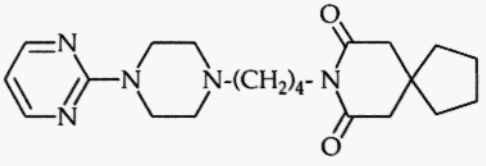
SYNTHESIS OF 3-AMINO-3-AMINOMETHYL-2*H*-1-BENZOPYRAN AND SPIRO[1-BENZOPYRAN-3(2*H*),2'-PIPERAZINE] DERIVATIVES

C. Comoy and G. Guillaumet*.
Laboratoire de Chimie Bioorganique et Analytique, URA CNRS n°499, Universite d'Orleans, B.P. 6759, 45067 ORLEANS Cedex 2, France.

Abstract : Preparation of 3-amino-3-aminomethyl-2*H*-1-benzopyran and spiro[1-benzopyran-3(2*H*),2'-piperazine] derivatives using the 2-hydroxy-5- or 6-methoxybenzaldehyde as starting material *via* the 5- or 6-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-one is described.

Introduction : During the last decade, serotonin (5-Hydroxytryptamine, 5-HT) has been implicated in various behavorial disorders such as anxiety, depression and insomnia (1-3). The discovery in 1981 of the 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) as a potent centrally active 5-HT receptor (4) and, subsequently, a selective 5-HT_{1A} receptor agonist (5), has led to an understanding of the 5-HT_{1A} receptors. Different chemical classes were known to have a high affinity for 5-HT_{1A} receptors (5-7), for example the piperazine class which presents the first agent to be approved for clinical use, Buspirone (Figure 1) (8,9).

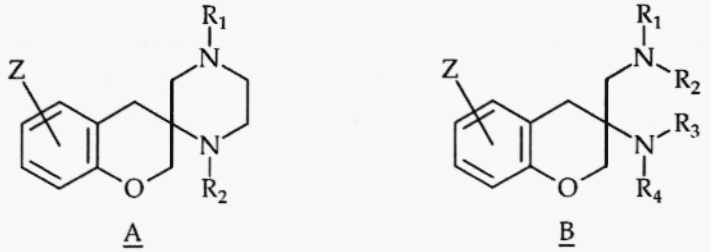
Figure 1



Buspirone

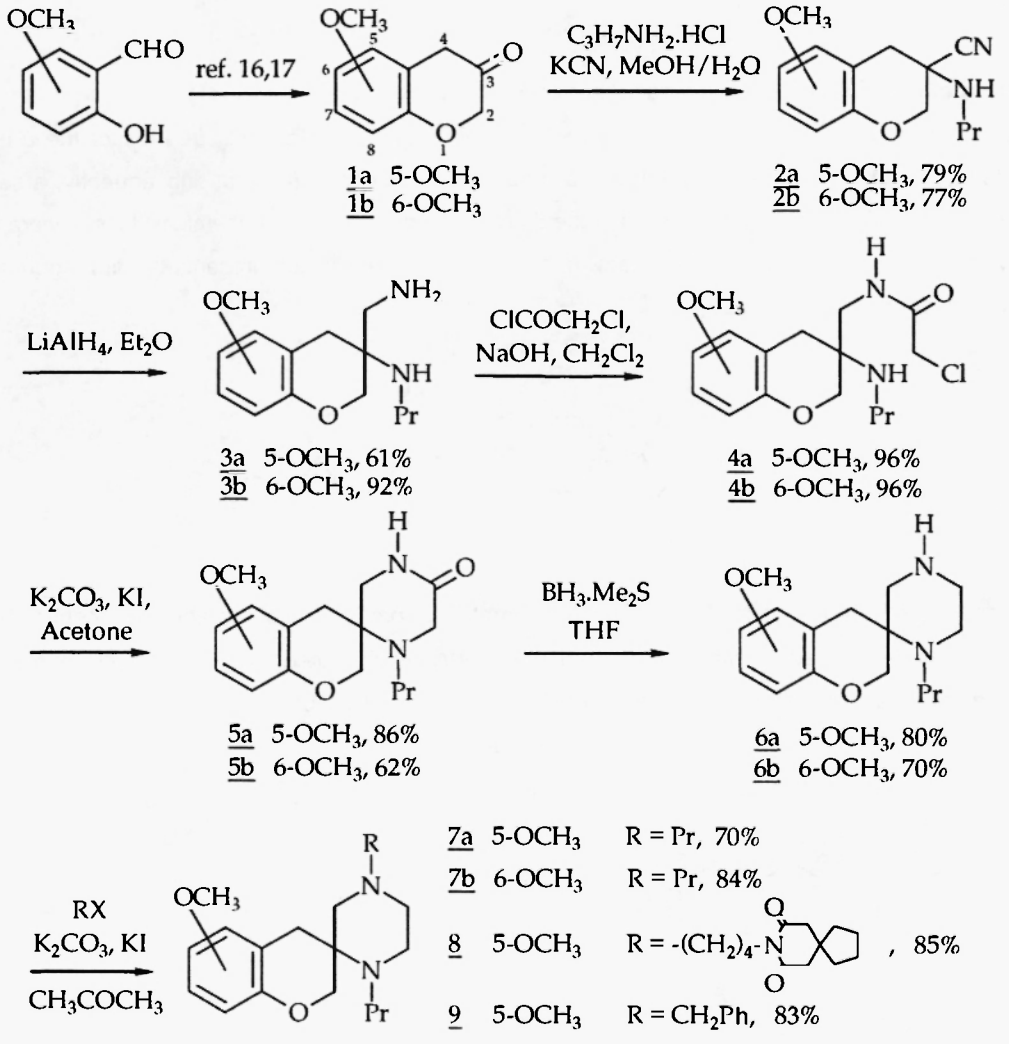
In connection with our research towards the elaboration of products liable to affect the central nervous system (CNS) (10-15), we have directed our work to the preparation of *N,N*-substituted-3,4-dihydrospiro[1-benzopyran-3(2*H*),2'-piperazines] A and *N,N*-substituted 3-amino-3-aminomethyl-3,4-dihydro-2*H*-1-benzopyrans B (Figure 2).

