxide **8a** depends on the medium acidity :

- at pH ≈ 0, two successive bielectronic waves are observed at - 0.65 and - 1.00 V SCE
- in acetic buffer, reduction occurs at - 1.10 V SCE in a single 4 electron wave
- in ammoniacal buffer, a single 2 electron wave appears at - 0.85 V SCE.

Tentatives of macroscale reductions on the bielectronic wave were again unsuccessfull, like for **2a**. But **8a** can be reduced in acetic buffer in a 4 electron process, leading to the 1,2-dihydropyridine derivative **9a** (Scheme 6) ; the latter is isolated as the hexafluorophosphate salt and purified by chromatography.

Compound **9a** displays two oxidation waves at + 0.9 and + 1.17 V SCE. The bielectronic oxidation leads selectively to the amino-naphtyridine **7a**.



Scheme 6

CONCLUSION

This paper illustrates the versatility of phenylhydroxylamine cyclizations according to the experimental conditions. Moreover, it shows the usefulness of the flow cell either in reductive or in oxidative process ; particularly, it is worthnoting the selective oxidation of the tricyclic dihydropyridine **2a** into the corresponding pyridine **8a** without modification of the amino group.

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EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and were not corrected. Purification by chromatography column were performed on 70-230 mesh silica gel or aluminium oxide neutral (Merck). TLC analyses were carried out on pre-coated plastic sheets silica gel $60F_{254}$ or aluminium oxide $60F_{254}$ neutral (type E). Elemental analyses were done at the "Service Central d'Analyse, Département Analyse Elémentaire (Vernaison)". IR spectra were recorded on a Nicolet 205 FT-IR instrument (KBr powder). NMR spectra were recorded on a Brucker AH 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 down field from TMS and coupling constant (J) in Hertz. The assigments were made using chemical shifts and coupling constants (^1J and long range coupling). ^{13}C NMR : broad band and gated decoupling spectra were recorded. Values with an asterisk* could be interverted.
Mass spectra was achieved on a Mat 311 double focusing instrument at the CRMPO with a source temperature of 170°C. An ion accelerating potential of 3 Kv and ionizing electrons of 70 ev.

Electrochemistry : Voltammetric investigations have been carried out at a vitreous carbon electrode.
Macroscale oxidations were performed in a flow cell [10]. The working electrode was a graphite felt cylinder (diameter : 50 mm ; thickness : 12 mm). The flow rate of the solution was regulated at 5 $ml.mn^{-1}$.
Macroscale reductions were performed either at mercury pool cathode at controled potential or in a flow cell.

Preparation of o-nitrobenzylidene (Z isomer)

10 g (0.0662 mole) of o-nitrobenzaldehyde (Merck) were dissolved in 8.45 g (0.0728 mole) of methyl acetoacetate (Aldrich). The mixture was then stirred over 24 hours with ten drops of piperidine. The solid mixture was taken up with 100 ml of methanol ; the Z isomer (11.865 g - 72% yield) was removed by succion.

m.p. (MeOH) : 102°C
Rf. (ether / petroleum ether (50/50) ; silica) : 0.24
I.R. (KBr) ν (cm^{-1}) : C=O (1780 and 1750) ; C=C (1675)
^1H NMR ($CDCl_3$) : CH_3-C=O (s:2.48) ; CH_3-O (s:3.60) ; H vinyl (s:8.08) ; 4H arom (d:7.43 ; 8.24 ; t:7.59, 7.68)
^{13}C NMR ($CDCl_3$) : 27.04 ; 52.28 ; 125.13 ; 129.90 ; 130.38 ; 130.55 ; 134.05 ; 136.27 ; 140.51 ; 147.03 ; 166.30 ; 194.54
M.S. m/e, rel.intensity % : 249 $[M]^{\cdot+}$ non observed ; 207 $[M\text{-}CH_2{=}C{=}O]^{\cdot+}$, 1 ; 203 $[M\text{-}\cdot NO_2]^+$ 10 ; 120, 34 ; 43, 100.
Exact mass : m/e = 207.0531 (calc. for $C_{10}H_9NO_4$ m/e = 207.05315)
Analysis : Calc.% C : 57.83 ; H : 4.42 ; N : 5.62 ; O : 32.13
Found % C : 58.14 ; H : 4.49 ; N : 5.60 ; O : 32.17

For attribution of the stereochemistry of the two alkenes one drop of deuteriated trifluoroacetic acid has been added to a solution of the previous compound in $CDCl_3$. Two novels methyl signals appeared at 2.20 and 3.88 ppm corresponding to the trans isomer.
NMR ^1H ($CDCl_3$) : CH_3-C=O (s:2.20) ; CH_3-O (s:3.88) ; H vinyl (s:8.07) ; 4H arom (d:7.21 ; 8.19 ; m:7.60)
NMR ^{13}C ($CDCl_3$ + CF_3CO_2D) : 31.21; 52.72 ; 124.09 ; 130.06 ; 130.32 ; 130.64 ; 131.04 ; 135.88 ; 139.54 ; 148.13 ; 164.36 ; 200.39.

