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Polynuclear Tetrazole-Containing Amino Acid Analogs

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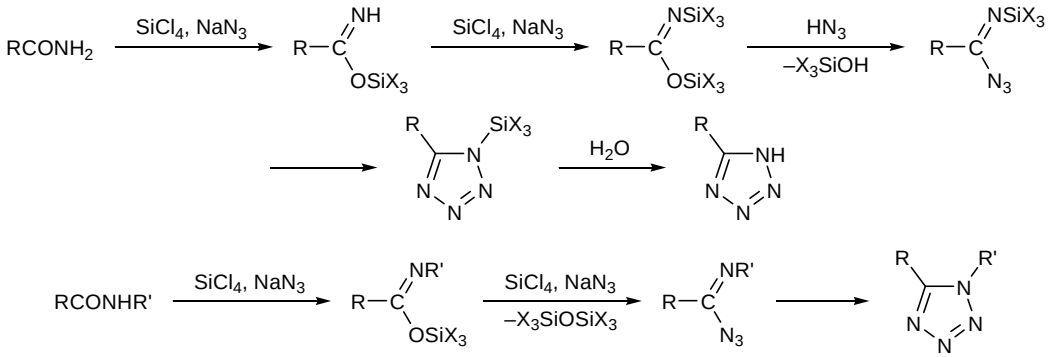
Abstract—New analogs of (D,L)-phenylalanine containing tetrazole rings were synthesized. The acidity constants of (D,L)-phenylalanine and (D,L)-tryptophane derivatives containing a tetrazole ring with no substituent on N^1 (pK_a = 3.0–3.1) and of the corresponding carboxylic acids (pK_a = 2.9–3.3) in aqueous methanol were determined by potentiometric titration.

Tetrazole-containing analogs of amino acids and peptides are important for the development of modern therapeutic agents due to their resistance to enzymatic cleavage and hydrolysis and the possibility for improving bioavailability and bioselectivity. A combination of such properties is favorable from the viewpoint of pharmacology, thus making these compounds attractive targets of organic synthesis. For example, Zabrocki *et al*. [1] proposed to modify peptides or particular amino acids with tetrazole fragments to obtain some peptidomimetics with a *cis*-blocked peptide bond. For this purpose, a secondary amine is generally treated with PCl_5 in the presence of quinoline, and intermediate imidoyl chloride is brought into reaction with a solution of hydrazoic acid [1, 2]. An alternative way of peptide bond modification with a tetrazole fragment involves the system PPh_3–DEAD–$TMSN_3$ [3]. It was also shown [4] that reactions of N-substituted carboxylic acid amides with trifluoromethanesulfonic anhydride (Tf_2O) and sodium azide give the corresponding 1,5-disubstituted tetrazoles [4]. El-Ahl *et al*. [5] recently proposed a procedure for the synthesis of tetrazoles from carboxamides using the system tetrachlorosilane–sodium azide. A probable mechanism of this process is shown in Scheme 1. The system $SiCl_4$–NaN_3 ensures preparation of both 1,5-disubstituted [6] and 1-unsubstituted tetrazoles [5, 6], and it can be applied to various substrates, amino acids among these. Following this procedure, tetrazole-containing analogs of (D,L)-phenylalanine, (D,L)-leucine [7], and (D,L)-tryptophane [8] were synthesized.

We have extended the above approach to the synthesis of structures containing both two and three tetrazole rings. As starting compound we used previously synthesized ditetrazole **I** [7]. It was treated with chloroacetamide in the presence of triethylamine to obtain tetrazolylacetamide **II**, and reaction of the latter with the system tetrachlorosilane–sodium azide gave compound **III** containing three differently substituted tetrazole rings. By alkaline hydrolysis of **II** we obtained tetrazolylacetic acid **IV** (Scheme 2). The syntheses were performed according to the procedures

Scheme 1.



$SiX_3 = SiCl_n(N_3)_{3-n}$, n = 0–3.

