SYNTHESIS OF FURO[3,2-*b*]PYRIDINE ANALOGUE OF EFAROXAN

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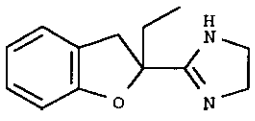
Abstract - 2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-ethyl-2,3-dihydrofuro[3,2-*b*]pyridine was synthesized in eight steps starting from 3-hydroxy-2-methylpyridine. The key step was a cyclization of a 2-chloromethyl-3-butyroxypyridine derivative. The target molecule is an aza analogue of efaroxan, a potent and selective antagonist of α_2-adrenoceptors.

α_2-Adrenoceptor antagonists have been studied for nearly two decades for their therapeutic applications in depression, owing to their noradrenergic enhancing activity in the central nervous system [1] The emergence of new theory for α_2-adrenoceptors antagonists in the treatement of neurodegenerative diseases [2] turned our attention to efaroxan **1** [3] and some related analogues. Dexefaroxan, the active enantiomer of efaroxan, is an imidazoline derivative possessing a high affinity and potent selectivity toward α_2-adrenoceptors In a preliminary discussion, Chapleo *et al.* [3] highlighted that the substitution of the aromatic ring and the position 2 of the 2,3-dihydrobenzofuran modulated the antagonistic activity at α_2-adrenoceptors. As a part of our study of efaroxan analogues we described here the synthesis and biological evaluation of the 4-aza **2** analogue of efaroxan.



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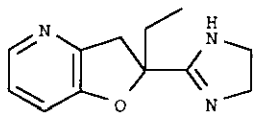

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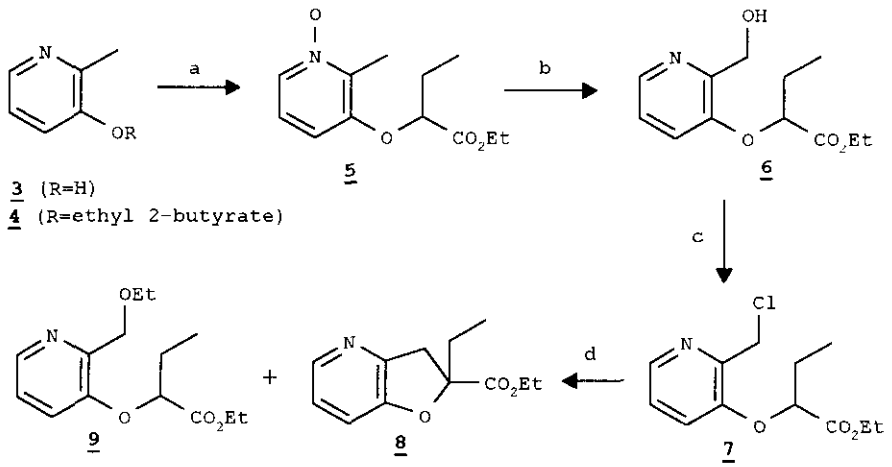
2,3-Dihydrofuro[3,2-*b*]pyridine derivatives have previously been obtained by thermal cyclization of 3-allyloxypyridine [4] or by a five membered ring cyclization between a sulfur ylide and a

benzyltrialkylammonium salt.[5] Our strategy was based on a cyclization of a chloromethylpyridyloxybutyric derivative 7 as the key step (Scheme 1).

