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Linear Polynuclear Tetrazole-Containing Compounds

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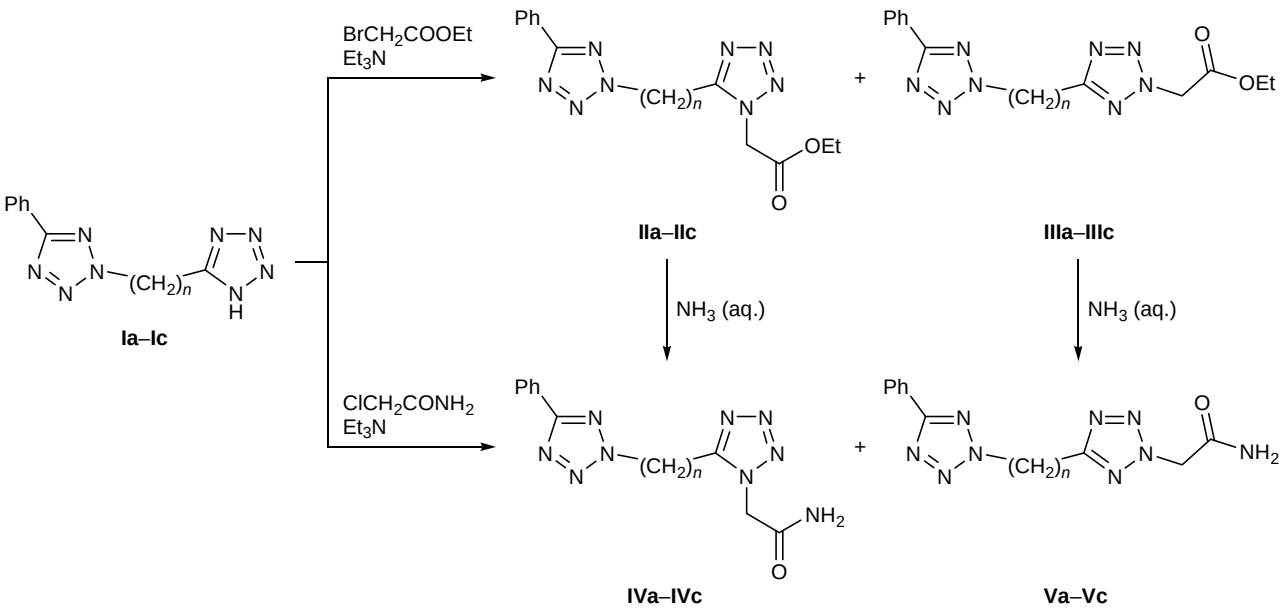
Abstract—Linear polynuclear tetrazole-containing compounds were synthesized. Alkylation of 5-[ω-(5-phenyl-2-tetrazolyl)alkyl]tetrazoles with ethyl bromoacetate and chloroacetamide gave the corresponding esters and amides. Treatment of the latter with tetrachlorosilane–sodium azide afforded compounds containing three tetrazole rings linked through polymethylene bridges. Acid ionization constants of the products possessing an NH-tetrazole ring (pK_a = 2.9–3.2) and the corresponding carboxylic acids (pK_a = 2.9–3.1) in aqueous methanol were determined by potentiometric titration.

In the recent years, much attention is given to 5-substituted tetrazoles and compounds possessing two or more tetrazole rings. Polynuclear tetrazoles are often difficult to obtain and explore. The series of such compounds includes both branched molecules containing only several NH-tetrazole rings and linear structures consisting of 1,5- and 2,5-disubstituted and NH-tetrazole rings. Polytetrazole derivatives may be used in various fields. The synthesis of branched polynuclear tetrazole-containing compounds (podands) was reported previously. Their molecular structure and physical properties suggest a strong complexing power toward metal ions. Effecting filter materials for profound purification of biological liquids from heavy metals and radioactive elements have been developed on the basis of some tetrazole podands [1, 2]. A promising line in this field of chemistry is the synthesis of macrocyclic tetrazole-containing compounds, e.g., analogs of 12-crown-4 [3]. In addition, polytetrazole fragments can be used as linkers in the design of

Scheme 1.



n = 1 (**a**), 2 (**b**), 3 (**c**).

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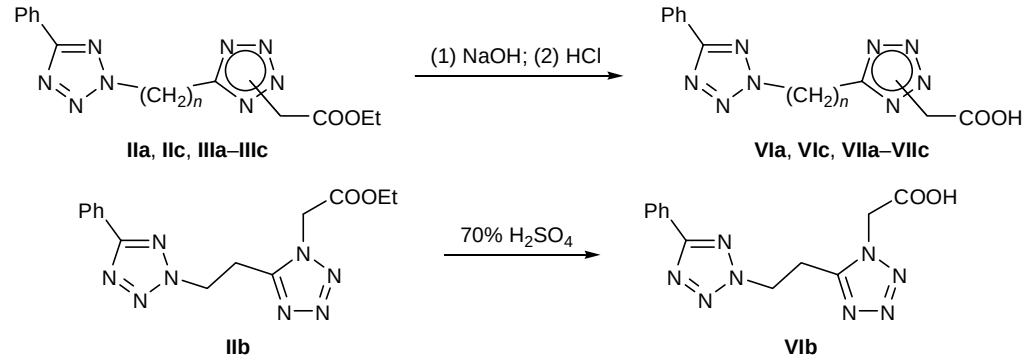
Scheme 2.



oligonucleotide systems [4]. Search for efficient procedures for the synthesis of new polynuclear tetrazoles and study of their physical and chemical properties seem to be important problems.