Figure 2



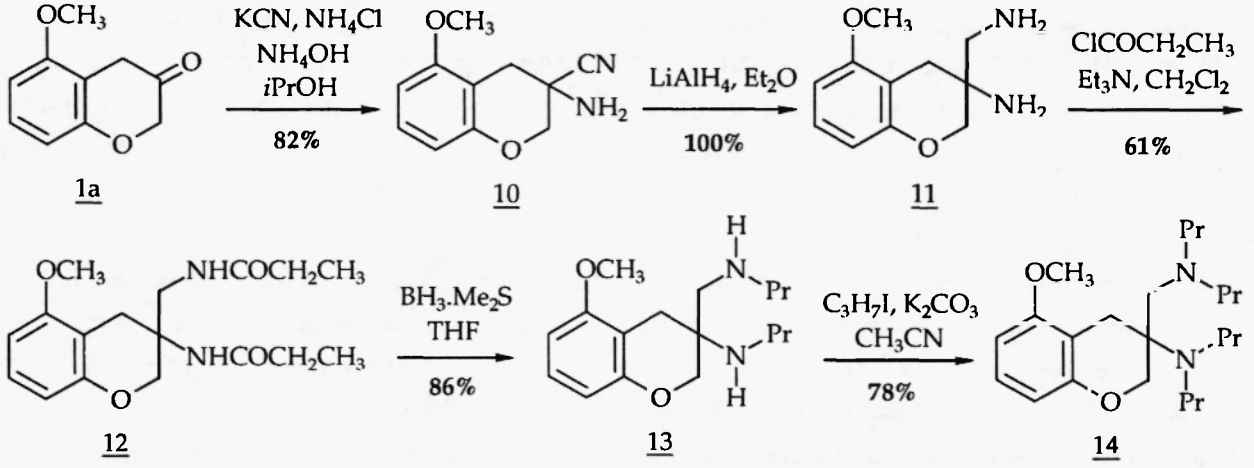
Results : The synthesis of piperazine derivatives of the A type (6-9) is illustrated in Scheme 1. The precursors 1a.b, 5- or 6-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-one (16,17), were obtained from 2-hydroxy-5- or 6-methoxy-benzaldehydes according to the procedure described by Wise *et al* (17). Ketones 1a.b were treated with propylamine hydrochloride and potassium cyanide in a mixture methanol/water as solvent to give the compounds 2a.b in 79 and 77% yields, respectively (18). Reduction of 2a.b with lithium aluminium hydride in refluxing diethyl ether afforded the expected diamines 3a.b in 61 and 92% yields, respectively. The next step was the formation of the piperazine ring. However, treatment of 3a.b with dibromoethane in several conditions such as triethylamine in toluene or diisopropylamine in acetonitrile did not give the desired derivatives. This difficulty was overcome by using another synthetic approach in three steps. The amines 3a.b were treated with 2-chloropropionyl chloride and a 1.2% sodium hydroxide solution as a base in methylene chloride (19) to give the required amides 4a.b in excellent yields (96%). Intramolecular *N*-alkylation in usual conditions provided the tricyclic derivatives 5a.b in 86 and 62% yields, respectively. Reduction of the amido groups with borane-dimethylsulfide complex (20) in refluxing tetrahydrofuran afforded the expected piperazines 6a.b in 80 and 70% yields, respectively. *N*-alkylation of 6a.b using potassium carbonate, in the presence of potassium iodide in acetone as solvent, gave the desired derivatives 7a.b, 8 and 9 in 70 and 84, 85 and 83% yields, respectively.

Scheme 1



The second part of our study dealing with the preparation of the analogue of the B type (14) is outlined in Scheme 2. A Strecker reaction (21) of ketone 1a in the presence of ammonium chloride and potassium cyanide in a mixture of isopropanol/28% ammonium hydroxide solution afforded the expected aminocyanide 10 in 82% yield. The nitrile was reduced with lithium aluminium hydride in refluxing diethyl ether to give the diamine 11 in quantitative yield. Unfortunately, reaction of 11 with 1-iodopropane and potassium carbonate in acetonitrile as a solvent did not provide the expected *N*-propylated derivative but led to the degradation of the starting material 11. So another pathway was used to elaborate the desired compound 14. *N*-Acylation of 11, by treatment with propionyl chloride in the presence of triethylamine in methylene chloride, gave the amide 12 in 61% yield. Reduction of 12 with borane-dimethylsulfide complex in refluxing tetrahydrofuran gave diamine 13 in 86% yield. The last step was the *N*-propylation of 13 with 1-iodopropane and potassium carbonate in acetonitrile to give the expected compound 14 in 78% yield.

Scheme 2



Pharmacology : The *N,N*-disubstituted-3,4-dihydrospiro[1-benzopyran-3(2*H*),2'-piperazine] derivatives 7a.b. 8, and 9 and the tetra-*n*-propyl compound 14 were shown to have no affinity with 5-HT_{1A} receptors.

Experimental : Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone, methylene chloride and *N,N*-dimethylformamide from diphosphorus pentoxide, and amines from potassium hydroxide. Column chromatographies were performed on silica gel (Kieselgel, 70-230 mesh for gravity columns and 230-400 mesh for flash columns). Analytical thin layer chromatography (tlc) was carried out on precoated plates (silica gel, Merck $60F_{254}$). Melting points were determined on a Köfler hotstage apparatus and were uncorrected. Infrared spectra were recorded on a PERKIN-ELMER 297 spectrometer. Mass spectra were recorded on a R-10-10-C NERMAG spectrometer. ^1H nmr spectra were recorded at 300 MHz on a BRUKER AM 300WB spectrometer. The coupling constants were recorded in hertz (Hz) and the chemical shifts were reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS) which was used as an internal standard.

