SYNTHESIS OF NEW ARYLETHANOLAMINE AND ARYLOXY-PROPANOLAMINE DERIVATIVES INCLUDING 1,4-BENZODIOXINE MOIETY

Sophie Boyé, Gérald Guillaumet, and Marie-Claude Viaud *

Institut de Chimie Organique et Analytique, associé au CNRS, Université d’Orléans, BP 6759, 45067 Orléans Cedex 2, France
E-mail: Marie-Claude Viaud <mc.viaud@univ-orleans.fr>

Abstract - The synthesis of new arylethanolamines and aryloxypropanolamines variously substituted on the nitrogen atom are described. Access to these compounds, which are potential β3-adrenergic ligands, involves, as key step, a reductive amination reaction between 2-amino alcohols and 1,4-benzodioxine aldehyde derivatives.

In 1967, β-adrenoceptors were classified into two subtypes β1 and β2.1 The recent discovery of a new β3-adrenoceptor subtype in adipocytes of rodents was first reported in 1984.2 There is now ample evidence that activation of β3-adrenergic receptor in adipose tissue stimulates both lipolysis2,3 and thermogenesis4 and offers the possibility of treating obesity and diabetes in man. An important contribution was made by Emorine et al. in 1989 when they reported the isolation of a gene which coded for the human β3-adrenergic receptor.5
Over the past decade, several classes of agonists for this receptor have been synthesized. But a major limitation of many current β3-agonists is low selectivity and efficiency in man such as BRL 37344, and the potential for stimulation of β1- and β2-receptor subtypes and subsequent side effects. Recently, functional properties of human β3-adrenoreceptor, evaluated in transfected Chinese Hamster Ovary (CHO) cells, showed that CL 314,514 was among the most selective and potent β3-adrenergic agonist and that (-)-Tertatolol displayed a very high affinity for this receptor (Figure 1).

The development of new families of β3-adrenergic ligands is a key way to elucidate the structure-activity relationship. In order to elaborate more potent and selective derivatives, we now report the synthesis of a novel class of aryloxypropanolamines and arylethanolamines, which are represented in Figure 2.

For the synthesis of this kind of compounds, we kept on the one hand the aryloxypropanolamine and arylethanolamine moieties respectively present in (-)-Tertatolol and BRL 37344 or CL 314,514. On the other hand, we focused our study on the replacement of the right-hand side aryl ring (BRL 37344) with a 1,4-benzodioxinic derivative, which is substituted by one or two carboxylic acid functions. Actually,
previous studies realised on CL 314,514 showed that the addition of a second carboxylic acid moiety improves selectivity against the β1- and β2-adrenoceptors. The 2,3-dihydro-1,4-benzodioxine ring, which are present in many natural and synthetic products, has generated much interest in medicinal chemistry. Contrary, the 1,4-benzodioxine analogs are less described, therefore they are pharmaceutical commodities of wide medical use. In addition this heterocycle was used as starting derivative for the access to aryloxypropanolamines which possess β-adrenergic blocking activity and antihypertensive properties. The retrosynthetic pathway utilised for the elaboration of the desired compounds (Figure 2) is outlined in Scheme 1. It involved, as key step, a reductive amination reaction between an appropriate aldehyde and an 2-amino alcohol.

Scheme 1

The Scheme 2 illustrates the synthesis of both 2-amino alcohols (4) and (6), obtained respectively from the 8-hydroxy-3,4-dihydro-2H-1-benzothiopyran (1) and the 3-chlorobenzaldehyde (5) commercially available.

Scheme 2
The treatment of compound (1) with epichlorhydrine in \( N,N \)-dimethylformamide in the presence of sodium hydride gave the oxirane (2) in 86% yield.\(^{13}\) This oxirane was converted in good yield by reaction with sodium azide into the azido alcohol (3) in a mixture of dioxane and water under reflux.\(^{14}\) Access to amine (4) was accomplished by catalytic hydrogenation in 83% yield. In parallel, the 2-(3-chlorophenyl)-2-hydroxyethanamine (6) was prepared from the 3-chlorobenzaldehyde (5) by action of trimethylsilyl cyanide in the presence of zinc iodide. The \( \alpha \)-silyloxy nitrile, generated \textit{in situ}, was subsequently reduced by using lithium aluminium hydride to provide the expected \( \beta \)-hydroxylamine (6)\(^{15}\) (Scheme 2).

The access to aldehyde (9) is described in Scheme 3. The synthesis of 1,4-benzodioxine starting material (7) was achieved by Baeyer-Villiger’s reaction from the 6-acetyl-1,4-benzodioxine-2-carboxylic acid ethyl ester which was prepared by a regioselective Friedel-Crafts acylation of 1,4-benzodioxine-2-carboxylic acid ethyl ester under classical conditions.\(^{16}\)

The phenol (7) was submitted to an \( O \)-alkylation with bromoacetaldehyde diethyl acetal via phase-transfer catalysis to give the aryl ether (8) in 74% yield.\(^{17}\) The deprotection of the diethyl acetal (8) was quantitatively achieved in the presence of concentrated hydrochloric acid to provide 9.
The diethyl acetal (8) is also an ideal precursor for the synthesis of aldehyde (12), which was disfunctionalized on the heterocyclic ring as shown in Scheme 4.