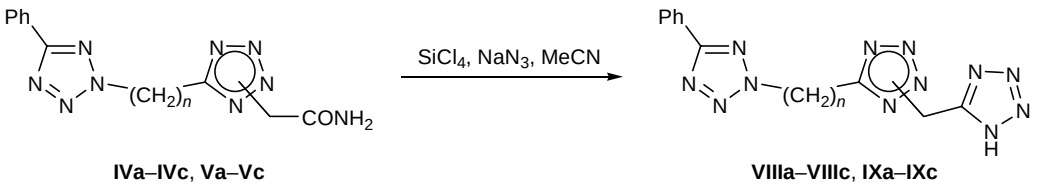
Tetrazolylacetamides are used as starting compounds for the preparation of linear polytetrazole-containing systems. Primary carboxylic acid amides can be converted into NH-tetrazoles by the action of tetrachlorosilane–sodium azide [5]. This approach may be applied to various substrates, including those derived from amino acids [6]. We have synthesized a series of previously unknown 5-[ω-(5-phenyl-2-tetrazolyl)-alkyl]-1(2)-tetrazolylacetic acids and their amides and ethyl esters. The amides were converted into the corresponding tritetrazoles by the action of $SiCl_4$–NaN_3.

One tetrazole ring in initial ditetrazole derivatives **Ia**–**Ic** contains an unsubstituted NH group [7]. It is known that alkylation of NH-tetrazoles gives as a rule mixtures of N^1- and N^2-substituted isomers [8]. Our results showed that mixtures of isomeric tetrazolylacetamides or ethyl tetrazolylacetates can be separated by fractional crystallization more readily than mixtures of analogous isomeric nitriles. By alkylation of 5-[ω-(5-phenyl-2-tetrazolyl)alkyl]tetrazoles with ethyl bromoacetate and chloroacetamide in the presence of triethylamine we obtained mixtures of the corresponding isomeric esters **IIa**–**IIc**/**IIIa**–**IIIc** and amides **IVa**–**IVc**/**Va**–**Vc** (Scheme 1). The isomers can be separated by fractional crystallization from alcohol or ether. Taking into account that amides **IVa**–**IVc** and **Va**–**Vc** melt above 100°C (126–188°C) and that esters **IIa**–**IIc**, **IIIa**, and **IIIb** are low-melting substances (mp 58–95°C), fractional crystallization is more convenient to separate the isomeric amides. Oily ester **IIIc** was separated from **IIc** by column chromatography.

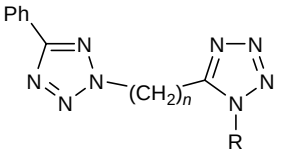
Carboxylic acids **VIa**, **VIc**, and **VIIa**–**VIIc** were obtained by alkaline hydrolysis of the corresponding esters and amides. Alkaline hydrolysis of ester **IIb** gave 5-phenyltetrazole as the major product, presumably as a result of retro-Michael reaction; therefore, it was subjected to acid hydrolysis to obtain acid **VIb** (Scheme 2). Treatment of amides **IVa**–**IVc** and **Va**–**Vc** with the system tetrachlorosilane–sodium azide in acetonitrile afforded tritetrazoles **VIIIa**–**VIIIc** and **IXa**–**IXc**, respectively (Scheme 3). It should be noted that the time necessary to complete the reaction with the N^1-isomers was longer by a factor of ~1.5 than for the N^2-isomers. Also, the reaction time appreciably increased in going from compounds having three methylene units to those possessing ethylene and methylene bridging groups in the initial ditetrazole.

Some specific features were observed in the ^1H and ^{13}C NMR spectra of the products. In going from amides **IV** and **V** to the corresponding tritetrazoles, the signal from the methylene protons neighboring to the terminal tetrazole ring shifts downfield by almost 1 ppm. Presumably, the reason is a strong electron-acceptor effect of the tetrazole ring. In the series of ditetrazolylmethane derivatives (n = 1), the chemical shifts of the CH_2CO protons are similar for both

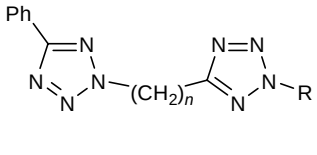
Scheme 3.