3-Cyano-3-n-propylamino-5-methoxy-3,4-dihydro-2H-1-benzopyran 2a : A solution of ketone 1a (4.500 g, 25.28 mmol) in methanol (MeOH) (50 ml) and *n*-propylamine hydrochloride (14.500 g, 151.00 mmol) in water (H_2O) (50 ml) was

cooled at -10°C. Potassium cyanide (9.850 g, 151.00 mmol) in H_2O (50 ml) was then added dropwise. The mixture was stirred overnight at room temperature. The crude product was extracted with methylene chloride (CH_2Cl_2), and purified by column chromatography (eluent : CH_2Cl_2/MeOH : 9/1). The expected compound 2a was obtained as a powder (4.930 g) in 79% yield; mp 83-84°C; ir (KBr) 3300 (NH), 2210 (CN), 1230 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.98 (t, 3H, CH_3, J = 7.3), 1.50-1.61 (m, 2H, CH_2CH_3), 1.42 (br s, 1H, NH), 2.74-2.88 (m, 3H, $CH_2CH_2CH_3$, CH_2Ar), 3.26 (dd, 1H, CH_2Ar, J = 16.6, J = 2.0), 3.82 (s, 3H, OCH_3), 3.90 (d, 1H, OCH_2, J = 10.7), 4.24 (dd, 1H, OCH_2, J = 10.7, J = 2.0), 6.48 (d, 1H, H_{6or8}, J = 8.1), 6.56 (d, 1H, H_{6or8}, J = 8.1), 7.12 (t, 1H, H_7, J = 8.1); *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7. 37; N, 11. 37. Found : C, 68.41 ; H, 7. 50; N, 11.55.

3-Cyano-3-n-propylamino-6-methoxy-3,4-dihydro-2H-1-benzopyran 2b : The compound 2b was prepared from the ketone 1b (1.810 g, 10.17 mmol) according to the method used for 2a. The product 2b was obtained after a column chromatography (eluent : CH_2Cl_2/MeOH : 99/1) as an oil (1.920 g) in 77% yield; ir (film) 3300 (NH), 2220 (CN), 1240 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.98 (t, 3H, CH_3, J = 7.4), 1.50-1.61 (m, 3H, NH, CH_2), 2,80 (t, 2H, $CH_2CH_2CH_3$, J = 7.2), 2.98 (d, 1H, CH_2Ar, J = 16.2), 3.24 (d, 1H, CH_2Ar, J = 16.2), 3.75 (s, 3H, OCH_3), 3.92 (d, 1H, OCH_2, J = 11.0), 4.23 (dd, 1H, OCH_2, J = 11.0, J = 2.0), 6.57 (d, 1H, H_5, J = 2.9), 6.73 (dd, 1H, H_7, J = 2.9, J = 8.9), 6.82 (d, 1H, H_8, J = 8.9); *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found : C, 67.99; H, 7.11; N, 11.13.

3-Aminomethyl-3-n-propylamino-5-methoxy-3,4-dihydro-2H-1-benzopyran 3a : To a suspension of lithium aluminium hydride (0.740 g, 1.94 mmol) in dry diethyl ether (Et_2O) (6 ml), a solution of 2a (2.390 g, 9.71 mmol) in Et_2O (25 ml) was added dropwise at 0°C . After refluxing for 4 h, the mixture was cooled to 0°C. Water (0.74 ml), 15 % sodium hydroxide solution (0.74 ml) and water again (2.2 ml) were successively added very slowly. After stirring for 15 min at 0° C, the salts were filtered then washed with Et_2O. The solvent was removed and the expected diamine 3a was obtained after a column chromatography (eluent : CH_2Cl_2/MeOH : 95/5) as an oil (1.470 g) in 61 % yield; ir (film) 3600-3300 (NH_2, NH), 1225 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.91 (t, 3H, CH_3, J = 7.3), 1.39-1.52 (m, 2H, CH_2CH_3), 1.70 (br s, 3H, NH_2, NH), 2.43-2.59 (m, 2H, $CH_2CH_2CH_3$), 2.66-2.75 (m, 4H, CH_2NH_2, CH_2Ar), 3.81 (s, 3H, OCH_3), 3.86 (d, 1H, OCH_2, J = 11.0), 3.93 (dd, 1H, OCH_2, J = 11.0, J = 1.5), 6.43 (d, 1H, H_{6or8}, J = 7.9), 6.50 (d, 1H, H_{6or8}, J = 7.9), 7.06 (t, 1H, H_7, J = 7.9); *Anal.* Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found : C, 66.98; H, 8.72; N, 10.99.

3-Aminomethyl-3-n-propylamino-6-methoxy-3,4-dihydro-2H-1-benzopyran 3b : The compound 3b was prepared from the amine 2b (0.400 g, 1.56 mmol) according to the method used for 3a. An analytical sample was obtained after a column chromatography (eluent : CH_2Cl_2/MeOH : 95/5). The crude derivative 3b was obtained as an oil (0.375 g) in 92% yield and was used without further purification in the next step; ir (film) 3700-3100 (NH_2, NH), 1250 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.92 (t, 3H, CH_3, J = 7.3), 1.39-1.52 (m, 2H, CH_2CH_3), 1.60-1.82 (m, 3H, NH, NH_2), 2.43-2.60 (m, 2H, $CH_2CH_2CH_3$), 2.65 (d, 1H, CH_2Ar, J = 16.2), 2.67 (d, 1H, CH_2NH_2, J = 13.2), 2.74 (d, 1H, CH_2NH_2, J = 13.2), 2.81 (d, 1H, CH_2Ar, J = 16.2), 3.75 (s, 3H, OCH_3), 3.86 (d, 1H, OCH_2, J = 11.0), 3.95 (dd, 1H, OCH_2, J = 11.0, J = 1.5), 6.58 (d, 1H, H_5, J = 2.9), 6.68 (dd, 1H, H_7, J = 2.9, J = 8.8), 6.76 (d, 1H, H_8, J = 8.8); *Anal.* Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found : C, 67.00; H, 8.69; N 10.93.

