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TETRAHEDRON

Synthesis of 3-Vinylpiperidines, 3-Ethylidenepiperidines and 5-Functionalized-1,2,3,4-tetrahydropyridines

Wim Aelterman and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

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Abstract : Reaction of 1-azapentadienyl anions, generated by deprotonation of N-(2-buten-1-ylidene)-alkylamines, with 1-bromo-3-chloropropane led to the formation of N-[2-(3-chloropropyl)-3-buten-1-ylidene]alkylamines. By reaction with nucleophiles and bases, the latter functionalized imines were converted into unsaturated piperidines, i.e. 3-vinylpiperidines, 3-ethylidenepiperidines, 5-vinyl-1,2,3,4-tetrahydropyridines and 5-(2-cyanoethyl)-1,2,3,4-tetrahydropyridines. 5-Vinyl-1,2,3,4-tetrahydropyridines proved to be suitable dienes in Diels-Alder reactions with N-phenylmaleimide, giving rise to octahydro-1*H*-pyrrolo[3,4*h*]quinoline-1,3-diones.

INTRODUCTION

ω-Halogenated imines, and more specifically δ-chloroimines, have been shown to be suitable building blocks for the synthesis of azaheterocycles.[1-5] For example, 1,5-dialkyl-1,2,3,4-tetrahydropyridines, which are useful synthons for alkaloid synthesis,[2] and the natural spreading agent stenusine[3] are easily accessible from δ-chloroimines. Azaheterocycles have been rarely synthesized from lithiated α,β-unsaturated imines by reaction with nitriles.[6] Unsaturated imines having a chloro atom at the δ-position have not yet been evaluated as building blocks for nitrogen-heterocycles. The combination of the insaturation and the ω-halogen in the imino molecule offers a synthetic potential for the synthesis of a variety of unsaturated piperidines and piperideines, which are otherwise difficultly accessible. In this paper, the synthesis of such unsaturated piperidines by a nucleophile- or base-induced cyclization of unsaturated δ-chloroimines is disclosed. Also the Diels-Alder reaction of conveniently prepared 5-vinyl-1,2,3,4-tetrahydropyridines with N-phenylmaleimide to form octahydro-1*H*-pyrrolo[3,4-*h*]quinoline-1,3-diones is reported.

RESULTS AND DISCUSSION

Anions derived from α,β-unsaturated imines can undergo attack at the α-position by reaction with alkyl halides.[7-10] Reaction with bifunctional electrophiles provides an interesting approach for the construction of azaheterocycles. A three-carbon fragment, halogenated at the terminus, was introduced at the α-position by reaction of conjugated 1-azaenolates **2** derived from N-(2-buten-1-ylidene)alkylamines with 1-bromo-3-chloro-

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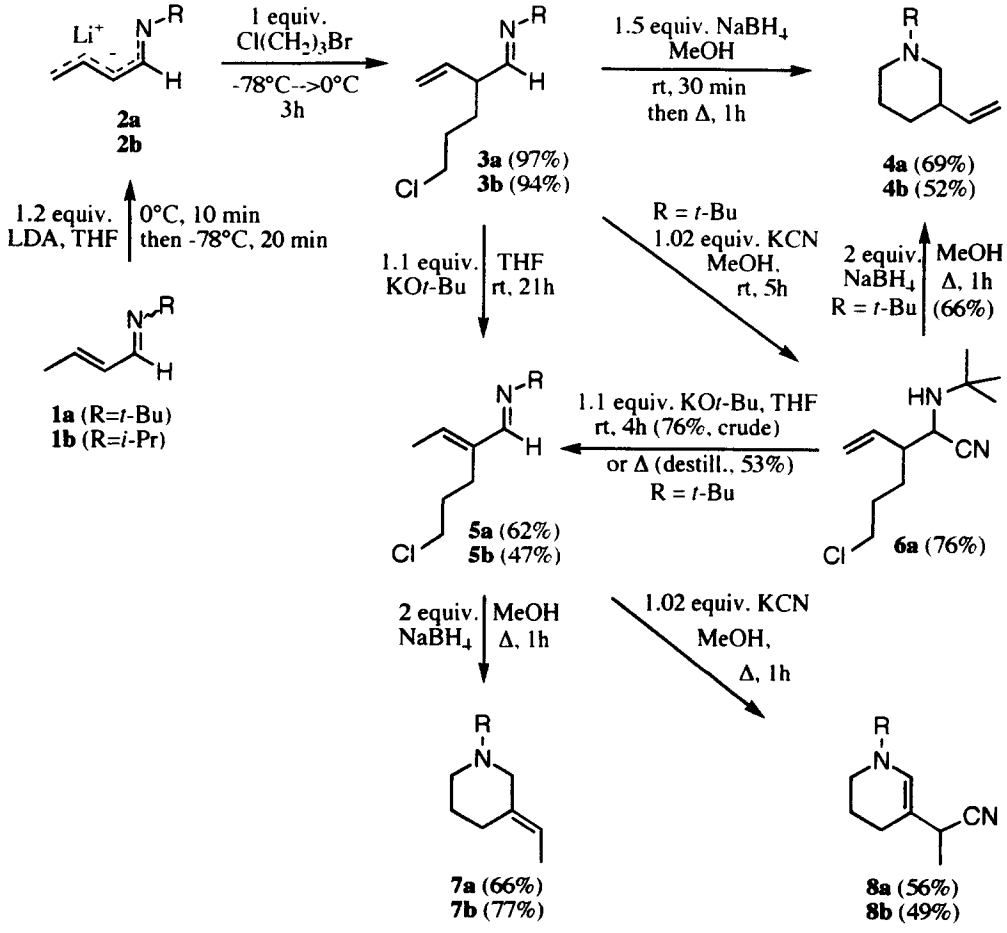
propane (Scheme 1). β,γ-Unsaturated imines **3**, carrying a γ-chloropropyl unit at the α-position, were obtained in excellent yields (94-97%) as crude products which had a satisfactory purity (> 95%; ^{1}H-NMR) to be used as such in the next step. These trifunctional compounds **3** were stable in the refrigerator for maximum two weeks, but attempts to purify aldimines **3** by distillation failed. Reductive cyclization of the δ-chloroimines **3** with sodium borohydride in methanol under reflux gave 1-alkyl-3-vinylpiperidines **4** in acceptable yields (52-69%) after purification by flash chromatography (Scheme 1). As demonstrated for the N-*tert*-butylderivative, vinylpiperidine **4a** was also accessible by treatment of the α-aminonitrile **6a**, obtained by reaction of aldimine **3a** with potassium cyanide in methanol at room temperature, with sodium borohydride in methanol under reflux (66% yield). The 3-vinylpiperidine ring[11] is a characteristic structural unit of the *Cinchona* alkaloids, including medicinally important derivatives such as quinine and cinchonamine.[12-13]



