HETEROCYCLES, Vol. 60, No. 12, 2003, pp. 2621 - 2630
Received, 14th July, 2003, Accepted, 26th September, 2003, Published online, 30th September, 2003

SYNTHESIS OF 2(*3H*)-BENZOXAZOLONE DERIVATIVES AS POTENTIAL MELATONIN RECEPTOR LIGANDS

Christophe Mésangeau[1], Jacques H. Poupaert[2], Pascal Carato[1*], and Saïd Yous[1]

[1]Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques et Biologiques de Lille, 3, rue du Professeur Laguesse, BP 83, F-59006 Lille, France. Fax: 03 20 96 43 75; e-mail: pcarato@phare.univ-lille2.fr

[2]Unité de Chimie Pharmaceutique, Ecole de Pharmacie, Faculté de Médecine, Université Catholique de Louvain, Avenue E. Mounier 73 (UCL 7343), B-1200 Bruxelles, Belgium

Abstract – This article reports the synthesis of new 2(*3H*)-benzoxazolone-based ligands for the melatonin receptors in which an acetamidopropyl side-chain was incorporated. Construction of the acetamidopropyl moiety was achieved *via* a Wadsworth-Emmons approach. Although these compounds can be seen as derivatives of *N*-[3-(3-methoxyphenyl)propyl]acetamide (MPPA), which is the exact analogue of melatonin in which the 1,2-indole nitrogen atoms are deleted, they exhibit lower affinities for the melatonin receptors probably due to an unfavourable steric bulk and hydrophilic interactions.

Melatonin (*N*-acetyl-5-methoxytryptamine, MT), a neurohormone principally synthesized and secreted by the pineal gland during the dark period in animal and humans[1,2] plays a central role in the regulation of circadian rhythm and, as a chronobiotic, can provide valuable therapy in the management of jet lag[3] and sleep disorders[4] particularly those occasioned by shift work. Melatonin exerts its effects through at least three targets : two G-protein-coupled receptors, MT_1 and MT_2,[5,6] and a binding site, MT_3/QR_2.[7] In the course of our search for new melatonin receptor ligands, we previously reported[8-10] various series of analogues involving the use of naphthalene, benzofuran, benzothiophene, and tetralin as central template. Most of them exhibited high affinity on both MT_1 and MT_2 receptors. As a part of this ongoing research program, the 2(*3H*)-benzoxazolone heterocycle[11] was also investigated as pivotal structure for the β-acetamidoethyl side-chain but the resulting analogues (6-AEB, Figure 1) showed only moderate affinities for the melatonin receptors.

In recent years, Garrat *et al.*[12] described compounds with a phenyl moiety bearing the acetamidoethyl (MPEA) and the acetamidopropyl side-chain (MPPA) as structurally simplified ligands of melatonin receptors and showed that MPPA possessed better affinities than its lower homologue. In accordance with previous publication of our group and Garrat's report, we decided to replace the ethylene moiety of 6-AEB by a propylene side-chain (6-APB). As part of this search, we also decided to synthesise the 5-isomer of this compound (5-APB) and to limit the conformational freedom of the acetamidopropyl side-chain of compound (**12**) by preparing compound (**17**) in which this chain is embedded into a cyclic structure (Figure 1).