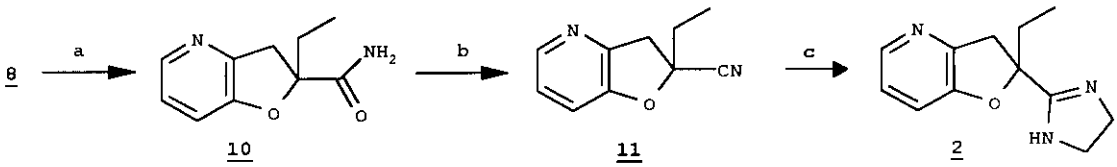
3-Hydroxy-2-methylpyridine 3 was used as the starting material. Reaction with ethyl 2-bromobutyrate in acetonitrile in the presence of K_2CO_3 furnished the butyric derivative 4 in 83% yield. The introduction of an hydroxy function on the methyl group in position 2 of the pyridine ring was achieved *via* a modified Boekelheide reaction[6] The first step was the oxidation of the pyridine by *meta*-chloroperbenzoic acid at room temperature. The *N*-oxide 5, obtained in 93% yield, was treated with trifluoroacetic anhydride at room temperature in THF. The rearranged product, obtained as its trifluoroacetic salt, was directly hydrolyzed by an aqueous $NaHCO_3$ solution, to obtain 80% yield of the hydroxymethyl derivative 6 This latter compound 6 was converted into the chloromethyl derivative 7 with thionyl chloride in methylene chloride.



a) i Ethyl 2-bromobutyrate/K_2CO_3/MeCN 83%, ii MCPBA/CH_2Cl_2 93%;
b) i $(CF_3CO)_2O$/THF/rt quant., ii $NaHCO_3$/THF/H_2O 80%; c) $SOCl_2/CH_2Cl_2$ quant.
d) i *tert*-BuOK/dioxane/rt, ii EtOH/$SOCl_2$ 30%

Scheme 1

The cyclization step of 7 was achieved with potassium *tert*-butoxide in dioxane at room temperature. Because of its high sensitivity toward basic media, the acid derivative of 8 obtained as the main product which was directly reesterified to 8 with thionyl chloride in ethanol Careful purification by chromatograhy furnished the pure cyclized compound 8 in 30% unoptimized yield. In this cyclization step the major by-product was determined as the open chain derivative 9 based on its ^{1}H-NMR spectrum showing two different ethoxy groups.



a) NH_4OH/MeOH 27%; b) P_2O_5/toluene 74%; c) i MeONa/EtOH, ii ethylenediamine/HCl 86%

Scheme 2

Conversion of the ester function to an imidazoline system was achieved according to a standard procedure[3] (Scheme 2). Treatment of the ester **8** with aqueous ammonia in methanol furnished the amide **10** in poor unoptimized yield (27%). Dehydration of the intermediate amide derivative by P_2O_5 in refluxing toluene gave the cyano derivative **11** in 74% yield The imidazoline **2** was finally obtained through the formation of the imidate in basic medium, followed by reaction with ethylenediamine in presence of hydrochloric acid in 86% yield.

In the receptor binding experiments [7] **2** showed a 20 fold decrease in affinity towards α_2-adrenoceptors, compared with efaroxan

EXPERIMENTAL

General notes :

All solvents and reagents used were commercially available in 'pure for synthesis' grade, and used without further purification unless otherwise indicated. The reaction progress was monitored by TLC on silica gel plates 60F-254 (Merck art. 1.05554). Flash chromatography was run on silica gel 60-chromagel, 35-70µ. Melting points were taken on a Electrothermal IA9300 melting point apparatus and are uncorrected. NMR spectra were measured on a BRUCKER DPX400 (^{1}H, 400 MHz) spectrometer in DMSO-d_6 with tetramethylsilane as internal standard. Elemental analyses were performed on a microanalyser Fisons 1108

Ethyl 2-[2'-methylpyridin-3'-yloxy]butyrate : 4

A mixture of 3-hydroxy-2-methylpyridine **3** (2 g, 18.3 mmol), ethyl 2-bromobutyrate (2.98 mL, 3.93 g; 20.2 mmol) and potassium carbonate (5 1 g, 36.6 mmol) in 100 mL of acetonitrile was heated at 70°C for 16 h After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed successively with a 1N NaOH solution and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give 3 4 g of **4** as an crude oil (83 %) ^{1}H NMR · 8.01 (dd,1H, J=3 4 and 2.6 Hz, $H_{6'}$), 7.16 (m,

2H, $H_{4'}$ and $H_{5'}$), 4.90 (dd, J=6 3 and 5.4 Hz, H_2), 4.13 (m, 2H $CH_3C\underline{H_2}O$), 2.40 (s, 3H, CH_3), 1.94 (m, 2H, $2H_3$), 1.16 (t, 3H, J=7.0 Hz, $C\underline{H_3}CH_2O$), 1.01 (t, 3H, J=7.4 Hz, $3H_4$).