Scheme 4

The corresponding acid (10) was obtained after saponification by a solution of sodium hydroxide (10%) with a good yield. The functionalization of 1,4-benzodioxine heterocycle can be mainly achieved through hydrogen-metal interchange with alkyllithium reagents. Thus, the diester (11) was readily prepared by metalation of 1,4-benzodioxine compound (10) with lithium diisopropylamide in tetrahydrofuran at -78°C followed by addition of carbon dioxide. The crude diacid, which was thus generated in situ, was straightforwardly treated with anhydrous ethanol in the presence of triphenylphosphine and diethyl azodicarboxylate according to Mitsunobu methodology to provide the expected diester (11) in an overall yield of 50%. The deprotection of the diethyl acetal (11) was quantitatively accomplished as previously described in the presence of concentrated hydrochloric acid.

The expected arylethanolamine and aryloxypropanolamine derivatives were prepared by a reductive amination reaction of aldehydes (9) or (12) with the required β-hydroxylamines (4) or (6). Performed in
the presence of sodium cyanoborohydride and zinc chloride in methanol, this reaction gave the desired derivatives (13, 14, 15 and 16), respectively in 83, 63, 71 and 70% yields (Scheme 5).

The last step involved the saponification of monoesters (13, 15) and diesters (14, 16) which was accomplished in satisfactory yields, in spite of purification difficulties, by using a solution of sodium hydroxide (10%) followed by a treatment with hydrochloric acid. The desired acids (17, 18, 19 and 20) were obtained by this sequence as hydrochloride salts. It must be noted that the acidic hydrolysis using Dowex resin in refluxing water, which was usually applied to other analogous series, didn't lead to corresponding acids but to the degradation of the starting material.
In conclusion, this paper reported the elaboration of a new class of arylenthalamines and aryloxypropanolamines which were substituted on the nitrogen atom with a 1,4-benzodioxine moiety. In the course of this synthesis, we needed procedures permitting functionalization of the homocycle and the heterocycle of 1,4-benzodioxine derivatives.

Activities of compounds (17, 18, 19 and 20) were determined in vitro by their ability to bind and to stimulate cyclic AMP production in CHO cells that have been transfected with the human β3-adrenoceptor genes. The pharmacological tests proved that these compounds could be potent and relatively selective β3-agonist ligands.

**EXPERIMENTAL SECTION**

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Proton NMR were recorded on a Bruker AM-300 WB spectrometer. The chemical shifts are reported per million (δ, ppm) downfield from tetramethylsilane (TMS) which was used as internal standard and the coupling constants are recorded in Hertz (Hz). Infrared spectra were obtained with a Perkin-Elmer FT Paragon
1000 PC spectrophotometer. Mass spectra were recorded on a R 10-10C Nermag (70 eV) apparatus. Microanalysis were performed on a Perkin-Elmer 240 C instrument. Organic solvents were purified when necessary by the methods described by D.D. Perin, W.L.F. Armarego and D.R. Perin (Purification of Laboratory Chemicals; Pergamon: Oxford, 1986) or purchased from Sigma-Aldrich Chimie. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254) and spots were visualised with UV light or on an alcohol solution of ammonium cerium (IV) nitrate. Column chromatography was performed with Kieselgel 60 (70-230 mesh) silica gel (Merck) for gravity columns and Kieselgel 60 (230-400 mesh) silica gel (Merck) for flash columns. All anhydrous reactions were performed in over-dried glassware under an atmosphere of argon.

For facilities of understanding NMR spectra, we decided to put a prime for the aromatic protons of thiochroman moiety.