3-n-Propylamino-3-(chloroacetyl)aminomethyl-5-methoxy-3,4-dihydro-2H-1-benzopyran 4a : A solution of amine

3a (1.370 g, 5.48 mmol) in CH_2Cl_2 (12 ml) was vigorously stirred with a 1.2 % sodium hydroxide solution (24 ml) before chloroacetylchloride (0.805 g, 7.12 mmol) in CH_2Cl_2 (3 ml) was added dropwise at 0°C. The same sodium hydroxide solution was then used drop by drop in order to maintain the pH about 9. When this value became stable, the separated organic layer was dried and the solvent was removed. After a column chromatography (eluent : CH_2Cl_2/ MeOH : 9/1) the expected compound 4a was obtained as a sticky solid (1.720 g) in 96 % yield; ir (KBr) 3390 and 3300 (NH), 1665 (CO), 1230 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.92 (t, 3H, **CH_3**, J = 7.3), 1.37-1.53 (m, 2H, **CH_2CH_3**), 1.53 (br s, 1H, NH), 2.43-2.59 (m, 2H, **$CH_2CH_2CH_3$**), 2.50 (d, 1H, **CH_2**Ar, J = 17.1), 2.81 (dd, 1H, **CH_2**Ar, J = 17.1, J = 1.8), 3.24-3.39 (m, 2H, **CH_2**NCO), 3.80 (d, 1H, O**CH_2**, J = 11.5), 3.82 (s, 3H, O**CH_3**), 3.97 (dd, 1H, O**CH_2**, J = 11.5, J = 1.8), 4.08 (s, 2H, **CH_2**Cl), 6.45 (d, 1H, **H_{6or8}**, J = 8.2), 6.51 (d, 1H, **H_{6or8}**, J = 8.2), 7.08 (t, 1H, **H_7**, J = 8.2), 7.45 (br s, 1H, NHCO); *Anal.* Calcd for $C_{16}H_{23}N_2O_3Cl$: C, 58.80; H, 7.09; N, 8.57; Cl, 10.87. Found : C, 59.07; H, 7.28; N, 8.72; Cl, 11.03.

3-n-Propylamino-3-(chloroacetyl)aminomethyl-6-methoxy-3,4-dihydro-2H-1-benzopyran 4b : The compound 4b was prepared from the amine 3b (0.230 g, 0.92 mmol) and 2-chloroacetylchloride (0.135 g, 1.20 mmol) according to the method used for 4a. The desired derivative 4b was obtained after a column chromatography (eluent : CH_2Cl_2/MeOH : 9/1) as an oil (0.290 g) in 96% yield; ir (film) 3500-3140 (NH, NHCO), 1660 (CO), 1210 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.90 (t, 3H, **CH_3**, J = 7.3), 1.37-1.62 (m, 3H, N**H**, **CH_2CH_3**), 2.42-2.60 (m, 2H, **$CH_2CH_2CH_3$**), 2.69 (d, 1H, **CH_2**Ar, J = 16.2), 2.81 (dd, 1H, **CH_2**Ar, J = 16.2, J = 2.0), 3.27 (dd, 1H, **CH_2**NH, J = 13.8, J = 5.1), 3.34 (dd, 1H, **CH_2**NH, J = 13.8, J = 5.1), 3.74 (s, 3H, O**CH_3**), 3.79 (d, 1H, O**CH_2**, J = 10.7), 3.98 (dd, 1H, O**CH_2**, J = 10.7, J = 2.0), 4.09 (s, 2H, **CH_2**Cl), 6.57 (d, 1H, **H_5**, J = 2.9), 6.69 (dd, 1H, **H_7**, J = 8.8, J = 2.9), 6.77 (d, 1H, **H_8**, J = 8.8), 7.44 (br s, 1H, NHCO); *Anal.* Calcd for $C_{16}H_{23}N_2O_3Cl$: C, 58.80; H, 7.09; N, 8.57; Cl, 10.87. Found : C, 58.97; H, 7.32; N 8.65; Cl, 10.99.

5-Methoxy-3,4-dihydro-5'-oxo-1'-n-propylspiro[1-benzopyran-3(2H),2'-piperazine] 5a : A mixture of the compound 4a (1.720 g, 5.27 mmol) dissolved in dry acetone (20 ml), potassium carbonate (2.181 g, 15.80 mmol) and potassium iodide (catalytic quantity) was refluxed for 24 h. After hydrolysis, the product was extracted with CH_2Cl_2. The crude product was chromatographied (eluent : CH_2Cl_2/MeOH : 95/5) to give the compound 5a as an oil (1.320 g) in 86 % yield; ir (film) 3600-3100 (NH), 1665 (CO), 1225 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.90 (t, 3H, **CH_3**, J = 7.3), 1.40-1.55 (m, 2H, **CH_2CH_3**), 2.38-2.48 (m, 1H, **$CH_2CH_2CH_3$**), 2.53-2.62 (m, 1H, **$CH_2CH_2CH_3$**), 2.69 (d, 1H, **CH_2**Ar, J = 17.0), 2.87 (dd, 1H, **CH_2**Ar, J = 17.0, J = 2.0), 3.23 (dd, 1H, **CH_2**NHCO, J = 12.1, J = 3.2), 3.34 (d, 1H, **CH_2**NHCO, J = 12.1), 3.38 (d, 1H, **CH_2**CO, J = 18.1), 3.53 (d, 1H, **CH_2**CO, J = 18.1), 3.83 (s, 3H, O**CH_3**), 4.02 (d, 1H, O**CH_2**, J = 10.6), 4.08 (dd, 1H, O**CH_2**, J = 10.6, J = 2.0), 6.06 (br s, 1H, **NH**CO), 6.46 (d, 1H, **H_{6or8}**, J = 8.2), 6.50 (d, 1H, **H_{6or8}**, J = 8.2), 7.08 (t, 1H, **H_7**, J = 8.2); *Anal.* Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found : C, 66.22; H, 7.70; N, 9.77.