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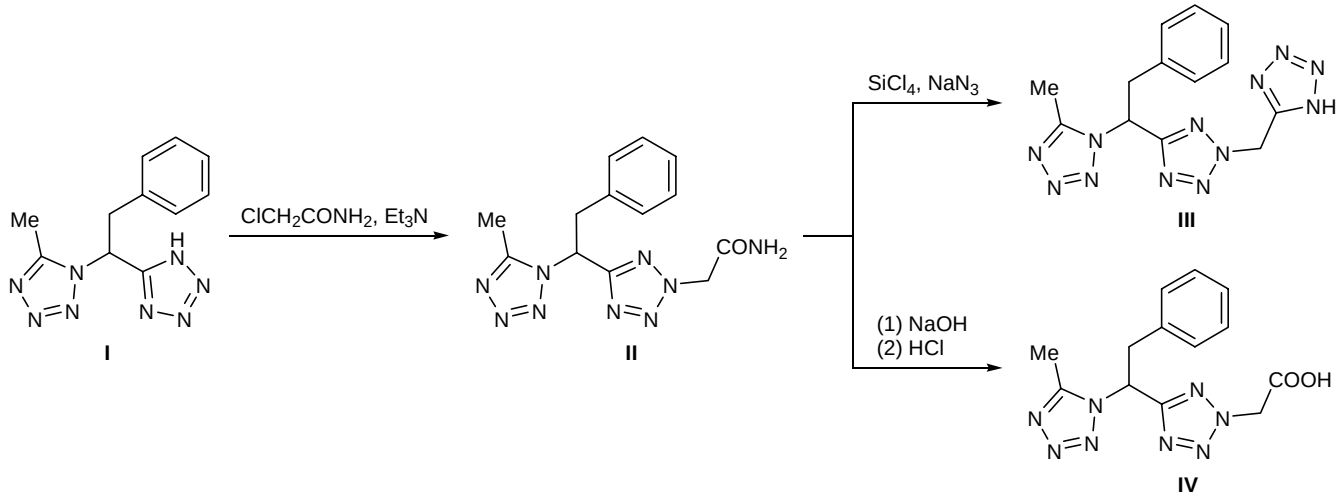
Scheme 2.



described in [7, 8]. The alkylation of ditetrazole **I** afforded a mixture of isomers, N^2-isomer **II** prevailing. Pure compound **II** was isolated by recrystallization from ethanol.

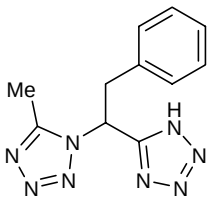
Low toxicity and high resistance to biochemical decomposition are the main factors responsible for successful application of tetrazole derivatives as isosteric analogs of carboxy group in molecular design of medical agents [9]. Furthermore, pK_a values of carboxylic acids and the corresponding NH-tetrazoles differ only slightly [10]. In the present work we determined by potentiometric titration acidity constants of some previously synthesized compounds **V**–**VII** [7, 8], as well as of the new polynuclear tetrazole-containing analogs of (D,L)-phenylalanine (compounds **III** and **IV**) (see below). It is seen that the pK_a values of the examined NH-tetrazoles and the corresponding carboxylic acids are very similar, in keeping with the known relation. On the other hand, the NH and COOH acidities of compounds **I** and **III**–**VII** are relatively high, presumably due to electron-acceptor effect of the tetrazole rings.

EXPERIMENTAL

Potentiometric measurements were performed using a pH-121 potentiometer equipped with an ESL-43-07 glass electrode, an EVL-1M3 silver chloride electrode, and a temperature-controlled cell (25°C). The titration was carried out in 50% aqueous methanol which was freed from carbon dioxide; a 0.1 N solution of sodium hydroxide was used as titrant, and a 0.1 N solution of sodium nitrate, as supporting electrolyte. The pK_a values were calculated as described in [11]. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer at 300 and 75 MHz, respectively, using DMSO-d_6 as solvent and reference. The progress of reactions and the purity of products were monitored by TLC on Kieselgel 60 F_{254} plates (Merck) using $CHCl_3$–MeOH (9:1 or 95:5) as eluent; spots were visualized with UV light.

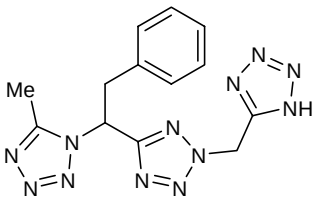
(*R*,*S*)-5-[1-(5-Methyl-1-tetrazolyl)-2-phenylethyl]-2-tetrazolylacetamide (II). Chloroacetamide, 4.77 g (0.051 mol), was added with stirring to a mixture of 10.9 g (0.043 mol) of compound **I**, 90 ml of acetonitrile, and 5.16 g (0.051 mol) of triethylamine. The mixture was heated for 6–7 h under reflux (TLC), the solvent was removed under reduced pressure, and the residue was treated with a 1:1 ethyl acetate–water mixture. The organic phase was separated, the solvent was removed under reduced pressure, and the residue was recrystallized from a minimal amount of ethanol. Yield 8.91 g (67%), light yellow crystals. An analytical sample was obtained by repeated recrystallization from ethanol, mp 133–135°C. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.65–3.80 m (1H, C**H**$_2$Ph), 3.92 d.d (1H, C**H**$_2$Ph, J = 5.1, 13.8 Hz), 5.48 s (2H, C**H**$_2$CO), 6.59 d.d (1H, CH, J = 5.1, 10.9 Hz), 7.10–7.25 m (5H, H_{arom}), 7.24 br.s and 7.56 br.s (1H each, $CONH_2$). ^{13}C NMR spectrum, δ_C, ppm: 8.1 (CH_3); 37.8 (**C**H_2Ph); 54.4 (**C**H_2CO); 54.8 (CH); 127.2, 128.4, 129.1, 135.4 (C_{arom}); 152.5 (**C**CH_3); 163.0 (**C**CH), 165.7 (**C**ONH_2). Found, %: C 50.10; H 5.25; N 40.38. $C_{13}H_{15}N_9O$. Calculated, %: C 49.83; H 4.83; N 40.24.