Acidity constants (25°C) of compounds **VI**–**IX**



VIa–**VIc**, **VIIIa**–**VIIIc**



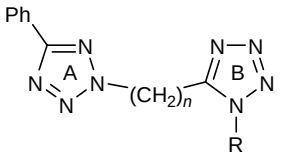
VIIa–**VIIc**, **IXa**–**IXc**

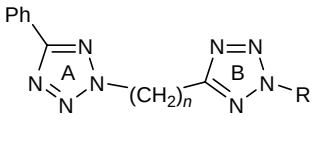
VI, **VII**, R = $HOCOCH_2$; **VIII**, **IX**, R = 5-tetrazolylmethyl.

n	NH acids		OH acids	
	comp. no.	pK_a	comp. no.	pK_a
1	**VIIIa**	3.03±0.06	**VIa**	2.96±0.04
2	**VIIIb**	3.01±0.05	**VIb**	3.01±0.05
3	**VIIIc**	3.06±0.06	**VIc**	2.95±0.05
1	**IXa**	2.93±0.05	**VIIa**	2.91±0.06
2	**IXb**	3.01±0.05	**VIIb**	3.01±0.06
3	**IXc**	3.15±0.06	**VIIc**	3.09±0.05

regioisomers. By contrast, the chemical shifts of protons in the bridging methylene group depend on the position of the substituent in ring B (Scheme 4). In the series of ethylene-bridged compounds (*n* = 2), the position of substituent in ring B insignificantly affects the chemical shift of the nearest CH_2 protons, while in compounds with a trimethylene bridge (*n* = 3) this effect is much stronger.

Scheme 4.





R = EtOCOC**H**$_2$, NH_2COC**H**$_2$, HOCOC**H**$_2$, HCN_4C**H**$_2$, *n* = 1–3.

Different regioisomers are characterized by different chemical shifts of the carbon atoms in the tetrazole rings [9]. The C^5 signal in the ^{13}C NMR spectra of 2,5-disubstituted tetrazoles appears at δ_C 160–165 ppm, and the corresponding signal from 1,5-disubstituted and NH-tetrazole rings is located at δ_C 150–155 ppm. The ^{13}C NMR spectra of the compounds synthesized in the present work were in full agreement with the above general relations.

The low toxicity and 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 [10]. It is important that pK_a values of carboxylic acids and the corresponding NH-tetrazoles differ insignificantly [11]. We determined the acidity constants of tetrazolylacetic acids **VI** and **VII** and NH-tetrazoles **VIII** and **IX** in aqueous methanol by potentiometric titration (see table). It is seen that, in keeping with the above stated, the pK_a values of NH-tetrazoles and the corresponding acids are very similar. Moreover, there is almost no difference between the pK_a values of the respective N^1- and N^2-isomers. Fairly strong acidity of the examined compounds is likely to result from electron-acceptor effect of the ditetrazole fragment.

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 [12]. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer at 300 and 75 MHz, respectively, using acetone-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. All the products, except for **IIIc** and **VIb**, were colorless crystalline substances.

General procedure for the synthesis of ethyl tetrazolylacetates IIa–IIc and IIIa–IIIc. Triethylamine, 51.5 mmol, was added under stirring to a suspension of 47 mmol of ditetrazole **I** in 70 ml of acetonitrile. Ethyl bromoacetate, 51.5 mmol, was then added, and the mixture was stirred for 5–6 h under reflux. The solvent was removed under reduced pressure, a 1:1 mixture of methylene chloride with water was added to the residue, and the organic phase was separated and washed in succession with two portions of a 5% solution of Na_2CO_3, water, 2% hydrochloric acid, and two portions of water. The solvent was removed under reduced pressure, and the isomeric products were separated by repeated crystallization from ethanol or diethyl ether.

Ethyl 5-(5-phenyl-2-tetrazolylmethyl)-1(2)-tetrazolyl acetates (IIa/IIIa). Yield 96% (mixture of isomers), isomer ratio 1:1 (according to the ^1H NMR data). Isomer **IIa**: Yield 29%, mp 95°C (from Et_2O).

^{1}H NMR spectrum, δ, ppm: 1.21 t (3H, CH_3, *J* = 7.3 Hz), 4.14 q (2H, OCH_2, *J* = 7.3 Hz), 5.72 s (2H, CH_2CO), 6.55 s (2H, NCH_2C), 7.50–7.60 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.2 (CH_3); 45.7 (**C**H_2CO); 49.4 (N**C**H_2C); 63.2 (OCH_2); 127.5, 128.0, 130.0, 131.6 (C_{arom}), 151.0 (CH_2**C**N); 166.3 (Ph**C**); 166.6 (CO). Found, %: C 49.28; H 4.42; N 36.01. $C_{13}H_{14}N_8O_2$. Calculated, %: C 49.68; H 4.49; N 35.65. Isomer **IIIa**: Yield 37%, mp 58°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, CH_3, *J* = 7.3 Hz), 4.23 q (2H, OCH_2, *J* = 7.3 Hz), 5.73 s (2H, CH_2CO), 6.40 s (2H, NCH_2C), 7.50–7.55 m (3H, H_{arom}), 8.10–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.2 (CH_3); 48.3 (**C**H_2CO); 54.3 (N**C**H_2C); 62.9 (OCH_2); 127.4, 128.1, 129.9, 131.3 (C_{arom}); 161.3 (CH_2**C**N), 166.0 (Ph**C**), 166.2 (CO). Found, %: C 49.65; H 4.76; N 36.09. $C_{13}H_{14}N_8O_2$. Calculated, %: C 49.68; H 4.49; N 35.65.