8-(2,3-Epoxypropoxy)-3,4-dihydro-2H-1-benzothiopyran (2). To a suspension of sodium hydride (0.32 g, 13.3 mmol) (60% dispersion in oil) in N,N-dimethylformamide (5 mL) was added a solution of thiochromanol (1) (1 g, 6 mmol) in dimethylformamide (10 mL) at room temperature. The reaction mixture was stirred at 60°C over 15 min. Then, epichlorhydrine (3.8 mL, 48.1 mmol) was added to the reaction mixture and the stirring was continued for 1 h at 60°C. After cooling, the solvent was evaporated and the resulting residue was hydrolysed with water, extracted with dichloromethane and dried over magnesium sulfate. After evaporation of organic layer, the resulting product was purified by column flash chromatography (eluent: petroleum ether/dichloromethane, 50/50) to provide epoxide (2) (1.14 g, 86%) as a white solid: mp 38-40°C; IR (KBr): 1230 (C-O-C) cm⁻¹; ¹H NMR (CDCl₃) δ: 2.04-2.13 (m, 2H, S-CH₂-CH₂), 2.79-2.85 (m, 3H, CH₂-Ar, ArO-CH₂-CH-CH(H)), 2.89 (t, J = 4.4 Hz, 1H, ArO-CH₂-CH-CH(H)), 2.97-3.02 (m, 2H, S-CH₂), 3.34-3.40 (m, 1H, ArO-CH₂-CH), 4.08 (dd, J = 5.1, 11.0 Hz, 1H, ArO(CH(H))-CH), 4.22 (dd, J = 3.7, 11.0 Hz, 1H, ArO(CH(H))-CH), 6.67 and 6.69 (2d, J = 7.4 Hz, 2H,
H5, H7), 6.92 (t, J = 7.4 Hz, 1H, H6). Anal. Calcd for C12H14O2S: C, 64.84; H, 6.35. Found: C, 64.78; H, 6.53.

8-[(2-Hydroxy-3-azido)propoxy]-3,4-dihydro-2H-1-benzothiopyran (3). To a solution of oxirane (2) (5.6 g, 25.2 mmol) in a mixture of dioxane (70 mL) and water (20 mL), was added sodium azide (2.29 g, 35.3 mmol) and then, the mixture was stirred under reflux for 6 h. After cooling and evaporation of the solvents under reduced pressure, the residue was hydrolysed with water and extracted with dichloromethane. The organic layers were dried over magnesium sulfate and evaporated to dryness. The crude azido alcohol (3) (5.84 g, 84%) was obtained as a white solid which was used without further purification in the next step: mp 61-63°C; IR (KBr): 1240 (C=O-C), 2100 (N3), 3110-3600 (O-H) cm⁻¹; 1H NMR (CDCl3 + D2O) δ: 2.05-2.14 (m, 2H, S-CH2-CH2), 2.83 (t, J = 5.9 Hz, 2H, CH2-Ar), 2.98-3.03 (m, 2H, S-CH2), 3.54 (d, J = 5.2 Hz, 2H, CH2-N3), 4.01-4.19 (m, 3H, O-CH2-CH), 6.67 and 6.72 (2d, J = 8.1 Hz, 2H, H5, H7), 6.95 (t, J = 8.1 Hz, 1H, H6).

8-[(2-Hydroxy-3-amino)propanoxy]-3,4-dihydro-2H-1-benzothiopyran (4). The azido alcohol (3) (2.5 g, 7.54 mmol) was dissolved in ethanol (40 mL). To this solution was added Lindlar palladium (0.200 g) and the mixture was hydrogenated (50 psi) in a Parr shaker at room temperature during 18 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude amino alcohol was purified by crystallisation from ether to give the pure product (4) (1.5 g, 83%) as a pale grey solid: mp 145-147°C; IR (KBr): 1250 (C=O-C), 3280 and 3340 (N-H), 3000-3400 (O-H) cm⁻¹; 1H NMR (CDCl3 + D2O) δ: 2.05-2.14 (m, 2H, H3), 2.82 (t, J = 6.3 Hz, 2H, H4), 2.86-3.03 (m, 4H, H2,-CH2-NH2), 3.91-4.10 (m, 3H, -O-CH2-CH), 6.68 and 6.71 (2d, J = 7.9 Hz, 2H, H5, H7), 6.94 (t, J = 7.9 Hz, 1H, H6). Anal. Calcd for C12H17O2S: C, 60.22; H, 7.16; N, 5.85; S, 13.40. Found: C, 60.37; H, 7.09; N, 5.91; S, 13.28.

2-(3-Chlorophenyl)-2-hydroxyethanamine (6). To a mixture of 3-chlorobenzaldehyde (5) (1.5 g, 10.7 mmol) and trimethylsilyl cyanide (1.57 mL, 11.7 mmol), zinc iodide (1 g, 1.1 mmol) was added.
After stirring for 20 min at room temperature under argon, anhydrous ether (15 mL) was added following addition by portion of lithium aluminium hydride (0.810 g, 21.4 mmol) at a rate which maintained gentle reflux of the reaction mixture. Stirring was continued under reflux for 2 h. After the decomposition of the excess lithium aluminium hydride and filtration of inorganic material, the crude amino alcohol (6) (1.80 g, quantitative yield) was isolated as an orange oil; IR (film): 3010-3520 (O-H), 3300 and 3350 (N-H) cm⁻¹; ¹H NMR (CDCl₃ + D₂O) δ: 2.77 (dd, J = 7.6, 12.6 Hz, 1H, CH(H)-NH₂), 3.03 (dd, J = 4.0, 12.6 Hz, 1H, CH(H)-NHz), 4.57-4.63 (m, 1H, CH-CH₂), 7.20-7.31 (m, 3H, H₃, H₅, H₆), 7.37 (s, 1H, H₂).

