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SYNTHESIS AND ACIDITY OF 5-PHENYLTETRAZOL-2-YLALKANOIC ACIDS AND THE CORRESPONDING 5-(5-PHENYLTETRAZOL-2-YLALKYL)TETRAZOLES

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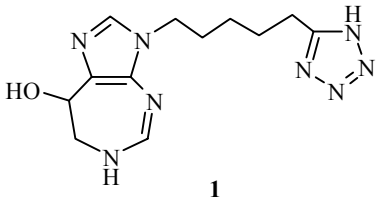
We have obtained 5-phenyltetrazol-2-ylalkanoic acids and their derivatives containing terminal nitrile, amide, and tetrazol-5-yl groups. Tetrazolylalkanoic acids with two (pK_a 4.93) and three (pK_a 5.45) bridging methylene groups are weaker acids than the corresponding ditetrazoles (pK_a 4.68 and 5.29 respectively). However, the acidity of 5-phenyltetrazol-2-ylacetic acid (pK_a 3.12), is higher than acidity of the corresponding ditetrazole (pK_a 3.27).

Keywords: ditetrazoles, tetrazoles, tetrazolylalkanoic acids, acidity.

In medicinal chemistry, the NH-unsubstituted tetrazole ring is considered as a metabolically stable substitute for carboxyl group. Recently in synthesis of novel biologically active substances, considerable attention has been paid to tetrazol-5-ylalkyl synthons [1]. The 5-(tetrazol-5-yl)amyl radical has been used in the molecular design of a modified AMP deaminase inhibitor (**1**) [2]. Recently a new potential inhibitor of thymidylate synthetases, ZD 9331, containing 2-(tetrazol-2-yl)ethyl substituent has been synthesized [3], so methods are being actively developed for directed synthesis of biologically active compounds containing tetrazol-5-ylalkyl moiety [4].



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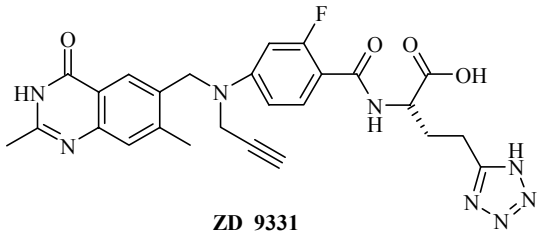

ZD 9331

In this work, we have synthesized and studied 5-phenyltetrazol-2-ylalkanoic acids and their derivatives containing terminal nitrile, amide, and tetrazol-5-yl groups.

Alkylation of NH-unsubstituted tetrazoles by various electrophilic agents is widely used for synthesis of disubstituted tetrazoles [5]. We used this reaction for synthesis of nitriles and amides of tetrazolylalkanoic acids.

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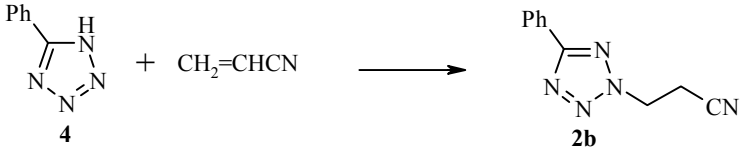
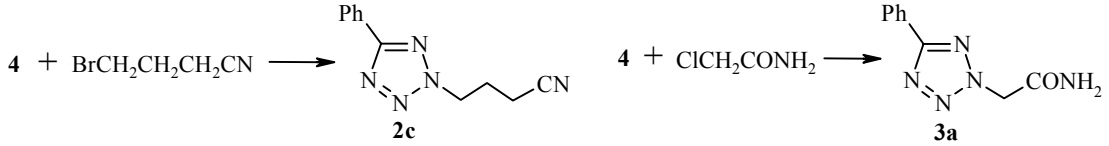
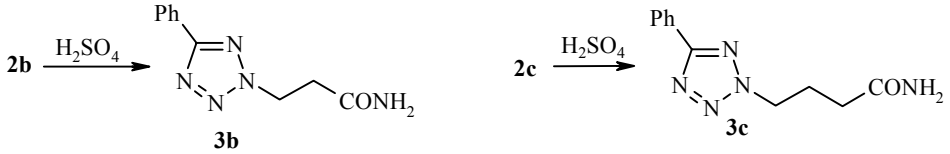
Nitriles of 5-phenyltetrazol-2-ylalkanoic acids **2b,c** and amide of 5-phenyltetrazol-2-ylacetic acid (**3a**) were obtained by alkylation of 5-phenyltetrazole (**4**) by acrylonitrile in the presence of triethylamine (Michael's method) or by nitriles or amides of the corresponding haloalkanoic acids.