Scheme 1

The β,γ-unsaturated imines **3** were easily isomerized in the more stable conjugated enimines **5** upon treatment with potassium *t*-butoxide in THF at room temperature. Reaction of α-amino-γ,δ-unsaturated nitrile **6a** with potassium *t*-butoxide in THF resulted in a dehydrocyanation and isomerization, also leading to α,β-unsaturated imine **5a**. When purification of the α-aminonitrile **6a** by distillation was tried, the same rearrangement occurred and the α,β-unsaturated imine **5a** was obtained as the sole product in 53% yield. The α,β-unsaturated imines **5** were successfully converted into 3-ethylidenepiperidines **7** and 5-(1-cyanoethyl)-1,2,3,4-tetrahydropyridines **8**, respectively, by reaction with sodium borohydride and potassium cyanide in methanol under reflux (Scheme 1). The formation of the tetrahydropyridines **8** is explained by a Michael-addition of cyanide to the β-position of the carbon-carbon double bond and subsequent ring closure (MIRC-reaction). This type of reaction is a Michael-induced ring closure (MIRC reaction) by which the transient 1-azaenolate gives an intramolecular alkylation of the nitrogen atom by the alkyl chloride at the terminus. The 3-ethylidenepiperidines **7** were obtained as *E*-isomers exclusively. The stereochemistry of compound **7a** was established by NOE NMR experiments (^{1}H NMR, 270 MHz, $CDCl_3$) (Fig. 1). Irradiation of the protons at C4 resulted in a NOE (6%) at

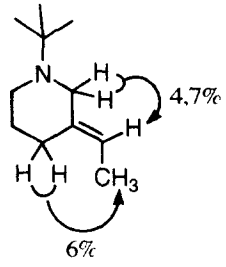
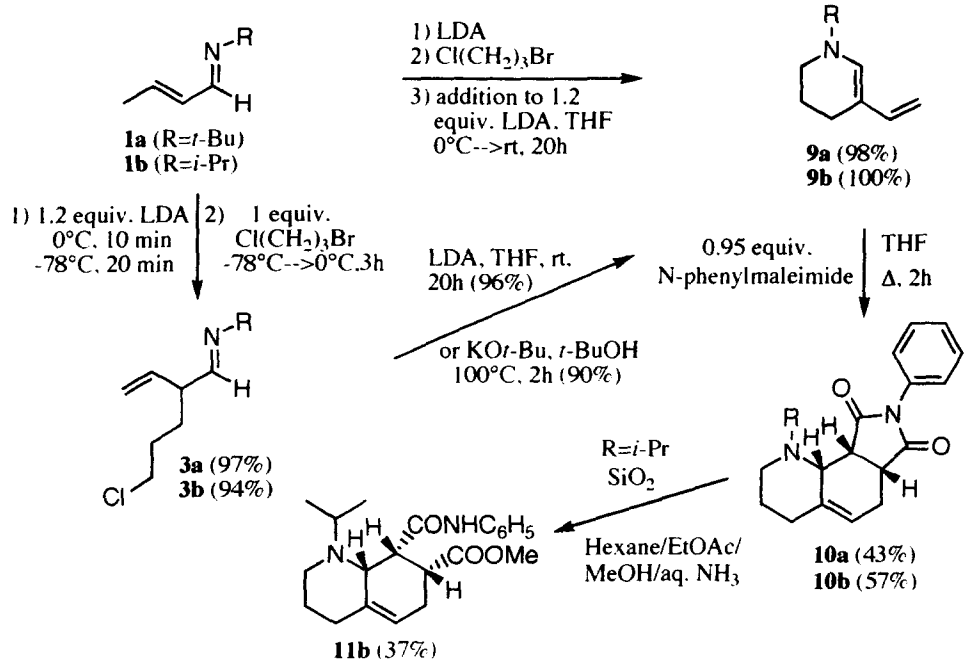


Fig. 1 : NOE effects observed for **7a**

the methyl protons of the ethylidene group. Also a NOE enhancement (4.7%) at the vinylic proton was observed when the methylene protons at C2 were irradiated. The 3-ethylidenepiperidine unit[14] is found in the structure of a large number of alkaloids, such as ervitsine,[15] geissoschizine,[16] strictamine,[15] pericyclivine,[17] ramiflorine,[18] ervatamine,[19] vinoxine,[15] pleiocarpamine[15] and akuammiline.[15]

The δ-chloroaldimines **3** could also be cyclized to the corresponding cyclic enamines by reaction with bases. Enimines **1** were converted into six-membered cyclic aminodienes **9** by a one pot synthesis consisting of deprotonation with LDA, subsequent alkylation with 1-bromo-3-chloropropane and ring closure with LDA (Scheme 2). The cyclic enamines **9**, which were obtained in excellent yields (98-100%), could not be purified by distillation or chromatography but they were pure enough (> 95%; ^{1}H NMR) to be used as such.[20] The 5-ethenyl-1,2,3,4-tetrahydropyridines **9** were also accessible in a two-step sequence from enimines **1** by treatment of the intermediate δ-chloroimines **3** with LDA in THF at room temperature or potassium *t*-butoxide in *t*-butanol at 100°C (2.5 h).

Electron-rich 1,3-dienes, such as **9**, are an important class of compounds because of their applications in organic synthesis, mainly in [4+2] cycloaddition reactions.[21,22] Indeed, piperidines **9** react under rather mild reaction conditions (2h reflux in THF) with N-phenylmaleimide to furnish stereoselectively the Diels-Alder



Scheme 2

endo-cycloadducts **10**, which were obtained as pure crystalline materials after flash chromatography (hexane/ethyl acetate) in 42-57% overall yield from **3** (Scheme 2). The stereochemistry of the octahydro-1*H*-pyrrolo-[3,4*h*]-quinoline-1,3-diones **10**, which was in agreement with results described in the literature from Diels-Alder reactions between other 1-amino-2,4-dienes and N-phenylmaleimide,[23-26] was established by NMR studies (^{1}H-^{1}H-coupling constants, NOE experiments) (Fig. 2 and 3). Thus, irradiation of H_{9a} (compound **10a**) effected a NOE enhancement of the signals for H_{9b} (6.7%) (Fig. 3), while ^{1}H-^{1}H-coupling constants between H_{9a}-H_{9b} (6.60 Hz) and H_{3a}-H_{9a} (8.74 Hz) matched completely those reported in the literature for a closely related endo-cycloaddition product (Fig. 2).[23]

When purification of the Diels-Alder product **10b** was performed by flash chromatography with a mixture of hexane / ethyl acetate / methanol ammonium hydroxide (25% NH_3 in H_2O) as eluent (ratio 78.2 : 19.5 : 2.0 : 0.3), the maleimide ring was opened with formation of compound **11b** (Scheme 2). The position of the N-phenylcarbamoyl group and the methoxycarbonylgroup was unraveled by DIFNOE experiments (Fig. 2). Irradiation of the H_8 proton resulted in a NOE enhancement at H_{8a} (6.1%), H_7 (5.5%) and at the carbamoyl proton (1.7%). Also, irradiation of the carbamoyl proton effected enhancement of the signals for H_8 (1.7%), and the CH (3.5%) and methyl groups (3.1%) of the N-isopropylamino substituent.