Ethyl 6-(2,2-diethylethoxy)-1,4-benzodioxine-2-carboxylate (8). Under argon, the phenol (7) (0.300 g, 1.4 mmol) was partly dissolved in toluene (6 mL) and refluxed for a complete dissolution. Potassium carbonate (2.61 g, 19 mmol) was added and the reaction mixture was stirred at reflux for 30 min. To this stirred mixture were added successively bromoacetaldehyde diethyl acetal (2.7 mL, 19 mmol) and tetrabutylammonium bromide (0.061 g, 0.19 mmol) and the reflux was continued for 2 days. After cooling, filtration on celite and evaporation of solvent, the residue was hydrolysed with water, extracted with dichloromethane. The organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate, 80/20) to furnish the desired acetal (8) (0.338 g, 74%) as a white solid: mp 50-52°C; IR (KBr): 1200-1290 (C-0-C), 1670 (C=C), 1720 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ: 1.23 (t, J = 7.1 Hz, 6H, O-CH₂-CH₃), 1.32 (t, J = 7.1 Hz, 3H, COOCH₂-CH₃), 3.56-3.80 (m, 4H, O-CH₂-CH₃), 3.90 (d, J = 5.2 Hz, 2H, O-CH₂-CH₂), 4.27 (q, J = 7.1 Hz, 2H, COOCH₂-CH₃), 4.77 (t, J = 5.2 Hz, 1H, -CH), 6.34 (d, J = 2.9 Hz, 1H, H₅), 6.43 (dd, J = 8.8, 2.9 Hz, 1H, H₇), 6.73 (d, J = 8.8 Hz, 1H, H₈), 6.91 (s, 1H, =CH); MS (EI) m/z 338 (M⁺). Anal. Calcd for C₁₇H₂₂O₇: C, 60.35; H, 6.55. Found: C, 60.18; H, 6.69.

Ethyl 6-(2-oxo-ethoxy)-1,4-benzodioxine-2-carboxylate (9). A stirred solution of acetal (8) (0.320 g, 0.95 mmol) in dioxane (2 mL) was treated with concentrated hydrochloric acid (2 mL). After 15 min at room temperature, the reaction mixture was hydrolysed with water and extracted with dichloromethane.
The organic layers were dried over magnesium sulfate. Evaporation of the solvent yielded the crude aldehyde (9) (0.237 g, 95%) as a colorless oil which was immediately used without further purification; IR (film): 1200-1290 (C-O-C), 1670 (C=C), 1720 and 1724 (C=O) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 1.32 (t, \(J = 7.1\) Hz, 3H, CH\(_2\)-CH\(_3\)), 4.28 (q, \(J = 7.1\) Hz, 2H, CH\(_2\)-CH\(_3\)), 4.48 (s, 2H, CH\(_2\)-CHO), 6.32 (d, \(J = 2.9\) Hz, 1H, H\(_5\)), 6.40 (dd, \(J = 8.8, 2.9\) Hz, 1H, H\(_7\)), 6.77 (d, \(J = 8.8\) Hz, 1H, H\(_8\)), 6.91 (s, 1H, =CH), 9.82 (s, 1H, CHO).

6-(2,2-Diethoxyethoxy)-1,4-benzodioxine-2-carboxylic acid (10). A solution of ester (8) (0.82 g, 2.42 mmol) in ethanol (30 mL) was basified with a 10% sodium hydroxide solution (9.7 mL, 24.2 mmol). After 2 h at room temperature, ethanol was removed \textit{in vacuo}. The residue was acidified with a solution of hydrochloric acid (2N) and the resulting precipitate was collected and dried to provide the desired acid (10) (0.675 g, 90%) as a white solid: mp 130-132°C; IR (KBr): 1200-1290 (C-O-C), 1671 (C=C), 1715 (C=O), 2500-3500 (O-H) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\) + D\(_2\)O) \(\delta\): 1.24 (t, \(J = 7.0\) Hz, 6H, O-CH\(_2\)-CH\(_3\)), 3.55-3.92 (m, 4H, O-CH\(_2\)-CH\(_3\)), 3.90 (d, \(J = 5.2\) Hz, 2H, O-CH\(_2\)-CH), 4.78 (t, \(J = 5.2\) Hz, 1H, -CH), 6.36 (d, \(J = 2.8\) Hz, 1H, H\(_5\)), 6.45 (dd, \(J = 8.8, 2.8\) Hz, 1H, H\(_7\)), 6.74 (d, \(J = 8.8\) Hz, 1H, H\(_8\)), 7.03 (s, 1H, =CH).

