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SYNTHESIS AND CHARACTERIZATION OF SOME LINEAR SULFUR-CONTAINING ANALOGUES OF QUISQUALIC ACID

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Abstract: The compounds such as 3-(1-(benzyloxy)-3-(ethoxycarbonyl)thioureido)-2-(tert-butoxycarbonyl)propanoic acid and 2-amino-4-(1-(benzyloxy)-3-(ethoxycarbonyl)thioureido)-butanoic acid have been synthesized respectively via an opening reaction of α -(*N*-Boc) amino- β -lactone and a reaction of substitution carried out on γ -iodohomoalanine. The structures of the synthesized compounds were established by ¹H-NMR, MS data and elemental analysis.

Keywords: Quisqualic acid, Substitution reaction, Glutamate receptor.

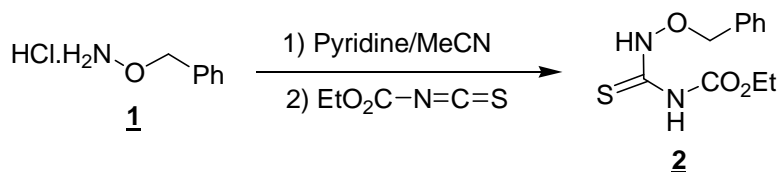
1. Introduction

Quisqualic acid is a natural product isolated from the seeds of *Quisqualis indica* and *Quisqualis fructus* [1,2]. This derivative has been reported to be a strong agonist for AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and group I metabotropic glutamate receptors [3,4]. Thus, after administration of quisqualate, these analogues become active at concentrations at which they are otherwise inactive [5].

In continuation of our research interest in heterocyclic amino acids [6-14], we report here our results concerning the synthesis of some new compounds, as 3-(1-(benzyloxy)-3-(ethoxycarbonyl)thioureido)-2-(tert-butoxycarbonyl)propanoic acid **6** and 2-amino-4-(1-(benzyloxy)-3-(ethoxycarbonyl)thioureido)butanoic acid **8**, linear sulfur-containing analogues of quisqualic acid through, as key step, an opening reaction of α -(*N*-Boc) amino- β -lactone and a reaction of substitution carried out on γ -iodohomoalanine.

2. Results and Discussion

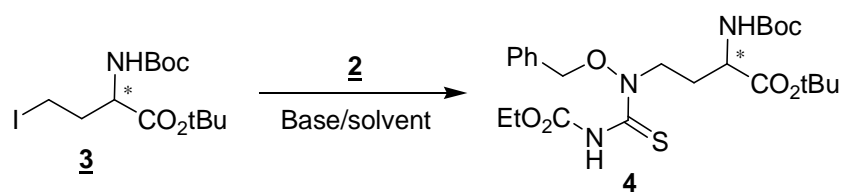
To synthesize the product giving access to the linear sulfur-containing analogues of quisqualic acid, we performed the condensation of *O*-benzyl hydroxylamine with ethoxycarbonyl isothiocyanate according to the following reaction (Scheme 1):



Scheme 1: Synthesis of thiourea derivative **2**

O-benzyl hydroxylamine hydrochloride **1** is treated with 1.5 equivalent of pyridine and 1.2 equivalent of ethoxycarbonyl isothiocyanate in acetonitrile to lead to *N*-ethoxycarbonyl-*N*-

benzylhydroxythiourea **2**. The later was obtained first by conducting the neutralization of the hydrochloride with an equivalent of triethylamine in methanol. The condensation reaction of the O-benzyl hydroxylamine is then carried in THF, under nitrogen atmosphere for 16 hours, to lead to product **2** with a yield of about 90%. Mass spectrometry (FAB, $[M+H]^+$ ($m/z=255$), 1H NMR spectrum analysis (250 Hz) and microanalysis show well that it is product **2**. The first way of synthesis of a linear sulfur-containing; higher analogue of quisqualic acid consists of the modification of the side chain of the γ -iodohomoalanine **3** by nucleophilic substitution reaction using as reagent the derivative of thiourea **2** (Scheme 2).