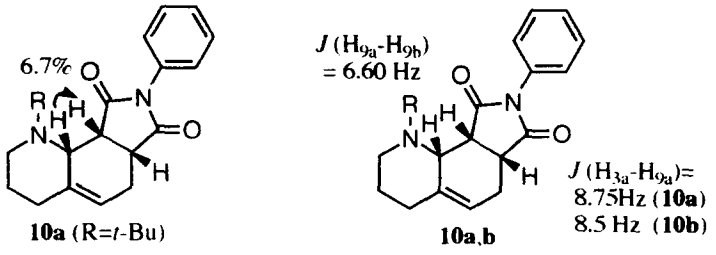


Fig. 2 : Determination of the stereochemistry of the tricyclic compounds **10a,b**

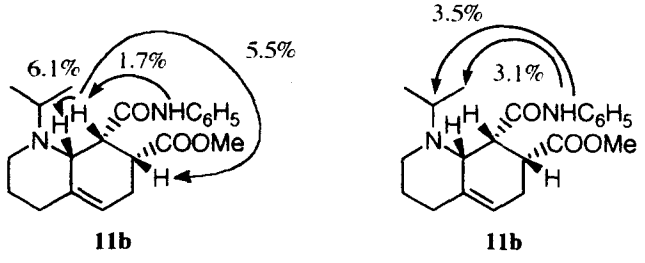


Fig. 3 : Determination of the stereochemistry of the bicyclic compound **11b**

EXPERIMENTAL PART

General methods. NMR spectra were recorded on a Jeol EX 270 NMR spectrometer (270 MHz for ^{1}H-NMR, 68 MHz for ^{13}C-NMR). IR spectra were obtained using a Perkin Elmer 1310 spectrophotometer. Mass spectra were recorded on a Varian MAT 112 mass spectrometer (70 eV) using a GC-MS coupling or the direct inlet system. Melting points were measured with a Büchi 535 melting point apparatus. TLC was performed on silica gel plates Kieselgel $60F_{254}$ (layer thickness 0.25 mm). Column chromatography was carried out on a glass column with Merck Silicagel 60 (particle size 40-63 μm).

N-(2-Buten-1-ylidene)alkylamines (1). To a solution of freshly distilled crotonaldehyde (0.3 mol) in dry CH_2Cl_2 (30 mL) was added $MgSO_4$ (0.3 mol) and the appropriate amine (0.36 mol). The solution was stirred for 20h at room temperature. After filtration of the drying agent and removal of the solvent *in vacuo*, the crude α,β-unsaturated imines **1** were distilled *in vacuo* (**1a** : 79%, bp. 36-38°C/11 mmHg (Lit.[27] : bp. 52-54°C/ 75 mmHg); **1b** : 72%, bp. 48-49°C/45 mmHg (Lit[27] : bp. 41°C/15 mmHg)).

N-[2-(3-Chloropropyl)-3-buten-1-ylidene]-*tert*-butylamine (3a). A solution of lithium diisopropylamide was freshly prepared from 3.94 g (39 mmol) of diisopropylamine in 40 mL of THF to which 14.4 mL of 2.5 M *n*-butyllithium (36 mmol) was added at 0°C under a nitrogen atmosphere. The aldimine **1a** (3.75 g, 30 mmol) was dissolved in THF (30 mL) and added dropwise. The solution was stirred for 10 min at 0°C after which time it was cooled to -78°C and further stirred for 20 min. At -78°C a solution of 4.72 g (30 mmol) of 1-bromo-3-chloropropane in 40 mL of THF was added *via* syringe and the solution further stirred for 3h,

during which the temperature was allowed to raise from -78°C to -30°C. After quenching of the reaction with 50 mL of saturated NH_4Cl solution, the mixture was added to ice-cooled 0.5 N NaOH (100 mL) and extracted with diethyl ether (3 x 50 mL). After drying (K_2CO_3) during 2h and concentration *in vacuo*, 5.85 g (97%) of β,γ-unsaturated imine **3a** (purity 95%) was obtained, which was used as such in the next step. ^{1}H-NMR ($CDCl_3$) : δ 1.18 (9H, s, CMe_3); 1.55-1.90 (4H, m, $CHC\underline{H}_2C\underline{H}_2$); 2.91 (1H, ~ quintet, J=6.7 Hz, CH); 3.55 (2H, t, J=6.3 Hz, CH_2Cl); 5.04 and 5.16 (2H, m, $CH=C\underline{H}_2$); 5.77 (1H, ddd, J=16.7, 10.9, 7.26 Hz, $\underline{H}C=CH_2$); 7.40 (1H, d, J=6.27 Hz, CH=N). ^{13}C-NMR ($CDCl_3$) : δ 29.15 and 30.02 ($CH\underline{C}H_2\underline{C}H_2$); 29.63 ($C\underline{Me}_3$); 44.83 ($CH_2Cl$); 49.36 (CH); 56.82 ($\underline{C}Me_3$); 116.39 ($CH=\underline{C}H_2$); 137.75 ($\underline{C}H=CH_2$); 159.48 (CH=N). IR (NaCl) : 1665, 1637 cm^{-1} (C=N, C=C). MS m/z (%) : 201/3 (M^+, 4); 186/8(13); 166(100); 152(5); 139(5); 124(8); 110(100); 96(23); 93(12); 83(12); 82(26); 77(6); 68(8); 57(50); 55(13); 53(8); 44(10); 42(13).