\textit{Anal.} Calcd for C\(_{15}\)H\(_{18}\)O\(_7\): C, 58.06; H, 5.85. Found: C, 58.11; H, 5.98.

Diethyl 6-(2,2-Diethoxyethoxy)-1,4-benzodioxine-2,3-dicarboxylate (11). Under an argon atmosphere at -78°C, 2M lithium diisopropylamide in tetrahydrofuran (3.22 mL, 6.45 mmol) was added dropwise to a stirred solution of the acid (10) (0.500 g, 1.61 mmol) in dry tetrahydrofuran (20 mL). After 4 h at -78°C, carbon dioxide bubbled into the reaction mixture for 30 min. Then, the cooling bath was removed and the temperature was allowed to warm to room temperature. After hydrolysis with a solution of hydrochloric acid (2N), the crude product was extracted with ethyl acetate. The organic layers were dried over magnesium sulfate and evaporated to dryness. The residue was taken up with tetrahydrofuran (20 mL) and to this solution, thus obtained, were added triphenylphosphine (1.26 g, 4.83 mmol) and anhydrous ethanol (0.3 mL, 4.83 mmol). The stirring was continued at room temperature for 10 min and then, diethyl
azodicarboxylate (0.76 mL, 4.83 mmol) was added slowly under an argon atmosphere at 0°C. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue hydrolysed with water. After extraction with ethyl acetate, the organic layers were dried over magnesium sulfate and evaporated in vacuo. The crude product was purified by column chromatography (eluent: petroleum ether/ethyl acetate, 90/10) to afford the compound (11) (0.330 g, 50%) as a colorless oil; IR (film): 1200-1290 (C-O-C), 1668 (C=C), 1739 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ: 1.24 (t, J = 7.0 Hz, 6H, O-CH₂-CH₃), 1.33 and 1.34 (2t, J = 7.2 Hz, 6H, COOCH₂-CH₃), 3.54-3.82 (m, 4H, O-CH₂-CH₃), 3.90 (d, J = 5.3 Hz, 2H, O-CH₂-CH), 4.30 and 4.31 (2q, J = 7.2 Hz, 4H, COOCH₂-CH₃), 4.77 (t, J = 5.3 Hz, 1H, -CH), 6.39-6.48 (m, 2H, H₅, H₇), 6.71 (d, J = 9.2 Hz, 1H, H₈); MS (Cl) m/z 411 (M⁺+1). Anal. Calcd for C₂₀H₂₄O₈: C, 58.53; H, 6.39. Found: C, 58.45; H, 6.33.

Diethyl 6-(2-oxo-ethoxy)-1,4-benzodioxine-2,3-dicarboxylate (12). The aldehyde (12) was prepared from the acetal (11) according to the method used for the product (9). The expected compound (12) was obtained with a quantitative yield as a colorless oil which was used without further purification in the next step; IR (film): 1200-1290 (C-O-C), 1668 (C=C), 1740 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ: 1.32 and 1.33 (2t, J = 7.1 Hz, 6H, CH₂-CHO), 4.29 and 4.30 (2q, J = 7.1 Hz, 4H, CH₂-CHO), 4.50 (d, J = 1.0 Hz, 2H, CH₂-CHO), 6.39-6.77 (m, 3H, H₅, H₇, H₈), 9.81 (t, J = 1.0 Hz, 1H, -CHO); MS (Cl) m/z 337 (M⁺+1).

Ethyl 6-[2-[2-hydroxy-3-(3,4-dihydro-2H-1-benzothiopyran-8-yloxy)propyl]ethoxy]-1,4-benzodioxine-2-carboxylate (13). To a stirred solution of aldehyde (9) (0.100 g, 0.378 mmol) and amine (4) (0.362 g, 1.51 mmol) in methanol (5 mL) at room temperature and under argon, was added a solution of sodium cyanobrohydride (0.026 g, 0.414 mmol) and zinc chloride (0.066 g, 0.207 mmol) in methanol (1 mL). The resulting solution was stirred at room temperature for 1 h. After methanol was evaporated under reduced pressure, the residue was hydrolysed with water and extracted with dichloromethane. The combined extracts were washed with water, dried over magnesium sulfate and evaporated to dryness. A column flash chromatography (eluent: dichloromethane/methanol, 100/0 to 95/5) gave the expected
product (13) (0.153 g, 83%) as a white solid: mp 73-75°C; IR (KBr): 1190-1280 (C-O-C), 1650 (C=C), 1720 (C=O), 2900-3400 (O-H and N-H) cm⁻¹; ¹H NMR (CDCl₃ + D₂O) δ: 1.26 (t, J = 7.3 Hz, 3H, OCH₂-CH₃), 1.98-2.06 (m, 2H, S-CH₂-CH₂), 2.76 (t, J = 5.9 Hz, 2H, CH₂-Ar), 2.80-2.93 (m, 4H, S-CH₂, C(OH)H-CH₂-NH), 2.95 (t, J = 5.1 Hz, 2H, NH-CH₂-CH₂-O), 3.92 (t, J = 5.1 Hz, 2H, NH-CH₂-CH₂-O), 3.96-4.02 (m, 3H, O-CH₂-C(OH)H), 4.22 (q, J = 7.3 Hz, 2H, OCH₂-CH₃), 6.26 (d, J = 2.9 Hz, 1H, H₅), 6.36 (dd, J = 8.8, 2.9 Hz, 1H, H₇), 6.61 and 6.64 (2d, J = 7.4 Hz, 2H, H₅, H₇), 6.67 (d, J = 8.8 Hz, 1H, H₈), 6.85 (s, 1H, =CHI, 6.90 (t, J = 7.4 Hz, 1H, H₆); MS (Cl/NH₃) m/z 488 (M⁺+1). Anal. Calcd for C₂₉H₂₉NO₇S: C, 61.59; H, 6.00; N, 2.87; S, 6.58. Found: C, 61.71; H, 6.08; N, 2.78; S, 6.66.