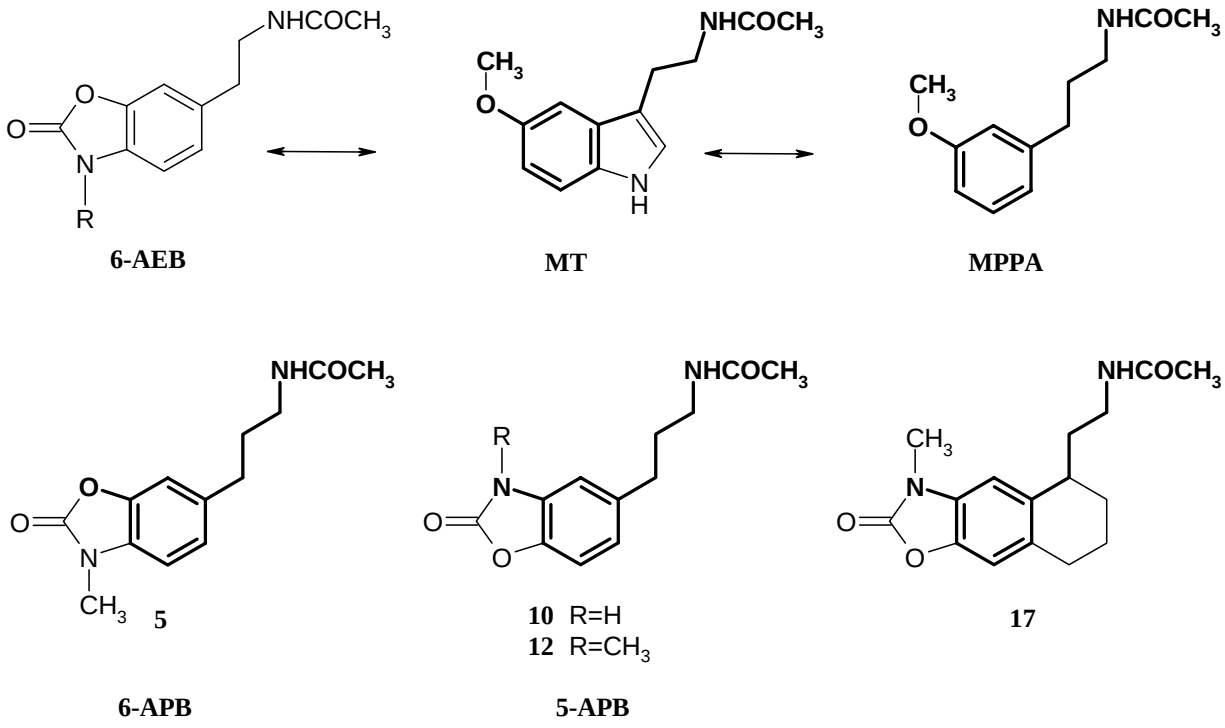
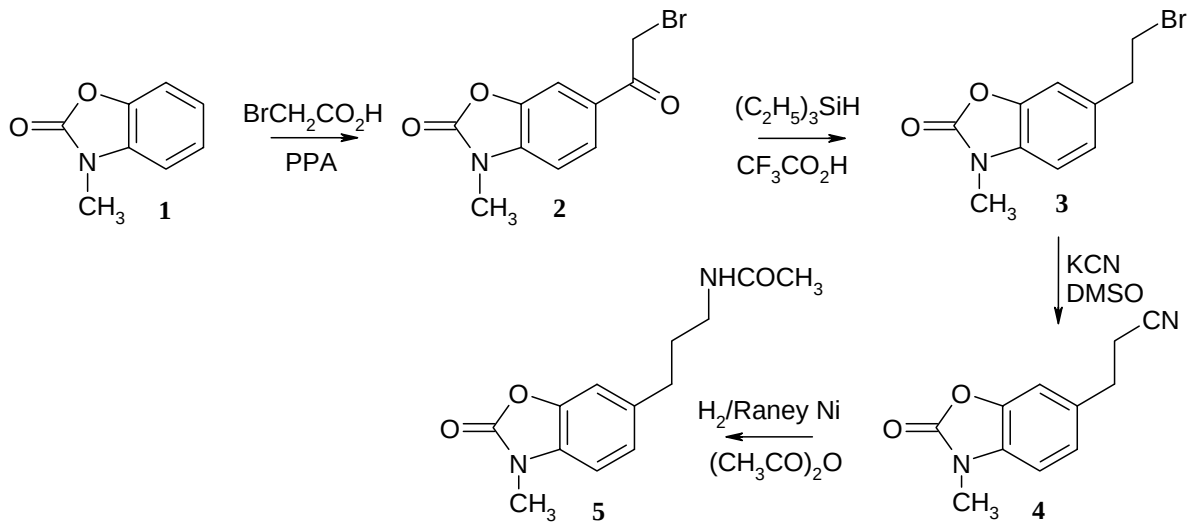


