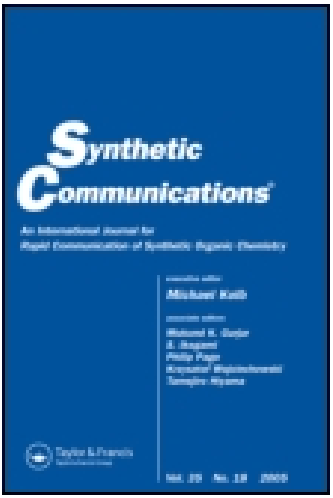

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Photochemical Synthesis of Spirocyclohexylisoquinolines, Analogues of (±)-Galanthamine and (±)-Lycoramine

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PHOTOCHEMICAL SYNTHESIS OF SPIROCYCLOHEXYLISOQUINOLINES, ANALOGUES OF (±)-GALANTHAMINE AND (±)-LYCORAMINE.

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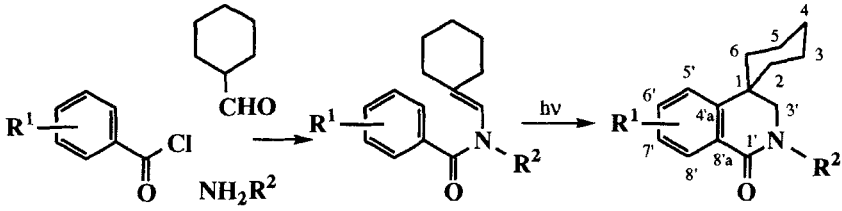
ABSTRACT : Photocyclization of *N*-arylenamides **10**, **15** and **16** led efficiently to spirotricyclic δ-lactams **5**, **6** and **7**. Compound **7** was easily and stereospecifically transformed in two steps into spirocyclohexylisoquinolines **3** and **4** which show structural analogies with some *Amaryllidaceae* alkaloids, galanthamine **1** and lycoramine **2**.

There has been considerable interest in the development of synthetic routes to spirocycloalkylisoquinolines due to their particular skeletons.[1] These compounds exhibit indeed structural analogies with natural products having important biological activities such as *Amaryllidacea* alkaloids. Thus, galanthamine **1**, a long acting centrally-active competitive acetylcholinesterase inhibitor, should be of great interest in the treatment of Alzeimer's disease[2]; lycoramine **2** inhibits the formation of peptide bond in protein synthesis[2] and many syntheses of these two compounds and derivatives or analogues have been reported (figure 2).[3]

For a number of years, we have been involved with the photocyclization of *N*-arylenamides easily obtained from primary amines, ketones or aldehydes and aromatic acylchlorides (figure 1).[4]

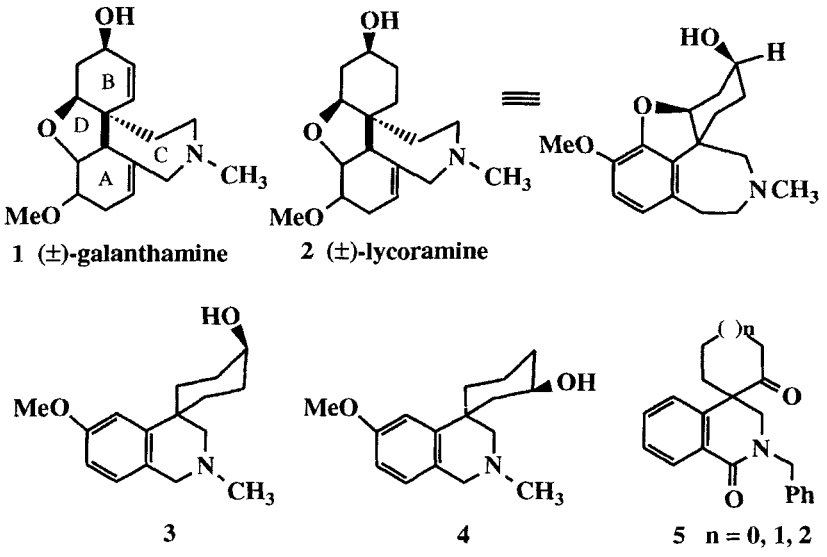
* to whom correspondence should be addressed

FIG. 1



Molecular Modelling studies of natural products galanthamine **1**, lycoramine **2** and tricyclic compound **3**, show structural similarities between these molecules (figure 2), although some differences can be observed between both frameworks : the spirocompound **3**, indeed, does not possess the tetrahydrofuran ring present in the natural products and exhibit a six-membered B ring instead of a seven-membered one. Nevertheless, the conformation of the B ring of compounds **3** and **4**, determined by molecular mechanics and AM1 calculations, is exclusively a chair conformation and is very similar to that of **1** and **2** (figures 1 and 2).