Diethyl 6-[2-[2-hydroxy-3-(3,4-dihydro-2H-1-benzothiopyran-8-olox)propylamino]ethoxy]-1,4-benzodioxine-2,3-dicarboxylate (14). Compound (14) was prepared similarly to 13 using appropriate aldehyde (12) and amine (4) and was obtained with a yield of 63% as a colorless oil; IR (film): 1200-1290 (C-O-C), 1667 (C=C), 1732 and 1737 (C=O), 3100-3710 (O-H and N-H) cm⁻¹; ¹H NMR (CDCl₃ + D₂O) δ: 1.34 and 1.35 (2t, J = 7.1 Hz, 6H, OCH₂-CH₃), 2.02-2.14 (m, 2H, S-CH₂-CH₂), 2.82 (t, J = 6.0 Hz, 2H, CH₂-Ar), 2.91-3.04 (m, 6H, S-CH₂, CH₂-NH-CH₂), 3.98 (t, J = 5.1 Hz, 2H, NH-CH₂-CH₂-O), 4.00-4.15 (m, 3H, O-CH₂-C(OH)H), 4.29 and 4.30 (2q, J = 7.1 Hz, 4H, OCH₂-CH₃), 6.38-6.75 (m, 5H, H₅, H₇, H₈, H₅, and H₇), 6.94 (t, J = 7.8 Hz, 1H, H₆); MS (Cl/NH₃) m/z 560 (M⁺+1). Anal. Calcd for C₂₈H₃₃N₂O₉S: C, 60.09; H, 5.94; N, 2.50; S, 5.73. Found: C, 59.97; H, 5.88; N, 2.63; S, 5.84.

Ethyl 6-[2-[2-hydroxy-2-(3-chlorophenyl)ethylamino]ethoxy]-1,4-benzodioxine-2-carboxylate (15). Compound (15) was prepared similarly to 13 using appropriate aldehyde (9) and amine (6) and was obtained with a yield of 71% as a white solid: mp 110-112°C; IR (KBr): 1200-1290 (C-O-C), 1670 (C=C), 1725 (C=O), 3000-3500 (O-H), 3300 (N-H) cm⁻¹; ¹H NMR (CDCl₃ + D₂O) δ: 1.32 (t, J = 7.1 Hz, 3H, OCH₂-CH₃), 2.72 (dd, J = 9.0, 12.2 Hz, 1H, C(OH)H-CH(H)-NH), 2.94-3.03 (m, 3H, CH(H)-NH-CH₂), 3.96 (t, J = 5.1 Hz, 2H, NH-CH₂-CH₂-O), 4.28 (q, J = 7.1 Hz, 2H, OCH₂-CH₃), 4.68
(dd, J = 3.6, 9.0 Hz, 1H, C(OH)H), 6.30 (d, J = 2.9 Hz, 1H, H₅), 6.41 (dd, J = 8.8, 2.9 Hz, 1H, H₇), 6.75 (d, J = 8.8 Hz, 1H, H₈), 6.91 (s, 1H, =CH), 7.21-7.38 (m, 4H, H₆, H₈), 8.44; N, 3.34. Found: C, 59.98; H, 5.28; Cl, 8.73; N, 3.28.