In all cases, we observed formation of two regioisomers: $N_{(1)}$- and $N_{(2)}$-disubstituted tetrazoles. The $N_{(2)}$-isomers were isolated from the mixture by fractional crystallization.

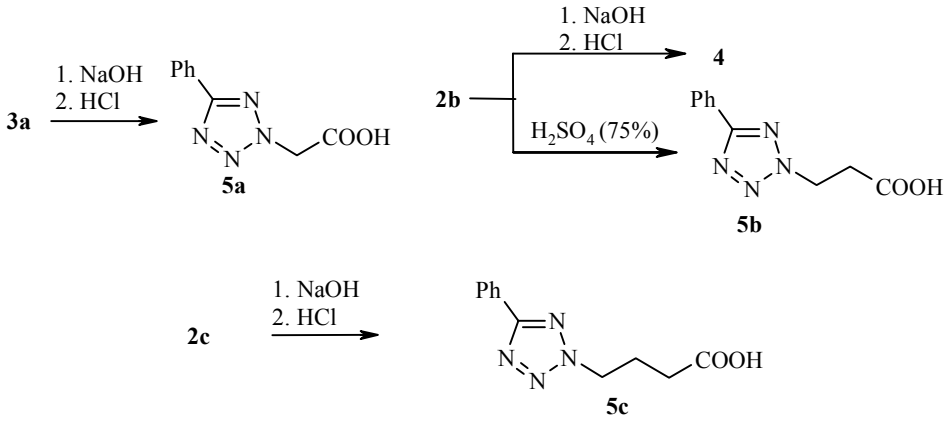




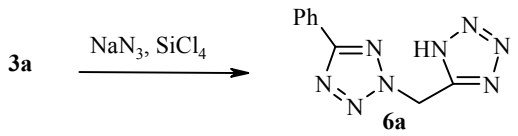
Amides of 5-phenyltetrazol-2-ylpropionic (**3b**) and 5-phenyltetrazol-2-ylbutanoic (**3c**) acids were obtained by reaction of the corresponding nitriles **2b,c** with conc. H_2SO_4.



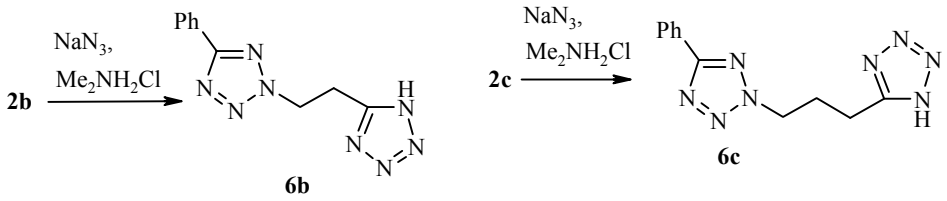
When amide **3a** and nitrile **2c** were treated with an aqueous solution of NaOH followed by acidification, we obtained the corresponding 5-phenyltetrazol-2-ylalkanoic acids **5a** and **5c** in good yield. At the same time, our attempts to obtain acids **5b** by base hydrolysis of nitrile **2b** were unsuccessful: instead of the expected carboxylic acid, we isolated tetrazole **4**. It was shown earlier that on cleavage of 1-(β-cyanoethyl)-5R-tetrazoles in alkaline medium, the corresponding NH-unsubstituted 5-R-tetrazoles were formed [6, 7]. A similar process probably also occurs under similar conditions in the case of 2-(β-cyanoethyl)-5R-tetrazoles. At the same time, the target compound **5b** could be synthesized by treatment of nitrile **2b** with 75% H_2SO_4.