N-[2-(3-Chloropropyl)-3-buten-1-ylidene]isopropylamine (3b). The same procedure as described for the preparation of **3a** provided crude product **3b** in 94% yield. ^{1}H-NMR (C_6D_6) : δ 1.11 and 1.12 (2x3H, 2xd, J=6.27 Hz, $CH\underline{Me}_2$); 1.25-1.62 (4H, m, $CHC\underline{H}_2C\underline{H}_2$); 2.61-2.75 (1H, m, $C\underline{H}CH_2$); 3.10 (2H, t, J=6.26 Hz, CH_2Cl); 3.05-3.15 (1H, m, $C\underline{H}Me_2$); 4.95 and 4.97 (2x1H, m, $CH=C\underline{H}_2$); 5.61 (1H, ddd, J=17.4, 10.1, 7.92 Hz, $C\underline{H}=CH_2$); 7.23 (1H, d, J=4.96 Hz, CH=N). ^{13}C-NMR ($CDCl_3$) : δ 23.58 and 23.72 (Me_2); 28.59 and 29.60 ($CH\underline{C}H_2\underline{C}H_2$); 44.21 ($CH_2Cl$); 48.28 ($\underline{C}HCH_2$); 60.81 ($\underline{C}HMc_2$); 116.10 ($CH=\underline{C}H_2$); 137.11 ($\underline{C}H=CH_2$); 161.90 (C=N). IR (NaCl) 1650, 1630 cm^{-1} (C=N, C=C). MS m/z (%) : 187/9 (M^+, 2); 172(3); 152(100); 136(15); 124(7); 110(21); 108(5); 96(7); 95(4); 94(5); 93(7); 82(9); 67(6); 55(8); 53(5); 43(13).

3-Ethenyl-1-*tert*-butylpiperidine (4a). To an ice-cooled solution of 3 mmol (0.60 g) of aldimine **3a** in 5 mL of dry methanol was added 4.5 mmol (0.17 g) of sodium borohydride. The solution was stirred for 30 min at room temperature and then refluxed for 1h. The reaction mixture was poured into water (20 mL), extracted with CH_2Cl_2 (3x10 mL) and dried ($MgSO_4$). Purification of crude **4a** by flash chromatography using CH_2Cl_2/MeOH/NH_4OH (25% in H_2O) (96.5:2.9:0.6) as eluent resulted in 0.35 g (69%) of pure 3-ethenyl-1-*tert*-butylpiperidine **4a**. R_f=0.31. ^{1}H-NMR ($CDCl_3$) : δ 1.06 (1H, qd, J=11.6, 4.4 Hz, $NCH_2CH_2\underline{H}CH$); 1.07 (9H, s, Me_3); 1.55 (1H, qt, J=11.6, 2.7 Hz, $NCH_2\underline{H}CH$); 1.64-1.80 (2H, m, $NCH_2HC\underline{H}HC\underline{H}$); 1.80 (1H, t, J=10.88 Hz, $N\underline{H}CH$); 1.97 (1H, td, J=11.6, 2.7 Hz, $NHC\underline{H}$); 2.13-2.29 (1H, m, $NCH_2C\underline{H}$); 2.99 (2H, dt, J=10.88, 1.65 Hz, $N\underline{H}CH$ and $NHC\underline{H}$); 4.95 (1H, ddd, J=10.39, 1.65, 0.99 Hz, $\underline{H}CH=CH$); 5.02 (1H, dt, J=17.49, 1.65 Hz, $HC\underline{H}=CH$); 5.75 (1H, ddd, J=17.49, 10.39, 6.93 Hz, $CH_2=C\underline{H}$). ^{13}C-NMR ($CDCl_3$) : δ 26.00 and 30.58 ($NCH_2\underline{C}H_2\underline{C}H_2$); 26.09 ($C\underline{Me}_3$); 41.18 ($NCH_2\underline{C}H$); 46.22 and 52.16 (2x$NCH_2$); 53.92 ($\underline{C}Me_3$); 113.29 ($CH=\underline{C}H_2$); 142.17 ($\underline{C}H=CH_2$). IR (NaCl) : 1640 cm^{-1} (C=C). MS m/z (%) : 167 (M^+, 13); 152(100); 142(1); 111(2); 110(5); 95(2); 82(7); 81(3); 70(10); 67(6); 57(21); 55(7); 54(3); 44(26). Anal. Calcd. for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found : C, 79.14; H, 12.66; N, 8.33.

3-Ethenyl-1-isopropylpiperidine (4b). The same procedure as described for the preparation of **4a** provided **4b** in 52% yield from **3b** after purification by flash chromatography using CH_2Cl_2/MeOH/NH_4OH

(25% in H_2O) (96.5:2.9:0.6) as eluent. R_f=0.29. ^{1}H-NMR ($CDCl_3$) : δ 1.04 (6H, d, J=6.60 Hz, $\underline{Me}_2CH$); 0.96-1.14 (1H, m, $NCH_2CH_2\underline{H}CH$); 1.44-1.90 (3H, m, $NCH_2C\underline{H}_2HC\underline{H}$); 1.88 (1H, t, J=10.88 Hz, $N\underline{H}CHCH$); 2.05 (1H, td, J=11.56, 2.7 Hz, $N\underline{H}CHCH_2$); 2.14-2.33 (1H, m, $C\underline{H}CH=CH_2$); 2.72 (1H, septet, J=6.60 Hz, $C\underline{H}Me_2$); 2.70-2.84 (2H, $\underline{H}CHNHC\underline{H}$); 4.96 (1H, ddd, J=10.1, 1.65, 1.2 Hz, $\underline{H}CH=CH$); 5.03 (1H, dt, J=172, 1.65 Hz, $HC\underline{H}=CH$); 5.74 (1H, ddd, J=17.2, 10.1, 6.93 Hz, $CH_2=C\underline{H}$). ^{13}C-NMR ($CDCl_3$) : δ 18.11 and 18.29 (2xMe); 25.53 and 30.65 ($NCH_2\underline{C}H_2CH_2$); 40.68 ($NCH_2\underline{C}H$); 49.00 and 54.70 (2x$NCH_2$); 54.75 ($\underline{C}HMe_2$); 113.40 ($CH=\underline{C}H_2$); 141.88 ($\underline{C}H=CH_2$). IR (NaCl) : 1643 cm^{-1} (C=C); 2958, 2924, 1380, 1178, 910 cm^{-1}. MS m/z (%) : 153 (M^+, 10) : 138(100); 111(8); 110(6); 95(5); 86(8); 70(15); 67(9); 56(23); 44(14); 43(11); 42(10); 41(17). Anal. Calcd. for $C_{10}H_{19}N$: C, 78.37; H, 12.50; N, 9.14. Found : C, 78.51; H, 12.52; N, 9.10.