6-Methoxy-3,4-dihydro-5'-oxo-1'-n-propylspiro[1-benzopyran-3(2H),2'-piperazine] 5b : The compound 5b was prepared from the compound 4b (2.090 g, 6.40 mmol) according to the method used for 5a. The expected derivative 5b was obtained after a column chromatography (eluent : CH_2Cl_2/ MeOH : 95/5) as a solid (1.150 g) in 62% yield; mp 124-125°C; ir (KBr) 3160 (NHCO), 1700-1640 (CO), 1240 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.89 (t, 3H, **CH_3**, J = 7.3), 1.40-1.56 (m, 2H, **CH_2CH_3**), 2.40-2.62 (m, 2H, **$CH_2CH_2CH_3$**), 2.83 (dd, 1H, **CH_2**Ar, J = 16.2, J = 1.5), 2.97 (d, 1H, **CH_2**Ar, J = 16.2), 3.26 (dd, 1H, **CH_2**NHCO, J = 13.1, J = 3.1), 3.31 (dd, 1H, **CH_2**NHCO, J = 13.1, J = 4.4), 3.35 (d, 1H, **CH_2**CO, J = 17.8), 3.53 (d, 1H, **CH_2**CO, J = 17.8), 3.75 (s, 3H, O**CH_3**), 4.03 (d, 1H, O**CH_2**, J = 10.6), 4.08 (dd, 1H, O**CH_2**,

J = 10.6, J = 1.5), 5.87 (m, 1H, NHCO), 6.62 (d, 1H, H_5, J = 2.9), 6.70 (dd, 1H, H_7, J = 8.9, J = 2.9), 6.77 (d, 1H, H_8, J = 8.9); *Anal.* Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found : C, 66.27; H, 7.71; N 9.79.

5-Methoxy-3,4-dihydro-1'-n-propylspiro[1-benzopyran-3(2H),2'-piperazine) 6a : Borane-dimethyl sulfide complex (4.55 ml, 2M in tetrahydrofuran solution, 9.1 mmol) was added dropwise to a solution of 5a (1.320 g, 4.55 mmol) in dry tetrahydrofuran (THF) (40 ml). The solution was heated under reflux for 16 h. The solvent was evaporated and the residue was heated on a steam bath for 1.5 h with 2M hydrochloric acid solution (90 ml) and methanol (45 ml). After cooling at room temperature, the solution was made alkaline by using a 2M sodium hydroxide solution. The product was extracted with CH_2Cl_2 and the expected amine 6a was obtained after a column chromatography (eluent : CH_2Cl_2/MeOH : 9/1) as an oil (1.000 g) in 80 % yield; ir (film) 3680-3100 (NH), 1240 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.86 (t, 3H, CH_3, J = 7.3), 1.37-1.50 (m, 2H, CH_2CH_3), 2.08 (br s, 1H, NH), 2.35-2.44 (m, 2H, $CH_2CH_2CH_3$), 2.66 (d, 1H, CH_2N, J = 17.1), 2.86 (d, 1H, CH_2N, J = 17.1), 2.71 (t, 2H, CH_2N, J = 4.7), 2.91-2.97 (m, 2H, CH_2N), 2.76 (s, 2H, CH_2Ar), 3.83 (s, 3H, OCH_3), 4.02 (s, 2H, OCH_2), 6.42 (d, 1H, H_{6or8}, J = 8.2), 6.47 (d, 1H, H_{6or8}, J = 8.2), 7.04 (t, 1H, H_7, J = 8.2); ms (CI/NH_3) *m/z* : 277 (M^++1); *Anal.* Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found : C, 69.41; H, 8.62; N, 9.98.

6-Methoxy-3,4-dihydro-1'-n-propylspiro[1-benzopyran-3(2H),2'-piperazine] 6b : The compound 6b was prepared from the compound 5b (1.080 g, 3.72 mmol) according to the method used for 6a. The desired product 6b was obtained after a column chromatography (eluent : CH_2Cl_2/MeOH : 9/1) as a solid (0.715 g) in 70% yield; mp 89-90°C; ir (film) 3280 (NH), 1240 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.87 (t, 3H, CH_3, J = 7.3), 1.35-1.50 (m, 2H, CH_2CH_3), 1.68 (br s, 1H, NH), 2.30-2.48 (m, 2H, $CH_2CH_2CH_3$), 2.60-2.97 (m, 6H, CH_2N), 2.77 (s, 2H, CH_2Ar), 3.74 (s, 3H, OCH_3), 4.01 (s, 2H, OCH_2), 6.63-6.68 (m, 2H, $H_{5\,7}$), 6.74 (d, 1H, H_8, J = 8.1); *Anal.* Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found : C, 69.50; H, 8.82; N 10.21.