Figure 1

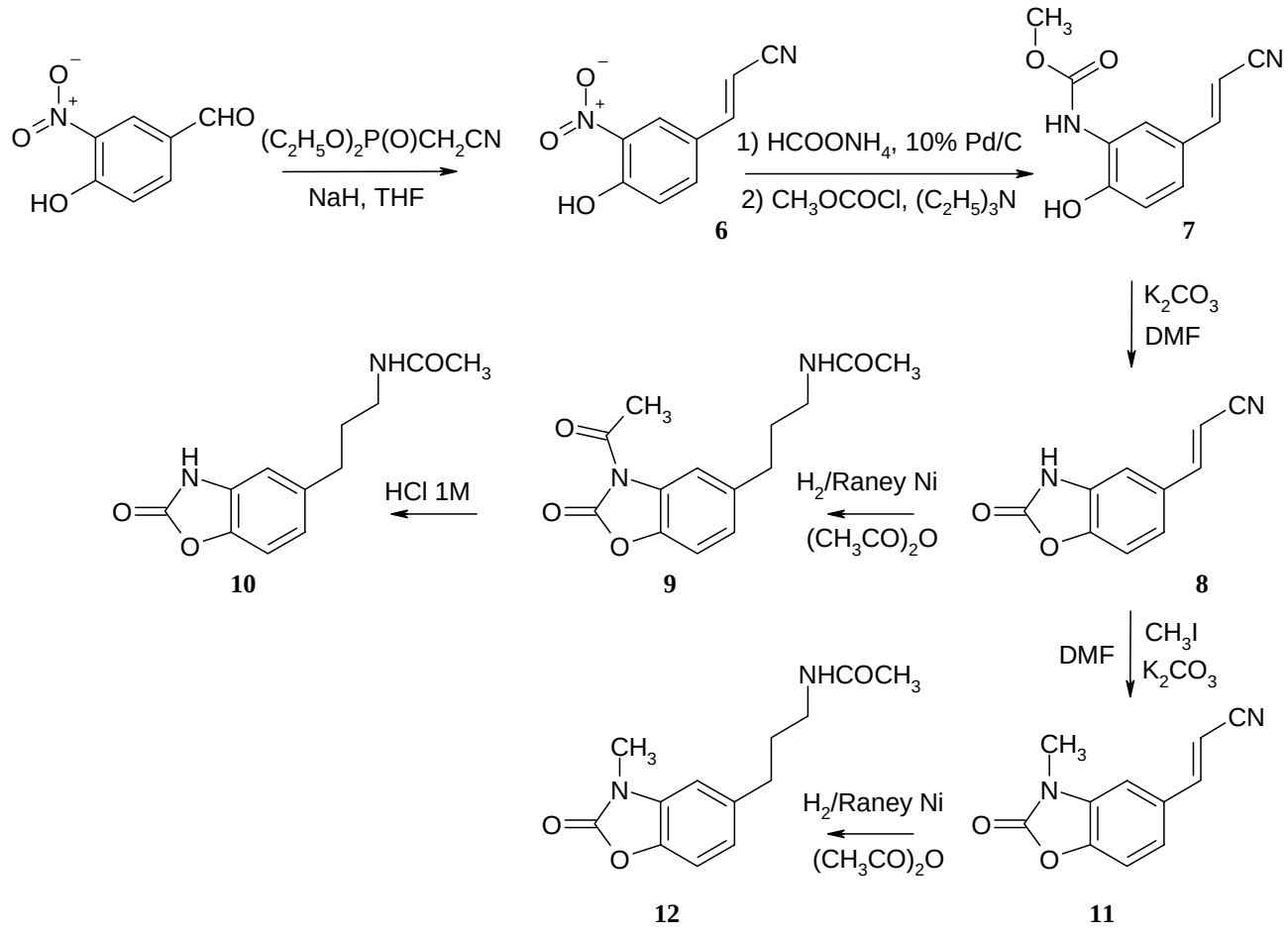
RESULTS AND DISCUSSION

Compound (**5**) was prepared as outlined in Scheme 1. The bromoacetyl derivative (**2**) was obtained by a Friedel-Crafts acid-catalyzed acylation of **1** using bromoacetic acid and polyphosphoric acid (70 % yield). Subsequent reduction of the ketone carbonyl group was performed using triethylsilane in trifluoroacetic acid (83 % yield) as previously described.[13,14] Substitution of the bromoethyl derivative (**3**) with potassium cyanide in DMSO led to **4** (83 % yield) which was then hydrogenated in the presence of Raney nickel as catalyst in acetic anhydride to give the *N*-acetyl derivative (**5**) (71 % yield).