FIG. 2



1 (±)-galanthamine **2** (±)-lycoramine

3 **4** **5** n = 0, 1, 2

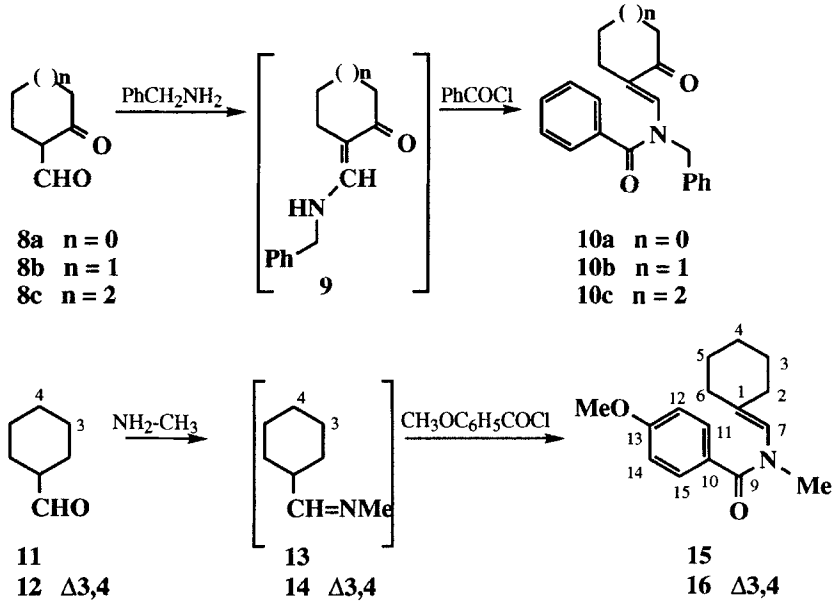
Furthermore, the necessary hydroxyl and methoxyl substituents[2c] could easily be introduced at the right position using our flexible photochemical synthesis.

Therefore, we report herein the synthesis of substituted spirocyclohexyl-isoquinolines **3** and **4** from the appropriate *N*-arylenamide **16.** The photo-cyclisation of enamides **10, 15** and **16** provided δ-lactams **5, 6** and **7.** Compound **7** was then transformed, in two steps, into the tricyclic derivatives **3** and **4.**

Preparation of arylenamides

N-arylenamides **10, 15** and **16** were conveniently prepared in one pot and very good yields by acylation of the non-isolated imines **9, 13** and **14** with benzoyl or *para*-methoxyanisoyl chloride.[5] The imines resulted from the condensation of *N*-methyl or *N*-benzylamine with the already described aldehydes **8a**[6], **8b**[7] and **8c**[7] or with the commercially available aldehydes **11** and **12** (figure 3).

FIG. 3

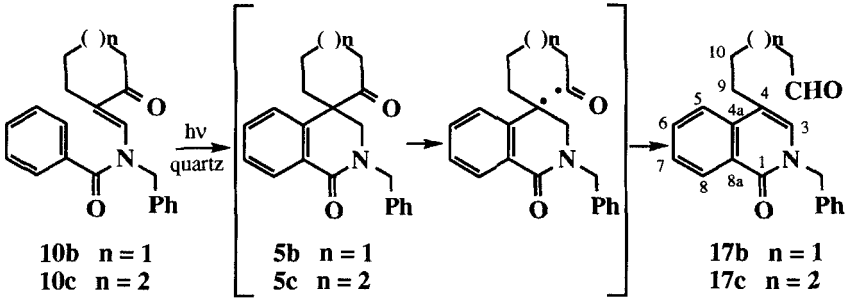


Photocyclization of *N*-arylenamides 10, 15 and 16

Photocyclisation of **10,** using a 400W medium pressure mercury lamp, at room temperature, provided the aldehydes **17b** and **17c** when the reaction was performed in a quartz immersion-well[8], which is transparent up to 200 nm (figure

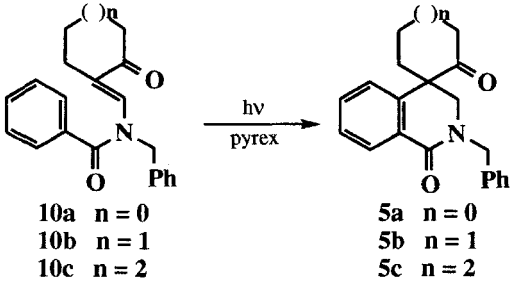
4). These compounds resulted from the Norrish I α-cleavage[9] of the spiroketones intermediates **5b** and **5c**.

FIG. 4



The use of a pyrex reactor with a cut off wavelength of 300 nm avoids the Norrish 1 cleavage and spiroketones **5** are thus obtained in good yields (figure 5).

FIG. 5



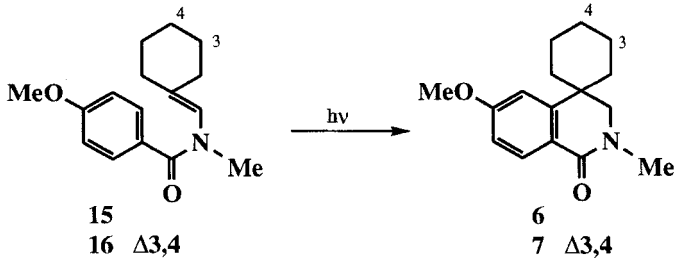
Enamides **15** and **16** led efficiently to the spiroisoquinolines **6** and **7**, the best yields being obtained when the irradiation was performed in a quartz immersion-well (figure 6).

The structures of all the photoproducts were deduced from their spectral data (^{1}H-NMR, IR, ^{13}C-NMR, high resolution mass spectroscopy or C, H, N analysis).