Compound 1a

3,26 g (3.96 mmole) of 3-aminocrotononitrile (Aldrich) was added to a suspension of the alkene **1** (Z isomer, 9g, 3.61 mmole) in methanol (80 ml). The mixture was warmed at 60°C until complete dissolution and was then refluxed for 18 hours. The mixture was cooled at 5°C, the desired product crystallized in the reaction mixture. Recrystallization in methanol gave 7.7 g of yellow powder (70% yield).
m.p. (methanol) : 228-230°C (dec)
Rf. (ether / silica) : 0.37
I.R. (KBr) ν (cm^{-1}) : N-H (3300) ; C≡N (2200) ; C=O (1710) ; C=C (1655)
^1H NMR (DMSO d_6) : N_1-H (s,broad:9.34) ; CH_3-2 (s:2.24) ; CH_3-O (s:3.34) ; H_4 (s:5.11) ; CH_3-6 (s:2.08) ; H9 or H_{12} (d:7.55-7.79) ; H_{10} or H_{11} (t:7.44-7.69)
^{13}C NMR (DMSO d_6) : CH_3-2 (17.46) ; C-2 (147.55)* ; C-3 (99.71) ; C=O (166.23) ; CH_3-O (50.66) ; C-4 (34.92); C-5 (83.36) ; C≡N (118.98) ; CH_3-6 (18.29) ; C-6 (147.66)* ; C-7 (140.87) ; C-8 (146.68) ; C-9 (123.06) ; C-10 or C-11 (128.02 ; 133.71) ; C-12 (131.11).
M.S. m/e, rel.intensity % : 313 $[M]^{\cdot+}$ 9 ; 296 $[M\text{-}OH]^+$, 100 ; 266, 34 ; 251, 60 ; 191, 95.
Exact mass : m/e = 313.1071 (calc. for $C_{16}H_{15}N_3O_4$ m/e = 313.10625)
Analysis : Calc.% C : 61.34 ; H : 4.79 ; N : 13.42 ; O : 20.45
Found % C : 61.00 ; H : 4.67 ; N : 13.25 ; O : 20.45

Compound 1b

A solution of 50% NaOH aq (40 ml) was added to 4 g (1.28 mmole) of **1a** dissolved in 200 ml of CH_2Cl_2 containing 2.5 ml of dimethylsulfate and 2.5 g of tetrabutylammonium hydrogenosulfate (Janssen). The two phases are vigourously stirred for 30 mn at room temperature. The organic layer was washed by a solution of ammonia (5%), HCl (5%) and water (x3). After drying over $MgSO_4$ and distillation 3 g (71%) of **1b** were obtained after recrystallization in ethanol.
m.p. (ethanol) : 144°C
Rf. (CH_2Cl_2/ silica) : 0.55
I.R. (KBr) ν (cm^{-1}) : C≡N (2200) ; C=O (1700) ; C=C (1650)

^1H NMR ($CDCl_3$) : CH_3-N_1 (s:3.27) ; CH_3-2 (s:2.50) ; CH_3-O (s:3.48) ; H_4 (s:5.35) ; CH_3-6 (s:2.28) ; H_9 or H_{12} (d:7.40-7.69) ; H_{10} or H_{11} (t:7.32-7.52)
^{13}C NMR ($CDCl_3$) : CH_3-N_1 (34,24) ; CH_3-2 (16.53) ; C-2 (149.54) ; C-3 (104.51) ; C=O (167.04) ; CH_3-O (51.33) ; C-4 (35.20) ; C-5 (87.71) ; C≡N (119.47) ; CH_3-6 (19.10) ; C-6 (150.26) ; C-7 (139.96) ; C-8 (148.34) ; C-9 (123.53) ; C-10 (127.86)* ; C-11 (133.12)* ; C-12 (130.69). For attribution of CH_3-2, C-2 ; CH_3-6 ; C-6, irradiation at 2.28 and 2.50 ppm.
M.S. m/e, rel.intensity % : 327 $[M]^{\cdot+}$ 5 ; 311 $[M-O]^+$, 16 ; 310 $[M-OH]^+$, 100 ; 280, 26 ; 265, 31 ; 204 $[M-C_6H_4NO]^+$, 88.
Exact mass : m/e = 327.1225 (calc. for $C_{17}H_{17}N_3O_4$ m/e = 327.12190)
Analysis : Calc.% C : 62.39 ; H : 5.20 ; N : 12.84 ; O : 19.57
Found % C : 62.29 ; H : 4.98 ; N : 12.84 ; O : 19.73

