Tetrazole-containing derivatives of 4-amino-3-phenylbutanoic acid

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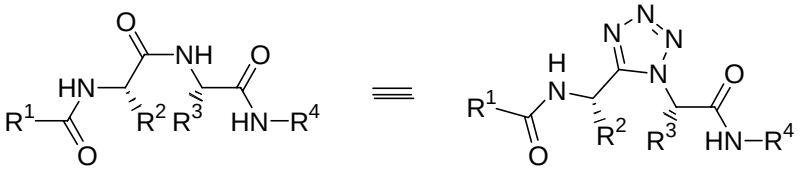
The paper is dedicated to Professor Alexander Pozharsky on his 70th birthday

Abstract
The molecule 4-amino-3-phenylbutanoic acid contains amino and carboxy terminal groups. The reactivity of both groups was utilized for preparation of corresponding tetrazole-containing derivatives. The terminal amino group was directly replaced by a tetrazol-1-yl fragment through reaction of 4-amino-3-phenylbutanoic acid hydrochloride with triethyl orthoformate and sodium azide in acetic acid. 4-Amino-3-phenylbutanoic acid was converted into 4-(tetrazol-1-yl)-3-phenylbutanoic acid and also methyl 4-(5-methyltetrazol-1-yl)-3-phenylbutanate in 79 and 45% yields, respectively.

Keywords: Tetrazoles, 4-amino-3-phenylbutanoic acid, heterocyclization, esterification, acylation

Introduction

The tetrazole ring as an analog and metabolically stable substitute of a carboxy group is extensively used in molecular design and in the synthesis of modified amino acids and peptidomimetics.[1] Certain analogs of natural amino acids containing one or several tetrazole rings have been synthesized.[2]



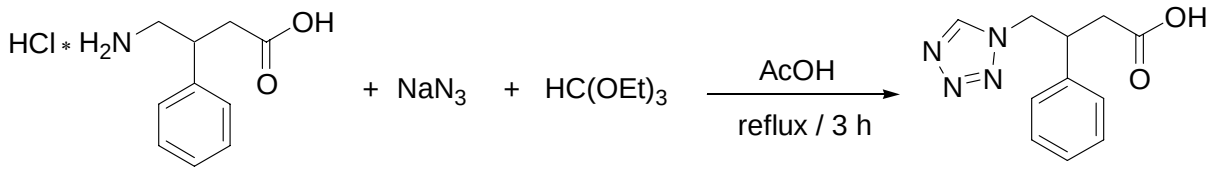
cis-amide tetrazole isostere

R^1, R^2 ,R^3, R^4 – amino acid side chains

4-Aminobutanoic acid (GABA) was historically the first nootropic drug.[3] 4-Amino-3-phenylbutanoic **1**, the corresponding hydrochloride **1a** (Phenibutium), and some other derivatives of acid **1** belong to a new generation of nootropic drugs.[4] The introduction of a tetrazole ring into the molecule of 4-amino-3-phenylbutanoic acid **1**, and also of some derivatives of this substrate might afford promising metabolically stable analogs. We report here on the synthesis of 4-(tetrazol-1-yl)-3-phenylbutanoic acid and methyl 4-(5-methyltetrazol-1-yl)-3-phenylbutanoate, the first tetrazole-containing derivatives and analogs of 4-amino-3-phenylbutanoic acid **1**.

Results and Discussion

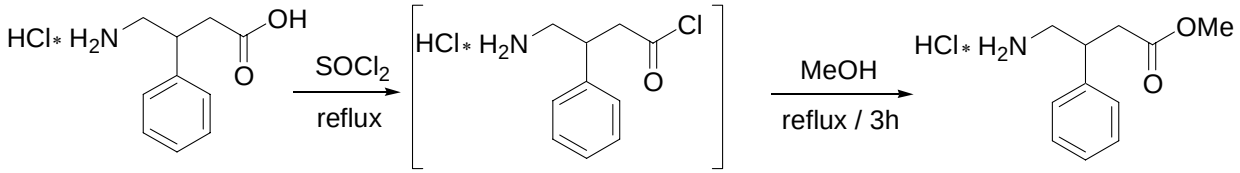
The conversion of an amino group of a primary amine into a tetrazole ring effected by a triethyl orthoformate - sodium azide system in acetic acid is well documented.[5] However, this procedure was not formerly applied to the conversion of amino acids into the corresponding tetrazole-containing derivatives. We demonstrated that the amino group of compound **1** reacted with the above-mentioned reagents to afford a tetrazole derivative, 4-(tetrazol-1-yl)-3-phenylbutanoic acid **2**.