5-Phenyl-2-(tetrazol-5-ylmethyl)-tetrazole (**6a**) was synthesized from amide **3a**, using a promising azidation system tetrachlorosilane–sodium azide, which can be used for synthesis of both NH-unsubstituted tetrazoles and 1,5-disubstituted tetrazoles from carboxylic acid amides [8].



1-(5-Phenyltetrazol-2-yl)-2-(tetrazol-5-yl)ethane (**6b**) and 1-(5-phenyltetrazol-2-yl)-3-(tetrazol-5-yl)propane (**6c**) were synthesized by 1,3-dipolar cycloaddition of dimethylammonium azide to nitriles **2b** and **2c** respectively at 110°C in DMA. Advantages of this azidation agent have been considered earlier in [9]. As a result of azidation of nitrile **2b**, along with the expected tetrazole **6b** we detected tetrazole **4**, which probably is formed upon thermal decomposition of the starting nitrile. In order to eliminate this side reaction, the process was conducted under relatively mild conditions (3 h, 90°C). In contrast to nitrile **2b**, harsher conditions are required for conversion of nitrile **2c** to the corresponding tetrazole **6c** (33 h, 110°C).



One reason why the tetrazole ring can be used in medicinal chemistry as an analog of the carboxyl group is their similar acid properties. Accordingly, it is of interest to compare the acidity of the synthesized carboxylic acids **5a-c** and tetrazoles **6a-c**.

In this work, we used potentiometric titration to determine the acid constants for the synthesized tetrazolylalkanoic acids and the corresponding NH-unsubstituted ditetrazoles (Table 1).

The data obtained allow us to see a trend toward a decrease in acidity as the number of bridging methylene groups increases, which is due to weakening of the inductive acceptor effect of the 5-phenyltetrazol-2-yl substituent.

Interesting results come from comparing the acid constants found. ω-(5-Phenyltetrazol-2-yl)alkanoic acids **5b,c**, with two and three bridging methylene groups, are weaker acids than the corresponding ditetrazoles **6b,c**. However, the acidity of tetrazolylacetic acid **5a**, containing only one methylene bridging group, has a slightly higher acidity than the corresponding tetrazole **6a**.

TABLE 1. Acidity of Compounds **5a-c** and **6a-c** (50% methanol, 25°C)

Compound	pK_a	Compound	pK_a
5a	3.12 ± 0.05*	**6a**	3.27 ± 0.03
5b	4.93 ± 0.04	**6b**	4.68 ± 0.02
5c	5.45 ± 0.03	**6c**	5.29 ± 0.03

* p*K*a 3.31 (50% ethanol, 25°C) [10].

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300 and 75 MHz respectively); the solvent and internal standard was acetone-d_6. Potentiometric titration was carried out in 50% MeOH at 25°C; the titrant was NaOH solution (0.1 mol/l), the supporting electrolyte was $NaNO_3$ solution (0.1 mol/l). The constants were calculated by the method [11]. The course of the reactions and the purity of the compounds obtained were monitored by TLC on Merck Kieselgel 60 F254 plates in the system $CHCl_3$–MeOH, 9:1, visualization in UV light.