Compound 2a

0.5 g (1.6 mmole) of **1a** was dissolved in a mixture (150 ml) of acetic buffer (0.5 $mol.l^{-1}$) and ethanol (1/2). The solution was electrolysed at a mercury pool cathode at - 0.9 V/SCE. After consumption of 4F per mole and complete cyclization of the hydroxylamine (6 hours), ethanol was evaporated under vacuum. The aqueous phase was basified by $NaHCO_3$ and vigourously shaked with 100 ml of CH_2Cl_2 until **2a** precipitated in the organic phase. After filtration 0.4 g (83% yield) of **2a** was obtained as a yellow powder.
m.p. (CH_2Cl_2) : > 260°C (dec)
Rf. (CH_2Cl_2/MeOH (80/20) ; silica) : 0.14
I.R. (KBr) ν (cm^{-1}) : N-H (3400) ; NH_2 (3000) ; C=O (1700) ; C=C (1675)
^1H NMR (DMSO d_6) : CH_3-O (s:3.55) ; CH_3-2 or CH_3-4 (s:1.92-2.23) ; H-N_3 (s:broad, 8.68) ; H_{10b} (s:4.48)-; H_7 or H_{10} (d:6.70-7.64) ; H_8 or H_9 (t:7.05-7.20)
^{13}C NMR (DMSO d_6) : CH_3-O (50.61) ; C=O (168.06) ; C-1 (96.79) ; C-2 (147.63)* ; CH_3-2 or CH_3-4 (16.80-18.52) ; C-4 (133.88) ; C-4a (93.62) ; C-5 (147.78)* ; C-6a (138.71) ; C-7 (116.03) ; C-8 or C-9 or C-10 (121.49-123.80-126.05) ; C-10a (131.41) ; C-10b (34.05)
M.S. m/e, rel.intensity % : 299 $[M]^{\cdot+}$, 24 ; 297 $[M-H_2]^{\cdot+}$, 8 ; 281 $[M-H_2O]^{\cdot+}$, 100 ; 250, 50.
Exact mass : m/e = 299.1285 (calc. for $C_{16}H_{17}N_3O_3$ m/e = 299.12698)

Compound 2b

0.5 g (1.5 mmole) of **1b** was dissolved in a mixture (150 ml) of ammonium acetate (0.5 $mol.l^{-1}$) and ethanol (1/2). The electrolysis was performed at - 1.1 V/SCE at a mercury pool cathode. After consumption of 3.6F per mole the electrolysis was stopped. The ethanolic mixture was separated from mercury and the hydroxylamine was cyclizised at 5°C under nitrogen for 12 hours. Ethanol was evaporated under nitrogen, the aqueous phase was then extracted by 100 ml of CH_2Cl_2 (x 2). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness. **2a** was purified by chromatography (silica, 25 g), polar impurities were eluted first with [CH_2Cl_2/MeOH - 95/5] ; the desired product was eluted when increasing the proportion of methanol from 5 to 30%. Distillation of the solvent gave a glassy product which was taken up with ether (0.3 g ; 63% yield).
m.p. (ether) : 180°C (dec)
Rf. (CH_2Cl_2/MeOH (70/30) ; silica) : 0.70
I.R. (KBr) ν (cm^{-1}) : NH_2 (3000) ; C=O (1700) ; C=C (1650)
^1H NMR ($CDCl_3$) : CH_3-2 or CH_3-4 (s:2.09-2.45) ; CH_3-N_3 (s:3.02) ; CH_3-O (s:3.55) ; H_{10b} (s:4.61) ; H_7 or H_{10} (d:6.78-7.68) ; H_8 or H_9 (t:7.03-7.16)
^{13}C NMR ($CDCl_3$) : CH_3-O (51.26) ; C=O (169.20) ; C-1 (98.85)* ; C-2 (150.36) ; CH_3-N_3 (51.26) ; CH_3-2 or CH_3-4 (17.60-17.65); C-4 (139.96) ; C-4a (98.79)* ; C-5 (151.27) ; C-6a (138.00) ; C-7 (116.42) ; C-8 or C-9 or C-10 (121.97-124.88-126.56) ; C-10a (132.29) ; C-10b (34.02)
M.S. m/e, rel.intensity % : 313 $[M]^{\cdot+}$ 1.72 ; 297 $[M-O]^+$, 7 ; 296 $[M-OH]^+$, 3 ; 282, 10 ; 280, 11 ; 18, 100.
Exact mass : m/e = 313.1423 (calc. for $C_{17}H_{19}N_3O_3$ m/e = 313.14263)

Compounds 3a and 3b

0.5 g (1.6 mmole) of **1a** was dissolved in a mixture (0.5 l) of sodium acetate (0.15 $mol.l^{-1}$) + NaOH aq. (2.5 $mmol.l^{-1}$) and ethanol (1/1). The solution was reduced at a graphite felt cathode (intensity red = 105 mA) and was collected under nitrogen. 2 ml of acetic acid were added and the ethanol was distilled off. **3a** was obtained as a creamy product which was washed twice with water and dissolved in ethanol, distillation under vacuum and nitrogen gave a pale yellow powder (0.2 g ; 47%). **3b** precipitated and was taken up by ethanol which was removed by succion giving 0.2 g of pale yellow powder.