Scheme 1

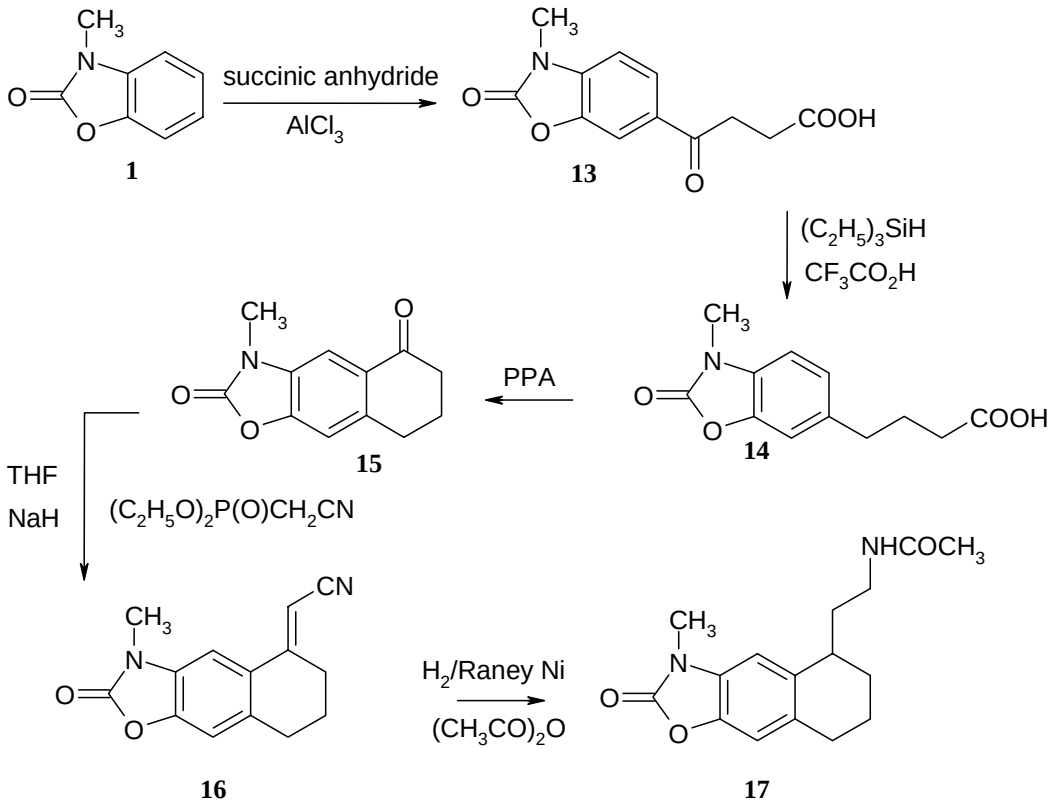
The key intermediate in the synthesis of compounds (**10**) and (**12**) is the nitrile (**8**) which was prepared as shown in Scheme 2.