Ethyl 5-[2-(5-phenyl-2-tetrazolyl)ethyl]-1(2)-tetrazolylacetates (IIb/IIIb). Yield 84% (mixture of isomers), isomer ratio 1:1 (^{1}H NMR). Isomer **IIb**: Yield 31%, mp 67°C (from Et_2O). ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, CH_3, *J* = 7.1 Hz), 3.84 t (2H, NCH_2C**H**$_2$C, *J* = 7.1 Hz), 4.23 q (2H, OCH_2, *J* = 7.1 Hz), 5.29 t (2H, NC**H**$_2CH_2C$, *J* = 7.1 Hz), 5.33 s (2H, CH_2CO), 7.50–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.9 (CH_3); 23.5 (NCH_2**C**H_2C); 48.5 (**C**H_2CO); 50.6 (N**C**H_2CH_2C); 63.0 (OCH_2); 127.3, 128.4, 129.8, 131.2 (C_{arom}), 154.0 (CH_2CH_2**C**); 165.6 (Ph**C**); 166.9 (CO). Found, %: C 50.99; H 5.08; N 34.10. $C_{14}H_{16}N_8O_2$. Calculated, %: C 51.21; H 4.91; N 34.13. Isomer **IIIb**: Yield 24%, mp 70°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3, *J* = 7.1 Hz), 3.76 t (2H, NCH_2C**H**$_2$C, *J* = 6.9 Hz), 4.20 q (2H, OCH_2, *J* = 7.1 Hz), 5.22 t (2H, NC**H**$_2CH_2$, *J* = 6.9 Hz), 5.60 s (2H, CH_2CO), 7.50–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.3 (CH_3); 26.0 (NCH_2**C**H_2C); 51.6 (**C**H_2CO); 53.9 (N**C**H_2CH_2); 62.8 (OCH_2); 127.3, 128.5, 129.8, 131.1 (C_{arom}); 163.9 (CH_2CH_2**C**); 165.5 (Ph**C**); 166.4 (CO). Found, %: C 50.85; H 4.85; N 33.86. $C_{14}H_{16}N_8O_2$. Calculated, %: C 51.21; H 4.91; N 34.13.

Ethyl 5-[3-(5-phenyl-2-tetrazolyl)propyl]-1(2)-tetrazolylacetates (IIc/IIIc). Yield 91% (mixture of isomers), isomer ratio 1:1 (^{1}H NMR). A part of N^1-isomer **IIc** was isolated by crystallization from ethanol. The remaining isomer mixture was separated by column chromatography on silica gel using chloroform as eluent. Isomer **IIc**: Yield 39%, mp 68°C (from Et_2O). ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3, *J* = 7.3 Hz), 2.65 quint (2H, CH_2C**H**$_2CH_2$, *J* = 7.3 Hz), 3.10 t (2H, NCH_2CH_2C**H**$_2$C, *J* = 7.3 Hz), 4.20 q (2H, OCH_2, *J* = 7.3 Hz), 4.95 t (2H, NC**H**$_2CH_2$, *J* = 6.5 Hz), 5.44 s (2H, CH_2CO), 7.50–7.60 m (3H, H_{arom}), 8.10–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.3 (CH_3); 20.5 (NCH_2CH_2**C**H_2C); 27.0 (CH_2**C**H_2CH_2); 48.4 (**C**H_2CO); 52.7 (N**C**H_2CH_2); 62.9 (OCH_2); 127.4, 128.6, 129.8, 131.1 (C_{arom}); 156.1 ($NCH_2CH_2CH_2$**C**); 165.6 (Ph**C**); 167.0 (CO). Found, %: C 52.86; H 5.78; N 33.01. $C_{15}H_{18}N_8O_2$. Calculated, %: C 52.62; H 5.30; N 32.73. Isomer **IIIc**: Yield 32%, oily substance. ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, CH_3, *J* = 7.3 Hz), 2.58 quint (2H, CH_2C**H**$_2CH_2$, *J* = 7.3 Hz), 3.07 t (2H, NCH_2CH_2C**H**$_2$C, *J* = 7.3 Hz), 4.23 q (2H, OCH_2, *J* = 7.3 Hz), 4.90 t (2H, NC**H**$_2CH_2$, *J* = 6.9 Hz), 5.61 s (2H, CH_2CO), 7.45–7.60 m (3H, H_{arom}), 8.10–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.3 (CH_3); 22.9 (NCH_2CH_2**C**H_2C); 28.0 (CH_2**C**H_2CH_2); 52.9 (**C**H_2CO); 53.9 (N**C**H_2CH_2); 62.8 (OCH_2); 127.4, 128.6, 129.8, 131.1 (C_{arom}); 165.6 (Ph**C**), 166.4 ($NCH_2CH_2CH_2$**C**), 166.6 (CO). Found, %: C 53.02; H 5.77; N 33.22. $C_{15}H_{18}N_8O_2$. Calculated, %: C 52.62; H 5.30; N 32.73.