Compound 3a
m.p. (ethanol) : 210°C (dec)
Rf. (CH_2Cl_2/MeOH (95/15) ; silica) : 0.24
I.R. (KBr) ν (cm^{-1}) : N-OH (3326) ; C≡N (2200) ; C=O (1672) ; C=C (1630)
^1H NMR (DMSO d_6) : CH_3 (s:2.02) ; CH_3 (s:2.07) ; H_{10} (s:4.40) ; 1H (t:7.08) ; 2H (m:7.23) ; 1H (d:7.35)
^{13}C NMR (DMSO d_6) : C≡N (120.93) ; C-1 (77.48) ; CH_3-2 or CH_3-4 (17.87-16.47); C-2 (150.02) ; C-4 (140.71) ; C-4a (97.06) ; C-5 (163.59) ; C-6a (137.82) ; C-7 (111.75) ; C-8 or C-9 or C-10 (121.93-122.2-127.1) ; C-10a (127.51) ; C-10b (34.19)
M.S. m/e, rel.intensity % : 267 $[M]^{\cdot+}$, 46 ; 266 $[M-H]^+$, 53 ; 265 $[M-H_2]^{\cdot+}$, 17 ; 250 $[M-OH]$, 100 ; 249 $[M-H_2O]^{\cdot+}$, 87 ; 221, 33.
Exact mass : m/e = 267.0994 (calc. for $C_{15}H_{13}N_3O_2$ m/e = 267.10077)

Compound 3b
m.p. (ethanol) : 210°C (dec)
I.R. (KBr) ν (cm^{-1}) : N-OH (3253) ; C≡N (2196) ; C=O (1672) ; C=C (1639)
^1H NMR (DMSO d_6) : CH_3-2 (s:2.30) ; CH_3-4 (s:2.27) ; CH_3-N_3 (3.09) ; H_{10b} (s:4.34) ; 4H arom (7.05-7.32) ; H-O (s, broad : 10.32)
^{13}C NMR (DMSO d_6) : C≡N (121.20) ; C-1 (79.38) ; CH_3-2 (19.35); C-2 (143.82) ; CH_3-N_3 (33.36) ; CH_3-4 (15.20) ; C-4 (152.96) ; C-4a (99.81) ; C-5 (163.10) ; C-6a (137.58) ; C-7 (112.00) ; C-8 or C-9 or C-10 (122.33-127.24) ; C-10a (127.28) ; C-10b (34.12)
for attribution of CH_3-2 ; C-2 ; CH_3-4 ; C-4 irradiation at 2.30 and 2.27 ppm
M.S. m/e, rel.intensity % : 281 $[M]^{\cdot+}$, 21 ; 265 $[M-O]^+$, 15 ; 250, 24 ; 236, 10
Exact mass : m/e = 281.1165 (calc. for $C_{16}H_{15}N_3O_2$ m/e = 281.11642)

Compound 5a
1 g (3.2 mmole) of dihydropyridine **1a** was dissolved in a mixture (1 l) of acetic buffer (0.5 $mol.l^{-1}$) and ethanol (4/6). The solution was oxidized at a graphite felt anode (intensity ox = 52 mA). Ethanol was distilled off. The aqueous phase was basified by $NaHCO_3$ and extracted with CH_2Cl_2 (100 ml). After drying ($MgSO_4$) the organic layer was concentrated and purified on silica (ether / petroleum ether (1/1). **5a** was obtained as a white product and recrystallized in ether (0.6 g ; 60% yield).
m.p. (ether) : 121°C
Rf. (ether/petroleum ether ; 50/50 ; silica) : 0.37
I.R. (KBr) ν (cm^{-1}) : C≡N (2200) ; C=O (1750)
^1H NMR (DMSO d_6) : CH_3-2 or CH_3-6 (s:2.61 or 2.75) ; CH_3-O (s:3.48) ; H_9 or H_{12} (d:7.54-8.36) ; H_{10} or H_{11} (t:7.85-7.94)
^{13}C NMR (DMSO d_6) : CH_3-2 (23.582) ; C-2 (161.74)* ; C-3 (124.39) ; C=O (165.67) ; CH_3-O (52.58) ; C-4 (149.68) ; C-5 (106.49) ; C≡N (115.34) ; C-6 (159.07)* ; CH_3-6 (23.582) ; C-7 (129.61) ; C-8 (146.66) ; C-9 (124.86) ; C-10 or C-11 or C-12 (130.89-131.41-134.58)
M.S. m/e, rel.intensity % : 311 $[M]^{\cdot+}$, non observed ; 280 $[M-O\text{-}Me]^+$,3 ; 265, 100 ; 249, 9.
Exact mass : m/e = 280.07258 (calc. for $C_{15}H_{10}N_3O_3$ m/e = 280.07221)
Analysis : Calc.% C : 62.00 ; H : 4.27 ; N : 13.35 ; O : 20.38
Found % C : 61.74 ; H : 4.18 ; N : 13.50 ; O : 20.58