Synthesis of spirocyclohexylisoquinolines 3 and 4

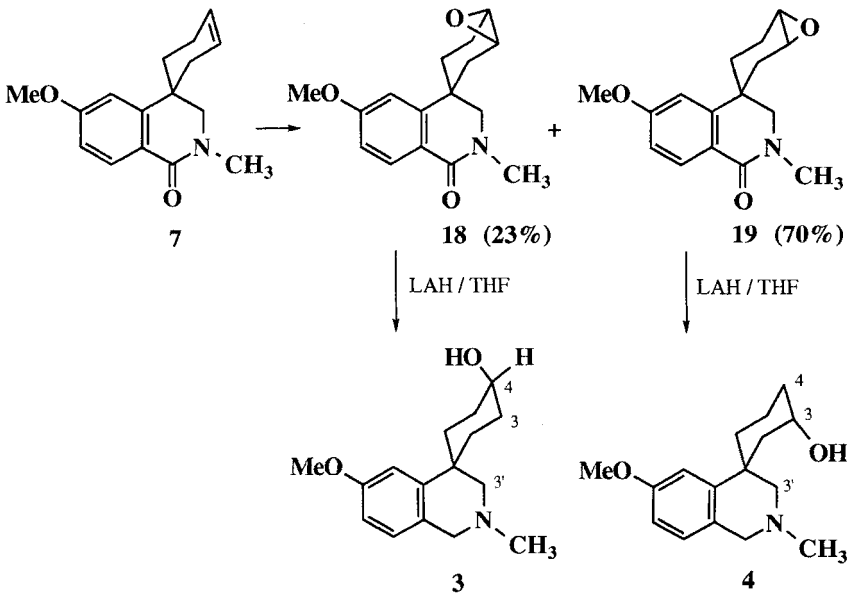
The epoxidation of **7** was achieved using *meta*-chloroperbenzoic acid and led

FIG. 6



to the *endo* and *exo* epoxides **18** and **19** mixture[10], in a 94% overall yield (figure 7).

FIG. 7



The two isomers could easily be separated by flash chromatography. The *exo* compound was the major product (7/3) and resulted from the attack of the reagent on the less hindered face of C ring, as shown by Molecular Modelling (figure 7).

Treatment of each isomer with LAH in THF induced stereospecifically *trans*-diaxial ring opening of the epoxides following by reduction of the lactam function.

The tricyclic spirocompounds **3** and **4** were fully characterized. Their ^1H NMR spectra exhibited, in particular, a singlet at 2.58 ppm for the two hydrogen at the C-3' position of the symmetrical alcohol **3** which appeared as an AB system centred at 2.9 ppm (J_{AB} = 12 Hz) for **4**. Moreover, the stereochemistry was demonstrated by the J H-3, H-4 coupling constants of 10 Hz for **4** and 8 Hz for **3**, respectively.

In conclusion, this three-step route provides a short, concise and stereospecific synthesis of substituted spirocycloalkylisoquinolines **3**, **4** and **5**, in overall yields ranging from 45% to 70%, starting from readily available and inexpensive precursors. Although they exhibit structural analogies with galanthamine **1** and lycoramine **2**, **3** and **4** do not present anticholinergic activities.

EXPERIMENTAL

Infrared spectra were obtained on a Perkin-Elmer 815 spectrometer. NMR spectra were performed on a Bruker AC spectrometer, at 400MHz for ^1H and 100 MHz for ^{13}C NMR or on a JEOL C 60 H and a JEOL FX 60 (15.08 MHz) with $CDCl_3$ as solvent and TMS as internal standard. EIMS, HRMS and microanalyses were recorded at the Service Central d'Analyse of Vernaison (France). Irradiation were carried out in a pyrex or a quartz immersion-well, using a medium pressure mercury lamp (Philips 400W), in freshly distilled benzene, MeOH or CH_3CN. Flash chromatography was carried out on Merck silica gel 60 (230-400 mesh). Yieds are reported for isolated products which were pure by NMR and TLC. Molecular Modelling was performed using the SYBYL 6.03 software package[11], on a Silicon Graphics Personal Iris 4D35TG workstation. Structures were built within SYBYL and minimized using the Tripos force field Maximin2, in vacuo conditions. The geometries were then optimized by AM1 calculations (MOPAC version 5.0).[12]

General procedure for the preparation of enamides

To a solution of 1.1 equivalents of amine in anhydrous benzene was added 1.0 equivalent of the carbonyl derivative (aldehyde or ketone). The reaction mixture was heated at reflux in a Dean and Stark apparatus. The resulting imine solution was allowed to cool at 0 °C and 1.5 equivalents of NEt_3 followed by 1.2 to 1.3 equivalents of acide chloride were added. The crude reaction mixture was stirred at this temperature until the reaction was complete. The solvent was then evaporated

and AcOEt was added to the residue. The solution was dried over $MgSO_4$ and filtered. The solution was concentrated under reduced pressure and purified by flash column chromatography eluting with gradient of mixtures of AcOEt/hexane.

General procedure for the irradiation of enamides

* **Method A** : A solution of enamide (500mg) in anhydrous acetonitrile, benzene or methanol (V = 150ml), was irradiated in a quartz immersion-well. The solvent was removed by rotary evaporation. Flash column chromatography of the resulting oil was done on silicagel eluting with a AcOEt/hexane mixture .