3-(3-Chloropropyl)-2-(N-*tert*-butylamino)-4-pentenenitrile (6a). To a solution of aldimine **3a** (1.21 g, 6 mmol) in 15 mL of dry methanol was added potassium cyanide (0.40 g, 6.12 mmol). The mixture was stirred for 5h at room temperature, then poured into H_2O (30 mL) and extracted with CH_2Cl_2 (3x20 mL). After drying ($MgSO_4$), filtration and evaporation of the solvent *in vacuo*, 1.04 g (76%) of nitrile **6a** was obtained. The crude product **6a** was used as such; purification by distillation resulted in a conversion into the imine **5a**. ^{1}H-NMR ($CDCl_3$) (two pairs of diastereomers; 60/40) : δ 1.15 and 1.16 (2x9H, 2xs, CMe_3); 1.56-1.91 (8H, m, $CHC\underline{H}_2C\underline{H}_2$); 2.21-2.36 (2H, m, $C\underline{H}CHCN$); 3.40-3.54 (2H, m, $C\underline{H}CN$); 3.54 (4H, t, J=6.1 Hz, CH_2Cl); 5.19-5.32 (4H, m, $C\underline{H}_2=CH$); 5.55-5.74 (2H, m, $CH_2=C\underline{H}$). ^{13}C-NMR ($CDCl_3$) : δ 27.38, 28.34 and 30.06, 30.17 ($CH\underline{C}H_2\underline{C}H_2$); 29.18 and 29.36 ($C\underline{Me}_3$); 44.56 and 44.62 ($CH_2Cl$); 47.92 and 48.59 ($\underline{C}HCHCN$); 48.03 ($\underline{C}HCN$); 51.12 and 51.23 ($\underline{C}Me_3$); 119.71 and 120.05 ($\underline{C}H_2=CH$); 121.63 and 121.90 (C≡N); 136.13 and 136.35 ($\underline{C}H=CH_2$). IR (NaCl) : 3335 cm^{-1} (NH), 2225 cm^{-1} (C≡N); 1640 cm^{-1} (C=C). MS m/z (%) : same as for compound **3a** (thermal transformation during GC-MS).

N-[2-(3-Chloropropyl)-2-buten-1-ylidene]-*tert*-butylamine (5a). To a solution of 2.01 g (10 mmol) of aldimine **3a** in 25 ml of THF was added 1.23 g (11 mmol) of potassium *tert*-butoxide. After 21h of stirring at room temperature, the mixture was poured into H_2O (40 mL) and extracted with diethyl ether (3x25 mL). The combined ether extracts were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was distilled (45-52°C/0.03 mmHg) to afford 1.25 g (62%) of pure **5a** as an oil. ^{1}H-NMR ($CDCl_3$) : δ 1.17 (9H, s, Me_3C); 1.86 (3H, d, J=6.93 Hz, $\underline{Me}CH$); 1.91 (2H, ~ quintet, J=7.0 Hz, $C\underline{H}_2CH_2Cl$); 2.52 (2H, t, J=7.26 Hz, $C\underline{H}_2C=CH$); 3.51 (2H, t, J=6.93 Hz, CH_2Cl); 5.93 (1H, q, J=6.93 Hz, $C\underline{H}Me$); 7.71 (1H, s, HC=N). ^{13}C-NMR ($CDCl_3$) : δ 14.07 ($\underline{Me}CH$); 22.68 ($\underline{C}H_2C=CH$); 29.70 ($C\underline{Me}_3$); 31.61 ($\underline{C}H_2CH_2Cl$); 45.08 (CH_2Cl); 56.35 ($\underline{C}Me_3$); 135.56 ($\underline{C}H=C$); 140.48 (=$C_{quat.}$); 157.70 (CH=N). IR (NaCl) : 1645, 1630 cm^{-1} (C=N, C=C). MS m/z (%) : 201 (M^+, 2); 186(9); 166(74); 152(4); 150(2); 146(3); 144(3); 139(3); 138(4); 130(2); 124(3); 110(100); 108(8); 96(21); 94(9); 93(11); 82(24); 81(7); 80(6); 77(5); 68(6); 67(10); 57(61); 55(13); 53(11).

N-[2-(3-Chloropropyl)-2-buten-1-ylidene]isopropylamine (5b). The same procedure as described for the preparation of **5a** provided **5b** in 47% yield after purification by distillation (34-38°C/0.005 mmHg). ^{1}H-

NMR ($CDCl_3$) : δ 1.15 (6H, d, J=6.26 Hz, Me_2); 1.86 (3H, d, J=7.1 Hz, MeCH=); 1.92 (2H, ~ quintet, J~7.1 Hz, CH_2CH_2Cl); 2.52 (2H, t, J=7.25 Hz, CH_2C=CH); 3.32 (1H, septet, J=6.26 Hz, $CHMe_2$); 3.52 (2H, t, J=6.7 Hz, CH_2Cl); 5.93 (1H, q, J=7.1 Hz, CH=C); 7.74 (1H, s, CH=N). ^{13}C-NMR ($CDCl_3$) : δ 14.09 (MeCH=C); 22.84 (CH_2C=); 24.20 (Me_2); 31.52 (CH_2CH_2Cl); 44.98 (CH_2Cl); 61.11 ($CHMe_2$); 136.26 (CH=C); 139.85 (=$C_{quat.}$); 161.26 (C=N). IR (NaCl) : 1624 cm^{-1} (C=N, C=C). MS m/z (%). 187/9 (M^+, 2); 172(4); 152(100); 136(18); 124(7); 110(34); 108(7); 96(5); 95(4); 94(5); 93(7); 88(3); 82(9); 68(5); 67(6); 55(10); 53(6).

(E)-3-Ethylidene-1-*tert*-butylpiperidine (7a). To a solution of aldimine **5a** (0.40 g, 2 mmol) in methanol (5 mL) was added 4 mmol (0.15 g) of sodium borohydride. The stirred mixture was refluxed for 1h, poured into H_2O (20 mL), extracted with CH_2Cl_2 (3x10 mL) and dried ($MgSO_4$). Purification of crude **7a** by flash chromatography using hexane/ethyl acetate (5:95) as eluent resulted in 0.20 g (66%) of pure **7a**. R_f=0.25. ^{1}H-NMR ($CDCl_3$) : δ 1.09 (9H, s, Me_3); 1.58 (3H, d, J=6.60 Hz, MeCH); 1.56-1.66 (2H, m, CH_2CH_2N); 2.13 (2H, t, J=6.4 Hz, $CH_2CH_2CH_2N$); 2.61 (2H, t, J=6.4 Hz, CH_2CH_2N); 2.96 (2H, s, NCH_2C=CH); 5.30 (1H, q, J=6.60 Hz, CH=). ^{13}C-NMR ($CDCl_3$) : δ 12.87 (MeCH); 25.96 (Me_3); 26.29 ($NCH_2CH_2CH_2$); 26.67 (NCH_2CH_2); 46.99 (NCH_2CH_2); 53.89 (CMe_3); 55.15 (NCH_2C=); 117.98 (=CH); 136.31 (=$C_{quat.}$). IR (NaCl) : 2965, 1358, 1220, 1202 cm^{-1} (ν_{max}). MS m/z (%) : 167 (M^+, 18); 152(100); 110(13); 96(12); 95(21); 84(2); 82(5); 81(2); 80(2); 70(4); 68(4); 67(10); 58(13); 57(6); 55(7); 44(6); 41(13). Anal. Calcd. for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found : C, 78.93; H, 12.63; N, 8.39.

