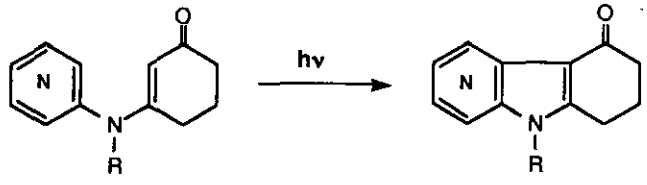
SYNTHESIS OF AZACARBAZOLES

Yves Blache[1], Olivier Chavignon[2], Marie E. Sinibaldi-Troin[3], Alain Gueiffier[1], Jean C. Teulade[2*], Yves Troin[3], and Jean C. Gramain[3]

1) Laboratoire de Chimie Organique, URA-CNRS 1111, Faculté de Pharmacie, 34060 Montpellier, France 2) Groupe de Recherche en Pharmacochimie, Faculté de Pharmacie, 63001 Clermont-Fd, France 3) Laboratoire de Chimie des Substances Naturelles, URA-CNRS 485, Université Blaise Pascal, 63177 Aubiere France

Abstract - Photocyclization of N-Benzylenaminone (**7**) led to azacarbolinones products which were fragmented to unexpected aldehydes (**9**) and (**11**).

Interest in carbazole alkaloids has increased considerably during the past years[1-3] and this was the result of the potential pharmacological activity[4] of new types of substances including pyrido[b]carbazoles e.g. ellipticine.[5] Moreover, carbazoles are part of the framework of many complex alkaloids isolated from plants belonging for example to the Aspidosperma and Strychnos families. In spite of their structural specificity, most of carbazole alkaloids, especially when they are selectively functionalized, are difficult to prepare.[1-3] Recently, a new approach to this framework by using a photocyclization of arylenaminones as the key step has been described[6] and used for the elaboration of Aspidosperma alkaloids.[7] Our program consists of an extent of this methodology and is more reliable to azaindolic structures since it has been demonstrated that nitrogen atom led to potentiality or modification of pharmacological activity.[8] We present here our results on the photocyclization of azaenaminones (**1**) precursors of azacarbazoles synthons (**2**) (Scheme 1).

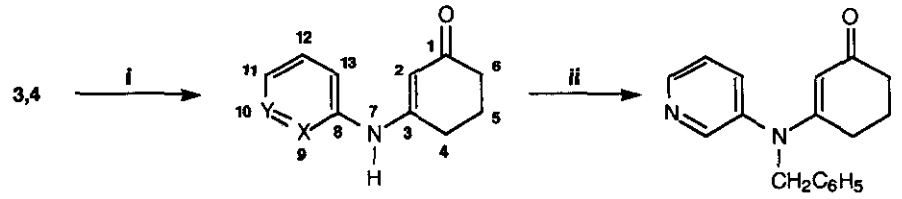


1 R = H or benzyl **2** R = H or benzyl

Scheme 1

The first step in the synthesis is the preparation of the starting materials (**1**). This was realized by slight changes of the reaction parameters (concentration, temperature, stoichiometry) of the previously described methodology.[6] So, condensation of 2 and 3-aminopyridines (**3,4**) with an excess of cyclohexanedione at low concentration gave high yields of the enamino ketones (**5**) and (**6**). The use of the same approach with 4-aminopyridine failed.

Transformation of secondary enaminone (**6**) to tertiary enamino ketone (**7**) by N-alkylation was realized in quantitative yield (see experimental part). In the same conditions or even under drastic reaction conditions (DMF, reflux, 3 h.) it was impossible to protect compound (**5**) (Scheme 2).