Compound 5b
The nitrophenyl dihydropyridine **1b** (1 g, 3.1 mmole) was dissolved in a mixture (0.5 l) of sulfuric acid aq (0.5 $mol.l^{-1}$) and ethanol 1/1. The solution was oxidized at a graphite felt anode (i_{ox} = 98 mA). The ethanol was distilled off and the resulting solution was extracted by CH_2Cl_2 (x 2) and ether ; 3 g of NH_4PF_6 were added to the aqueous phase, a white precipitate of pyridinium hexafluorophosphate (**5b**) separated and was taken up with boiling ethanol (1.2 g ; 83% yield).
m.p. (ethanol) : 260°C (dec)
Rf. (CH_2Cl_2/MeOH : 9/1 ; silica) : 0.44
I.R. (KBr) ν (cm^{-1}) : C≡N (2275, weak) ; C=O (1750) ; C=C (1600)
^1H NMR (CD_3CN) : CH_3-N_1 (s:3.56) ; CH_3-2 (s:2.85) ; CH_3-O (s:4.16) ; CH_3-6 (s:3.06) ; H_9 or H_{12} (d:7.42 or 8.40) ; H_{10} or H_{11} (7.91 or 7.98)
^{13}C NMR (CD_3CN) : CH_3-N_1 (43.94) ; CH_3-2 (21.62) ; C-2 (164.12) ; C-3 (132.52) ; CH_3-O (54.91) ; C=O (164.12) ; C-4 (157.48) ; C≡N (113.51) ; C-5 (115.05) ; CH_3-6 (22.82) ; C-6 (162.58) ; C-7 (128.64) ; C-8 (147.33) ; C-9 (126.72) ; C-10 or C-11 or C-12 (131.07-133.98-136.38) ; for attribution of CH_3-2 ; C-2 ; CH_3-6 ; C-6 irradiation at 2.85 and 3.07 ppm.

FAB$^+$: 326.2

M.S. m/e, rel.intensity % : 325 $[M]^{\cdot+}$, 90 ; 310 $[M-CH_3]^+$, 100 ; 294, 9 ; 266, 25 ; 107, 61.

Exact mass : m/e = 325.1046 (calc. for $C_{17}H_{15}N_3O_4$ m/e = 325.10625)

Analysis : Calc.% C : 43.31 ; H : 3.40 ; N : 8.92 ; P : 6.58 ; F : 24.20
Found % C : 42.84 ; H : 3.43 ; N : 8.84 ; P : 6.38 ; F : 23.19

Compound 6a

0.6 g (1.9 mmole) of nitrophenyl pyridine **5a** was dissolved in a mixture (150 ml) of acetic buffer (0.5 mol.l^{-1}) and ethanol (1/1). Reduction at - 1 V SCE consumed 4F per mole of substrate ; **6a** precipitated during the electrolysis (0.36 g ; 75% yield).

m.p. (ethanol) : 210°C

I.R. (KBr) ν (cm^{-1}) : O-H (2800) ; C≡N (2200) ; C=O (1640)

^1H *NMR*(DMSO d_6) : CH_3-2 (s:2.83) ; CH_3-4 (s:3.09) ; H_7 and H_8 (d, (J=4Hz):7.84) ; H_9 (m:7.46) ; H_{10} (d:9.21) ; H-O (s,broad:11.5) ; for attribution irradiation at 7.84 ppm.

^{13}C *NMR* (DMSO d_6) : C≡N (118.56) ; C-1 (99.09) ; CH_3-2 (24.44) ; C-2 (164.47) ; CH_3-4 (27.78) ; C-4 (164.94) ; C-4a (117.33) ; C-5 (155.76) ; C-6a (138.68) ; C-7 (113.25) ; C-8 or C-9 or C-10 (122.56-125.18-133.63) ; C-10a (113.67) ; C-10b (140.53) ; for attribution of CH_3-2 ; C-2 irradiation at 2.835 ppm.

M.S. m/e, rel.intensity % : 265 $[M]^{\cdot+}$, 38 ; 249 $[M-O]^+$, 100 ; 248 $[M-OH]^+$, 44 ; 221, 33 ; 204, 13.