(E)-3-Ethylidene-1-isopropylpiperidine (7b). The same procedure as described for the preparation of **7a** provided **7b** in 77% yield after flash chromatography using CH_2Cl_2/MeOH/NH_4OH (25% in H_2O) (94.7:5.0:0.3) as eluent. R_f=0.27. ^{1}H-NMR ($CDCl_3$) : δ 1.05 (6H, d, J=6.60 Hz, Me_2); 1.59 (3H, d, J=6.60 Hz, MeCH=); 1.58-1.69 (2H, m, NCH_2CH_2); 2.15 (2H, ~t, J=6.27 Hz, $NCH_2CH_2CH_2$); 2.56 (2H, ~t, J~5.4 Hz, NCH_2CH_2); 2.68 (1H, septet, J=6.60 Hz, $CHMe_2$); 2.93 (2H, s, NCH_2C=); 5.31 (1H, q, J=6.60 Hz, =CH). ^{13}C-NMR ($CDCl_3$) : δ 12.74 (MeCH=); 18.49 (Me_2); 26.25 and 26.34 ($NCH_2CH_2CH_2$); 49.54 (NCH_2CH_2); 54.45 ($CHMe_2$); 58.17 (NCH_2C=); 118.04 (=CH); 135.78 (=$C_{quat.}$). IR (NaCl) : 2918-2959, 1377, 1324, 1174 cm^{-1} (ν_{max}). MS m/z (%) : 153 (M^+, 26); 138(100); 124(5); 110(18); 96(10); 95(30); 93(5); 82(7); 81(5); 80(3); 79(4); 77(3); 70(5); 69(5); 67(15); 58(5); 56(10); 55(12); 54(5); 53(7); 44(12); 41(24). Anal. Calcd. for $C_{10}H_{19}N$: C, 78.37; H, 12.50; N, 9.14. Found : C, 78.50; H, 12.49; N, 9.11.

5-(1-Cyanoethyl)-1,2,3,4-tetrahydro-1-*tert*-butylpyridine (8a). A solution of 0.40 g (2 mmol) aldimine **5a** in 5 mL dry methanol was treated with 0.133 g (2.04 mmol) of potassium cyanide. The reaction mixture was stirred for 1h under reflux, poured into 20 mL of H_2O and extracted with CH_2Cl_2 (3x10 mL). The combined extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (hexane/ethyl acetate : 4/1; R_f=0.31) to provide 0.21 g (56%) of pure compound **8a**. Note : the flash chromatography should be performed quickly (within 20 min; column of 15 cm long) in order to minimize decomposition of the cyclic enamine **8a**. ^{1}H-NMR ($CDCl_3$) : δ 1.16 (9H, s, Me_3); 1.38 (3H, d, J=7.26 Hz, MeCH); 1.87 (2H, quintet,

J=5.9 Hz, $NCH_2C\underline{H}_2$); 1.99-2.05 (2H, m, $C\underline{H}_2C$=CH); 2.91-3.02 (2H, m, NCH_2); 3.19 (1H, q, J=7.26 Hz, CHCN); 6.25 (1H, s, C=CH). ^{13}C-NMR ($CDCl_3$) : δ 18.29 (<u>Me</u>CH); 22.26 ($\underline{C}H_2C$=CH); 22.84 ($NCH_2\underline{C}H_2$); 27.65 (Me_3); 31.45 (<u>C</u>HCN); 41.40 (NCH_2); 54.54 ($\underline{C}Me_3$); 103.09 (=$C_{quat.}$); 122.39 (C≡N); 129.54 (=CH). IR (NaCl) : 2230 cm^{-1} (C≡N); 1645 cm^{-1} (C=C). MS m/z (%) : 192 (M^+, 17); 177(43); 136(13); 135(8); 134(6); 121(100); 94(6); 82(17); 81(8); 80(10); 57(24); 44(35); 42(10); 41(25). Anal. Calcd. for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N, 14.57. Found : C, 88.04; H, 10.48; N, 14.56.

5-(1-Cyanoethyl)-1,2,3,4-tetrahydro-1-isopropylpyridine (8b). The same procedure as described for the preparation of **8a** provided **8b** in 49% yield after flash chromatography (hexane/ethyl acetate : 4/1; R_f=0.33). ^{1}H-NMR ($CDCl_3$) : δ 1.08 (6H, d, J=6.60 Hz, $CH\underline{Me}_2$); 1.37 (3H, d, J=7.26 Hz, <u>Me</u>CH); 1.82-1.92 (2H, m, $NCH_2C\underline{H}_2$); 1.98-2.09 (2H, m, $NCH_2CH_2C\underline{H}_2$); 2.85-2.90 (2H, m, NCH_2); 3.16 (1H, septet, J=6.60 Hz, $C\underline{H}Me_2$); 3.17 (1H, q, J=7.26 Hz, CHC≡N); 5.98 (1H, s, =CH). ^{13}C-NMR ($CDCl_3$) : δ 18.24 (<u>Me</u>CHCN); 19.87 (Me_2); 22.48 and 22.60 ($NCH_2\underline{C}H_2\underline{C}H_2$); 31.05 (<u>C</u>HC≡N); 42.44 (NCH_2); 53.94 ($\underline{C}HMe_2$); 102.05 (=$C_{quat.}$); 122.32 (C≡N); 131.59 (=CH). IR (NaCl) : 2223 cm^{-1} (C≡N); 1651 cm^{-1} (C=C). MS m/z (%) : 178 (M^+, 21); 163(100); 148(5); 135(7); 121(35); 108(5); 94(6); 82(6); 81(7); 80(9); 67(5); 53(5); 43(8); 41(14). Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found : C, 74.16; H, 10.14; N, 15.67.