5 X=N Y=CH
6 X=CH Y=N

7

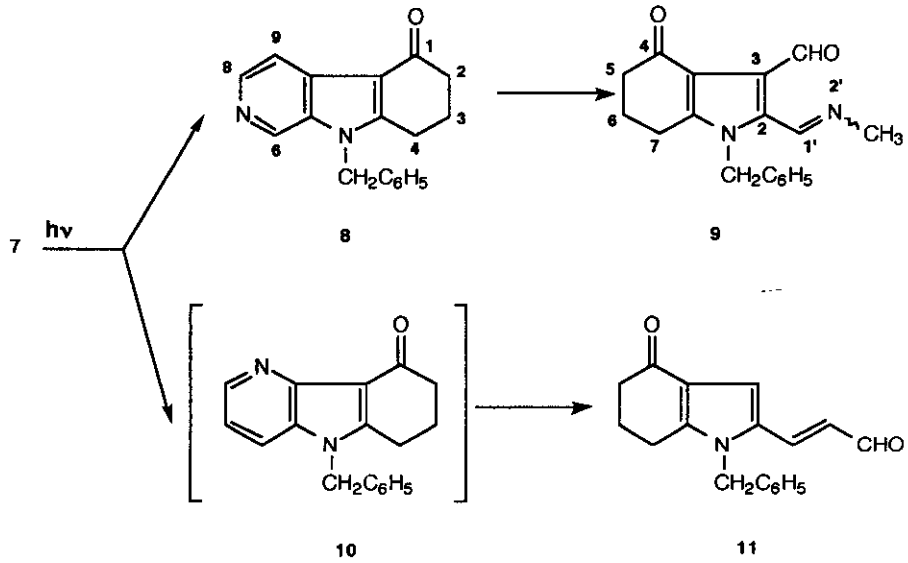
Reagents and conditions : (*i*) cyclohexanedione, p-toluenesulfonic acid / toluene , reflux (7 h) ; (ii) NaH, dry toluene, benzyl chloride, reflux (2 h)

Scheme 2

Photocyclization of enamino ketones (**5**, **6** and **7**) was conducted in a deoxygenated benzene or benzene/MeOH (1:1) solution at 22°C with a medium pressure mercury uv lamp (400 W) during 2 or 3 hours. Photocylization of **5** or **6** gave only starting materials as previously reported from arylenaminones.[6] In the photocyclization of **7**, formation of two regioisomers were expected.[9] Irradiation of **7** gave a mixture of compounds (**8**), (**9**) and (**11**) in 60%, 10%, 5% yield, respectively. No hexahydrocarbazole structures were identified in the crude mixture (Scheme 3).

Structure of **8** and unexpected and unstable bicyclic compounds (**9**) and (**11**) were well established on the basis of their spectral data. The structure of the regioisomeric compound (**8**) [m/z : 276(M^+), 248 and 91(100%)] was supported by spectral data with in particular ν_{max} (KBr) 1680(C=O) and δ ($CDCl_3$) 8.14 (1H, d, H-9), 8.41(1H, d, H-8) and 8.70(1H, s, H-6) which prove that cyclization occurs at the para position of the pyridinic azote. In addition, the aldehydic compound (**9**) is issued via the indolic structure (**8**). The ^{1}H-nmr spectrum

showed the N-methyl and CHO signals at δ :2.85 and 9.90, respectively. This structural assignment was consistent by mass spectral evidence [m/z : 294(M^+), 225 and 91(100%)]. For compound (**11**), ir spectrum (KBr) indicated the presence of two carbonyl absorptions at ν_{max} 1680 and 1693. In the ^{1}H-nmr spectrum, the formyl proton was found at δ ($CDCl_3$), 9.49(1H, d). In addition to the benzyl signals, proton assignment was made on the basis of NOE effects, proton coupling constants and gave unequivocally the following values : H-3(7.20), H-5, 5'(2.78), H-6,6'(2.19), H-7,7'(2.55). Trans-relationship between H-1' and H-2' was evident from the observation of a positive NOE effect. The ^{13}C-nmr spectrum, in accord with the proposed structure, revealed the presence of 14 sp^2 carbons, participating in two carbonyl groups and an olefinic double bond conjugated with the aldehydic carbon.



Reagents and conditions : C_6H_6/MeOH, irradiation (400W Uv lamp, 3 h), Pyrex reactor

Scheme 3

These results showed that **7** cyclizes to either of the two positions on the pyridine ring preferentially to the γ-position to give **8** rather than **10**. In addition, uv spectrum of **8** showed a large absorption in a range near 300 nm and could act as an internal filter for the reaction (some starting compound still remained). Compounds (**9**) and (**11**) were photoreactive products issued from C-N cleavage of azacarbazoles (**8**) and (**10**), respectively.