2-(2-Cyanoethyl)-5-phenyltetrazole (2b). Et_3N (20.2 g, 0.2 mol) was added with stirring to suspension of tetrazole **4** (28.9 g, 0.2 mol) in MeCN (100 ml), acrylonitrile (15.9 g, 0.3 mol) was added to the homogeneous solution obtained and the reaction mass was held for 3 days at room temperature. MeCN was distilled off, the remaining viscous oil was dissolved in CH_2Cl_2 and washed twice with 5% Na_2CO_3 solution, water, 2% HCl solution, and twice more with water. CH_2Cl_2 was distilled off, the oil obtained crystallized after some time. After recrystallization from 70% aqueous ethanol, we obtained 23.1 g (58%) of nitrile **2b,** free of the $N_{(1)}$ isomer (monitored by TLC); mp 56°C (mp 55-57°C [11]). ^1H NMR spectrum, δ, ppm, *J* (Hz): 3.40 (2H, t, *J* = 6.4, CH_2CN); 5.14 (2H, t, *J* = 6.4, $\underline{CH_2}CH_2CN$); 7.51-7.59 (3H, m, Ph); 8.10-8.19 (2H, m, Ph). ^{13}C NMR spectrum, δ, ppm: 18.6 ($\underline{C}H_2CN$); 49.5 ($\underline{C}H_2CH_2CN$); 117.6 (CN); 127.4, 128.2, 129.9, 131.3 (Ph); 165.9 (CN_4). Found, %: C 60.35; H 4.88; N 35.09. $C_{10}H_9N_5$. Calculated, %: C 60.29; H 4.55; N 35.15.

2-(3-Cyanopropyl)-5-phenyltetrazole (2c). Et_3N (10.1 g, 0.1 mol) was added with stirring to suspension of tetrazole **4** (14.5 g, 0.1 mol) in MeCN (50 ml), γ-bromobutyronitrile (14.8 g, 0.1 mol) was added to the homogeneous solution obtained and the reaction mass was held for 1 day at room temperature. Triethylammonium bromide precipitate formed was filtered out, MeCN was distilled off, the remaining viscous oil was dissolved in CH_2Cl_2 and washed in a separatory funnel twice with 5% Na_2CO_3 solution, water, 2% HCl solution, and twice more with water. CH_2Cl_2 was distilled off, the oil obtained was recrystallized from ethanol 3-4 times until a pure substance was formed (monitored by TLC). Obtained 9.6 g (45%) of nitrile **2c**, free of the $N_{(1)}$ isomer; mp 36-37°C. ^1H NMR spectrum, δ, ppm, *J* (Hz): 2.46 (2H, q, *J* = 6.8, $\underline{CH_2}CH_2CN$); 2.69 (2H, t, *J* = 7.1, CH_2CN); 4.90 (2H, t, *J* = 6.6, $\underline{CH_2}CH_2CH_2CN$); 7.49-7.58 (3H, m, Ph); 8.09-8.18 (2H, m, Ph). ^{13}C NMR spectrum, δ, ppm: 14.8 ($\underline{C}H_2CN$); 26.0 ($\underline{C}H_2CH_2CN$); 52.2 ($\underline{C}H_2CH_2CH_2CN$); 119.5 (CN); 127.3, 128.4, 129.8, 131.1 (Ph); 165.6 (CN_4). Found, %: C 62.15; H 5.11; N 33.05. $C_{11}H_{11}N_5$. Calculated, %: C 61.96; H 5.20; N 32.84.