Scheme 2

Treatment of 4-hydroxy-3-nitrobenzaldehyde with diethyl cyanomethylphosphonate and NaH in tetrahydrofuran according to the Wadsworth-Emmons[15] reaction gave the nitrile (**6**) (70 % yield). The stereochemistry of this compound was assigned on the basis of the coupling constant values of the ethylenic protons (J = 16.4 Hz), which were consistent with the values expected for the *(E)*-stereoisomer. Selective reduction of the nitro group of **6** was accomplished with ammonium formate and palladium on charcoal in methanol and the amino group was immediately converted into methyl carbamate (**7**) (70 % yield) by treatment in ethyl acetate with methyl chloroformate and triethylamine. Compound (**7**) was finally heated in DMF in the presence of potassium carbonate to afford the benzoxazolinonic compound (**8**) (70 % yield). The *N*-acetyl derivative (**10**) was obtained by hydrogenation of **8** in the presence of Raney nickel in acetic anhydride (76 % yield) and selective desacetylation of **9** by treatment in 1M HCl (82 % yield). On the other hand, *N*-methylation of **8** with methyl iodide and potassium carbonate in DMF gave **11** (71 % yield) which upon reduction of the nitrile group in acetic anhydride provided **12** (37 % yield).

Compound (**17**) was prepared in five steps starting from 3-methyl-2(*3H*)-benzoxazolone (Scheme 3).



Scheme 3

Tetralone (**15**) was obtained according to previously described procedure. [16] The acid (**13**) was obtained *via* a Friedel-Crafts acylation of the starting material with succinic anhydride using the $AlCl_3$-DMF reagent. Reduction of the ketone carbonyl group of **13** gave **14**. This compound was then cyclised to the tetralone (**15**) (69 % yield) by heating in polyphosphoric acid. The acetonitrile (**16**) was prepared from **15** *via* a Wadsworth-Emmons reaction (46 % yield). Assignment of its configuration was not easy by ^{1}H-NMR spectrum due to the absence of neighboring protons on the vicinal carbon and was therefore tentatively ascribed on the basis of molecular mechanisms (MM2) and semi-quantum mechanisms calculations (PM3 and PM3 COSMO). Indeed, by the MM2 method, a difference of steric energy of 3.0 Kcal/mol in favor of the E-isomer while the PM3 and PM3 COSMO methods gave a difference of heat of formation of 2.2 and 3.3 Kcal/mol, respectively, always in favor of the E-isomer. In all cases thus, the E-configuration was favored. Compound (**16**) was finally hydrogenated in acetic anhydride as described above to give **17** (47 % yield).

In conclusion, this article reports the synthesis of new 2(*3H*)-benzoxazolone-based ligands for the melatonin receptors in which an acetamidopropyl side-chain was incorporated. Construction of the acetamidopropyl moiety was expeditiously achieved by Wadsworth-Emmons approach. While there is a considerable body of literature pertinent to the structure activity - relationships of MT_1 receptor ligands, including detailed ComFa studies,[17] the MT_2 receptor has been by far less intensively investigated. Among the newly synthesized melatonin analogs, the only compounds that showed noticeable affinities for melatonin receptors were compounds (**12**) and (**17**) (IC_{50}: $6.7.10^{-6}$M and $1.43.10^{-7}$M, respectively), and this only at MT_2 receptor sites. All other compounds exhibited disappointingly IC_{50}'s>10^{-5} M, both at MT_1 and MT_2 receptor sites. Although the compounds we report here can be effectively considered as close modifications of *N*-[3-(3-methoxyphenyl)propyl]acetamide (MPPA), which is as a matter of fact the exact analogue of melatonin in which the 1,2-indole nitrogen atoms have been deleted, they demonstrated much lower affinities for the melatonin receptors most likely due to unfavourable steric bulk and hydrophilic interactions. Among all the original ligands obtained, compound (**17**) in view of the selectivity for MT_2 it exhibited (IC_{50} MT_1/MT_2 = 8.2) has been selected as a valuable lead compound for further elaborations of selective MT_2 receptor ligands.

EXPERIMENTAL

Melting points were determined on a Büchi SMP-535 apparatus and are uncorrected. IR spectra were recorded on a Brüker Vector 22 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Brüker AC 300 instrument in DMSO-d_6 using TMS as an internal reference. Elemental analysis were

performed by the analytical center of C.N.R.S. of Vernaison (France) and are within -/+ 0.4 of the theoretical values.