5-Ethenyl-1-*tert*-butyl-1,2,3,4-tetrahydropyridine (9a). A solution of lithium diisopropylamide was freshly prepared from 2.62 g (26 mmol) of diisopropylamine in 25 mL of THF to which 9.6 ml of 2.5 M *n*-butyllithium (24 mmol) was added at 0°C under a nitrogen atmosphere. The aldimine **1a** (2.50 g, 20 mmol) was dissolved in THF (20 mL) and added dropwise. The solution was stirred for 10 min at 0°C after which time it was cooled to -78°C and further stirred for 20 min. At -78°C a solution of 3.15 g (20 mmol) of 1-bromo-3-chloropropane in 20 ml of THF was added *via* syringe and the solution was further stirred for 3h, during which the temperature was allowed to raise from -78°C to room temperature. This solution was slowly added *via* a small tube under nitrogen to an ice cooled solution of 24 mmol of lithium diisopropylamide, prepared as described above. This solution was stirred for 20h during which the mixture was allowed to reach room temperature. The mixture was added to ice-cooled 0.5N NaOH (100 mL) and extracted with diethyl ether (3x50 mL). After drying ($MgSO_4$) and concentration *in vacuo*, 3.24 g (98%) of crude piperideine **9a** was obtained, which was used as such in the next step. ^{1}H-NMR ($CDCl_3$) : δ 1.19 (9H, s, Me_3); 1.80-1.92 (2H, m, $CH_2C\underline{H}_2CH_2$); 2.12 (2H, t, J=6.4 Hz, $C\underline{H}_2C$=CH); 3.03 (2H, t, J=5.5 Hz, NCH_2); 4.47 (1H, dd, J=10.55, 1.65, <u>H</u>CH=); 4.57 (1H, dd, J=17.1, 1.65 Hz, HC<u>H</u>=CH); 6.30 (1H, dd, J=17.1, 10.55 Hz, H_2C=C<u>H</u>); 6.39 (1H, s, NCH=C). ^{13}C-NMR ($CDCl_3$) : δ 20.86 ($\underline{C}H_2C$=CH); 22.61 ($CH_2\underline{C}H_2CH_2$); 27.98 ($C\underline{Me}_3$); 41.74 (NCH_2); 54.75 ($\underline{C}Me_3$); 100.32 ($\underline{C}H_2$=CH); 108.28 (<u>C</u>=CH); 134.52 (N<u>C</u>H=C); 139.15 (<u>C</u>H=CH_2). IR (NaCl) 1655, 1620 cm^{-1} (C=C). MS m/z (%) : 165 (M^+, <1); 150(8); 137(2); 109(4); 108(3); 94(3); 84(7); 82(8); 81(16); 80(16); 67(9); 57(100); 55(5); 53(4); 44(19); 42(8); 41(29). Anal. Calcd. for $C_{11}H_{19}N$: C, 79.93; H, 11.59; N, 8.47. Found : C, 79.95; H, 11.62; N, 8.44.

5-Ethenyl-1-isopropyl-1,2,3,4-tetrahydropyridine (9b). The same procedure as described for the preparation of **9a** provided crude **9b** in quantitative yield. ^{1}H-NMR ($CDCl_3$) : δ 1.11 (6H, d, J=6.60 Hz, Me_2); 1.78-1.94 (2H, m, $NCH_2C\underline{H}_2$); 2.15 (2H, ~t, J~6.27 Hz, $C\underline{H}_2CH_2CH_2N$); 2.97 (2H, ~t, J~5.5 Hz, NCH_2); 3.20 (1H, septet, J=6.60 Hz, $C\underline{H}Me_2$); 4.47 (1H, dd, J=10.55, 1.65 Hz, $\underline{H}CH$=CH); 4.58 (1H, dd, J=17.3, 1.65 Hz, HC$\underline{H}$=CH); 6.14 (1H, s, NC$\underline{H}$=C); 6.30 (1H, dd, J=17.3, 10.55 Hz, C$\underline{H}$=CH_2). ^{13}C-NMR ($CDCl_3$) : δ 20.27 (Me_2); 20.99 and 22.21 ($NCH_2C\underline{H}_2C\underline{H}_2$); 42.91 ($NCH_2$); 54.23 ($\underline{C}HMe_2$); 100.18 ($\underline{C}H_2$=CH); 107.58 (NCH=$\underline{C}$); 136.37 (N$\underline{C}$H=C); 138.67 ($\underline{C}H$=$CH_2$). IR (NaCl) : 1621 cm^{-1} (C=C); 2960, 1277, 1178 cm^{-1} (ν_{max}). MS m/z (%) : 151 (M^+, 46); 136(100); 108(10); 106(4); 94(4); 93(4); 91(4); 81(5); 80(6); 79(6); 77(4); 68(8); 67(10); 53(5); 43(5). Anal. Calcd. for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found : C, 79.62; H, 11.35; N, 9.27.

9-*tert*-Butyl-2-phenyl-3aβ,4,6,7,8,9,9aβ,9bβ-octahydro-1*H*-pyrrolo[3,4-*h*]quinoline-1,3-dione (10a). To a solution of diene **9a** (0.43 g, 2.6 mmol) in dry THF (5 mL) was added 0.43 g (2.47 mmol) of N-phenylmaleimide. The mixture was heated under reflux for 2h. After evaporation of the solvent, crude adduct **10a** was purified by rapid (within 20 min, column 15.0 cm) flash chromatography using hexane/ethyl acetate/methanol (76:19:5) as eluent to afford 0.38 g (43%, based on 2.47 mmol) of pure **10a**. R_f=0.27. Mp. 64-65°C. ^{1}H-NMR ($CDCl_3$) : δ 1.24 (9H, s, Me_3); 1.29-1.48 and 1.67-1.78 (2H, m, $NCH_2C\underline{H}_2$); 2.03-2.30 (3H, m, $NCH_2CH_2C\underline{H}_2$ and C=CH$\underline{H}$CH); 2.79 (1H, ddd, J=14.68, 7.42, 1.65 Hz, C=CHHC$\underline{H}$); 2.88 (1H, td, J=10.6, 5.7 Hz, N$\underline{H}$CH); 3.11-3.26 (2H, m, NHC$\underline{H}$ and $C=CHCH_2C\underline{H}$); 3.30 (1H, dd, J=8.74, 6.6 Hz, NCHC$\underline{H}$); 3.96 (1H, dm, J=6.60 Hz, NCH); 5.56 (1H, dm, J=7.42 Hz, C=CH); 7.15-7.48 (5H, m, C_6H_5). ^{13}C-NMR ($CDCl_3$) : δ 23.45 ($NCH_2C\underline{H}_2$); 23.66 ($C=CH\underline{C}H_2$); 27.85 (Me_3); 28.77 ($NCH_2CH_2\underline{C}H_2$); 41.15 ($C=CHCH_2\underline{C}H$); 42.73 (NCH_2); 48.05 (NCH$\underline{C}$H); 54.27 (NCH); 55.22 ($\underline{C}Me_3$); 117.21 (C=$\underline{C}$H); 126.50, 128.37 and 129.05 (=CH's); 132.29 (NCH$\underline{C}$=CH); 143.14 (=$C_{quat.}$); 177.44 and 179.17 (2xC=O). IR (KBr) : 1708 cm^{-1} (C=O). MS m/z (%) : 338 (M^+, 17); 223(17); 173(17); 166(27); 165(100); 164(16); 151(17); 150(34); 149(42); 135(17); 129(18); 121(19); 109(70); 94(21); 91(25); 86(66); 84(97); 57(31); 47(35); 41(35). Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found : C, 74.80; H, 7.70; N, 8.25.