Diethyl 6-[2-[2-hydroxy-2-(3-chlorophenyl)ethylamino]ethoxy]-1,4-benzodioxine-2,3-dicarboxylate (16). Compound (16) was prepared similarly to 13 using appropriate aldehyde (12) and amine (6) and was obtained with a yield of 70% as a colorless oil; IR (film): 1200-1290 (C-O-C), 1668 (C=C), 1733 and 1738 (C=O), 3130-3680 (O-H), 3318 (N-H) cm⁻¹; ¹H NMR (CDCl₃ + D₂O) δ: 1.34 and 1.35 (2t, J = 7.1 Hz, 6H, OCH₂-CH₃), 2.72 (dd, J = 9.1, 12.2 Hz, 1H, C(OH)H-CH(H)-NH), 2.90-3.08 (m, 3H, CH(H)-NH-CH₂), 3.97 (t, J = 5.1 Hz, 2H, NH-CH₂-CH₂-O), 4.30 and 4.31 (2q, J = 7.1 Hz, 4H, OCH₂-CH₃), 4.69 (dd, J = 3.5, 9.1 Hz, 1H, C(OH)H), 6.37-6.46 (m, 2H, H₅, H₇), 6.72 (d, J = 8.8 Hz, 1H, H₈), 7.12-7.41 (m, 4H, H₆, H₈); MS (Cl/NH₃) m/z 493 (M⁺+1). Anal. Calcd for C₂₄H₂₆N₂O₈Cl: C, 58.60; H, 5.33; Cl, 7.15; N, 2.92. Found: C, 58.81; H, 5.29; Cl, 7.15; N, 2.92.

6-[2-[2-Hydroxy-3-(3,4-dihydro-2H-1-benzo(thiopyran-8-yl)propylamino)ethoxy]-1,4-benzodioxine-2-carboxylic acid hydrochloride (17). A suspension of ester (13) (0.092 g, 0.19 mmol) in ethanol (5 mL) was treated with a 10% sodium hydroxide solution (0.75 mL, 1.9 mmol). After 2 h at room temperature, ethanol was removed in vacuo. The residue was hydrolysed with a solution of hydrochloric acid (3N) and the resulting solution was stirred at 0°C for 12 h. The solid obtained was filtered off and then washed with water and acetone to give the desired acid (17) (0.090 g, 93%) as a white solid: mp 112-114°C (decomp); IR (KBr): 1180-1260 (C-O-C), 1640 (C=O), 1690 (C=O), 2500-3700 (O-H and N-H) cm⁻¹; ¹H NMR (DMSO-d₆ + D₂O) δ: 1.80-1.92 (m, 2H, S-CH₂-CH₂), 2.66 (t, J = 6.0 Hz, 2H, CH₂-Ar), 2.82 (t, J = 6.0 Hz, 2H, S-CH₂), 3.05 (dd, J = 9.5, 12.9 Hz, 1H, C(OH)H-CH(H)-N), 3.21 (dd, J = 2.6, 12.9 Hz, 1H, C(OH)H-CH(H)-N), 3.29 (t, J = 5.1 Hz, 2H,
HETEROCYCLES, Vol. 45, No. 3, 1997 551

N-CH₂-CH₂-O), 3.85 (dd, J = 6.0, 9.5 Hz, 1H, O-CH(H)-C(OH)H), 3.96 (dd, J = 4.3, 9.5 Hz, 1H, O-CH(H)-C(OH)), 4.06-4.20 (m, 3H, C(OH)H, N-CH₂-CH₂-O), 6.48 (dd, J = 8.6, 2.6 Hz, 1H, H₇), 6.52 (d, J = 2.6 Hz, 1H, H₅), 6.62 and 6.69 (2d, J = 7.7 Hz, 2H, H₅, H₇), 6.74 (d, J = 8.6 Hz, 1H, H₈), 6.86 (t, J = 7.7 Hz, 1H, H₆), 7.10 (s, 1H, =CH); MS (Cl/NH₃) m/z 460 (M⁺+1). Anal. Calcd for C₂₃H₂₃NO₇S.HCl: C, 55.70; H, 5.28; N, 2.82; S, 6.46; Cl, 7.15. Found: C, 55.63; H, 5.32; N, 2.89; S, 6.18; Cl, 7.02.

6-[2-[2-Hydroxy-3-(3,4-dihydro-2H-1-benzothiopyran-8-yloxy)propylamino]ethoxy]-1,4-benzodioxine-2,3-dicarboxylic acid hydrochloride (18). The compound (18) was prepared from the ester (14) according to the method used for the product (17). The expected hydrochloride (18) was obtained with a yield of 83% as a yellow solid: mp 118-120°C (decomp); IR (KBr): 1160-1260 (C-0-C), 1509 (C=O), 1589 (C=C), 2060-3800 (O-H and N-H) cm⁻¹; ¹H NMR (DMSO-d₆ + D₂O) δ: 1.90-2.05 (m, 2H, S-CH₂-CH₂), 2.76 (t, J = 6.1 Hz, 2H, CH₂-Ar), 2.94 (t, J = 6.1 Hz, 2H, S-CH₂), 3.10 (dd, J = 9.5, 12.8 Hz, 1H, C(OH)-CH(H)-N), 3.24 (dd, J = 3.0, 12.8 Hz, 1H, C(OH)-CH(H)-N), 3.29-3.38 (m, 2H, N-CH₂-CH₂-O), 3.94 (dd, J = 6.1, 9.8 Hz, 1H, O-CH(H)-C(OH)), 4.05 (dd, J = 4.4, 9.8 Hz, 1H, O-CH(H)-C(OH)), 4.07-4.22 (m, 3H, C(OH)H, N-CH₂-CH₂-O), 6.57 (dd, J = 8.5, 2.7 Hz, 1H, H₇), 6.62 (d, J = 2.7 Hz, 1H, H₅), 6.72 and 6.79 (2d, J = 7.7 Hz, 2H, H₅, H₇), 6.87 (d, J = 8.5 Hz, 1H, H₈), 6.95 (t, J = 7.7 Hz 1H, H₆); MS (Cl/NH₃) m/z 460 (M⁺+1-CO₂). Anal. Calcd for C₂₃H₂₃NO₇S.HCl: C, 53.38; H, 4.85; Cl, 6.57; N, 2.59; S, 5.94. Found: C, 53.51; H, 4.93; Cl, 6.37; N, 2.42; S, 6.03.

