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SYNTHESIS OF NEW HIGHER HOMOLOGUES OF QUISQUALIC ACID

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Abstract: *The compounds such as methyl 2-(tert-butoxycarbonyl)-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoate and 2-amino-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoic acid, higher homologues of quisqualic acid, have been synthesized in a first time via N-alkylation reaction of 4-phenyl-1,2,4-oxadiazolidine-3,5-dione by alkyl 2-(tert-butoxycarbonyl)-4-iodobutanoate in presence of potassium carbonate as base in dry acetone. The structures of the synthesized compounds were established by ^{1}H-NMR, MS data and elemental analysis.*

KEYWORDS: Quisqualic Acid, N-Alkylation Reaction, Glutamate Receptor.

INTRODUCTION

Quisqualic acid is a naturally occurring compound activating glutamate non-NMDA receptors and glutamate mGlu receptors [1]. Furthermore, quisqualate has an unresolved effect on synaptic transmission. Hence, quisqualate is able to induce an enhanced sensitivity of neurons to depolarization by analogues of 2-amino-4-phosphonobutyric acid (AP4) [2], phenylglycine, and homoibotenic acid (HIBO). Thus, after administration of quisqualate, these analogues become active at concentrations at which they are otherwise inactive [3].

In continuation of our research interest in heterocyclic amino acids [4-10], we report here our results concerning the synthesis of new compounds, as methyl 2-amino-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoate **4a** and *tert*-butyl 2-amino-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoate **4b**, higher homologues of quisqualic acid, through *N*-alkylation reaction, as key step, between 4-phenyl-1,2,4-oxadiazolidine-3,5-dione and methyl or *tert*-butyl 2-(*tert*-butoxycarbonyl)-4-iodobutanoate.

RESULTS AND DISCUSSION

The synthesis of the compounds **3a** and **3b** for the first time is carried out under the following conditions: to a sodium hydride suspension (0.44 mmol) previously washed with hexane in *N*,*N*-dimethylformamide, 0.44 mmol of 4-phenyl-1,2,4-oxadiazolidine-3,5-dione **2** is added. After one hour of stirring at room temperature, 0.44 mmol of methyl 2-(*tert*-butoxycarbonyl)-4-iodobutanoate **1a** (same for *tert*-butyl 2-(*tert*-butoxycarbonyl)-4-iodobutanoate **1b**) dissolved in 5mL of *N*,*N*-dimethylformamide was added to the reaction medium. The reaction is carried out at room temperature, then it is monitoring by thin layer chromatography. But the

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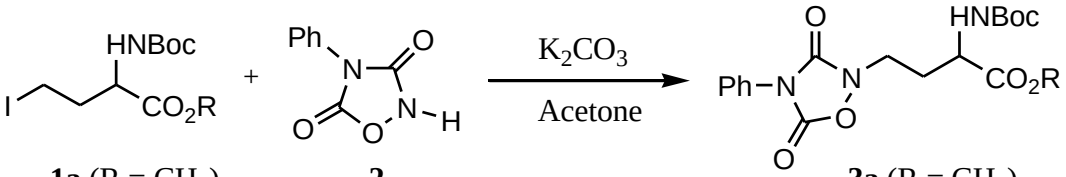
desired compounds **3a** and **3b** were obtained after treatment of the crude reaction mixture and purification in a low yield of about 25%. This performance has been significantly increased to 70% when operating at high dilution in acetone and increasing the number of equivalents of K_2CO_3 until 3 (Scheme 1).



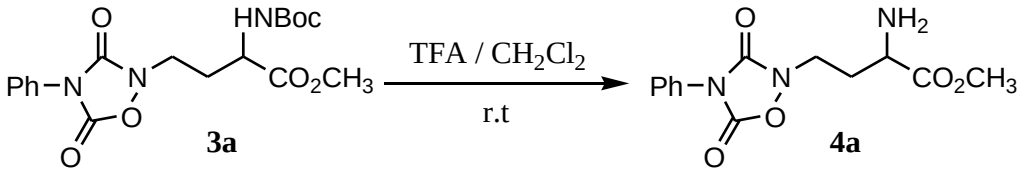
1a (R = CH_3)
1b (R = tBu)

2

3a (R = CH_3)
3b (R = tBu)

Scheme 1: ***Synthesis of the N-protected esters*** **3a** ***and*** **3b**

The acid cleavage of Boc group in the case of *N*-protected methyl ester **3a**, with trifluoroacetic acid in methylene chloride [11], leads to the corresponding amino ester **4a** with a yield of about 90% (Scheme 2). The hydrolysis of this ester, using alkali conditions (1 eq. of NaOH 2N), did not give the expected product but leads to several unidentified and inseparable products and no trace of starting material was observed at the end of purification.