9-Isopropyl-2-phenyl-3aβ,4,6,7,8,9,9aβ,9bβ-octahydro-1*H*-pyrrolo[3,4-*h*]quinoline-1,3-dione (10b). The same procedure as described for the preparation of **10a** provided **10b** in 57% yield after flash chromatography (ethyl acetate/hexane : 9/1). R_f=0.33. ^{1}H-NMR ($CDCl_3$) : δ 0.99 and 1.22 (2x3H, 2xd, J=6.7 Hz, $\underline{Me}_2$CH); 1.58-1.70 (2H, m, $NCH_2C\underline{H}_2$); 2.11-2.39 (4H, m, N$\underline{H}$CHCH$_2$C$\underline{H}_2$ and =CH$\underline{H}$CH); 2.79 (1H, ddd, J=14.84, 7.58, 1.98 Hz, =CHHC$\underline{H}$); 3.03 (1H, ddd, J=10.9, 6.3, 4.3 Hz, NHC$\underline{H}$); 3.21 (1H, ddd, J=8.5, 6.43, 1.98 Hz, $=CHCH_2C\underline{H}$); 3.44 (1H, d, J=6.60 Hz, NC$\underline{H}$); 3.45 (1H, septet, J=6.7 Hz, C$\underline{H}$Me$_2$); 3.54 (1H, dd, J=8.5, 6.60 Hz, NCHC$\underline{H}$); 5.57-5.66 (1H, m, C$\underline{H}$=C); 7.16-7.47 (5H, m, C_6H_5). ^{13}C-NMR ($CDCl_3$) : δ 14.16 and 20.97 (2xMe); 22.44 ($NCH_2\underline{C}H_2$); 23.83 ($C=CH\underline{C}H_2$); 27.64 ($NCH_2CH_2\underline{C}H_2$); 40.77 (NCHCH$\underline{C}$H); 41.44 ($NCH_2$); 42.19 (NCH$\underline{C}$H); 48.70 ($\underline{C}HMe_2$); 58.58 (N$\underline{C}$HCH); 118.42 (=$\underline{C}HCH_2$);

126.56, 128.37 and 129.02 (=CH's); 132.22 (NCH<u>C</u>=CH); 141.52 (=$C_{quat.}$ N); 175.36 and 178.94 (C=O). IR (NaCl) : 1685-1711 cm^{-1} (C=O). MS m/z (%) : 324 (M^+, 4); 309(3); 281(2); 191(1); 176(1) ; 175(3); 151(100); 136(37); 119(3); 108(3); 106(3); 102(4); 93(4); 91(6); 84(7); 77(4); 43(6). Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.63. Found : C, 74.13; H, 7.45; N, 8.60.

1-Isopropyl-7-methoxycarbonyl-1,2,3,4,6,7,8,8α-octahydro-8-(N-phenylaminocarbonyl)quinoline (11b). This product was obtained in 37% yield after flash chromatography of crude **10b** with hexane/ethyl acetate/methanol/NH_4OH (25% in H_2O) (78.2:19.5:2.0:0.3) as eluent. R_f=0.39. Mp 182.1-163.6°C. ^{1}H-NMR ($CDCl_3$) : δ 1.04 and 1.21 (2x3H, 2xd, J=6.60 Hz, Me_2CH); 1.53 (1H, qt, J=13.0, 3.63 Hz, $NCH_2\underline{H}CH$); 1.81 (1H, ABm, J=13.0 Hz, $NCH_2HC\underline{H}$); 2.03-2.42 (4H, m, $N\underline{H}CHCH_2CH_2$ and =CH<u>H</u>CH); 2.51-2.69 (2H, m, =CHHC<u>H</u>C<u>H</u>COOMe); 3.17 (1H, dq, J=11.3, 2.9 Hz, NHC<u>H</u>); 3.53 (1H, septet, J=6.60 Hz, C<u>H</u>Me_2); 3.52-3.63 and 3.77-3.85 (2x1H, 2xm, NC<u>H</u>C<u>H</u>CONH); 3.80 (3H, s, OMe); 5.47 (1H, dd, J=4.8, 2.5 Hz, C<u>H</u>=C); 6.97-7.06, 7.22-7.29 and 7.47-7.54 (5H, m, C_6H_5); 12.20 (1H, s, broad, CONH). ^{13}C-NMR ($CDCl_3$) : 12.52 and 21.22 (<u>Me</u>$_2$CH); 24.67 (C=CH<u>C</u>H_2); 24.94 ($NCH_2\underline{C}H_2$); 33.30 ($NCH_2CH_2\underline{C}H_2$); 42.01 (<u>C</u>HCOOMe); 42.55 (<u>C</u>HCONH); 42.78 (NCH_2); 47.04 (<u>C</u>HMe_2); 52.00 (OMe); 59.23 (N<u>C</u>HC=CH); 119.40, 123.38, 123.60 and 128.89 (=CH's); 133.08 and 140.03 (=$C_{quat.}$); 169.11 and 173.49 (2xC=O). IR (KBr) : 1737 cm^{-1} (C=O); 1596, 1554, 1198 cm^{-1} (ν_{max}). MS m/z (%) : no M^+ ; 341 (M^+ -Me, 2); 325(2); 313(3); 236(3); 220(2); 206(2); 192(2); 178(3); 151(100); 136(30); 119(3); 106(5); 93(4); 91(6); 77(4); 70(3); 58(5); 43(8). Anal. Calcd. for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found : C, 70.92; H, 7.90; N, 7.86.

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