General procedure for the synthesis of tetrazolylacetamides IVa–IVc and Va–Vc. *a*. Triethylamine, 20 mmol, was added to a suspension of 13 mmol of ditetrazole **Ia**–**Ic** in 50 ml of acetonitrile, and 20 mmol of chloroacetamide was added to the resulting solution. The mixture was stirred for 8–15 h under reflux, the solvent was removed under reduced pressure, and a 1:1 mixture of ethyl acetate with water was added to the residue. The organic phase was separated and washed in succession with two portions of a 5% solution of Na_2CO_3, water, 2% hydrochloric acid, and two portions of water. The solvent was removed under reduced pressure, and the isomeric products were separated by repeated crystallization from ethanol or diethyl ether.

b. Ethyl ester **IIa**–**IIc** or **IIIa**–**IIIc**, 16 mmol, was dissolved in 40 ml of ethanol, 160 mmol of 25% aqueous ammonia was added, the mixture was heated for 0.5 h at 60–70°C and cooled, and the precipitate was filtered off.

5-(5-Phenyl-2-tetrazolylmethyl)-1-tetrazolylacetamide (IVa). Yield 73% (*b*), mp 188°C (frm EtOH). ^{1}H NMR spectrum, δ, ppm: 5.56 s (2H, CH_2CO), 6.49 s (2H, NCH_2C), 7.01 br.s (1H, $CONH_2$), 7.50–7.60 m (4H, H_{arom}, $CONH_2$), 8.05–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 46.1 (CH_2CO); 50.3

(N**C**H_2C); 127.5, 128.0, 129.9, 131.4 (C_{arom}); 151.3 (NCH_2**C**); 166.1 (Ph**C**); 166.9 (CO). Found, %: C 46.76; H 4.56; N 44.49. $C_{11}H_{11}N_9O$. Calculated, %: C 46.31; H 3.89; N 44.19.

5-[2-(5-Phenyl-2-tetrazolyl)ethyl]-1-tetrazolylacetamide (IVb). Yield 79% (*b*), mp 160°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 3.80 t (2H, NCH_2C**H**$_2$C, *J* = 7.3 Hz), 5.28 t (2H, NC**H**$_2$CH_2C, *J* = 7.3 Hz), 5.37 s (2H, CH_2CO), 6.97 br.s and 7.43 br.s (1H each, $CONH_2$), 7.50–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 23.8 (NCH_2**C**H_2C); 49.5 (**C**H_2CO), 50.8 (N**C**H_2CH_2C); 127.4, 128.5, 129.9, 131.2 (C_{arom}); 154.2 (NCH_2C**H**$_2$); 165.6 (Ph**C**); 167.2 ($CONH_2$). Found, %: C 47.88; H 4.51; N 42.49. $C_{12}H_{13}N_9O$. Calculated, %: C 48.16; H 4.38; N 42.12.

5-[3-(5-Phenyl-2-tetrazolyl)propyl]-1-tetrazolylacetamide (IVc). Yield 81% (*b*), mp 126°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.65 quint (2H, CH_2C**H**$_2$CH_2, *J* = 7.3 Hz), 3.08 t (2H, NCH_2CH_2C**H**$_2$C, *J* = 7.3 Hz), 4.95 t (2H, NC**H**$_2$CH_2, *J* = 6.5 Hz), 5.27 s (2H, CH_2CO), 6.86 br.s and 7.35 br.s (1H each, $CONH_2$), 7.50–7.55 m (3H, H_{arom}), 8.10–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 20.8 (NCH_2CH_2-**C**H_2C); 27.0 (CH_2**C**H_2CH_2); 49.3 (**C**H_2CO); 52.9 (N**C**H_2CH_2CH_2); 127.4, 128.6, 129.9, 131.1 (C_{arom}); 156.3 (NCH_2CH_2CH_2**C**); 165.6 (Ph**C**); 166.6 (CO). Found, %: C 49.46; H 4.37; N 41.25. $C_{13}H_{15}N_9O$. Calculated, %: C 49.83; H 4.83; N 40.23.

5-(5-Phenyl-2-tetrazolylmethyl)-2-tetrazolylacetamide (Va). Yield 84% (*b*), mp 170°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 5.52 s (2H, CH_2CO), 6.34 s (2H, NCH_2C), 6.89 br.s and 7.32 br.s (1H each, $CONH_2$), 7.50–7.60 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 48.3 (**C**H_2CO); 55.5 (N**C**H_2C); 127.4, 128.2, 129.9, 131.4 (C_{arom}); 161.1 (NCH_2**C**); 166.0 (Ph**C**); 166.3 (CO). Found, %: C 46.13; H 4.11; N 44.48. $C_{11}H_{11}N_9O$. Calculated, %: C 46.31; H 3.89; N 44.19.

5-[2-(5-Phenyl-2-tetrazolyl)ethyl]-2-tetrazolylacetamide (Vb). Yield 85% (*b*), mp 161°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 3.74 t (2H, NCH_2C**H**$_2$C, *J* = 7.3 Hz), 5.20 t (2H, NC**H**$_2$CH_2C, *J* = 7.3 Hz), 5.41 s (2H, CH_2CO), 6.78 br.s and 7.12 br.s (1H each, $CONH_2$), 7.50–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 26.1 (NCH_2**C**H_2C); 51.7 (CH_2CO); 55.2 (N**C**H_2CH_2C); 127.4, 128.6, 129.9, 131.1 (C_{arom}); 163.8 (NCH_2C**H**$_2$); 165.6 (Ph**C**); 166.6 (CO). Found, %: C 48.33; H 4.78; N 42.20. $C_{12}H_{13}N_9O$. Calculated, %: C 48.16; H 4.38; N 42.12.