3-(3-Methyl-2(*3H*)-benzoxazol-6-yl)propionitrile (4)

To a suspension of potassium cyanide (5.6 g, 86 mmol) in DMF (250 mL) was slowly added compound (**3**) (12.5 g, 49 mmol). The mixture was stirred at 60°C for 24 h and poured into water. The precipitate was filtered, washed with water and dried. Recrystallization from toluene-cyclohexane (9-1) afforded **4** (8.96 g, 83 %) as white solid. mp 145-147°C. IR ν 2241, 1763 cm^{-1}. ^1H NMR δ 2.82 (t, J = 6.3 Hz, 2H) ; 2.92 (t, J = 6.3 Hz, 2H) ; 3.25 (s, 3H) ; 7.15 (d, J = 7.7 Hz, 1H) ; 7.20 (d, J = 7.7 Hz, 1H) ; 7.32 (s, 1H). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.50; H, 5.06; N, 13.64.

***N*-[3-(3-Methyl-2(*3H*)-benzoxazol-6-yl)propyl]acetamide (5)**

A solution of **4** (1.2 g, 6 mmol) in acetic anhydride (150 mL) was hydrogenated over Raney nickel (0.2 g) under pressure (60 bar) at 60°C for 6 h. After filtration and evaporation, the residue was dissolved in methylene chloride, washed with 0.1 M NaOH, dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallization from ethyl acetate afforded **5** (1.06 g, 71 %) as white solid. mp 128-130°C. IR ν 3304, 1766, 1635 cm^{-1}. ^1H NMR δ 1.68 (qu, J = 6.8 Hz, 2H) ; 1.80 (s, 3H) ; 2.60 (t, J = 6.8 Hz, 2H) ; 3.02 (m, 2H) ; 3.30 (s, 3H) ; 7.06 (d, J = 8.0 Hz, 1H) ; 7.15 (d, J = 8.0 Hz, 1H) ; 7.21 (s, 1H) ; 7.86 (br s, 1H). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.75; H, 6.58; N, 11.35.

(*E*)-3-(4-Hydroxy-3-nitrophenyl)acrylonitrile (6)

Under stirring and N_2, a solution of diethyl cyanomethylphosphonate (23.3 mL, 144 mmol) in anhydrous THF (40 mL) was added dropwise to a mixture of 60 % NaH (5.7 g, 144 mmol) in anhydrous THF (100 mL) cooled at 0°C. After 1 h, a solution of 4-hydroxy-3-nitrobenzaldehyde (8 g, 48 mmol) in anhydrous THF (40 mL) was added dropwise and the mixture was stirred at rt for 1 h. The mixture was then poured into water and 1M HCl was added until pH 2.0. The precipitate was collected by filtration, washed with water and dried. Recrystallization from toluene afforded **6** (6.39 g, 70 %) as yellow solid. mp 178°C. IR ν 3260, 2216 cm^{-1}. ^1H NMR δ 6.43 (d, J = 16.4 Hz, 1H) ; 7.18 (d, J = 8.6 Hz, 1H) ; 7.64 (d, J = 16.4 Hz, 1H) ; 7.85 (dd, J = 8.6, 2.2 Hz, 1H) ; 8.21 (d, J = 2.2 Hz, 1H) ; 11.70 (s, 1H). Anal. Calcd for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 57.02; H, 3.25; N, 14.62.

(*E*)-*N*-[5-(2-Cyanovinyl)-2-hydroxyphenyl]methyl carbamate (7)

To a stirred suspension of **6** (4.5 g, 23.7 mmol) and palladium on charcoal (1.2 g) in methanol (80 mL) at 40°C was added anhydrous ammonium formate (9 g, 142 mmol). The resulting mixture was stirred at

40°C for 1 h and the catalyst was removed by filtration through a celite pad. The filtrate was evaporated under reduced pressure, then the residue was taken up in water and extracted with ethyl acetate. Triethylamine (4.9 mL, 35 mmol) and methyl chloroformate (2.2 mL, 28.5 mmol) were added to the solution at 0°C. The mixture was stirred for 1 h, washed with 0.5 M HCl and with water. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallization from toluene afforded **7** (3.62 g, 70 %) as white solid. mp 183-186°C. IR ν 3367, 3187, 2213, 1694 cm^{-1}. ^1H NMR δ 3.65 (s, 3H) ; 6.13 (d, J = 16.7 Hz, 1H) ; 6.88 (d, J = 8.5 Hz, 1H) ; 7.27 (dd, J = 8.5, 1.5 Hz, 1H) ; 7.51 (d, J = 16.7 Hz, 1H) ; 7.78 (s, 1H) ; 8.50 (br s, 1H) ; 10.46 (br s, 1H). Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.41; H, 4.52; N, 12.99.