5-Methoxy-3,4-dihydro-1',4'-di-n-propylspiro[1-benzopyran-3(2H),2'-piperazine] 7a : The compound 7a was prepared from amine 6a (0.150 g, 0.54 mmol) according to the method used for 5a. The product 7a was obtained after a column chromatography (eluent CH_2Cl_2/MeOH : 9/1) as an oil (0.121 g) in 70 % yield; ir (film) 1240 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.82 (t, 3H, CH_3, J = 7.3), 0.86 (t, 3H, CH_3, J = 7.3), 1.33-1.50 (m, 4H, CH_2CH_3), 2.21 (t, 2H, CH_2N, J = 7.4), 2.25-2.56 (m, 4H, $CH_2CH_2CH_3$), 2.42 (t, 2H, CH_2N, J = 7.3), 2.64 (d, 1H, CH_2Ar, J = 17.5), 2.77 (t, 2H, CH_2N, J = 5.2), 2.85 (d, 1H, CH_2Ar, J = 17.5), 3.81 (s, 3H, OCH_3), 3.97 (d, 1H, OCH_2, J = 10.3), 4.06 (d, 1H, OCH_2, J = 10.3), 6.43 (d, 1H, H_{6or8}, J = 8.2), 6.49 (d, 1H, H_{6or8}, J = 8.2), 7.05 (t, 1H, H_7, J = 8.2); ms (CI/NH_3) *m/z* : 319 (M^++1); *Anal.* Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found : C, 71.75; H, 9.60; N, 8.93.

6-Methoxy-3,4-dihydro-1',4'-di-n-propylspiro[1-benzopyran-3(2H),2'-piperazine] 7b : The compound 7b was prepared from the amine 6b (0.690 g, 2.50 mmol) according to the method used for 5a. After a column chromatography (eluent : CH_2Cl_2/MeOH : 9/1) the desired derivative 7b was obtained as an oil (0.670 g) in 84% yield; ir (film) 1210 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.82 (t, 3H, CH_3, J = 7.3), 0.87 (t, 3H, CH_3, J = 7.3), 1.32-1.50 (m, 4H, CH_2CH_3), 2.20 (d, 1H, CH_2N, J = 7.7), 2.24 (d, 1H, CH_2N, J = 7.7), 2.30-2.59 (m, 6H, $CH_2CH_2CH_3$, CH_2N), 2.66-2.80 (m, 2H, CH_2N), 2.88 (s, 2H, CH_2Ar), 3.75 (s, 3H, OCH_3), 4.00 (s, 2H, OCH_2), 6.60-6.69 (m, 2H, $H_{5\,7}$), 6.74 (d, 1H, H_8, J = 8.1); *Anal.* Calcd for

$C_{19}H_{30}N_2O_2$: **C**, 71.66; H, 9.50; N, 8.80. Found : C, 71.79; H, 9.63; N, 8.91.

5-Methoxy-3,4-dihydro-4'-{4"-(8"-azaspiro[4.5] decane-7,9-dione)butyl}-1'-n-propylspiro[1-benzopyran-3(2H), 2'-piperazine] 8 : The compound 8 was prepared from amine 6a (0.150 g, 0.54 mmol) and 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (0,247 g, 0,81 mmol) according to the method used for 5a. The expected product 8 was obtained after a column chromatography (eluent : CH_2Cl_2/MeOH : 9/1) as an oil (0.230 g) in 85 % yield; ir (film) 1680 and 1735 (CO), 1230 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.85 (t, 3H, CH_3, J = 7.3), 1.33-1.50 (m, 10H, CH_2CH_3, CH_2), 1.65-1.71 (m, 4H, CH_2), 2.25 (t, 2H, CH_2N, J = 7.4), 2.28 (s, 2H, CH_2N), 2.35-2.50 (m, 4H, $CH_2CH_2CH_3$, CH_2N), 2.55 (s, 4H, $NCOCH_2$), 2.64 (d, 1H, CH_2Ar, J = 17.5), 2.76 (t, 2H, CH_2N, J = 5.1), 2.80 (d, 1H, CH_2Ar, J = 17.5), 3.71 (t, 2H, CH_2NCO, J = 7.2), 3.82 (s, 3H, OCH_3), 3.96 (d, 1H, OCH_2, J = 10.4), 4.06 (d, 1H, OCH_2, J = 10.4), 6.43 (d, 1H, H_{6or8}, J = 8.2), 6.49 (d, 1H, H_{6or8}, J = 8.2), 7.04 (t, 1H, H_7, J = 8.2); ms (CI/NH_3) *m/z* : 498 (M^++1); *Anal.* Calcd for $C_{29}H_{43}N_3O_4$: C, 69.99; H, 8.71; N, 8.44. Found C, 70.08; H, 8.85; N, 8.52.

5-Methoxy-3,4-dihydro-4'-benzyl-1'-n-propylspiro[1-benzopyran-3(2H),2'-piperazine] 9 : The compound 9 was prepared from amine 6a (0.210 g, 0.76 mmol) and benzyl bromide (0.195 g, 1.14 mmol) according to the method used for 5a . After column chromatography (eluent : CH_2Cl_2/MeOH : 9/1), the expected product 9 was isolated as an oil (0.230 g) in 83 % yield; ir (film) 1245 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.85 (t, 3H, CH_3, J = 7.3), 1.33-1.48 (m, 2H, CH_2CH_3), 2.30-2.53 (m, 6H, CH_2Ar, CH_2N, $CH_2CH_2CH_3$), 2.64 (d, 1H, CH_2N, J = 17.5), 2.78 (t, 2H, CH_2N, J = 5.3), 2.93 (d, 1H, CH_2N, J = 17.5), 3.43 (d, 1H, CH_2Ph, J = 13.2), 3.49 (d, 1H, CH_2Ph, J = 13.2), 3.85 (s, 3H, OCH_3), 4.06 (s, 2H, OCH_2), 6.43 (d, 1H, H_{ar}, J = 8.3), 6.44 (d, 1H, H_5, J = 8.3), 7.03 (t, 1H, H_7,J = 8.3), 7.13-7.30 (m, 5H, H_8); ms (CI/NH_3) *m/z* : 367 (M^++1); *Anal.* Calcd for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found : C, 75.24; H, 8.11; N, 7.50.