Exact mass : m/e = 265.0853 (calc. for $C_{15}H_{11}N_3O_2$ m/e = 265.08512)

Analysis : Calc.% C : 67.92 ; H : 4.15 ; N : 15.85 ; O : 12.08
Found % C : 67.87 ; H : 4.14 ; N : 15.57 ; O : 12.19

Compound 6b

0.8 g (2.4 mmole) of **1b** was dissolved in a mixture (0.5 l) of sulfuric acid aq (0.5 mol.l^{-1}) and ethanol (1/1). After being oxidized (i_{ox} = 78 mA) the solution was reduced by a second passage throught a graphite felt cathode (i_{red} = 156 mA). After removal of the ethanol, **6b** was precipitated by the addition of 3 g of NH_4PF_6. The product was taken up with boiling ethanol and gave 0.650 g (65% yield) of an orange powder.

m.p. (ethanol) : > 260°C (dec)

I.R. (KBr) ν (cm^{-1}) : O-H (3210) ; C≡N (2250, weak) ; C=O (1650)

^1H *NMR* (CD_3CN) : CH_3-2 (s:3.16) ; CH_3-N_3 (s:4.20) ; CH_3-4 (s:3.45) ; H_7 (d:7.91) ; H_8 or H_9 (t:7.57 or 8.01) ; H_{10} (d:9.27)

^{13}C *NMR* (CD_3CN) : C≡N (116.90) ; C-1 (107.14) ; CH_3-2 (22.84) ; C-2 (162.40) ; CH_3-N_3 (43.91) ; CH_3-4 (21.85) ; C-4 (166.85) ; C-4a (121.83) ; C-5 (154.82) ; C-6a (139.55) ; C-7 (114.77) ; C-8 or C-9 or C-10 (125.29-128.37-138.56) ; C-10a (113.37) ; C-10b (145.63) ; for attribution of CH_3-2 ; C-2 ; CH_3-4 ; C-4 irradiation at 3.16 and 3.45 ppm.

FAB$^+$: 280.2

M.S. m/e, rel.intensity % : 279 $[M]^{\cdot+}$, 3; 263 $[M-O]^+$,30 ; 262 $[M-OH]^+$, 30 ; 248, 18 ; 104, 67 ; 85, 52 ; 20, 100

Exact mass : m/e = 279.1013 (calc. for $C_{16}H_{13}N_3O_2$ m/e = 279.10077)

Analysis : Calc.% C : 45.18 ; H : 3.29 ; N : 9.88 ; P : 7.29 ; F : 26.82
Found % C : 45.12 ; H : 3.32 ; N : 9.85 ; P : 7.19 ; F : 26.22

Compound 8a

1 g (3.2 mmole) of **1a** was dissolved in a mixture (1 l) of acetic buffer (0.5 mol.l^{-1}) and ethanol (1/1). The solution was reduced at a graphite felt cathode (i_{red} = 102 mA) and collected under nitrogen. After complete cyclization at 5°C, the solution of **2a** was oxidized on a graphite felt anode (i_{ox} = 51 mA). After the removal of ethanol the aqueous phase was basified with $NaHCO_3$ and extracted by 150 ml of CH_2Cl_2 (x 3). The combined organic layer were dried ($MgSO_4$) and concentrated to dryness. Pure **8a** was obtained by sonication of the product mixture (CH_2Cl_2) and by chromatography of the mother liquor (Silica : CH_2Cl_2/MeOH 5%) (0.6 g - 63% yield).

m.p. (CH_2Cl_2) : 230°C (dec)

Rf. (CH_2Cl_2/MeOH ; 80/20 ; silica) : 0.60

I.R. (KBr) ν (cm^{-1}) : NH_2 (3350) ; C=O (1760) ; C=C (1600)

^1H *NMR* (DMSO d_6) : CH_3-O (s:4.02) ; CH_3-2 or CH_3-4 (s:2.56 or 3.11) ; -NH_2 (s, broad:7.80) ; H_7 or H_{10} (d:7.97 -8.56) ; H_8 or H_9 (t:7.58-7.88)

^{13}C *NMR* (DMSO d_6) : CH_3-O (53.34) ; C=O (170.19) ; C-1 (120.32) ; CH_3-2 or CH_3-4 (22.16 or 27.09) ; C-2 or C-4 (151.81 or 156.70) ; C-4a (112.29) ; C-5 (145.34) ; C-6a (138.55) ; C-7 (118.16) ; C-8 or C-9 or C-10 (124.64-124.87-132.04) ; C-10a (116.79) ; C-10b (129.77)

M.S. m/e, rel.intensity % : 297 $[M]^{\cdot+}$, 43 ; 281 $[M-O]^+$, 100 ; 280 $(M-OH]^+$, 42 ; 250, 38
Exact mass : m/e = 297.1118 (calc. for $C_{16}H_{15}N_3O_3$ m/e = 297.11133)
Analysis : Calc.% C : 64.65 ; H : 5.05 ; N : 14.14 ; O : 16.16
Found % C : 64.48 ; H : 4.89 ; N : 13.86 ; O : 16.08