* **Method B** : A solution of enamide (500mg) in anhydrous acetonitrile or in a 1/1 benzene/methanol solution (V =150ml) was irradiated in a pyrex immersion-well. The solvent was evaporated and the crude residue was chromatographied on silicagel using a AcOEt/hexane mixture as eluent.

***N*-(2-oxocyclopentanylidene), *N*-benzylbenzamide 10a**

Enamide **10a** was prepared from 2-hydroxymethylenecyclopentanone **8a** (1g, 8.9 mmol), benzylamine (0.957g, 8.93mmol) and benzoyl chloride (1.63g, 11.6mmol) in 90% yield (2.45g; 2/8 AcOEt/hexane as eluent).

10a : UV (EtOH, λ) 298 nm (15526). IR (CCl_4) 1720, 1685. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.78-1.85 (m, 2H, 2H-4), 2.22 (t, 2H, *J* = 7.9 Hz, 2H-5), 2.58 (td, 2H, *J* = 7.2 and 2.2 Hz, 2H-3), 5.25 (s, 2H, NCH_2Ph), 7.20-7.60 (m, 10H, H aromatic), 7.70 (s, 1H, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 20.1, 27.6, 37.7, 48.8, 118.1, 125.9, 127.4, 128.6, 128.7, 128.8, 134.0, 137.1, 135.4, 172.3, 207.2. EIMS, m/z : 305 (3), 277 (14), 249 (29), 211 (23), 200 (52), 158 (27), 105 (100), 91 (51), 77 (61). HRMS : calc. for $C_{20}H_{19}NO_2$: 305.1330, found : 305.1404.

***N*-(2-oxocyclohexanylidene), *N*-benzylbenzamide 10b**

Enamide **10b** was prepared from 2-hydroxymethylenecyclohexanone **8b** (1g, 7.94mmol), benzylamine (0.851g ; 7.94mmol) and benzoyl chloride (1.45g, 10.3mmol) in 95 % yield (2.3g, 2/8 AcOEt/hexane as eluent).

10b : mp 82-84 °C (ether), UV (EtOH, λ) 276 nm (14705). IR (CCl_4) 1685, 1654. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.34-1.40 (m, 2H, 2H*-5), 1.39-1.65 (m, 2H, 2H*-4), 1.80-1.87 (td, 2H, *J* = 7 Hz and 1.5 Hz, 2H-6), 2.27 (t, 2H, *J* = 6.7 Hz, 2H-3), 4.58 (s, 2H, NCH_2Ph), 7.15 (s, 1H, H-7), 7.30-7.59 (m, 10H, H

aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 23.1, 27.5, 40.1, 51.7, 127.6, 127.8, 128.1, 128.7, 129.9, 131.2, 134.9, 136.0, 136.7, 170.8, 200.2. Anal. calc. for $C_{21}H_{21}NO_2$: C 78.97, H 6.63, N 4.39; found : C 79.06, H 6.37, N 4.48.

***N*-(2-oxocycloheptanylidene), *N*-benzylbenzamide 10c**

Enamide **10c** was prepared from 2-hydroxymethylenecycloheptanone **8c** (1g, 7.14mmol), benzylamine (0.765g, 7.14mmol) and benzoyl chloride (1.30g, 9.28mmol) in 94 % yield (2.23g; 2/8 AcOEt/hexane as eluent).

10c : mp 110-112 °C (ether), UV (EtOH, λ) 291nm (14270). IR (CCl_4) 1680, 1669. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.00-1.10 (m, 2H, 2H-5), 1.39-1.50 (m, 4H, 2H-6, 2H-4), 2.10-2.15 (m, 2H, 2H-7), 2.25-2.35 (m, 2H, 2H-3), 4.90 (s, 2H, NCH_2Ph), 6.35 (s, 1H, H-8), 7.20-7.59 (m, 10H, H aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 23.8, 30.5, 30.7, 33.5, 44.1, 50.5, 127.2, 127.8, 127.9, 128.4, 128.6, 130.5, 131.9, 133.4, 135.6, 136.5, 171.2, 203.9. Anal. calc. for $C_{22}H_{23}NO_2$: C 79.25, H 6.95, N 4.20; found : C 79.12, H 6.85, N 4.31;

***N*-(cyclohexanylidene), *N*-methyl-*p*-methoxybenzamide 15**

Enamide **15** was prepared from cyclohexanecarboxaldehyde **11** (4.45g, 0.04mol), methylamine (1.86g, 0.06mol) and anisoyl chloride (6.82g, 0.04mol) in 47 % yield (4.87g; 3/7 AcOEt/hexane as eluent).

15 : oil, IR (CCl_4) 1640. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.25-2.18 (m, 10H), 3.25 (s, 3H, NCH_3), 4.07 (s, 3H, OCH_3), 6.10 (s, 1H, H-7), 7.05-8.05 (m, 4H, H aromatic). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 25.9 (C-4), 27.1 (C*-5), 27.4 (C*-3), 32.5 (C*-2), 36.1 (C*-6), 54.9 (OCH_3 and NCH_3), 112.5 (C-11 and C-15), 123.5 (C-7), 128.2 (C-12 and C-14), 130.2 (C-10), 138.1 (C-1), 160.6 (C-13), 170.4 (C-9). Anal. calc. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found : C 73.83, H 8.01, N 5.58

***N*-(cyclohex-3-enylidene), *N*-methyl-*p*-methoxybenzamide 16**

Enamide **16** was prepared from cyclohex-3-enecarboxaldehyde **12** (4.41g, 0.04mol), methylamine (1.86g, 0.06mol) and anisoyl chloride (6.82g, 0.04mol) in 60 % yield (6.17g; 3/7 AcOEt/hexane as eluent).