6-[2-[2-Hydroxy-2-(3-chlorophenyl)ethylamino]ethoxy]-1,4-benzodioxine-2-carboxylic acid hydrochloride (19). The compound (19) was prepared from the ester (15) according to the method used for the product (17). The expected hydrochloride (19) was obtained with a yield of 74% as a white solid: mp 118-120°C (decomp); IR (KBr): 1160-1260 (C-0-C), 1509 (C=O), 1589 (C=C), 2060-3800 (O-H and N-H) cm⁻¹; ¹H NMR (DMSO-d₆ + D₂O) δ: 3.04 (dd, J = 10.2, 12.5 Hz, 1H, C(OH)H-CH(H)-N),
(dd, J = 2.7, 12.5 Hz, 1H, C(OH)H-CH(H)-N), 3.33 (t, J = 5.2 Hz, 2H, N-CH$_2$-CH$_2$-O), 4.14 (t, J = 5.2 Hz, 2H, N-CH$_2$-CH$_2$-O), 4.91 (dd, J = 2.7, 10.2 Hz, 1H, C(OH)H), 6.48 (d, J = 2.8 Hz, 1H, H$_5$), 6.54 (dd, J = 8.8, 2.8 Hz, 1H, H$_7$), 6.77 (d, J = 8.8 Hz, 1H, H$_8$), 7.04 (s, 1H, =CH), 7.28-7.42 (m, 4H, H$_{arom}$); MS (Cl/NH$_3$) m/z 392 (M$^+$+1). Anal. Calcd for C$_{19}$H$_{18}$NO$_6$Cl.HCl: C, 53.29; H, 4.47; Cl, 16.56; N, 3.27. Found: C, 53.35; H, 4.28; Cl, 16.61; N, 3.11.

6-[2-[2-Hydroxy-2-(3-chlorophenyl)ethylamino]ethoxy]-1,4-benzodioxine-2,3-dicarboxylic acid hydrochloride (20). The compound (20) was prepared from the ester (16) according to the method used for the product (17). The expected hydrochloride (20) was obtained with a yield of 78% as a yellow solid: mp 94-96°C (decomp); IR (KBr): 1160-1210 (C-O-C), 1509 (C=O), 1591 (C=C), 2060-3700 (O-H and N-H) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$ + D$_2$O) $\delta$: 3.05 (dd, J = 10.7, 12.7 Hz, 1H, C(OH)H-CH(H)-N), 3.26 (dd, J = 2.7, 12.7 Hz, 1H, C(OH)H-CH(H)-N), 3.39 (t, J = 4.8 Hz, 2H, N-CH$_2$-CH$_2$-O), 4.23 (t, J = 4.8 Hz, 2H, N-CH$_2$-CH$_2$-O), 5.00 (dd, J = 2.7, 10.7 Hz, 1H, C(OH)H), 6.55 (dd, J = 8.8, 2.7 Hz, 1H, H$_7$), 6.60 (d, J = 2.7 Hz, 1H, H$_8$), 6.85 (d, J = 8.8 Hz, 1H, H$_8$), 7.25-7.55 (m, 4H, H$_{arom}$); MS (Cl/NH$_3$) m/z 392 (M$^+$+1-CO$_2$). Anal. Calcd for C$_{20}$H$_{18}$NO$_6$Cl.HCl: C, 50.86; H, 4.06; Cl, 15.01; N, 2.97. Found: C, 50.68; H, 4.19; Cl, 15.17; N, 3.08.

ACKNOWLEDGMENTS

We are grateful to A.D.I.R. Company (Courbevoie, France) for its multiform support. We thank also ORIL (Bolbec, France) for the synthesis of compound (1) and Mr A. Petit (Technologie SERVIER, Orléans, France) for some NMR assignments.

REFERENCES


Received, 5th December, 1996