(*R*,*S*)-5-[1-(5-Methyl-1-tetrazolyl)-2-phenylethyl]-2-(5-tetrazolylmethyl)tetrazole (III). A reactor equipped with a reflux condenser (capped with a drying tube) and a magnetic stirrer was charged with 5.0 g



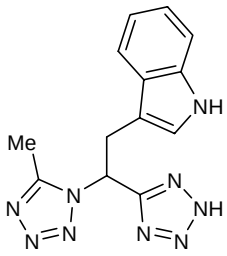
I

pK_a 2.99 ± 0.06



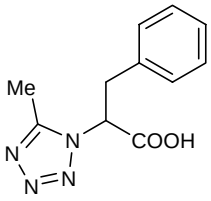
III

3.06 ± 0.05



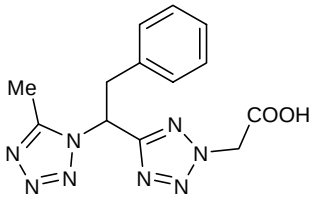
VI

3.13 ± 0.05



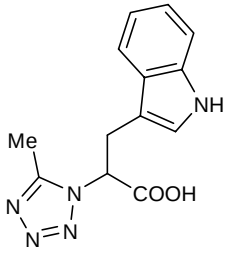
V

pK_a 3.03 ± 0.06



IV

2.90 ± 0.06



VII

3.27 ± 0.06

(0.016 mol) of amide **II**, 3.11 g (0.048 mol) of sodium azide, and 70 ml of acetonitrile, and a solution of 5.42 g (0.032 mol) of tetrachlorosilane in 20 ml of acetonitrile was added with stirring. The mixture was heated for 6 h under reflux and analyzed by TLC for initial amide **II**. If necessary, additional amounts of the reactants were added. This procedure was repeated every 6 h until initial amide **II** disappeared completely. The overall reaction time was 33 h. The mixture was then poured in small portions into a solution of sodium carbonate, maintaining the pH value greater than 7. The precipitate of silicic acid was filtered off, charcoal was added to the filtrate, and the mixture was stirred for 0.5 h and filtered. A solution of sodium nitrite was added to the filtrate, and the mixture was slowly acidified to pH 2 by adding dilute hydrochloric acid. The solution was cooled, and the precipitate was filtered off. Yield 2.63 g (49%), colorless crystalline substance, mp 70–73°C. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.65–3.75 m (1H, C**H**$_2$Ph), 3.90 d.d (1H, C**H**$_2$Ph, J = 5.1, 13.8 Hz), 6.48 s (2H, NCH_2C), 6.58 d.d (1H, CH, J = 5.8, 10.2 Hz), 7.15–7.25 m (5H, Ph), 12.28 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 8.1 (CH_3); 37.9 (**C**H_2Ph); 46.5 (N**C**H_2C); 54.3 (CH); 127.3, 128.5, 129.2, 135.3 (C_{arom}); 152.6 (CH_3**C**); 152.9 (NCH_2**C**), 163.7 (CH). Found, %: C 45.77; H 5.34; N 49.85. $C_{13}H_{14}N_{12}$. Calculated, %: C 46.15; H 4.17; N 49.68.

(*R*,*S*)-5-[1-(5-Methyl-1-tetrazolyl)-2-phenylethyl]-2-tetrazolylacetic acid (IV). Amide **II**, 2.5 g (0.008 mol), was dissolved in a solution of 0.96 g (0.024 mol) of sodium hydroxide in 50 ml of water on heating to the boiling point, and the solution was kept for 1 h at room temperature. It was diluted with 50 ml of water, acidified to pH 2 with hydrochloric acid, and cooled. The precipitate was filtered off and recrystallized from 50% ethanol. Yield 1.95 g (78%), colorless crystalline substance, mp 184–185°C. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.70–3.80 m (1H, C**H**$_2$Ph), 3.90–4.00 m (1H, C**H**$_2$Ph), 5.76 s (2H, CH_2CO), 6.55–6.70 m (1H, CH), 7.15–7.30 m (5H, H_{arom}), 13.80 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 8.1 (CH_3); 37.9 (**C**H_2Ph); 53.9 (**C**H_2CO); 54.4 (CH); 127.3, 128.5, 129.2, 135.4 (C_{arom}); 152.5 (CH_3**C**); 163.3 (CH**C**); 167.2 (COOH). Found, %: C 49.30; H 4.78; N 35.67. $C_{13}H_{14}N_8O_2$. Calculated, %: C 49.68; H 4.49; N 35.65.

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