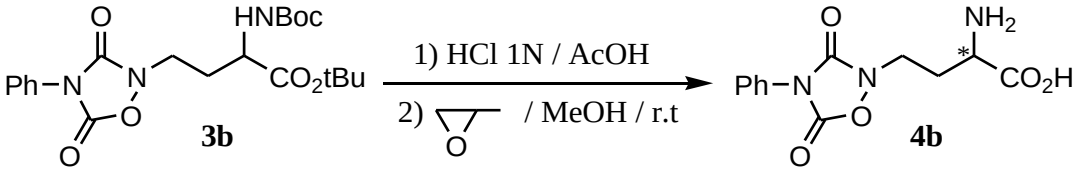


3a

4a

Scheme 2: ***N-Boc deprotection of N-protected ester*** **3a**

To avoid any degradation or cyclization and due to its ease of deprotection, the *N*-Boc *tert*-butyl ester group was chosen. Thus, the product **4b** is obtained as the optically pure α-amino acid by treatment of compound **3b** with HCl(1N)/AcOH at room temperature for two hours (Scheme 3), followed by precipitation in methanol by the propylene oxide. The desired compound **4b** was getting with an almost quantitative yield.



3b

4b

Scheme 3: ***Synthesis of the optically pure α-amino acid*** **4b**

Experimental Section

The melting points were determined using a Büchi melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded with a Bruker AVANCE 250 operating at 250 MHz. Chemical shifts (δ) are given in ppm and are reported relative to tetra-methylsilane TMS and coupling constants (*J*) are given in hertz. Peaks are described as singlet (s), doublet (d), triplet (t) and multiplet (m). All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F_{254}) and spots were

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visualized under UV light or by exposure to vaporised iodine. The purification was performed by column chromatography on silica gel columns 60 Merck. Optical rotations were measured in *tBu*OMe and CH_2Cl_2 on a Perkin-Elmer 241 MC polarimeter with a 10 cm cell (concentration C given in g/mL). The mass spectra were recorded on a JOEL JMX-DX 300 mass spectrometer at Fast Atom Bombardment (FAB). The elemental analyses were performed on a Thermo Scientific Flash EA analyzer. The purification was performed by column chromatography on silica gel 60 Merck (Kieselgel $60F_{254}$ Merck Fertigplatten).

N-alkylation reaction of 4-phenyl-1,2,4-oxadiazolidine-3,5-dione: Synthesis of the N-protected esters **3a** *and* **3b**: A mixture of 4-phenyl-1,2,4-oxadiazolidine-3,5-dione **2** (89 mg, 0.5 mmol) and potassium carbonate (207 mg, 1.5 mmol) in 20 mL of dry acetone was stirred at room temperature. After one hour, the methyl 2-(*tert*-butoxycarbonyl)-4-iodobutanoate **1a** (or *tert*-butyl 2-(*tert*-butoxycarbonyl)-4-iodobutanoate **1b**) (171.5 mg, 0.5 mmol) dissolved in 10 mL of dry acetone was added to the reaction medium. After stirring at room temperature for 24 hours, the solvent was evaporated under vacuum and the residue was extracted with ether. The organic layer was dried with sodium sulfate (Na_2SO_4) and the solvent was removed. The resulting crude is purified by column chromatography on silica gel using ether/hexane as eluent to afford the pure *N*-protected esters **3a** and **3b**.