16 : oil, IR (CCl_4) 1640, 1660. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.65-2.65 (m, 6H), 3.15 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 5.35 (s, 1H, H-7), 5.50-5.75

(m, 2H, H-3 H-4), 6.80-7.40 (m, 4H, H aromatic). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 26.4 (C-5), 27.0 (C*-6), 28.8 (C*-2), 55.2 (OCH_3 and NCH_3), 112.9 (C-11 and C-15), 124.5 (C-4), 124.9 (C-3), 127.0 (C-7), 128.4 (C-12 and C-14), 130.4 (C-10), 134.2 (C-1), 161.0 (C-13), 170.6 (C-9). Anal. calc. for $C_{16}H_{19}NO_2$: C 74.68, H 7.44, N 5.18; found : C 74.35, H 7.14, N 5.25.

2-Benzyl-1-oxo-4-(formylpentyl) isoquinoline 17b

Irradiation of **10b** (0.2g, 0.63mmol) using the method A led to 0.12g of **17b** (yield = 60 % ; 3/7 AcOEt/hexane as eluent) when the reaction was conducted 2 hours in acetonitrile, to 126mg of **17b** (yield = 63 %) when the reaction was performed in benzene for 50 minutes and to 142mg of **17b** (yield = 71 %) when the reaction was done in methanol for 1hour 55 minutes.

17b : oil, IR (CCl_4) 2720, 1730, 1660, 1630. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.60-1.70 (m, 4H, 2H-10, 2H-11), 2.45-2.50 (m, 2H, 2H-9), 2.60-2.65 (m, 2H, 2H-12), 5.20 (s, 2H, NCH_2Ph), 6.95 (s, 1H, H-3), 7.30-7.70 (m, 9H, H aromatic), 8.55 (d, 1H, J = 13 Hz, H-5), 9.75 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 21.8, 28.9, 29.4, 43.6, 51.6, 116.1, 122.7, 126.7, 127.8, 128.2, 128.7, 128.8, 130.3, 131.2, 136.5, 137.1, 161.9, 202.1. EIMS, m/z : 319 (2), 248 (16), 91 (100), 65 (8). HRMS : calc. for $C_{21}H_{21}NO_2$: 319.1572, found : 319.1559.

2-Benzyl-1-oxo-4-(formylhexyl) isoquinoline 17c

Irradiation of **10c** (0.2g, 0.60mmol) using the method A led to 118 mg of **17c** (yield = 59 %; 3/7 AcOEt/hexane as eluent) in acetonitrile (1 hour), 134mg of **17c** (yield = 67 %) when the reaction was done in methanol for 45 minutes and 120mg of **17c** (yield = 60 %) when the cyclization was conducted in benzene for 50 minutes.

17c : oil, IR (CCl_4) 2720, 1730, 1660, 1630. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.32-1.40 (m, 2H, 2H-11), 1.57-1.66 (m, 4H, 2H-10, 2H-12), 2.39 (t, 2H, J = 7.2 Hz, 2H-9), 2.62 (t, 2H, J = 7.6 Hz, 2H-13), 5.20 (s, 2H, NCH_2Ph), 6.90 (s, 1H, H-3), 7.30-7.65 (m, 8H, H aromatic), 8.50 (d, 1H, J = 8 Hz, H-5), 9.75 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 21.5, 28.8, 29.1, 29.2, 43.7, 51.5, 116.3, 122.4, 126.6, 126.7, 127.8, 127.9, 128.7, 128.8, 128.9, 132.2, 136.5, 137.1, 161.9, 202.3. EIMS, m/z : 333 (14), 248 (33), 91 (100), 65 (8). HRMS : calc. for $C_{22}H_{23}NO_2$: 333.1729, found : 333.1730.

2'-Benzyl-1'-oxospiro-[1,4'-cyclopentan-2-one-(3'*H*)-isoquinoline] 5a

Irradiation of **10a** (0.2mg, 0.66mmol) for 18 hours in a 1/1 benzene-methanol mixture using the method B gave 100mg of **5a** (yield = 50 %) which was purified by chromatography (2/8 AcOEt/hexane as eluent).

5a : oil, IR (CCl_4) 1720, 1660. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.95-2.05 (m, 4H, 2H-4, 2H-5), 2.40-2.50 (m, 2H, 2H-3), 3.18 (AB spectrum, 2H, J = 13.3 Hz, Δν = 205 Hz, 2H-3'), 3.18 (AB spectrum, 2H, J = 14.7 Hz, Δν = 257 Hz, NCH_2Ph), 6.85-8.20 (m, 9H, H aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 18.5, 36.4, 39.5, 50.4, 53.2, 124.5, 126.9, 127.8, 127.9, 128.8, 132.4, 136.7, 141.3, 163.7, 218.7. EIMS, m/z : 305 (48), 248 (17), 214 (15), 186 (73), 158, (12), 119 (15), 105 (20), 91 (100), 77 (11). HRMS : calc. for $C_{20}H_{19}NO_2$: 305.1404, found : 305.1415.