3-Amino-3-cyano-5-methoxy-3,4-dihydro-2H-1-benzopyran 10 : Ammonium chloride (0.360 g, 6.73 mmol) and potassium cyanide (0.440 g, 6.73 mmol) were mixed. A solution of ammonium hydroxide (28% NH_3 in water) (5 ml) and a solution of 5a (0.300 g, 1.68 mmol) in isopropanol (3 ml) were successively added. The mixture was stirred at room temperature for 40 h. After hydrolysis with a sodium carbonate solution, the product was extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate and the solvents were removed. The crude product was purified by column chromatography (eluent : CH_2Cl_2) and gave the expected amine 10 as a solid (0.280 g) in 82 % yield; mp 109-110°C; ir (film) 3380 and 3300 (NH_2), 2220 (CN), 1230 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.90 (br s, 2H, NH_2), 2.81 (d, 1H, CH_2Ar, J = 16.9), 3.25 (dd, 1H, CH_2Ar, J = 16.9, J = 1.5), 3.82 (s, 3H, OCH_3), 3.90 (d, 1H, OCH_2, J = 11.0), 4.19 (dd, 1H, OCH_2, J = 11.0, J = 1.5), 6.49 (d, 1H, H_{6or8}, J = 8.1), 6.56 (d, 1H, H_{6or8}, J = 8.1), 7.14 (t, 1H, H_7, J = 8.1); *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found : C, 64.42; H, 5.87; N, 13.60.

3-Amino-3-aminomethyl-5-methoxy-3,4-dihydro-2H-1-benzopyran 11 : The compound 11 was prepared from cyanide 10 (0.760 g, 3.72 mmol) according to the method used for 3a. The expected diamine 11, which was used in the next step without further purification, was obtained as an oil (0.775 g) in quantitative yield. An analytical sample was obtained after a flash column chromatography (eluent : CH_2Cl_2/MeOH : 9/1); ir (film) 3500-3200 (NH_2), 1240 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.50 (br s, 4H, NH_2), 2.50 (d, 1H, CH_2Ar, J = 16.9), 2.62 (d, 1H, CH_2Ar, J = 16.9), 2.67 (d, 1H, CH_2NH_2, J = 13.0), 2.74 (d, 1H, CH_2NH_2, J = 13.0), 3.78 (d, 1H, OCH_2, J = 10.2), 3.81 (s, 3H, OCH_3), 3.89 (d, 1H,

OCH_2, J = 10.2), 6.44 (d, 1H, H_{6or8}, J = 8.3), 6.52 (d, 1H, H_{6or8}, J = 8.3), 7.07 (t, 1H, H_7, J = 8.3); *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found : C, 63.52; H, 7.82; N, 13.57.

N-(5-Methoxy-3-n-propionylamino-3,4-dihydro-2H-1-benzopyran-3-ylmethyl)propionamide 12 : Triethylamine (2 ml, 14.4 mmol) and propanoylchloride (0.490 g, 5.29 mmol) were added dropwise at 0°C to a solution of the diamine 11 (0.500 g, 2.40 mmol). The mixture was then stirred at room temperature for 1 h. After hydrolysis and extraction with CH_2Cl_2, the crude product was purified by column chromatography (eluent : CH_2Cl_2/MeOH : 9/1) and the compound 12 was obtained as an oil (0.470 g) in 61 % yield; ir (film) 3500 and 3360 (NH), 1640 and 1670 (CO), 1230 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.08 (t, 3H, CH_3, J =7.6), 1.20 (t, 3H, CH_3, J = 7.6), 2.24 (q, 2H, CH_2, J = 7.6), 2.30 (q, 2H, CH_2, J = 7.6), 2.50 (d, 1H, CH_2Ar, J = 16.9), 3.31-3.44 (m, 2H, CH_2Ar, CH_2NCO), 3.74 (dd, 1H, CH_2NCO, J = 14.3, J = 6.7), 3.80 (s, 3H, OCH_3), 3.82 (d, 1H, OCH_2, J = 11.1), 4.42 (dd, 1H, OCH_2, J = 11.1, J = 1.5), 6.38 (br s, 1H, NHCO), 6.47 (d, 1H, H_{6or8}, J = 8.3), 6.50 (d, 1H, H_{6or8}, J = 8.3), 6.71-6.79 (br s, 1H, NHCO), 7.08 (t, 1H, H_7, J = 8.3); ms (CI/NH_3) *m/z* : 321 (M^++1); *Anal.* Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found : C, 63.80; H, 7.67; N, 8.85.

(5-Methoxy-3-n-propylaminomethyl-3,4-dihydro-2H-1-benzopyran-3-yl)propylamine 13 : Borane-dimethyl sulfide complex (0.5 ml, 2M in tetrahydrofuran solution, 1.0 mmol) was added dropwise to a solution of the compound 12 (0.080 g, 0.25 mmol) in dry tetrahydrofuran (THF) (5 ml). The solution was heated under reflux for 24 h. The solvent was evaporated and the residue was heated on a steam bath for 1.5 h with 2M hydrochloric acid solution (10 ml) and methanol (5 ml). After cooling to room temperature, the solution was made alkaline by using a 2M sodium hydroxide solution. The product was extracted with CH_2Cl_2 then, after evaporation of solvents, chromatographied (eluent : CH_2Cl_2/MeOH : 9/1) to give 13 as an oil (0.063 g) in 86 % yield; ir (film) 3600-3100 (NH), 1230 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.93 (t, 3H, CH_3, J = 7.1), 0.90 (t, 3H, CH_3, J = 7.1), 1.38-1.60 (m, 4H, CH_2CH_3), 1.83 (br s, 2H, NH), 2.46-2.70 (m, 5H, CH_2Ar, $CH_2CH_2CH_3$), 2.64 (s, 2H, CH_2N), 2.79 (d, 1H, CH_2Ar, J = 17.2), 3.80 (s, 3H, OCH_3), 3.88 (d, 1H, OCH_2, J = 10.7), 4.00 (d, 1H, OCH_2, J = 10.7), 6.43 (d, 1H, H_{6or8}, J = 8.3), 6.50 (d, 1H, H_{6or8}, J = 8.3), 7.06 (t, 1H, H_7, J = 8.3); *Anal.* Calcd for $C_{17}H_{28}N_2O_2$: C, 69.83; H, 9.65; N, 9.58. Found : C, 69.71; H, 9.46; N, 9.32.