1a **2**

Scheme 1

We also carried out an alternative way of tetrazol-1-yl substituent introduction into the structure of an ester of 4-amino-3-phenylbutanoic acid**.** The corresponding synthesis route was based on the conversion of primary amides into 1,5-disubstituted tetrazoles.[2] In the first stage acid chloride **3** was obtained *in situ* and subsequently subjected to esterification into ester **4.**

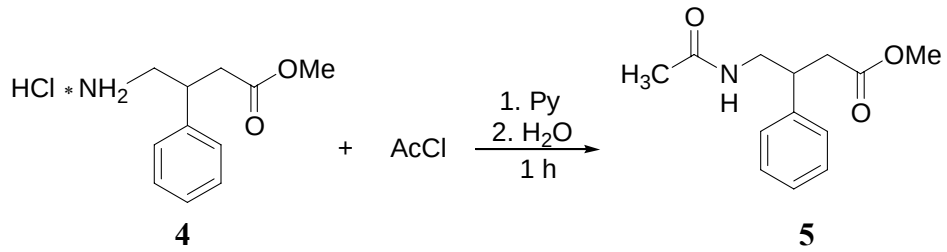


1 **3** **4**

Scheme 2

In the second stage, acylation of the terminal amino group was performed in pyridine

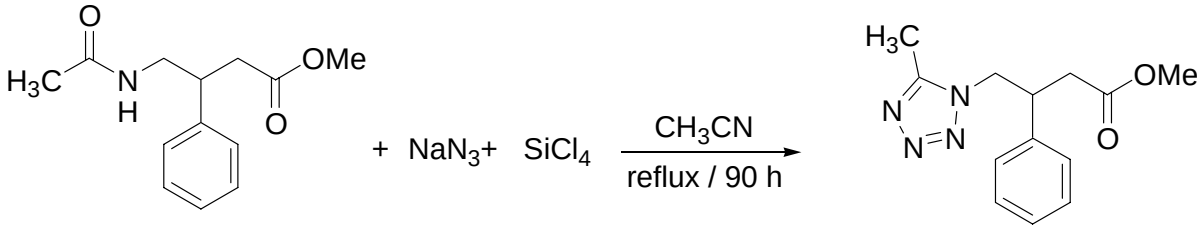
transforming ester **4** into amide **5.**



4 **5**

Scheme 3

Following the procedure,[2] we succeeded in converting amide **5** into tetrazole derivative **6.**



5 **6**

Scheme 4

Hence in this study we obtained the first representatives of tetrazole-containing analogs of 4-amino-3-phenylbutanoic acid.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer. IR spectra were recorded on a SHIMADZU FTIR-8400 spectrophotometer. Elemental analysis was performed on a Hewlett-Packard 185 C,H,N-analyzer semi-automatic instrument. Reaction progress was monitored by TLC on Merck Kieselgel $60F_{254}$ plates, and spots were visualized under UV light.

4-(Tetrazol-1-yl)-3-phenylbutanoic acid (2). Hydrochloride **1a** (21.5 g, 0.1 mol) and sodium azide (7.15 g, 0.11 mol) were added with stirring to a solution of triethyl orthoformate (60 g, 44 ml, 0.3 mol) and acetic acid (70 ml). The mixture was heated to 100 °C and kept at this temperature for 3 h. Then the reaction mixture was cooled, filtered, and the filtrate was evaporated in a vacuum. The residue was dissolved in acetone (100 ml), filtered, and the filtrate was evaporated in a vacuum. The residue was dissolved in distilled water (50 ml), and a

concentrated solution of sodium hydroxide was added thereto till pH ≈ 9-10. The solution was treated with activated carbon, filtered, and acidified with a concentrated solution of hydrochloric acid till pH ≈ 2 was reached. The precipitate was filtered off and recrystallized from ethanol to give the tetrazole **2 (**18.3 g, 79%), mp 175 °C, ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 12.23 (brs, 1H, O*H*), 9.01 (s, 1H, *H*C^5), 7.32 (m, 5H, C$_6$*H*$_5$), 4.78 (m, 2H, C*H*$_2$), 3.72 (quintet, *J* 8.5 Hz, 1H, C*H*), 2.74 (m, 2H, C*H*$_2$). ^{13}C NMR spectrum (75 MHz, DMSO-d_6) δ 172.4, 151.1, 140.0, 128.5, 127.7, 127.3, 51.9, 42.0, 37.5. IR (KBr, cm^{-1}) 3126, 2985, 2929, 1708, 1456, 1260, 1139, 1072, 1018, 981, 734, 704. Anal. Calcd for $C_{11}H_{12}N_4O_2$ (232): C, 56.89; H, 5.21; N, 24.12. Found: C, 56.75; H, 5.28; N, 24.01.