2'-Benzyl-1'-oxospiro-[1,4'-cyclohexan-2-one-(3'*H*)-isoquinoline] 5b

Irradiation of **10b** (0.2g, 0.63mmol) using the method B gave 146mg of **5b** (yield = 73 %; 2/8 AcOEt/hexane as eluent) when the reaction was conducted for 2 hours in a 1/1 benzene-methanol solution, and to 138mg of **5b** (yield = 69 %) when the reaction was performed in acetonitrile for 2 hours 15 minutes.

5b : mp 142-144 °C (ether), IR (CCl_4) 1715, 1660 . ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.45-1.55 (m, 1H, H-4), 1.65-1.75 (m, 2H, 2H-5), 1.85-2.05 (m, 3H, 2H-6, H-4), 2.15-2.25 (m, 2H, 2H-3), 3.52 (AB spectrum, 2H, J = 12.8 Hz, Δν = 131 Hz, 2H-3'), 4.80 (AB spectrum, 2H, J = 11.4 Hz, Δν = 134 Hz, NCH_2Ph), 7.19-7.51 (m, 8H, H aromatic), 8.22 (d, 1H, J = 7.6 Hz, H-5'). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 20.4, 26.2, 35.1, 38.8, 49.9, 51.6, 52.8, 124.9, 127.6, 127.7, 128.1, 128.7, 128.9, 129.4, 131.9, 136.8, 140.6, 164.1, 210.0. EIMS, m/z : 319 (37), 248 (14), 228 (17), 200 (46), 185 (7), 158 (9), 115 (12), 91 (100), 65 (13). HRMS calc. for $C_{21}H_{21}NO_2$: 319.1572, found : 319.1566.

2'-Benzyl-1'-oxospiro-[1,4'-cycloheptan-2-one-(3'*H*)-isoquinoline] 5c

Irradiation of **10c** (0.2g, 0.60mmol) using the method B gave 136mg of **4c** (yield = 68 %; 2/8 AcOEt/hexane as eluent) when the reaction was conducted for 1hour 10 minutes in a (1/1) benzene-methanol solution, and 130mg of **4c** (yield = 65 %) when the reaction was performed in acetonitrile for 2 hours.

5c : mp 125-127 °C (ether), IR (CCl_4) 1715, 1660. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.05-1.17 (m, 1H), 1.30-1.40 (m, 1H), 1.48-1.65 (m, 3H), 1.72-2.02 (m, 3H), 2.58 (t, 1H, J = 8.9 Hz, H-3), 2.68 (t, 1H, J = 8.9 Hz, H-3), 3.52 (AB spectrum, 2H, J = 13.4 Hz, Δν = 269 Hz, 2H-3'), 4.80 (AB spectrum, 2H, J = 14.4 Hz, Δν = 232 Hz, NCH_2Ph), 7.19-7.51 (m, 8H, H aromatic), 8.22 (d, 1H, H-5', J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 21.4, 26.8, 30.4, 34.2, 42.8, 50.2, 50.9, 51.6, 124.4, 127.4, 127.5, 127.7, 128.8, 129.2, 132.0, 129.4, 136.8, 141.9, 163.5, 213. Anal. calc. for $C_{22}H_{23}NO_2$: C 79.25, H 6.95, N 4.20, found : C 79.26, H 7.07, N 4.31;

2'-Methyl-6'-methoxy-1'-oxospiro-[1,4'-cyclohexane-(3'*H*)-isoquinoline] 6

Irradiation of **15** (1g, 3.85mmol) for 7 hours in methanol, using the method A, led to 370mg of **6** (yield = 37 %) which was purified by flash column chromatography (3/7 AcOEt/hexane as eluent).

6 : mp 132-134 °C (ether), IR (CCl_4) 1655. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.50-2.10 (m, 10H), 3.18 (s, 3H, NCH_3), 3.38 (s, 2H, 2H-3'), 4.05 (s, 3H, OCH_3), 7.05-8.05 (m, 8H, H aromatic). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 21.8 (C-4), 25.8 (C-3 and C-5), 33.5 (C-2 and C-6), 35.2 (C-3'), 37.2 (C-1), 53.7 (NCH_3), 55.2 (OCH_3), 108.8 (C-5'), 111.0 (C-7'), 121.4 (C-8'), 130.6 (C-4'a), 149.7 (C-8'a), 162.6 (C-6'), 164.6 (C-1'). Anal. calc. for $C_{16}H_{21}NO_2$ C 74.10, H 8.16, N 5.40, found : C 74.28, H 8.25, N 5.26.

2'-Methyl-6'-methoxy-1'-oxospiro-[1,4'-cyclohex-3-en-(3'*H*)-isoquinoline] 7

Irradiation of **16** (1g, 3.89mmol) for 7 hours in methanol, using the method B, gave 470mg of **7** (yield = 47 %) which was purified by flash column chromatography (3/7 AcOEt/hexane as eluent).