Compound 9a

0.5 g (1.7 mmole) of **8a** was dissolved in 10 cc of acetic acid and poured into 150 cc of acetic buffer (0.25 $mol.l^{-1}$). The electrolysis was carried out in a mercury pool cathode at - 1.35 V/SCE. After consumption of 4F per mole of substrate the solution was basified by $NaHCO_3$ and 2 g of NH_4PF_6 were added. The aqueous phase was then extracted with 150 cc of CH_2Cl_2 (x 2). After drying ($MgSO_4$) the organic phase was concentrated and chromatographied on alumina (10 g) polar impurities were first eluted with CH_2Cl_2 and MeOH (1%). The desired product **9a** was obtained when increasing the proportion of methanol to 5% giving 0.2 g (42%) of an highly fluorescent yellow powder.
Rf. (CH_2Cl_2/MeOH ; 95/5 ; alumina) : 0.25
I.R. (KBr) ν (cm^{-1}) : NH_3^+ (2800-3200) ; C=O (1750) ; PF_6 (850)
^1H NMR (CD_3CN) : CH_3-O (s:3.59) ; CH_3-2 (s:2.3) ; H-N_3 (d:broad:6.67) ; H-4 (qxd:4.61) ; CH_3-4 (d:J=7Hz, 1.23) ; -NH_2 (s, broad:7.03) ; H_7 , H_8, H_9, H_{10} (m:7.25 to 7.60)
^{13}C NMR (CD_3CN) : CH_3-O (51.85) ; C=O (169.05) ; C-1 (97.60) ; CH_3-2 (20.55) ; C-2 (160.80) ; CH_3-4 (18.14) ; C-4 (46.32) ; C-4a (111.40) ; C-5 (151.79) ; C-6a (143.16) ; C-7 (121.17) ; C-8 or C-9 or C-10 (124.18-127.51-131.48) ; C-10a (119.74) ; C-10b (140.34).

Compound 7a

N-oxyde compound **8a** was reduced according to previous procedure giving the intermediate amidine **9a**. The volume of the solution was then adjusted to 0.5 l with acetic buffer (0.5 $mol.l^{-1}$) and oxidized (i_{ox} = 55 mA). The solution was basified with Na_2CO_3 and extracted with 150 ml of CH_2Cl_2 (x 2). The combined organic layer were dried ($MgSO_4$) and concentrated to dryness, the material was taken up with ethanol (5 ml) and rapidly filtered giving 0.2 g (42%) of white powder.
m.p. (ethanol) : 228°C
Rf. (CH_2Cl_2/MeOH ; 99/1 ; alumina) : 0.25
I.R. (KBr) ν (cm^{-1}) : NH_2 (3470 and 3310) ; C=O (1770) ; C=C (1650)
^1H NMR (DMSO d_6) : CH_3-O (s:3.99) ; CH_3-2 (s:2.54) ; CH_3-4 (s:3.07) ; -NH_2 (s, broad:6.81) ; 4H arom (t:7.26 ; m:7.53 to 7.63 ; d:7.80)
^{13}C NMR (DMSO d_6) : CH_3-O (53.05) ; C=O (170.64) ; C-1 (120.02) ; CH_3-2 (22.18) ; C-2 (152.34) ; CH_3-4 (27.36) ; C-4 (158.19) ; C-4a (112.19) ; C-5 (155.70) ; C-6a (146.90) ; C-7 (121.97) ; C-8 or C-9 or C-10 (124.18-125.98-130.87) ; C-10a (117.03) ; C-10b (137.42) ; for attribution of CH_3-2 ; C-2 ; CH_3-4 ; C-4 irradiation at 2.54 and 3.06 ppm.
M.S. m/e, rel.intensity % : 281 $[M]^{\cdot+}$, 100 ; 250, 22 ; 222, 9
Exact mass : m/e = 281.1173 (calc. for $C_{16}H_{15}N_3O_2$ m/e = 281.11642)
Analysis : Calc.% C : 68.33 ; H : 5.34 ; N : 14.95 ; O : 11.39
Found % C : 67.21 ; H : 5.32 ; N : 14.85 ; O : 11.28

1-methoxycarbonyl-6-hydroxy-5-oxo-2,3-dimethyl 3,10 b dihydro-benzo(c)-[2,7]-naphtyridine