(*E*)-3-[2(*3H*)-benzoxazol-5-yl]acrylonitrile (8)

To a solution of **7** (2 g, 9.2 mmol) in DMF (60 mL) was added potassium carbonate (2.5 g, 18 mmol). The reaction mixture was heated under reflux for 20 min, poured into water and the precipitate was collected by filtration. Recrystallization from toluene-acetonitrile (1-1) afforded **8** (1.20 g, 70 %) as white solid. mp 261-264°C. IR ν 3348, 2210, 1776 cm^{-1}. ^1H NMR δ 6.45 (d, J = 16.0 Hz, 1H) ; 7.37 (m, 3H) ; 7.67 (d, J = 16.0 Hz, 1H) ; 11.90 (br s, 1H). Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.21; H, 3.35; N, 15.01.

***N*-[3-(3-Acetyl-2(*3H*)-benzoxazol-5-yl)propyl]acetamide (9)**

A solution of **8** (1.2 g, 6.5 mmol) in acetic anhydride (120 mL) was hydrogenated over Raney nickel (0.3 g) under pressure (50 bar) at 50°C for 30 h. After filtration and evaporation, the residue was dissolved in ethyl acetate, washed with an aqueous solution of potassium carbonate and with water. The solvent was dried ($MgSO_4$) and evaporated to dryness. Recrystallization from toluene afforded **9** (1.36 g, 76 %) as white solid. mp 149-153°C. IR ν 3319, 1797, 1719, 1642 cm^{-1}. ^1H NMR δ 1.67 (m, 2H) ; 1.80 (s, 3H) ; 2.60 (s, 3H) ; 2.64 (t, J = 7.4 Hz, 2H) ; 3.03 (m, 2H) ; 7.14 (d, J = 8.3 Hz, 1H) ; 7.32 (d, J = 8.3 Hz, 1H) ; 7.81 (s, 1H) ; 7.88 (br s, 1H). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.71; H, 5.92; N, 10.05.

***N*-[3-(2(*3H*)-Benzoxazol-5-yl)propyl]acetamide (10)**

A suspension of **9** (1.1 g, 4 mmol) in 1M HCl (40 mL) was heated at 50°C for 15 h and concentrated *in vacuo*. The resulting precipitate was collected by filtration and dried. Recrystallization from water-ethanol (1-1) afforded **10** (0.77 g, 82 %) as white solid. mp 164-166°C. IR ν 3345, 1761, 1625 cm^{-1}. ^1H NMR δ 1.63 (m, 2H) ; 1.80 (s, 3H) ; 2.57 (t, J = 7.5 Hz, 2H) ; 3.02 (m, 2H) ; 6.90 (m, 2H) ; 7.16 (d, J =

8.3 Hz, 1H) ; 7.86 (br s, 1H) ; 11.56 (br s, 1H). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.38; H, 6.01; N, 11.87.

(*E*)-3-(3-Methyl-2(*3H*)-benzoxazol-5-yl)acrylonitrile (11)

Potassium carbonate (3.1 g, 22.5 mmol) was added to a solution of **8** (1.4 g, 7.5 mmol) in DMF (30 mL). The reaction mixture was refluxed for 30 min and methyl iodide (0.7 mL, 11 mmol) was slowly added. After stirring at reflux for 30 min, the solution was poured into water and the precipitate was collected by filtration. Recrystallization from toluene afforded **11** (1.07 g, 71 %) as white solid. mp 220-222°C. IR ν 2214, 1771 cm^{-1}. ^1H NMR δ 3.34 (s, 3H) ; 6.47 (d, J = 16.8 Hz, 1H) ; 7.40 (m, 3H) ; 7.68 (d, J = 16.8 Hz, 1H). Anal. Calcd for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.82; H, 4.15; N, 14.24.