5-[3-(5-Phenyl-2-tetrazolyl)propyl]-2-tetrazolylacetamide (Vc). Yield 85% (*b*), mp 124°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.57 quint (2H, CH_2C**H**$_2$CH_2, *J* = 7.3 Hz), 3.05 t (2H, NCH_2CH_2C**H**$_2$C, *J* = 7.3 Hz), 4.91 t (2H, NC**H**$_2$CH_2CH_2, *J* = 6.9 Hz), 5.41 s (2H, CH_2CO), 6.82 br.s and 7.21 br.s (1H each, $CONH_2$), 7.50–7.55 m (3H, H_{arom}), 8.10–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 23.0 (NCH_2CH_2-**C**H_2C); 28.1 (CH_2**C**H_2CH_2); 53.0 (CH_2CO); 55.1 (N**C**H_2CH_2CH_2); 127.4, 128.6, 129.9, 131.1 (C_{arom}); 165.6 (Ph**C**); 166.2 (NCH_2CH_2CH_2**C**); 167.2 (CO). Found, %: C 50.24; H 4.87; N 40.53. $C_{13}H_{15}N_9O$. Calculated, %: C 49.83; H 4.83; N 40.23.

5-(5-Phenyl-2-tetrazolylmethyl)-1-tetrazolylacetic acid (VIa). Ester **IIa**, 3.4 g (11 mmol), was dissolved on heating in 40 ml (1.3 g, 32 mol) of aqueous sodium hydroxide. The solution was heated for 0.5 h at 70°C, cooled, and acidified to pH 1–2 with hydrochloric acid. The precipitate was filtered off and recrystallized from 70% aqueous alcohol. Yield 2.4 g (78%), mp 153°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 5.71 s (2H, CH_2CO), 5.79 br.s (1H, COOH), 6.56 s (2H, NCH_2C), 7.50–7.60 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 45.7 (**C**H_2CO); 49.2 (N**C**H_2C); 127.5, 127.9, 129.9, 131.5 (C_{arom}); 151.0 (NCH_2**C**); 166.2 (Ph**C**); 167.4 (CO). Found, %: C 46.36; H 3.71; N 39.35. $C_{11}H_{10}N_8O_2$. Calculated, %: C 46.16; H 3.52; N 39.15.

5-[2-(5-Phenyl-2-tetrazolyl)ethyl]-1-tetrazolylacetic acid (VIb). Ester **IIb**, 1.0 g (3 mmol), was added to 20 ml of 70% sulfuric acid, the mixture was heated for 1 h at 70°C, poured into 300 ml of water, and cooled, and the precipitate was filtered off and recrystallized from 40% ethanol. Yield 1.7 g (76%), mp 172°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 3.85 t (2H, NCH_2C**H**$_2$C, *J* = 7.3 Hz), 5.29 t (2H, NC**H**$_2$CH_2C, *J* = 7.3 Hz), 5.53 s (2H, CH_2CO), 7.50–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}), 8.80 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 23.5 (NCH_2**C**H_2C); 48.3 (**C**H_2CO); 50.6 (N**C**H_2CH_2C); 127.3, 128.4, 129.8, 131.2 (C_{arom}); 154.0 (NCH_2C**H**$_2$); 165.6 (Ph**C**); 167.7 (CO). Found, %: C 48.42; H 4.39; N 37.63. $C_{12}H_{12}N_8O_2$. Calculated, %: C 48.00; H 4.03; N 37.32.

5-[3-(5-Phenyl-2-tetrazolyl)propyl]-1-tetrazolylacetic acid (VIc) was synthesized as described above for acid **VIa**. Yield 92%, mp 129°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.66 quint (2H, CH_2C**H**$_2$-CH_2, *J* = 7.3 Hz), 3.13 t (2H, NCH_2CH_2C**H**$_2$C, *J* = 7.3 Hz), 4.95 t (2H, NC**H**$_2$CH_2CH_2, *J* = 6.5 Hz), 5.45 s

(2H, CH_2CO), 7.50–7.55 m (3H, H_{arom}), 8.10–8.15 m (2H, H_{arom}), 11.74 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 20.5 ($NCH_2CH_2\mathbf{C}H_2C$); 27.0 ($CH_2\mathbf{C}H_2CH_2$); 48.1 ($\mathbf{C}H_2CO$); 52.7 ($N\mathbf{C}H_2CH_2CH_2$); 127.3, 128.5, 129.8, 131.1 (C_{arom}); 156.1 (NCH_2CH_2-$CH_2\mathbf{C}$); 165.6 (Ph**C**); 167.8 (COOH). Found, %: C 49.36; H 4.27; N 36.00. $C_{13}H_{14}N_8O_2$. Calculated, %: C 49.68; H 4.49; N 35.65.

5-(5-Phenyl-2-tetrazolylmethyl)-2-tetrazolylacetic acid (VIIa) was synthesized as described above for acid **VIa**. Yield 93%, mp 154°C (from EtOH). ^1H NMR spectrum, δ, ppm: 5.73 s (2H, CH_2CO), 6.39 s (2H, NCH_2C), 7.50–7.60 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}), 11.83 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 48.3 ($\mathbf{C}H_2CO$); 54.1 ($N\mathbf{C}H_2C$); 127.4, 128.1, 129.9, 131.3 (C_{arom}); 161.2 ($NCH_2\mathbf{C}$); 166.0 (Ph**C**); 167.0 (CO). Found, %: C 45.94; H 3.45; N 39.44. $C_{11}H_{10}N_8O_2$. Calculated, %: C 46.16; H 3.52; N 39.15.