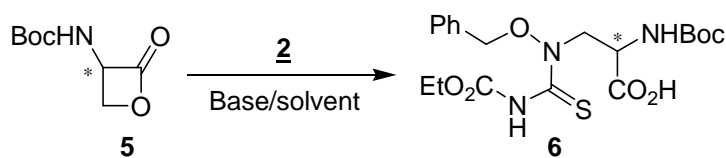


Scheme 2: Synthesis of the *N*-Boc amino ester **4**

Within sight of the literature, the use of the sodium hydride seems to be the method which would be appropriate best for the reactions of substitution, a test carried out in the DMF [15], leads after 76 hours of agitation at room temperature to the product **4** with a yield of only 50%. The yield could not be improved by modifications of the reaction conditions.

By against the use of potassium carbonate (2 equivalents), in acetone [16] (24 hours at 25°C) leads to a better result. The product **4** is obtained with a yield of about 90%; the purification being carried out by chromatography on silica gel column. The analysis of its 1H NMR spectrum (250 Hz) and its mass spectrum allowed us to confirm that it is indeed the substitute product.

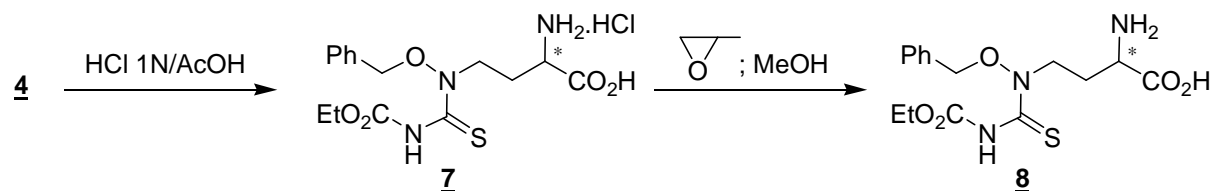
A second synthetic pathway of another linear analogue of the quisqualic acid consists in the opening of the lactone **5** with thiourea derivative **2**. The nucleophilic attack causes ring opening by rupture of the carbon-oxygen bond to directly generate the linear *N*-Boc sulfur-containing analogue of quisqualic acid (Scheme 3).



Scheme 3: Synthesis of the *N*-Boc amino acid **6**

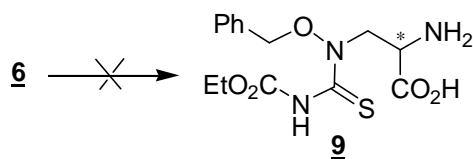
Two bases were used, sodium hydride in DMF and potassium carbonate, thereby obtaining the product **6** with a respectively yield of 20 and 40% (Scheme 3). The yield could not be improved by modifications of reaction conditions. Mass spectrometry (FAB, $[M+H]^+$ ($m/z=440$)) shows that the opening reaction has occurred.

To obtain free amino acids, we proceeded to the deprotection of amine and ester functions. The simultaneous cleavage of the *tert*-butyloxycarbonyl group and *tert*-butyl ester of compound **4** is carried out by a solution of HCl 1N in acetic acid [17] during 2 hours at room temperature. The amino acid hydrochloride **7** thus obtained is neutralized with propylene oxide in methanol to yield the free amino acid **8** with a yield of around 80% (Scheme 4).



Scheme 4: Synthesis of the optically pure α -amino acid **8**

Tests of cleavage of the Boc grouping of *N*-Boc amino acid **6** were carried out in order to obtain free corresponding amino acid (Scheme 5). Different methods are used namely HCl 1N/AcOH; HBr/AcOH [17], TFA in dichloromethane [18], trimethylsilyl chloride in *t*BuOH [19], *p*-toluenesulfonic acid in TFA [20,21] and boron tris(trifluoroacetate) in TFA [22].



Scheme 5: Synthesis essay of the free α -amino acid **9**

All these methods led, after treatment of the reaction mixture, to a complex mixture of products difficult to separate on a silica column.