7 : mp 124-126 °C (acetone-AcOEt), IR (CCl_4) 1660. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.90-2.24 (m, 6H), 3.10 (s, 3H, NCH_3), 3.37 (AB spectrum, 2H, 2H-3', J = 12 Hz, Δν = 92 Hz), 3.90 (s, 3H, OCH_3), 5.90 (s, 2H, H-3, H-4), 7.00-8.38 (m, 3H, H aromatic). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 22.3 (C-6), 30.7 (C-5), 33.7 (C-2), 35.4 (C-3'), 35.7 (C-1), 55.3 (NCH_3), 56.8 (OCH_3), 109.8 (C-4), 111.5 (C-3), 121.4 (C-5'), 125.3 (C-7'), 127.0 (C-8'), 130.7 (C-4'a), 148.1 (C-8'a), 162.6 (C-6'), 164.6 (C-1'). Anal. calc. for $C_{16}H_{19}NO_2$: C 74.68, H 7.44, N 5.44, found : C 74.42, H 6.99, N 5.41.

3,4-Epoxy-2'-methyl-6'-methoxy-1'-oxospiro-[1,4'-cyclohexane-(3'*H*)-isoquinolines] 18 and 19

To a solution of **7** (2g, 8mmol) in 50 ml of CH_2Cl_2 was added 1.5 equivalents of *meta*-chloroperbenzoic acid (2.3g, 12mmol). After 48 hours the resulting mixture was neutralized with an 5 % aqueous NaOH solution. The organic layer was washed with water and dried over $MgSO_4$. After filtration, the solvent was evaporated to give 2.05g (yield = 94 %) of a mixture of **18** and **19** which were separated by flash column chromatography (7/3 AcOEt/hexane as eluent) leading to 0.5g (yield = 23 %) of **18** and 1.48g (yield = 70 %) of **19**.

***endo* - 18** : mp 135-136 °C (ether), IR (CCl_4) 1660. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.40-2.20 (m, 6H), 3.10 (s, 3H, NCH_3), 3.15-3.40 (m, 2H, H-3 and H-4), 3.25 (s, 2H, 2H-3'), 3.80 (s, 3H, OCH_3), 6.90-8.10 (m, 3H, H aromatic). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 20.4 (C-5), 27.1 (C-6), 32.2 (C-2), 33.8 (C-4), 35.3 (C-3), 49.6 (C-1*), 50.9 (C-3'*), 54.9 (NCH_3), 55.2 (OCH_3), 108.6 (C-7'), 111.9 (C-5'), 120.9 (C-8'), 130.6 (C-4'a), 147.8 (C-8'a), 162.8 (C-6'), 164.4 (C-1'). Anal. calc. for $C_{16}H_{19}NO_3$: C 70.30, H 7.01, N 5.13; found : C 69.90, H 7.01, N 5.22

***exo* - 19** : mp 133-134 °C (ether), IR (CCl_4) 1660. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.40-2.40 (m, 6H), 3.30 (s, 3H, NCH_3), 3.40-3.60 (m, 2H, H-3, H-4), 3.50 (AB spectrum, 2H, J = 12 Hz, Δν = 75 Hz, 2H-3'), 4.00 (s, 3H, OCH_3), 6.90-8.20 (m, 3H, H aromatic). ^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.4 (C-5), 27.1 (C-6), 31.9 (C-2), 34.6 (C-4), 34.9 (C-3), 50.5 (C*-1), 52.3 (C*-3'), 55.2 (NCH_3) ; 59.2 (OCH_3), 110.7 (C-7'), 111.6 (C-5'), 121.2 (C-8'), 130.8 (C-4'a), 146.1 (C-8'a), 161.8 (C-6'), 163.9 (C-1'). Anal. calc. for $C_{16}H_{19}NO_3$: C 70.30, H 7.01, N 5.13; found : C 69.93, H 7.00, N 5.22.

4-Hydroxy-2'-methyl-6'-methoxyspiro-[1,4'-cyclohexane-(3'*H*)-isoquinoline] 3

A solution of **18** (0.5g, 1.83mmol) in 30 ml of anhydrous ether was added drop to drop at 0 °C to a suspension of LAH (0.56g, 14.6mmol) in ether (50 ml). After 12 hours, water was added and the solvent evaporated. The residue was dried over $MgSO_4$ to give **3** (0.45g, yield = 93 %).

3 : oil, IR (CCl_4) 3625. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.40-2.40 (m, 9H), 2.60 (s, 3H, NCH_3), 3.60-3.80 (m, 2H, 2H-1'), 3.05 (AB spectrum, 2H, J = 12 Hz, Δν = 90 Hz, 2H-3'), 4.00 (s, 3H, OCH_3), 4.30-4.40 (m, 1H, H-3, J = 10 Hz),

6.90-7.40 (m, 3H, H aromatic). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 16.9 (C-5), 32.3 (C-6), 36.5 (C-2), 38.3 (C-4), 42.6 (C-3'), 46.3 (C-1'), 54.9 (C-1), 58.4 (C-3), 62.9 (NCH_3), 66.9 (OCH_3), 110.8 (C-7'), 111.6 (C-5'), 126.7 (C-8'), 126.9 (C-4'a), 144.7 (C-8'a), 157.8 (C-6').

3-Hydroxy-2'-methyl-6'-methoxyspiro-[1,4'-cyclohexane-(3'*H*)-isoquinoline] 4

Reduction of **19** (0.5g, 1.83mmol) was accomplished as describe for **18** by treatment with LAH (0.56g, 14.6mmol). After evaporation of the solvent, the alcohol **4** (0.37g) was obtained (yield = 92 %) .