Ethyl 2-[2'-methyl-1'-oxypyridin-3'-yloxy]butyrate : 5

Technical 60% MCPBA (4.5g, 15.6 mmol) was added in small portions to a stirred solution of **4** (2 9 g, 13 mmol) in 100 mL of CH_2Cl_2. The mixture was kept at rt for 16 h, and then washed with an saturated aqueous $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give the crude compound **5** in 93% yield (2.89 g) as an oil. ^{1}H NMR · 7.95 (d, 1H, J=6 5 Hz, $H_{6'}$), 7.17 (dd, 1H, J=8.6 and 6.5 Hz, $H_{5'}$), 6.90 (d, 1H, J=8.6 Hz, $H_{4'}$), 4.97 (t, 1H, J=6.0 Hz, H_2), 4.12 (m, 2H, $CH_3C\underline{H_2}O$), 2 30 (s, 3H, CH_3), 1 92 (m, 2H, $2H_3$), 1 14 (t, 3H, J=7.2 Hz, $C\underline{H_3}CH_2O$), 0.97 (t, 3H, J=7.4 Hz, $3H_4$).

Ethyl 2-[2'-hydroxymethylpyridin-3'-yloxy]butyrate : 6

Trifluoroacetic anhydride (1.7 mL, 11.9 mmol) was added to a solution of **5** (570 mg, 2 38 mmol) in 15 mL of THF. The mixture was stirred at rt for 5 h and evaporated to dryness. Quantitative yield of the trifluoroacetic salt of the trifluoroacetylated alcohol (1 1 g) was obtained as a pale yellow amorphous powder. This crude compound was sufficiently pure for the next step ^{1}H NMR . 8.33 (d, 1H, J=5.5 Hz, $H_{6'}$), 8 03 (d, 1H, J=8.4 Hz, $H_{4'}$), 7 82 (dd, 1H, J=8.4 and 5.5 Hz, $H_{5'}$), 5.27 (t, 1H, J=5 9 Hz, H_2), 4 87 (s, 2H, $C\underline{H_2}OCOCF_3$), 4 12 (m, 2H, $CH_3C\underline{H_2}O$), 1 98 (m, 2H, $2H_3$), 1.16 (t, 3H, J=7.2 Hz, $C\underline{H_3}CH_2O$), 0.99 (t, 3H, J=7.3 Hz, $3H_4$).

The crude salt (1.1 g) was dissolved in 20 mL of an aqueous saturated $NaHCO_3$ solution The mixture was stirred at rt for 3 h, and then extracted with ether The organic layer was washed by brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound **6** was isolated with a 80% yield (455 mg of a light yellow oil). ^{1}H NMR . 8.11 (br s, 1H, $H_{6'}$), 7.23 (m, 2H, $H_{4'}$ and $H_{5'}$), 4.90 (t, 1H, J=6.3 Hz, H_2), 4.63 (dd, 1H, J=13 8 and 3.1 Hz, HA of $C\underline{H_2}OH$), 4.52 (dd, 1H, J=13.8 and 7.1 Hz, HB of $C\underline{H_2}OH$), 4 11 (m, 2H, $CH_3C\underline{H_2}O$), 1.91 (m, 2H, $2H_3$), 1.14 (t, 3H, J=7 2 Hz, $C\underline{H_3}CH_2O$), 0.98 (t, 3H, J=7 4 Hz, $3H_4$).