3. Experimental Section

The melting points were determined using a Büchi melting point apparatus and are uncorrected. The ¹H-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), triplet (t), quadruplet (q) and multiplet (m). All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm thick pre-coated silica gel plates (Merck Fertigplatten Kieselgel 60F₂₅₄) and spots were visualized under UV light or by exposure to vaporized iodine. The purification was performed by column chromatography on silica gel columns 60 Merck. Optical rotations were measured in *t*BuOMe and CH₂Cl₂ 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 60F₂₅₄ Merck Fertigplatten).

Synthesis of ethyl benzyloxycarbamothioylcarbamate **2:** To a solution of 50 mmols of *O*-benzylhydroxylamine in 100 mL of anhydrous THF is added dropwise, during a period of 15 minutes and at 0°C, 55 mmols of ethoxycarbonylisothiocyanate. The reaction mixture is then stirred at room temperature for 16 hours. After vacuum evaporation of the THF, the product is recrystallized from ether-hexane. Yield: 90%; white solid; mp: 100°C (ether-hexane); R_f: 0,72 (AcOEt-hexane: 2/1); ¹H-NMR (250 MHz, CDCl₃) δ (ppm): 1.28 (t, 3H, CH₃, *J* = 6 Hz), 4.19 (q, 2H, CH₂-CH₃, *J* = 6 Hz), 5.09 (s, 2H, CH₂-Ph), 7.39-7.58 (m, 5H, H_{arom}), 8.2 (s, 1H, NH-O), 11.6 (s, 1H, NH-CO); MS-FAB (Matrix: *m*-Nitro benzyl alcohol (NBA)): [M+H]⁺ = 255; Anal. Calcd. for [C₁₁H₁₄N₂O₃S]: C, 51.96; H, 5.51; N, 11.02; S, 12.60. Found: C, 51.84; H, 5.67; N, 11.08; S, 12.62.

a - Use of sodium hydride in DMF: To a sodium hydride suspension (0.44 mmol), previously washed with hexane in DMF, 0.44 mmol of thiourea **2** was added. After 30 minutes of stirring

at room temperature, 0.4 mmol of the γ -iodohomoalanine **3** or the lactone **5**, dissolved in the minimum of DMF was added to the reaction medium. The reaction is then carried out at room temperature for 76 hours. The treatment of the reaction is done as follows:

*In the case of the γ -iodohomoalanine **3**:* The solvent is evaporated in vacuo and the residue obtained is taken up in ethyl acetate. The organic phase is washed with water, dried over sodium sulfate and then concentrated under vacuum. The oil obtained is chromatographed on silica gel column (eluent: ether-hexane 1/3).

*In the case of lactone **5**:* After evaporation under vacuum of the DMF, the residue is taken up in water, the aqueous phase is then extracted with ethyl acetate to remove excess unreacted of reagent and of lactone. The pH was brought to 3 using a 1N HCl solution, the aqueous phase is then extracted with ethyl acetate (3 times). The extracts are combined, dried over sodium sulfate and the solvent is evaporated under vacuum, the oil obtained is purified on silica gel column (eluent: ethyl acetate-methanol 20/1).

b - Use of potassium carbonate: To a solution of thiourea derivative **2** (6 mmoles) in 25 mL of anhydrous acetone is added 12 mmoles of K_2CO_3 . After 30 minutes, the γ -iodohomoalanine **3** or the lactone **5** (5.53 mmoles), dissolved in the minimum of acetone was added and the reaction mixture agitated at room temperature during 24 hours. Treating the reaction is carried out identically to that previously reported for the use of sodium hydride in DMF.