5-[2-(5-Phenyl-2-tetrazolyl)ethyl]-2-tetrazolylacetic acid (VIIb) was synthesized as described above for acid **VIa**. Yield 91%, mp 146°C (from EtOH). ^1H NMR spectrum, δ, ppm: 3.76 t (2H, $NCH_2C\mathbf{H}_2C$, J = 7.1 Hz), 5.22 t (2H, $NC\mathbf{H}_2CH_2C$, J = 7.1 Hz), 5.61 s (2H, CH_2CO), 7.50–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}), 11.91 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 26.0 ($NCH_2\mathbf{C}H_2C$); 51.6 ($\mathbf{C}H_2CO$); 53.7 ($N\mathbf{C}H_2CH_2C$); 127.4, 128.5, 129.8, 131.1 (C_{arom}); 163.9 ($NCH_2CH_2\mathbf{C}$); 165.5 (Ph**C**); 167.2 (CO). Found, %: C 48.35; H 4.08; N 37.78. $C_{12}H_{12}N_8O_2$. Calculated, %: C 48.00; H 4.03; N 37.32.

5-[3-(5-Phenyl-2-tetrazolyl)propyl]-2-tetrazolylacetic acid (VIIc) was synthesized as described above for acid **VIa**. Yield 94%, mp 58°C (from EtOH). ^1H NMR spectrum, δ, ppm: 2.58 quint (2H, $CH_2C\mathbf{H}_2$-CH_2, J = 7.3 Hz), 3.08 t (2H, $NCH_2CH_2C\mathbf{H}_2C$, J = 7.3 Hz), 4.89 t (2H, $NC\mathbf{H}_2CH_2CH_2C$, J = 6.9 Hz), 5.62 s (2H, CH_2CO), 7.50–7.55 m (3H, H_{arom}), 7.74 br.s (1H, COOH), 8.10–8.15 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 22.8 ($NCH_2CH_2\mathbf{C}H_2C$); 27.9 ($CH_2\mathbf{C}H_2CH_2$); 52.9 (CH_2CO); 53.7 ($N\mathbf{C}H_2CH_2$-CH_2C); 127.3, 128.4, 129.7, 131.0 (C_{arom}); 165.4 (Ph**C**); 166.2 ($NCH_2CH_2CH_2\mathbf{C}$); 167.3 (CO). Found, %: C 49.86; H 5.20; N 35.31. $C_{13}H_{14}N_8O_2$. Calculated, %: C 49.68; H 4.49; N 35.65.

General procedure for the synthesis of tritetrazoles VIIIa–VIIIc and IXa–IXc. A reactor equipped with a reflux condenser (capped with a drying tube), stirrer, and thermometer was charged under stirring with 10.5 mmol of amide **IVa**–**IVc** or **Va**–**Vc**, 50 ml of acetonitrile, 21 mmol of sodium azide, and 21 mmol of tetrachlorosilane in 20 ml of acetonitrile. The mixture was heated for 6–7 h under reflux and analyzed by TLC for the initial amide. If necessary, additional amounts of the reactants (5.2 mmol of NaN_3 and 5.2 mmol of $SiCl_4$) were added. This procedure was repeated every 6 h until the initial amide disappeared completely. The mixture was then poured in small portions under stirring into a solution of sodium carbonate, maintaining the pH value above 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 1–2 by adding hydrochloric acid. The solution was cooled, and the precipitate was filtered off and recrystallized from ethanol.

5-(5-Phenyl-2-tetrazolylmethyl)-1-(5-tetrazolylmethyl)tetrazole (VIIIa). Reaction time 89 h. Yield 68%, mp 87°C (from EtOH). ^1H NMR spectrum, δ, ppm: 6.01 br.s (1H, NH), 6.48 s (2H, $C\mathbf{H}_2CNH$), 6.68 s (2H, NCH_2C), 7.50–7.55 m (3H, H_{arom}), 8.00–8.10 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 42.8 ($N\mathbf{C}H_2C$); 45.7 ($\mathbf{C}H_2CNH$); 127.5, 127.8, 129.9, 131.5 (C_{arom}); 150.8 ($NCH_2\mathbf{C}$); 155.4 ($CH_2\mathbf{C}NH$); 166.2 (Ph**C**). Found, %: C 42.24; H 3.06; N 53.73. $C_{11}H_{10}N_{12}$. Calculated, %: C 42.58; H 3.25; N 54.17.