EXPERIMENTAL

General. Ir spectra were recorded with a Perkin-Elmer 377 spectrophotometer. Absorption bands are expressed in centimeters (cm^{-1}) using polystyrene calibration and only noteworthy absorptions are listed. ^1H- and ^{13}C-nmr spectra were recorded on a Brüker EM-360 spectrometer working at 300 MHz (^1H-nmr) and 75 MHz (^{13}C-nmr). Chemical shift data are reported in ppm downfield δ from TMS. Coupling constants, J, are given in Hz; s, d, t and m indicate singlet, doublet, triplet and multiplet, respectively. Mass spectrometry was done on a LKB 2091 instrument. Irradiations were carried out in a pyrex glass vessel using a medium pressure mercury lamp (Philips 400 W). Before irradiation, the reaction mixture was flushed with a stream of argon to remove oxygen. Tlc was carried out on SiO_2 (Silica gel 60, Merck 0.0063-0.20 mm) and the spots were located with uv light. Flash column chromatography was carried out on SiO_2 (Silica gel 60, Merck 0.040-0.063 mm).

Preparation of enaminone (**5**) :A mixture of 2-aminopyridine (**3**) (3.3 g, 0.035 mol), 1,3-cyclohexanedione (3.8 g, 0.035 mol), p-toluenesulfonic acid (0.05 g) and toluene (175 ml) was refluxed under a Dean-Stark head for 7 h. After neutralization with solid K_2CO_3, the benzene solution was filtered. On cooling the filtrate gave a crystalline product. The precipitate was washed with ether, and extracted three times with CH_2Cl_2. After solvent removal, the residue was purified by chromatography on silica gel with CH_2Cl_2-MeOH (90:10, v/v) to provide **5** as a colorless oil. Treatment of the mixture with cold ether resulted in the crystallization of **5** as colorless prisms mp 180-182°C; ir (KBr) ν_{max} 3480, 3250, 1978, 1523; ^1H-nmr (300 MHz, DMSO-d_6) δ 1.91(m, 2H, H-5,5'), 2.20(t, 2H, J = 6.5 Hz, H-6,6'), 2.55(t, 2H, J = 6 Hz, H-4,4'), 6.85(s, 1H, H-2), 6.96(m, 1H, H-11), 7.02(d, 1H, $J_{12,13}$ = 8.5 Hz, H-13), 7.69(td, 1H, $J_{11,12}$ = 9 Hz, $J_{10,12}$ = 2 Hz, H-12), 8.28(d, 1H, $J_{10,11}$ = 5 Hz, H-10), 9.24(s, 1H, NH); ^{13}C-nmr (75 MHz, DMSO-d_6) δ 21.51(C-5), 28.68(C-6), 36.38(C-4), 104.78(C-2), 113.62(C-13), 117.19(C-11), 137.56(C-12), 147.37(C-10), 154.17(C-3), 158.04(C-8), 197.36(CO); Anal. Calcd for $C_{11}H_{12}N_2O$: C : 70.21; H : 6.38; N : 14.89. Found : C : 70.25; H : 6.31; N : 14.71.

Enaminone (**6**) :Enaminone (**6**), recrystallized from benzene, was obtained by the above procedure mp 165-167°C; ir (KBr) ν_{max} 3402, 3208, 1550, 1503; ^1H-nmr (300 MHz, DMSO-d_6) δ 1.90(m, 2H, H-5,5'), 2.18(t, 2H, J = 6.5 Hz, H-6,6'), 2.51(t, 2H, J = 6 Hz, H-4,4'), 3.34(s, 1H, NH), 7.40(m, 1H, H-10), 7.62(m, 1H, H-9), 8.32(dd, 1H, $J_{9,11}$ = 1.5 Hz, $J_{10,11}$ = 5 Hz, H-11), 8.40(d, $J_{9,13}$ = 2 Hz, H-13), 8.95(s, 1H, H-2);

^{13}C-nmr (75 MHz, DMSO-d_6) δ 21.41(C-5), 28.33(C-6), 36.34(C-4), 98.56(C-2), 123.84(C-9), 129.99 (C-10), 135.8(C-8), 144.32(C-13), 145.05(C-11), 161.78(C-3), 195.67(CO); Anal. Calcd for $C_{11}H_{12}N_2O$: C : 70.21; H : 6.38; N : 14.89. Found : C : 70.31; H : 6.25; N : 14.75.