*tert-butyl 4-(1-(benzyloxy)-3-(ethoxycarbonyl)thioureido)-2-(tert-butoxycarbonyl)butanoate **4**:* Yield: 90%; oil; Rf: 0,35 (ether-hexane: 3/1); 1H -NMR (250 MHz, $CDCl_3$) δ (ppm): 1.26 (t, 3H, CH_3 , $J = 6.6$ Hz), 1.44 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.85-2.28 (m, 2H, $CH_{2\beta}$), 2.8-3.0 (m, 2H, $CH_{2\gamma}$), 4.12-4.21 (q, 2H + 1H, CH_2-CH_3 , $CH-NH$, $J = 6.6$ Hz), 5.06 (s, 2H, CH_2-Ph), 7.36 (m, 5H, Harom), 7.97 (s, 1H, $NHBoc$), 11.6 (s, 1H, $NH-CO$); MS-FAB (Matrix: NBA): $[M+H]^+ = 512$; $[\alpha]_D = +4$ ($C = 6$, $CHCl_3$).

*3-(1-(benzyloxy)-3-(ethoxycarbonyl)thioureido)-2-(tert-butoxycarbonyl)propanoic acid **6**:* Yield: 40%; oil; 1H -NMR (250 MHz, $CDCl_3$) δ (ppm): 1.28 (t, 3H, CH_3 , $J = 7.13$ Hz), 1.46 (s, 9H, $C(CH_3)_3$), 3.2-3.55 (m, 2H, $CH_{2\beta}$), 4.17 (q, 2H, CH_2-CH_3 , $J = 7.13$ Hz), 4.45-4.62 (m, 1H, CH_α), 5.05 (s, 2H, CH_2-Ph), 7.39 (m, 5H, Harom), 7.9 (s, 1H, $NHBoc$), 10.5 (s, 1H, $NH-CO$); MS-FAB (Matrix: NBA): $[M+H]^+ = 440$; $[\alpha]_D = -13$ ($C = 1$, $CHCl_3$).

Acid hydrolysis of the tert-butylic ester and t-butyloxycarbonyl: To a solution of *N*-protected amino ester **4** (1 mmol) in 10 mL of 1N HCl/AcOH was stirred for two hours at room temperature. After evaporation under vacuum of the solvent, the amino acid hydrochloride **7** is crystallized from ether, solubilized in the minimum of methanol and neutralized with propylene oxide to lead to corresponding amino acid **8**.

*2-amino-4-(1-(benzyloxy)-3-(ethoxycarbonyl)thioureido)butanoic acid hydrochloride **7**:* Yield: quantitative; white solid; mp: 131°C (methanol-ether); MS-FAB (Matrix: NBA): $[M]^+ = 356$; Anal. Calcd. for $[C_{15}H_{22}N_3O_5S]$: C, 45.97; H, 5.61; N, 10.72; S, 8.17. Found: C, 45.82; H, 5.62; N, 10.50; S, 8.31.

*2-amino-4-(1-(benzyloxy)-3-(ethoxycarbonyl)thioureido)butanoic acid **8**:* Yield: 80%; white solid; mp: 143°C (water-methanol); 1H -NMR (250 MHz, $DMSO-d_6$) δ (ppm): 1.22 (t, 3H, CH_3 , $J = 6.6$ Hz), 1.7-2.2 (m, 2H, $CH_{2\beta}$), 2.7-3.1 (m, 2H, $CH_{2\gamma}$), 3.2-3.5 (m, 1H, CH_α), 4.1 (q, 2H, CH_2-CH_3 , $J = 6.6$ Hz), 5.09 (s, 2H, CH_2-Ph), 7.3-7.49 (m, 5H, Harom), 8.2 (s, 1H, $NH-CO$); MS-FAB (Matrix: NBA): $[M+H]^+ = 356$; Anal. Calcd. for $[C_{15}H_{21}N_3O_5S]$: C, 50.70; H, 5.91; N, 11.83; S, 9.01. Found: C, 50.59; H, 5.81; N, 11.68; S, 9.11; $[\alpha]_D = +13.97$ ($C = 0.465$, HCl 4N).

4. Conclusion

The works that we realized show the difficulty of synthesis of sulfur-containing analogues of quisqualic acid. The need for obtaining unprotected amino acids themselves represents an increased additional difficulty because of the multiple functions. Despite this, we have prepared the linear analogues of quisqualic and homoquisqualic acids while controlling the chirality in position 2.

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