5-[2-(5-Phenyl-2-tetrazolyl)ethyl]-1-(5-tetrazolylmethyl)tetrazole (VIIIb). Reaction time 80 h. The product contained an admixture of 5-phenyltetrazole which was removed by recrystallization from ethanol. Yield 33%, mp 135°C (from EtOH). ^1H NMR spectrum, δ, ppm: 4.01 t (2H, $NCH_2C\mathbf{H}_2C$, J = 7.3 Hz), 5.35 t (2H, $NC\mathbf{H}_2CH_2C$, J = 7.3 Hz), 6.28 s (2H, NCH_2C), 7.50–7.55 m (3H, H_{arom}), 8.05–8.10 m (2H, H_{arom}), 15.31 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.7 ($NCH_2\mathbf{C}H_2C$); 41.6 ($N\mathbf{C}H_2C$); 50.5 ($N\mathbf{C}H_2CH_2C$); 127.3, 128.3, 129.8, 131.1 (C_{arom}); 155.3 ($NCH_2\mathbf{C}$); 153.8 ($NCH_2CH_2\mathbf{C}$); 165.5 (Ph**C**). Found, %: C 44.64; H 3.83; N 51.92. $C_{12}H_{12}N_{12}$. Calculated, %: C 44.44; H 3.73; N 51.83.

5-[3-(5-Phenyl-2-tetrazolyl)propyl]-1-(5-tetrazolylmethyl)tetrazole (VIIIc). Reaction time 34 h. Yield 62%, mp 128°C (from EtOH). ^1H NMR spectrum, δ, ppm: 2.69 quint (2H, $CH_2C\mathbf{H}_2CH_2$, J = 7.3 Hz), 3.27 t (2H, $NCH_2CH_2C\mathbf{H}_2C$, J = 7.3 Hz), 4.97 t (2H, $NC\mathbf{H}_2CH_2CH_2$, J = 6.5 Hz), 6.19 s (2H, NCH_2C), 7.50–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}), 14.07 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.7 ($NCH_2CH_2\mathbf{C}H_2C$); 26.8 ($CH_2\mathbf{C}H_2CH_2$); 41.5 ($N\mathbf{C}H_2C$); 52.7 ($N\mathbf{C}H_2CH_2CH_2C$); 127.3, 128.5,

129.8, 131.1 (C_{arom}); 155.3 (NCH_2**C**); 155.8 (NCH_2-CH_2CH_2**C**); 165.5 (Ph**C**). Found, %: C 45.88; H 4.07; N 49.95. $C_{13}H_{14}N_{12}$. Calculated, %: C 46.15; H 4.17; N 49.68.

5-(5-Phenyl-2-tetrazolylmethyl)-2-(5-tetrazolylmethyl)tetrazole (IXa). Reaction time 45 h. Yield 73%, mp 125°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 6.37 s (2H, NCH_2C), 6.48 s (2H, C**H**$_2$CNH), 7.50–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}), 14.90 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 47.5 (**C**H_2CNH); 48.2 (N**C**H_2C); 127.4, 128.0, 129.9, 131.3 (C_{arom}); 154.5 (CH_2**C**NH); 161.6 (NCH_2**C**); 166.0 (Ph**C**). Found, %: C 42.42; H 2.93; N 54.46. $C_{11}H_{10}N_{12}$. Calculated, %: C 42.58; H 3.25; N 54.17.

5-[2-(5-Phenyl-2-tetrazolyl)ethyl]-2-(5-tetrazolylmethyl)tetrazole (IXb). Reaction time 65 h. Yield 64%, mp 144°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 3.74 t (2H, NCH_2C**H**$_2$C, J = 7.3 Hz), 5.19 t (2H, NC**H**$_2CH_2C$, J = 7.3 Hz), 6.35 s (2H, NCH_2C), 7.50–7.55 m (3H, H_{arom}), 8.05–8.10 m (2H, H_{arom}), 15.53 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 26.0 (NCH_2-**C**H_2C); 47.0 (N**C**H_2C); 51.5 (N**C**H_2CH_2C); 127.4, 128.5, 129.8, 131.1 (C_{arom}); 154.4 (NCH_2**C**); 164.4 (NCH_2CH_2**C**); 165.5 (Ph**C**). Found, %: C 44.78; H 3.94; N 52.12. $C_{12}H_{12}N_{12}$. Calculated, %: C 44.44; H 3.73; N 51.83.

5-[3-(5-Phenyl-2-tetrazolyl)propyl]-2-(5-tetrazolylmethyl)tetrazole (IXc). Reaction time 21 h. Yield 59%, mp 121°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.56 quint (2H, CH_2C**H**$_2CH_2$, J = 7.3 Hz), 3.05 t (2H, NCH_2CH_2C**H**$_2$C, J = 7.3 Hz), 4.89 t (2H, NC**H**$_2CH_2CH_2$C, J = 6.9 Hz), 6.39 s (2H, NCH_2C), 7.45–7.55 m (3H, H_{arom}), 8.05–8.15 m (2H, H_{arom}), 15.01 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.9 (NCH_2CH_2**C**H_2C); 27.8 (CH_2**C**H_2CH_2); 46.9 (N**C**H_2C); 52.9 (N**C**$H_2CH_2CH_2$); 127.3, 128.4, 129.7, 131.0 (C_{arom}); 154.3 (NCH_2**C**); 165.5 (Ph**C**); 166.7 ($NCH_2CH_2CH_2$**C**). Found, %: C 46.47; H 3.90; N 49.98. $C_{13}H_{14}N_{12}$. Calculated, %: C 46.15; H 4.17; N 49.68.

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