Methyl 4-amino-3-phenylbutanoate hydrochloride (4). Hydrochloride **1a** (21.5 g, 0.1 mol) was dissolved in methanol (300 ml) at room temperature, and thionyl chloride (17.9 g, 0.15 mol) was added thereto at a rate maintaining a weak boiling of the reaction mixture. The reaction mixture was then heated at reflux for 3 h and then it was cooled to room temperature. The separated precipitate was filtered off, dried in an air flow and recrystallized from methanol to give the hydrochloride **4 (**17.2 g, 75%), Mp 159 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.21 (brs, 3H, N*H*$_3^+$), 7.30 (m, 5H, C$_6$*H*$_5$), 3.80 (s, 3H, C*H*$_3$O), 3.39 (quintet, *J* 8.5 Hz, 1H, C*H*), 2.98-2.58 (m, 4H, C*H*$_2$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.0, 140.5, 128.6, 127.9, 127.2, 51.5, 43.5, 39.7, 37.9. IR (KBr, cm^{-1}) 3150, 2940, 1735, 734, 704. Anal. Calcd for $C_{11}H_{15}NO_2$*HCl (229.5): C, 57.52; H, 7.02; N, 6.10. Found: C, 57.10; H, 7.23; N, 6.02.

Methyl 4-(acetylamino)-3-phenylbutanoate (5). Hydrochloride **4** (11.35 g, 0.05 mol) was dissolved in dry pyridine (50 ml) at room temperature. On cooling to 0-5 °C, acetyl chloride (3.95 g, 0.05 mol) was added dropwise and the reaction mixture was maintained at this temperature for 1 h. Afterwards the solution was poured into an ice –water mixture (500 g). The precipitate was filtered off, dried in an air flow and recrystallized from ethyl ether to give the amide **5** (8 g, 68%), Mp 41 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (brs, 1H, N*H*), 7.30 (m, 5H, C$_6$*H*$_5$), 3.46 (s, 3H, C*H*$_3$O), 3.24 (m, 3H, C*H*+C*H*$_2$), 2.68 (m, 2H, C*H*$_2$), 1.77 (s, 3H, C*H*$_3$-C=O). ^{13}C NMR spectrum (75 MHz, DMSO-d_6) δ 172.0, 169.3, 142.0, 128.3, 127.5, 126.6, 51.1, 44.0, 37.7, 22.4. IR (KBr, cm^{-1}) 3321, 3314, 2998, 2964, 1730, 1653, 734, 704. Anal. Calcd for $C_{13}H_{17}NO_3$ (235): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.49; H, 7.23; N, 5.90.

Methyl 4-(5-methyltetrazol-1-yl)-3-phenylbutanoate (6). To a suspension of amide **5** (4.7 g, 0.02 mol) and sodium azide (2.6 g, 0.04 mol) in anhydrous acetonitrile (20 ml) was added, by small portions, a solution of $SiCl_4$ (6.8 g, 0.04 mol) in anhydrous acetonitrile (20 ml). The reaction mixture was heated to boiling and maintained at reflux with sampling every 6 h to control the conversion of initial amide **5** (TLC monitoring). When initial amide **5** was found in the reaction mixture, an extra amount of the azidizing agent was added (0.01 mol of NaN_3 and 0.01 mol of $SiCl_4$), and the heating was continued till complete conversion of amide **5** (TLC). On completion of the reaction the mixture was cooled to room temperature and then in small portions it was poured into a saturated solution of sodium carbonate (250 ml) maintaining pH > 7 (**CAUTION!**: the formation of explosive HN_3 is possible). The solution obtained was extracted with ethyl acetate (5 ×). The combined organic solutions were washed with distilled water and

dried with Na_2SO_4. Then the solvent was evaporated in a vacuum, and the residue was recrystallized from ethanol to give the tetrazole **6** (2.87 g, 45%), Mp 122 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40 (m, 5H, C_6H_5), 3.40 (s, 3H, CH_3O), 4.73 (m, 2H, CH_2), 3.69 (quintet, *J* 8.5 Hz, 1H, C*H*), 2.70 (m, 2H, CH_2), 2.40 (s, 3H, CH_3-C^5). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.5, 155.3, 142.1, 128.2, 127.6, 126.8, 52.3, 50.9, 42.1, 37.7. IR (KBr, cm^{-1}) 2980, 2960, 1732, 1450, 1265, 1140, 1070, 1010, 980, 730, 700. Anal. Calcd for $C_{13}H_{16}N_4O_2$ (260): C, 59.99; H, 6.20; N, 21.52. Found: C, 59.20; H, 6.53; N, 21.01.

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