Methyl 2-(tert-butoxycarbonyl)-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoate **3a**: Yield = 70% (138 mg, white powder); m.p: 109°C (ether/hexane); R_f = 0.3 (Ether/hexane 2/1); ^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.44 (s, 9H, $C(CH_3)_3$), 2.15 (m, 1H, CH_β), 2.35 (m, 1H, CH_β), 3.7 (s, 3H, OCH_3), 3.95 (m, 2H, N-CH_2-), 4.5 (m, 1H, CH_α), 5.25 (d, 1H, NH, *J* = 7.13 Hz), 7.5 (m, 5H, H_{arom}); MS-FAB (Matrix: m-Nitro benzyl alcohol (NBA)): M = 393, $(M+H)^+$ = 394, $(2M+H)^+$ = 787; Anal. Calcd. for [$C_{18}H_{23}N_3O_7$]: C, 54.84; H, 5.84; N, 10.66. Found: C, 54.82; H, 5.83; N, 10.65.

t-Butyl 2-(tert-butoxycarbonyl)-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoate **3b**: Yield = 70% (152 mg, white powder); m.p: 102°C (ether/hexane); R_f = 0.15 (ether/hexane 2/1). ^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.45 (s, 9H, $C(CH_3)_3$); 1.47 (s, 9H, $C(CH_3)_3$); 2.0 (m, 2H, $CH_{2\beta}$); 3.90 (t, 2H, N-CH_2-, *J* = 7.5 Hz); 4.2 (m, 1H, CH_α); 5.3 (d, 1H, NH, *J* = 9 Hz); 7.6 (m, 5H, H_{arom}). MS-FAB (Matrix: Thioglycerol (TG)): M = 435; $(M+H)^+$ = 436; $[\alpha]_D$ = + 9 (C = 1, $CHCl_3$).

Deprotection of N-Boc amino ester **3a**: *Synthesis of methyl 2-amino-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoate* **4a**: To 130 mg (0.33 mmol) of compound **3a** is added at 0°C a mixture of: TFA/CH_2Cl_2: 1/1-V/V (1.1 mmol of TFA); stirring for 30 minutes at room temperature. Evaporate the TFA without heating; retake by methanol and evaporated (the operation is performed several times until complete disappearance of TFA). The trifluoroacetate aminoester thus obtained is dissolved in CH_2Cl_2 and neutralized to pH = 7 with a hydrochloric acid solution 1N, the organic layer is extracted 2 times with water and then dried over $MgSO_4$. The resulting crude is purified by column chromatography on silica gel using ether as eluent to obtain the aminoester **4a**. Yield = 90% (87 mg, colorless oil); R_f = 0.18 (Ether); ^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.9 (m, 2H, NH_2); 2.0 (m, 2H, $CH_{2\beta}$); 3.55 (m, 1H, CH_α); 3.7 (s, 3H, OCH_3); 4.0 (t, 2H, -CH_2-N, *J* = 7.5 Hz); 7.6 (m, 5H, H_{arom}). MS-FAB (Matrix: Thioglycerol (TG)): M = 293; $(M+H)^+$ = 294; $(2M+H)^+$ = 587.

Deprotection of N-Boc amino ester **3b**: *Synthesis of 2-amino-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoic acid* **4b**: A solution of **3b** (82 mg, 0.28 mmol) in 10 mL of a hydrochloric acid solution (1N) in acetic acid was stirred for 2 hours at room temperature. After

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evaporation, the hydrochloride salt of the amino acid was crystallized by addition of anhydrous ether. The corresponding amino acid **4b** was precipitated with propylene oxide in methanol.

2-amino-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoic acid hydrochloride: Quantitative yield; m.p: 174°C (ether/methanol); ^{1}H-NMR (250 MHz, DMSO-d_6) δ(ppm): 1.5 (s, 3H, NH_3^+); 2.3 (m, 2H, $CH_{2\beta}$); 4.1 (m, 3H, -CH_2-N + CH_α); 7.5 (m, 5H, H_{arom}). MS-FAB (Matrix: Glycerol (GC)): M = 315; $(M\text{-}Cl)^+$ = 294; $(2M+H)^+$ = 280.

2-amino-4-(3,5-dioxo-4-phenyl-1,2,4-oxadiazolidin-2-yl)butanoic acid **4b**: Quantitative yield; m.p: 185°C (water/methanol); ^{1}H-NMR (250 MHz, D_2O) δ(ppm): 2.2 (m, 2H, $CH_{2\beta}$); 3.4 (m, 1H, -CH-N); 4.0 (m, 2H, -CH-N + CH_α); 7.0 (m, 5H, H_{arom}). MS-FAB (Matrix: Thioglycerol (TG)): M = 279; $(M + H)^+$ = 280; $[\alpha]_D$ = + 34 (C = 0.5, 4N HCl); Anal. Calcd. for [$C_{12}H_{13}N_3O_5$]: C, 51.59; H, 4.69; N, 15.00. Found: C, 51.57; H, 4.69; N, 14.87.

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