19 : oil, IR (CCl_4) 3630. ^1H NMR ($CDCl_3$, 60 MHz) : δ 1.30-2.20 (m, 9H), 2.40 (s, 3H, NCH_3), 3.50 (s, 2H, 2H-1'), 2.58 (s, 2H, 2H-3'), 3.80 (s, 3H, OCH_3), 3.90-4.10 (m, 1H, H-4, J = 8 Hz), 6.90-7.40 (m, 3H, H aromatic). ^{13}C NMR ($CDCl_3$, 15 MHz) : δ 28.5 (C-2 and C-6), 30.0 (C-3 and C-5), 37.9 (C-3'), 46.6 (C-1'), 55.0 (C-1), 58.7 (C-4), 59.8 (NCH_3), 64.7 (OCH_3), 111.0 (C-7'), 111.3 (C-5'), 126.5 (C-8'), 126.8 (C-4'a), 144.8 (C-8'a), 158.1 (C-6').

References and notes

1. (a) Krapcho, A.P. *Synthesis* **1978**, 77.(b) Martin, S.F. *Tetrahedron* **1980**, *36*, 419.
2. (a) Wildman, W.C. "The alkaloïds", Manske, R.H.F. Ed., Academic Press, New York **1968**, vol. 11, p. 307. (b) Fuganti, C. "The alkaloïds", Manske, R.H.F. Ed., Academic Press, New York **1975**, vol. 15, p. 83. (c) Han, S.; Sweeney, J.E.; Bachman, E.S.; Schweiger, E.J.; Forloni, G.; Coyle, J.T.; Davis, B.M. and Joullié, M.M. *Eur. J. Med. Chem.* **1992**, *27*, 673. (d) Shieh W.-C. and Carlson J.A. *J. Org. Chem.* **1994**, *59*, 5463.
3. (a) Hazama, N.; Irie, H.; Mizutani, T.; Shingu, T.; Takada, M.; Uyeo, S. and Yoshitake, A. *J. Chem. Soc. (C)* **1968**, 2947. (b) Misaka, Y.; Mizutani, T.; Sekido, M. and Uyeo, S. *J. Chem. Soc. (C)* **1968**, 2954. (c) Martin, S.F. and Garrison, P.J. *J. Org. Chem.* **1982**, *47*, 1513. (d) Sànchez, I.-H.; Soria, J.J.; Lopez, F.J.; Larraza, M.I. and Flores, H.J. *J. Org. Chem.* **1984**, *49*, 157. (e) Ackland, D. J. and Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2695. (f) Parker, K.A. and Kim, H.-J. *J. Org. Chem.* **1992**, *57*, 752. (g) Barton, D. H. R. and Kirby, G. W. *J. Chem. Soc.*

(C) **1962**, 806. (h) Kametani, T.; Yamaki, K.; Yagi, H. and Fukumoto, K. *J. Chem. Soc. (C)* **1969**, 2602. (i) Kametani, T.; Shishido, K.; Hayashi, E.; Seino, C.; Kohno, T.; Shibuya, S. and Fukumoto, K. *J. Org. Chem.* **1971**, *36*, 1295. (j) Szewczyk, J.; Lewin, A. H. and Carroll, F. I. *J. Heterocyclic Chem.* **1988**, *25*, 1809. (k) Vlahov, R.; Krikorian, D.; Spassov, G.; Chinova, M. ; Vlahov, I.; Parushev, S.; Snatzke, G.; Ernst, L.; Kieslich, K.; Abraham, W.-R. and Sheldrick, W. S. *Tetrahedron* **1989**, *45*, 3329. (l) Szewczyk, J.; Wilson, J. W.; Lewin, A. H. and Carroll, F. I. *J. Heterocyclic Chem.* **1995**, *32*, 195.

4. (a) Gramain, J.-C.; Mavel, S.; Troin, Y. and Vallée-Goyet, D. *Tetrahedron* **1991**, *47*, 7287. (b) Gramain, J.-C.; Troin, Y. and Vallée-Goyet, D. *Tetrahedron* **1991**, *47*, 7301.
5. (a) March, J. "Advanced Organic Chemistry. Reactions, Mechanisms, and Structure", Wiley, J. Ed., New York, **1985**, p 541. (b) Brossi, A. Dolan, L. A. and Teitel, S. *Org. Synth.* **1977**, *56*, 3.
6. Eaton, P.E. and Jobe, P. G. *Synth. Commun.* **1983**, 796.
7. Ainsworth, C. *Org. Synth.* **1963**, *4*, 536.
8. Ninomiya, I. and Naito, T. "Photochemical Synthesis", Katritzky, A.R.; Meth-Cohn, O. and Rees, C.W., Ed., Academic Press, Londres, **1989**, p. 221.
9. Iriarte, J.; Schaffner, K. and Jeger, O. *Helv. Chim. Acta.* **1964**, *47*, 1255.
10. The term *endo* was used for the epoxide on the side of the aromatic ring and the term *exo* designed the epoxide at the opposite of the aromatic ring.
11. Tripos Associates, 1699 S Harley Rd, Suite 303, St Louis, MO 63144. 12. Merz, K.M. and Besler B.H., version MOPAC 5.0 ESC, QCPE n°589, **1990**, with AM1 force field parameters.

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