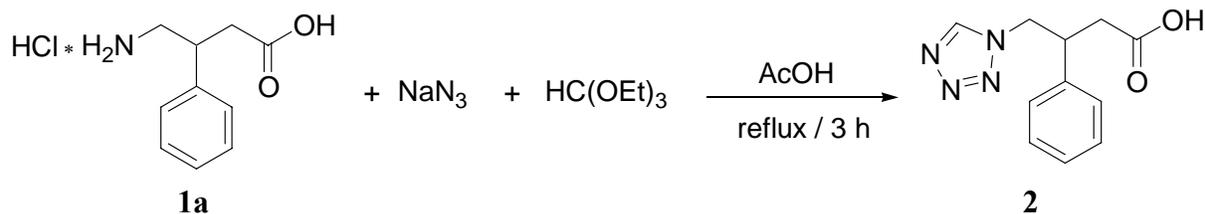


4-Aminobutanoic acid (GABA) was historically the first nootropic drug.³ 4-Amino-3-phenylbutanoic acid **1**, the corresponding hydrochloride **1a** (Phenibutium), and some other derivatives of acid **1** belong to a new generation of nootropic drugs.⁴ The introduction of a tetrazole ring into the molecule 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**.

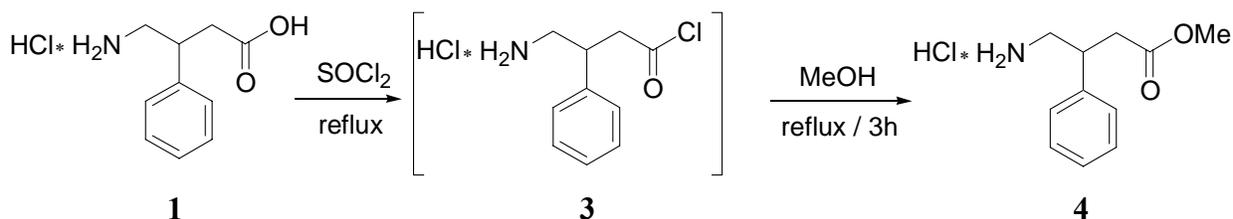
Results and Discussion

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**.



Scheme 1

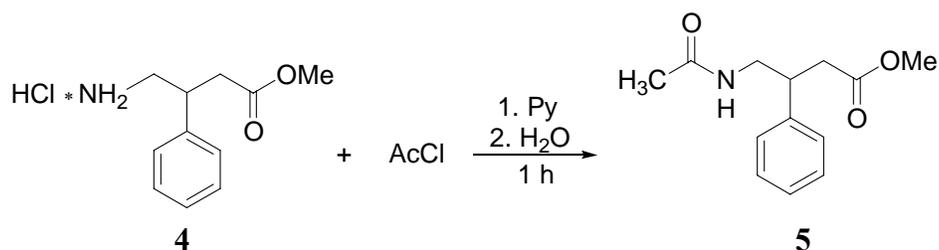
We also carried out an alternative way of tetrazol-1-yl substituent introduction into the structure of an ester of 4-amino-3-phenylbutanoic acid. The corresponding synthesis route was based on the conversion of primary amides into 1,5-disubstituted tetrazoles.² In the first stage acid chloride **3**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



Scheme 2

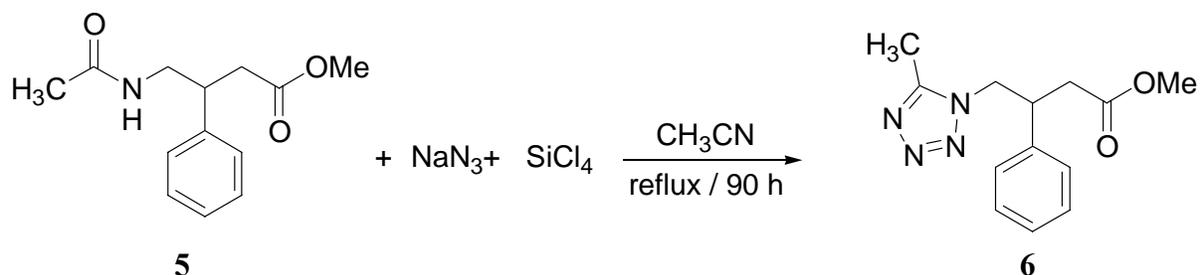
In the second stage, acylation of the terminal amino group was performed in pyridine

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



Scheme 3

Following the procedure,² we succeeded in converting amide **5** into tetrazole derivative **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. ¹H and ¹³C 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 60F₂₅₄ 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 \approx 9-10. The solution was treated with activated carbon, filtered, and acidified with a concentrated solution of hydrochloric acid till pH \approx 2 was reached. The precipitate was filtered off and recrystallized from ethanol to give the tetrazole **2** (18.3 g, 79%), mp 175 °C, ^1H NMR spectrum (300 MHz, DMSO- d_6): δ 12.23 (brs, 1H, OH), 9.01 (s, 1H, HC 5), 7.32 (m, 5H, C $_6$ H $_5$), 4.78 (m, 2H, CH $_2$), 3.72 (quintet, J 8.5 Hz, 1H, CH), 2.74 (m, 2H, CH $_2$). ^{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 $_4$ O $_2$ (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, ^1H NMR (300 MHz, DMSO- d_6): δ 8.21 (brs, 3H, NH $_3^+$), 7.30 (m, 5H, C $_6$ H $_5$), 3.80 (s, 3H, CH $_3$ O), 3.39 (quintet, J 8.5 Hz, 1H, CH), 2.98-2.58 (m, 4H, CH $_2$). ^{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, ^1H NMR (300 MHz, DMSO- d_6) δ 7.91 (brs, 1H, NH), 7.30 (m, 5H, C $_6$ H $_5$), 3.46 (s, 3H, CH $_3$ O), 3.24 (m, 3H, CH+CH $_2$), 2.68 (m, 2H, CH $_2$), 1.77 (s, 3H, CH $_3$ -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 \times). The combined organic solutions were washed with distilled water and

dried with Na₂SO₄. 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. ¹H NMR (300 MHz, DMSO-d₆) δ 7.40 (m, 5H, C₆H₅), 3.40 (s, 3H, CH₃O), 4.73 (m, 2H, CH₂), 3.69 (quintet, *J* 8.5 Hz, 1H, CH), 2.70 (m, 2H, CH₂), 2.40 (s, 3H, CH₃-C⁵). ¹³C NMR (75 MHz, DMSO-d₆) 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 C₁₃H₁₆N₄O₂ (260): C, 59.99; H, 6.20; N, 21.52. Found: C, 59.20; H, 6.53; N, 21.01.

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