N-Benzylation of enaminone (**6**) :To a suspension of sodium hydride (60 % dispersion in oil) (245 mg, 10.3 mmol) in 30 ml of dry toluene, under nitrogen, was added dropwise a solution of enaminone (**6**) (1.5 g, 7.9 mmol) dissolved in 200 ml of toluene. The mixture was refluxed for 1 h, followed by stirring at room temperature for another 1 h. The mixture was then cooled in an ice bath, and benzyl chloride (1.62 g, 12.9 mmol) was added portionwise and the solution was refluxed for 2 h. The reaction mixture was poured into cold water and the layers were separated. The aqueous phase was extracted (CH_2Cl_2) and the organic extracts were dried ($MgSO_4$). After solvent removal, the residue was purified on silica gel (SiO_2) with CH_2Cl_2-MeOH (90:10, v/v) as eluent to give 2.13 g (97% yield) of ketone (**7**) as an oil : ^{1}H-Nmr (300 MHz, $CDCl_3$) δ : 1.69(m, 2H, H-5,5'), 2.27(m, 4H, H-6,6' and H-4,4'), 4.81(s, 2H, CH_2), 5.35(s, 1H, H-2), 7.13(d, 1H, $J_{12,13}$ = 7 Hz, H-13), 7.23(m, 5H, H-Ph), 7.44(dd, 1H, $J_{11,12}$ = 4 Hz, H-12), 8.39(d, 1H, $J_{9,11}$= 2 Hz, H-9), 8.45(d, 1H, $J_{11,12}$ = 4 Hz, H-11);^{13}C-nmr (75 MHz, $CDCl_3$) δ 22.18(C-5), 28.21(C-6), 35.82(C4), 56.29(NCH_2), 102.45(C-2), 123.90(C-12), 126.72(C-Ph), 127.53(C-Ph), 128.65(C-Ph), 135.08(C-13), 135.81(C-Ph), 140.61(C-8), 148.19(C-9), 149.01(C-11), 164.18(C-3), 197.43(CO); Anal. Calcd for $C_{18}H_{18}N_2O$: C : 77.70; H : 6.47; N : 10.07. Found : C : 77.65; H : 6.52; N : 9.89.

Photocyclization of enaminone (**7**) : A solution of enaminone (**7**) (200 mg, 0.72 mmol) in C_6H_6/MeOH (300 ml, 1:1) was irradiated under argon during 3 h in a Pyrex reactor with a 400 W medium pressure uv lamp. After evaporation of the solvent, the residue was purified by flash chromatography (SiO_2), with AcOEt as eluent to give 10 mg (5% yield) of vinyl aldehyde (**11**) as viscous oil : Ir (KBr) ν_{max} 1693, 1680, 1120; ^{1}H-nmr (300 MHz, $CDCl_3$) δ : 2.19(m, 2H, H-6,6'), 2.55(t, 2H, J = 6 Hz, H-7,7'), 2.78(t, 2H, J = 5.5 Hz, H-5,5'), 5.28(s, 2H, NCH_2), 6.49(dd, 1H, $J_{1',2'}$ = 13 Hz, $J_{2',CHO}$ = 8 Hz, H-2'), 6.97(m, 2H, H-Ph), 7.20(s, 1H, H-3), 7.21(d, 1H, $J_{1',2'}$ = 13 Hz, H-1'), 7.35(m, 3H, H-Ph), 9.49(d, 1H, $J_{2',CHO}$ = 8 Hz, CHO) ; ^{13}C-nmr (75 MHz, $CDCl_3$) δ : 22.16, 23.17, 37.85, 47.58, 110.24, 122.04, 125.54, 126.18, 128.30, 129.40, 130.53, 135.51, 138.78, 148.19, 192.87, 193.90 ; ms (m/z, relative intensity) 279(M^+,25), 250(8), 188(22), 91(100); Anal. Calcd for $C_{18}H_{17}NO_2$: C : 77.42; H : 6.09; N : 5.02. Found : C : 77.40; H : 7.14; N : 4.92.