(3-Di-n-propylaminomethyl-5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)di-n-propylamine 14 : This compound 14 was prepared starting from the compound 13 (0.400 g, 1.37 mmol) and 1-iodopropane (6.986 g, 41.1 mmol) according to the method used for 5a. The expected derivative 14 was obtained after a column chromatography (eluent : CH_2Cl_2/MeOH : 9/1) as an oil (0.400 g) in 78 % yield; ir (film) 1230 (COC) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 0.83-0.94 (m, 12H, CH_3), 1.30-1.55 (m, 8H, CH_2CH_3), 2.36-2.61 (m, 11H, $CH_2CH_2CH_3$, CH_2Ar, CH_2N), 2.66 (d, 1H, CH_2Ar, J = 16.8), 3.81 (s, 3H, OCH_3), 3.84 (d, 1H, OCH_2, J = 10.8), 3.96 (d, 1H, OCH_2, J = 10.8), 6.43 (d, 1H, H_{6or8}, J = 8.2), 6.49 (d, 1H, H_{6or8}, J = 8.2), 7.05 (t, 1H, H_7, J = 8.2); ms (CI/NH_3) *m/z* : 377 (M^++1); *Anal.* Calcd for $C_{23}H_{40}N_2O_2$: C, 73.36; H, 10.71; N, 7.44. Found : C, 73.50; H, 10.89; N, 7.65.

Acknowledgements : We are specially grateful to I.R.I.S. (Institut de Recherches Internationales Servier) for a grant to C. Comoy. We thank also Mrs Le Floch for typing.

References :

(1) A.L. Johnston and S.E. File, Pharmacol. Biochem. Behav. 24, 1467 (1986)

(2) M.S. Eison, Psychopathology 17, 37 (1984)

(3) S.J. Peroutka and S.H. Snyder, J. Pharmacol. Exp. Ther. 216, 142 (1981)

(4) L.E. Arvidsson, U. Hacksell, J.L.G. Nilsson, S. Hjorth, A. Carlsson, P. Lindberg, D. Sanchez and H. Wikström, J. Med. Chem. 24, 921 (1981)

(5) Middlemiss and J.R. Fozard, Eur. J. Pharm. 90, 151 (1983)

(6) A.G. Romero and R.B. Mc Call, Ann. Rep. Med. Chem. 270, 21 (1992)

(7) R.W. Fuller and D.W. Robertson, Ann. Rep. Med. Chem. 26, 23 (1991)

(8) a) B.P. Richardson and D. Hoyer, Serotonin : From cell biology to pharmacology and therapeutics, Paoletti, R., Drodrecht : Kleewer (Ed), 1990, pp 265 b) A.P. Levy and L.D. Van der Kar, Life Sci. 51, 83 (1992) c) D.P. Taylor and S.L. Moon, Neuropeptides 19. 15 (1991)

(9) K.V. Kastenhoz and M.L. Crismon, Clin. Pharm. 3, 600 (1984)

(10) J.M. Cossery, H. Gozlan, U. Spampinato, C. Perdicakis, G. Guillaumet, L. Pichat and M. Hamon, Eur. J. Pharmacol. 140, 143 (1987)

(11) M. Al Neirabeyeh, D. Reynaud, T. Podona, L. Ou, C. Perdicakis, G. Coudert, G. Guillaumet, L. Pichat, A. Gahrib and N. Sarda, Eur. J. Med. Chem. 26, 497 (1991)

(12) G. Griebel, R. Misslin, M. Pawlowski, B. Guardiola-Lemaître, G. Guillaumet and J.G. Bizot Espiard, Neuroreport 3, 84 (1992)

(13) T. Besson, T. Podona, M.L. Baudin, G. Coudert and G. Guillaumet, Bioorg. Med. Chem. Lett. 3, 1935 (1993)

(14) T. Podona, B. Guardiola-Lemaître, D.H. Caignard, G. Adam, B. Pfeiffer, P. Renard and G. Guillaumet, J. Med. Chem. 37, 1779 (1994)

(15) C. Comoy, C. Marot, T. Podona, M.L. Baudin, L. Morin-Allory, G. Guillaumet, P. Renard, B. Pfeiffer, Caignard, M.C. Rettori, B. Guardiola-Lemaître and G. Adam, J. Med. Chem., to be published

(16) B. Andersson, H. Wikström and A. Hallberg, Acta Chem. Scand. 44, 1024 (1990)

(17) L.D. Wise, H.A. DeWald, E.S. Hawkins, D.M. Reynolds, T.G. Heffner, L.T. Meltzer and T.A. Pugsley, J. Med. Chem. 31, 688 (1988)

(18) G.M. Carrera Jr. and D.S. Garvey, J. Heterocycl. Chem. 29, 847 (1992)

(19) R. Perrone, F. Berardi, M. Leopoldo and V. Tortorella, J. Med. Chem. 35, 3045 (1992)

(20) C.F. Lane, Aldrichimica Acta 10, 41 (1977)

(21) D.D. Davey and W.C. Lumma Jr., J. Org. Chem. 54, 3211 (1989)

Received August 30, 1995