Ethyl 2-[2'-chloromethylpyridin-3'-yloxy]butyrate, hydrochloride : 7

Thionyl chloride (0.151 mL, 246 mg, 2 07 mmol) was added to a solution of **6** (450 mg, 1 88 mmol) in 10 mL of CH_2Cl_2. The solution was heated under reflux for 3 h and then evaporated to dryness to give the crude salt **7** in quantitative yield as an amorphous powder. ^{1}H NMR 8 22 (dd, 1H, J=4 6 and 1.6 Hz, $H_{6'}$), 7.53 (m, 2H, $H_{4'}$ and $H_{5'}$), 5.11 (dd, 1H, J=6 3 and 5.1 Hz, H_2), 4.92 (d, 1H, J=11 0 Hz, HA from CH_2Cl), 4.78 (d, 1H, J=11 0 Hz, HB from CH_2Cl), 4.12 (m, 2H, $CH_3C\underline{H_2}O$), 1.97 (m, 2H, $2H_3$), 1 15 (t, 3H, J=7.2 Hz, $C\underline{H_3}CH_2O$), 1 02 (t, 3H, J=7.4 Hz, $3H_4$).

Ethyl 2-ethyl-2,3-dihydrofuro[3,2-*b*]pyridine-2-carboxylate : 8

Potassium *tert*-butoxide (8 8 g, 78 mmol) was added to a solution of 7 (11.5 g, 39 mmol) in 250 mL of freshly distilled dioxane. After a slight exothermic reaction, the mixture was stirred at rt for 1 h. The solution was diluted by CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was dissolved in 100 mL of ethanol and treated with thionyl chloride (6 mL, 82 mmol). The mixture was heated at 60°C for 16 h and evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. After flash chromatography (CH_2Cl_2/acetone 98/2) of the residual oil, 2.6 g (30%) of cyclized compound **8** and 2.3 g (22%) of uncyclized compound **9** were obtained as oils. ^{1}H NMR · 8.01 (dd, 1H, J=4.9 and 1.4 Hz, H_5), 7.25 (dd, 1H, J=8.1 and 1.4 Hz, H_7), 7.12 (dd, 1H, J=8.1 and 4.9 Hz, H_6), 4.18 (q, 2H, J=7.0 Hz, $CH_3C\underline{H_2}O$), 3.52 (d, 1H, J=17.0 Hz, H_{3A}), 3 32 (d, 1H, J=17.0 Hz, H_{3B}), 2.01 (m, 2H, $CH_3C\underline{H_2}C$), 1.19 (t, 3H, J=7.0 Hz, $C\underline{H_3}CH_2O$), 0 90 (t, 3H, J=7 3 Hz, $C\underline{H_3}CH_2C$).

Ethyl 2-(2'-ethoxymethylpyridin-3'-yloxy)butyrate : 9

Pale yellow oil ^{1}H NMR · 8.11 (*m*, 1H, $H_{6'}$), 7.26 (*m*, 2H, $H_{4'}$ and $H_{5'}$), 4.92 (t, J=6.1 Hz, 1H, H_2), 4,65 (d, J=11 Hz, 1H, HA from $C\underline{H_2}OEt$), 4.46 (d, J=11 Hz, 1H, HB from $C\underline{H_2}OEt$), 4 12 (m, 2H, $CH_3C\underline{H_2}OCO$), 3 52 (m, 2H, $CH_3C\underline{H_2}O$), 1.94 (m, 2H, $2H_3$), 1 13 (m, 6H, $C\underline{H_3}CH_2OCO$ and $C\underline{H_3}CH_2O$), 1.00 (t, J=7 3 Hz, 3H, $3H_{4'}$).