Further elution gave keto aldehyde (**9**) recrystallized from benzene (21 mg, 10%), mp 80-82°C : Ir (KBr) ν_{max} 1732, 1670, 1477, 1262, 1110 ; ^{1}H-nmr (300 MHz, $CDCl_3$) δ : 2.21(m, 2H, H-6,6'), 2.58(t, 2H,J = 5.5 Hz, H-7,7'), 2.75(t, 2H, J = 5 Hz, H-5,5'), 2.85(s, 3H, CH_3), 5.18(s, 2H, NCH_2), 6.42(s, 1H, H-1'), 7,01(m, 2H, H-Ph), 7.42(m, 3H, H-Ph), 9.90(s, 1H, CHO); ms (m/z, relative intensity) 294(M^+, 2), 281(10), 238(12), 225(24), 91(100); Anal. Calcd for $C_{18}H_{18}N_2O_2$: C : 73.47; H : 6.12; N : 9.52. Found : C : 73.39; H : 6.27; N : 9.41. Fractions eluted with AcOEt/MeOH (9:1) on evaporation gave 60% (121 mg) of **8** as very pale yellow prisms (recrystallization solvent : benzene) and 20 mg (10% yield) of recovered enaminone (**7**). Compound (**8**) : mp 120-122°C; ir (KBr) ν_{max} 1680; ^{1}H-nmr (300 MHz, $CDCl_3$) δ : 2.24(m, 2H, H-3,3'), 2.59(t, 2H, J = 5 Hz, H-4,4'), 2.91(t, 1H, J = 5.5 Hz, H-2'), 5.39(s, 2H, NCH_2), 7.06(m, 2H, H-Ph), 7.30(m, 3H, H-Ph), 8.14(d, 1H, J = 5 Hz, H-9), 8.41(d, 1H, J = 5 Hz, H-8), 8.70(s, 1H, H-6) ; ^{13}C-nmr (75 MHz, $CDCl_3$) δ 22.22, 23.08, 37.64, 47.847, 115.72, 126.14, 128.14, 129.13, 130.60, 132.45, 134.06, 135.18, 141.90, 154.43, 193.58. ms (m/z, relative intensity) 276(M^+, 35), 248(30), 219(15),91(100); Anal. Calcd for $C_{18}H_{16}N_2O$: C : 78.26; H : 5.80; N : 10.14. Found : C : 78.09; H : 5.65; N : 10.11.

REFERENCES

1. H. P. Husson, in "the alkaloids", ed. by A. Brossi, Academic Press, New York, 1985, vol. 26, p. 1.
2. D. P. Chakraborty, in "Progr. Chem. Org. Nat. Products", eds N. Herz, H. Grisebach and G.W. Kirby, Springer Verlag, Vienna, 1977, vol. 34, p. 299.
3. P. Bhattacharyya and D. P. Chakraborty, in "Progr. Chem. Org. Nat. Products", Eds W. Herz, H. Grisebach, G. W. Kirby, and Ch. Tamm, Springer Verlag, Vienna, 1987, vol. 52, p. 159.
4. T. Naid, T. Kitahara, M. Kaneda, and S. Nakamura, J. Antibiotics, 1987, **40**, 157; M. H. Telaska, J. B. Gloer, D. T. Wichklow, and P. F. Dowd, J. Org. Chem., 1989, **54**, 4743.
5. P. Potier, Pure Appl. Chem. 1986, **58**, 737; V. K. Kansel, and P. Potier, Tetrahedron, 1986, **42**, 2389.
6. J. C. Gramain, H. P. Husson, and Y. Troin, Tetrahedron Lett., 1985, **26**, 2323.
7. M. Dufour , J. C. Gramain, H. P. Husson, M. E. Sinibaldi, and Y. Troin, J. Org. Chem., 1990, **55**, 5483; J. C. Gramain, H. P. Husson, and Y. Troin, J. Org. Chem., 1985, **50**, 5517.
8. F. Marsais, P. Pineau, F. Nivolliers, M. Mallet, A. Turck, A. Godard, and G. Queguiner, J. Org. Chem., 1992, **57**, 565.
9. D. Gardette, J. C. Gramain, M. E. Lepage, and Y. Troin, Can. J. Chem., 1989, **67**, 213.

Received, 5th July, 1993