1 g (2.9 mmole) of nifedipine was reduced according to previous procedure (compound **3a**). After removal of the ethanol, the aqueous phase was extracted by CH_2Cl_2 (x 2). The organic phase was dried ($MgSO_4$) and evaporated. The material was taken up by CH_2Cl_2 (10 ml) to give 0.5 g of a white powder.
m.p. (CH_2Cl_2) : 260°C
I.R. (KBr) ν (cm^{-1}) : O-H (3346) ; N-H (3260) ; C=O ester (1721) ; C=O hydroxamic acid (1680) ; C=C (1651)
^1H NMR (DMSO d_6) : CH_3-O (s:3.54) ; CH_3-2 (s:2.27) ; H-N_3 (s,broad:8.65) ; CH_3-4 (d,JH-N_4 = 1Hz ; 2.02) ; H-O (s,broad:10.10) ; H-7, H-8, H-9, H-10 (d:6.69(1H) ; m:6.97 (1H) ; m:7.18 (2H) ; H-10b (s:4.48)
^{13}C NMR (DMSO d_6) : CH_3-O (50.63) ; C=O (ester)(168.01) ; C-1 (99.33) ; CH_3-2 (18.45) ; C-2 (138.23) ; CH_3-4 (15.99) ; C-4 (140.05) ; C-4a (95.31) ; C-5 (164.24) ; C-6a (148.00) ; C-7 (111.46) ; *C-8 ; *C-9 ; *C-10 (121.83-122.29-126.20) ; C-10a (129.50) ; C-10b (34.54)
M.S. m/e, rel.intensity % : 300 $[M]^{\cdot+}$, 92 ; 285 $[M-CH_3]^+$, 98 ; 282 $[M-H_2O]^+$, 100 ; 251, 95 ; 240, 52.
Exact mass : m/e = 300.1116 (calc. for $C_{16}H_{16}N_2O_4$ m/e = 300,1110)

Crystal data for 1a

$C_{16}H_{15}O_4N_3$: Mr = 313.3, monoclinic, $P2_1/n$, a = 7.805(3), b = 14.484 (2), c = 13.741(3) Å, β = 99.44(2), V = 1532.3(6) $Å^{-3}$, Z = 4, Dx = 1.36 $Mg.m^{-3}$, λ MoKα) = 0.70926Å, μ = 0.93 cm^{-1}, F(000) = 656, T = 294 K, final R = 0.035 for 1211 observations.

The sample (0.20*0.20*0.40 mm) is studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$ = 50°, scan $\omega/2\theta$ = 1, t_{max} = 60 s, range HKL : H 0,9 K 0,17 L -16,16, intensity controls without appreciable decay (0.4 %) gives 3042 reflections from which 1211 independant (R_{int} = 0,016) with $I>2\sigma(I)$.

After Lorenz and polarization corrections the structure was solved with Direct Methods which reveal all the non hydrogen atoms of the molecule. After isotropic (R = 0.11), then anisotropic refinement (R = 0.081), the hydrogene atoms are found with a Fourier Difference (between 0.24 an 0.12 $eÅ^{-3}$). The whole structure was refined by the full-matrix least-square techniques (use of F magnitude ; x, y, z, βij for C,O and N atoms and x, y, z for H atoms ; 254 variables and 1211 observations ; $w = 1/\sigma(F_O)^2 = [\sigma^2(I) + (0.04F_O^2)^{2-1/2})$ with the resulting R =0.037, R_w = 0.035 and S_w = 0.88 (residual $\Delta\rho \leq 0.09$ $eÅ^{-3}$).

Atomic scattering factors from International Tables for X-ray Crystollography (1974). All the calculations were performed on a Digital MicroVAX 3100 computer with the MOLEN package (Enraf-Nonius, 1990).

Nomenclature

1a	5-methoxycarbonyl-3-cyano-2,6-dimethyl-4(o-nitrophenyl)-1,4 dihydropyridine
1b	5-methoxycarbonyl-3-cyano-1,2,6-trimethyl-4(o-nitrophenyl)-1,4 dihydropyridine
2a	5-amino-1-methoxycarbonyl-2,4-dimethyl-3,10b dihydrobenzo(c)[2,7]-naphtyridine-6-oxyde
2b	5-amino-1-methoxycarbonyl-2,3,4-trimethyl-3,10b dihydrobenzo(c)[2,7]-naphtyridine-6-oxyde
3a	1-cyano-6-hydroxy-5-oxo-2,4-dimethyl-3,10b dihydrobenzo(c)[2,7]-naphtyridine
3b	1-cyano-6-hydroxy-5-oxo-2,3,4-trimethyl-3,10b dihydrobenzo(c)[2,7]-naphtyridine
5a	5-methoxycarbonyl-3-cyano-2,6-dimethyl-4(o-nitrophenyl)-pyridine
5b	5-methoxycarbonyl-3-cyano-1,2,6-trimethyl-4(o-nitrophenyl)-pyridinium hexafluorophosphate
6a	1-cyano-6-hydroxy-5-oxo-2,4-dimethyl-benzo(c)[2,7]-naphtyridine
6b	1-cyano-6-hydroxy-5-oxo-2,3,4-trimethyl-benzo(c)[2,7]-naphtyridinium hexafluorophosphate
7a	5-amino-1-methoxycarbonyl-2,4-dimethyl-benzo(c)[2,7]-naphtyridine
8a	5-amino-1-methoxycarbonyl-2,4-dimethyl-benzo(c)[2,7]-naphtyridine 6-oxyde
9a	5-amino-1-methoxycarbonyl-2,4-dimethyl-3,4-dihydrobenzo(c)[2,7]-naphtyridine hexafluorophosphate

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10 Moinet, C. ; Raoult, E. *Bull. Soc. Chim. Fr.*, **1991**, 214.

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