2-Ethyl-2,3-dihydrofuro[3,2-*b*]pyridine-2-carboxamide : 10

A solution of **8** (1 g, 4 5 mmol) in 10 mL of a 36% ammonia water and 20 mL of methanol was stirred at rt for 16 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2, and washed with brine The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was purified by flash chromatography (CH_2Cl_2/MeOH 96/4) to give 230 mg (yield 27%) of pure **10** as a light yellow solid. ^{1}H NMR · 8 01 (dd, 1H, J=4 5 and 1 6 Hz, H_5),7 58 (broad s, 1H, NH), 7 44 (br s, 1H, NH), 7 15 (*m*, 2H, H_6 *and* H_7), 3.43 (d, 1H, J=17.0 Hz, H_{3A}), 3.19 (d, 1H, J=17 0 Hz, H_{3B}), 1 92 (m, 2H, $CH_3C\underline{H_2}C$), 0 90 (t, 3H, J=7.3 Hz, $C\underline{H_3}CH_2C$).

2-Ethyl-2,3-dihydrofuro[3,2-*b*]pyridine-2-carbonitrile : 11

A mixture of **10** (230 mg, 1.2 mmol), P_2O_5 (680 mg, 4 8 mmol) and 15 mL of toluene was refluxed for 3 h. The reaction mixture was cautiously treated with 10 mL of water and then extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give 155 mg (74%) of **11** as a crude oil. ^{1}H NMR : 8.16 (dd, 1H, J= 4 9 and 1.3 Hz, H_5), 7.38 (dd, 1H, J=8.3 and 1.3 Hz, H_7), 7 24 (dd, 1H, J= 8 3 and 4.9 Hz, H_6), 3.78 (d, 1H, J=17.0 Hz, H_{3A}), 3.58 (d, 1H, J=17.0 Hz, H_{3B}), 2 20 (q, 2H, J=7.3 Hz, $CH_3C\underline{H_2}C$), 1.13 (t, 3H, J=7.3 Hz, $C\underline{H_3}CH_2C$).

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-ethyl-2,3-dihydrofuro[3,2-*b*]pyridine : 2

A catalytic amount of sodium methoxide was added to a stirred solution of **11** (155 mg, 0 89 mmol) in 10 mL of ethanol. The reaction was kept at rt for 16 h. Then a 3.8 N HCl solution in isopropanol (0.703 mL, 2.7 mmol) and ethylenediamine (0.065 mL, 58,8 mg, 0.98 mmol) were added to the reaction mixture. The mixture was stirred at rt for another 48 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, and successively washed with an 1 N NaOH solution and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give 165 mg (86%) of **2** as an oil The dihydrochloride precipitated by addition of two equivalents of HCl in isopropanol to a solution of **2** in acetone (mp · 230°C.). ^{1}H NMR (free base): 7.96 (dd, 1H, J=3.8 and 2 4 Hz, H_5), 7.07 (m, 2H, H_6 and H_7), 6.52 (br s, 1H, NH), 3 72 (d, 1H, J=16.7 Hz, H_{3A}), 3 53 (m, 4H, imidazoline), 3.18 (d, 1H, J=16.7 Hz, H_{3B}), 1.95 (q, 2H, J=7.5 Hz, $CH_3C\underline{H_2}C$), 0 84 (t, 3H, J=7.5 Hz, $C\underline{H_3}CH_2C$). ^{1}H NMR (dihydrochloride) : 10 86 (br s, 2H, NH and HCl), 8.28 (dd, 1H, J=5 1 and 0.8 Hz, H_5), 8.11 (br s, 1H, HCl), 7.62 (dd, 1H, J=8.2 and 0 8 Hz, H_7), 7 48 (dd, 1H, J= 8 2 and 5.1 Hz, H_6), 3.95 (d, 1H, J= 17 8 Hz, H_{3A}), 3 88 (br s, 4H, imidazoline), 3.67 (d, 1H, J=17.8 Hz, H_{3B}), 2.28 (m, 2H, $CH_3C\underline{H_2}C$), 0.96 (t, 3H, J= 7.2 Hz, $C\underline{H_3}CH_2C$, Anal. Calcd for $C_{12}H_{15}N_3O$,2HCl: C, 49.67; H, 5.90; N, 14.48 Found C, 49.64; H, 6.19, N, 14 11.

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