***N*-[3-(3-Methyl-2(*3H*)-benzoxazol-5-yl)propyl]acetamide (12)**

Starting from **11** (1 g, 5 mmol) the reaction was carried out as described for **9**. Recrystallization from ethyl acetate afforded **12** (0.46 g, 37 %) as white solid. mp 137-138°C. IR ν 3308, 1757, 1627 cm^{-1}. ^1H NMR δ 1.70 (m, 2H) ; 1.81 (s, 3H) ; 2.62 (t, J = 7.6 Hz, 2H) ; 3.04 (m, 2H) ; 3.32 (s, 3H) ; 6.96 (d, J = 8.2 Hz, 1H) ; 7.12 (s, 1H) ; 7.22 (d, J = 8.2 Hz, 1H) ; 7.88 (br s, 1H). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.63; H, 6.59; N, 11.12.

3-Methyl-2,5-dioxo-cyclohexa(f)benzoxazole (15)

Under mechanical stirring, a mixture of polyphosphoric acid (50 g) and **14** (5 g, 21 mmol) was heated at 70°C for 2 h. After cooling, the reaction mixture was poured into ice. The precipitate was collected by filtration and dried. Recrystallization from acetonitrile afforded **15** (3.15 g, 69 %) as white solid. mp 172-174°C. IR ν 1755, 1625 cm^{-1}. ^1H NMR δ 2.03 (m, 2H) ; 2.61 (t, J = 6.1 Hz, 2H) ; 2.97 (t, J = 6.1 Hz, 2H) ; 3.36 (s, 3H) ; 7.33 (s, 1H) ; 7.65 (s, 1H). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.16; H, 5.16; N, 6.34.

(*E*)-(3-Methyl-2-oxocyclohexa(f)benzoxazol-5-ylidene)acetonitrile (16)

Under stirring and N_2, a solution of diethyl cyanomethylphosphonate (3.1 mL, 19 mmol) in anhydrous THF (20 mL) was added dropwise to a mixture of 60 % NaH (0.8 g, 19 mmol) in anhydrous THF (30 mL) cooled at 0°C. After 1 h, a solution of **15** (2.8 g, 13 mmol) in anhydrous THF (40 mL) was added dropwise and the mixture was stirred at rt for 1 h. The mixture was then poured into water and extracted with ether. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to dryness. Recrystallization from toluene-acetonitrile (4-1) afforded **16** (1.44 g, 46 %) as white solid. mp 258-262°C. IR ν 2204, 1775 cm^{-1}. ^1H NMR δ 1.83 (m, 2H) ; 2.80 (t, J = 5.9 Hz, 2H) ; 2.86 (t, J = 5.9 Hz, 2H) ;

3.33 (s, 3H) ; 6.28 (s, 1H) ; 7.20 (s, 1H) ; 7.70 (s, 1H). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.12; H, 5.15; N, 11.39.

***N*-[2-(3-Methyl-2-oxocyclohexa(f)benzoxazol-5-yl)ethyl]acetamide (17)**

Starting from **16** (1.4 g, 4.2 mmol) the reaction was carried out as described for **9**. Recrystallization from toluene afforded **17** (0.57 g, 47 %) as white solid. mp 121-123°C. IR ν 3299, 1775, 1634 cm^{-1}. ^1H NMR δ 1.70 (m, 9H) ; 2.80 (m, 3H) ; 3.14 (t, J = 5.6 Hz, 2H) ; 3.31 (s, 3H) ; 7.00 (s, 1H) ; 7.01 (s, 1H) ; 7.88 (br s, 1H). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.54; H, 7.14; N, 9.88.

ACKNOWLEDGEMENT

The authors are grateful to Dr. C. Bochu (Laboratoire d'Application de Résonance Magnétique Nucléaire de l'Université de Lille 2) for his help in the interpretation of the ^1H-NMR spectra.

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