5-Phenyltetrazol-2-ylethanoic Acid Amide (3a). Et_3N (10.1 g, 0.1 mol) was added with stirring to suspension of tetrazole **4** (14.5 g, 0.1 mol) in MeCN (50 ml), $ClCH_2CONH_2$ (9.4 g, 0.1 mol) was added to the homogenous solution obtained and the reaction mass was held for 1 day at room temperature. The triethylammonium chloride precipitate formed was filtered out, MeCN was distilled off, the residue was dissolved in CH_2Cl_2 and washed twice with 5% Na_2CO_3 solution, water, 2% HCl solution, and twice more with water. CH_2Cl_2 was distilled off, the residue was recrystallized from 50% ethanol. Obtained 13.8 g (68%) of amide **3a**, free of the $N_{(1)}$ isomer (monitored by TLC); mp 188°C (mp 187°C [12] and 186-186.5°C [13]). ^1H NMR spectrum, δ, ppm: 5.54 (2H, s, CH_2); 6.92 and 7.33 (2H, two br. s, $CONH_2$); 7.50-7.58 (3H, m, Ph); 8.09-8.18 (2H, m, Ph). ^{13}C NMR spectrum, δ, ppm: 55.4 (CH_2); 127.4, 128.5, 129.9, 131.2 (Ph); 165.7 (CN_4); 166.8 ($CONH_2$). Found, %: C 53.09; H 4.52; N 34.76. $C_9H_9H_5O$. Calculated, %: C 53.20; H 4.46; N 34.46.

5-Phenyltetrazol-2-ylpropanoic Acid Amide (3b). Nitrile **2b** (10.2 g, 0.05 mol) was added to conc. H_2SO_4 (50 ml), stirred until completely dissolved, and the reaction mass was held for 1 day at ~20°C. Then the mixture was added to water (500 ml) in small portions with stirring. The precipitate formed was filtered out and recrystallized from 50% ethanol. Obtained 9.6 g (88%) of amide **3b**; mp 126-127°C (mp 131-132°C [13] and 132°C [12]). ^1H NMR spectrum, δ, ppm, *J* (Hz): 3.07 (2H, t, *J* = 6.8, $\underline{CH_2}CONH_2$); 4.97 (2H, t, *J* = 7.0, $\underline{CH_2}CH_2CONH_2$); 6.44 and 7.03 (2H, two br. s, $CONH_2$); 7.49-7.57 (3H, m, Ph); 8.06-8.16 (2H, m, Ph).

^{13}C NMR spectrum, δ, ppm: 34.7 ($\underline{C}H_2CONH_2$); 50.0 ($\underline{C}H_2CH_2CONH_2$); 127.3, 128.7, 129.9, 131.1 (Ph); 165.4 (CN_4); 171.3 ($CONH_2$). Found, %: C 55.65; H 5.51; N 32.58. $C_{10}H_{11}N_5O$. Calculated, %: C 55.29; H 5.10; N 32.24.

5-Phenyltetrazol-2-ylbutanoic Acid Amide (3c) was obtained similarly to amide **3b** from nitrile **2c**. Yield 67%; mp 148-149°C. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.26-2.38 (4H, m, $\underline{CH_2}\underline{CH_2}CONH_2$; 4.80 (2H, t, *J* = 6.7, $\underline{CH_2}CH_2CH_2CONH_2$); 6.25 and 6.82 (2H, two br. s, $CONH_2$); 7.50-7.58 (3H, m, Ph); 8.09-8.17 (2H, m, Ph). ^{13}C NMR spectrum δ, ppm: 25.8 ($\underline{C}H_2CONH_2$); 32.0 ($\underline{C}H_2CH_2CONH_2$); 53.3 ($\underline{C}H_2CH_2CH_2CONH_2$); 127.4, 128.7, 129.9, 131.1 (Ph); 165.5 (CN_4); 173.7 ($CONH_2$). Found, %: C 57.38; H 5.39; N 30.48, $C_{11}H_{13}N_5O$. Calculated, %: C 57.13; H 5.67; N 30.28.

5-Phenyltetrazol-2-ylethanoic Acid (5a). Amide **3a** (10.2 g, 0.05 mol) was added to solution of NaOH (6.0 g, 0.15 mol) in water (50 ml). The mixture obtained was boiled with stirring until the precipitate was completely dissolved (~3 h), then it was added to water (150 ml) and acidified with HCl to pH ~2. The precipitate was filtered off and recrystallized from water. Obtained 9.5 g (93%) of acid **5a**; mp 184°C (mp 184-186°C [14] and 186-187°C [15]). ^{1}H NMR spectrum, δ, ppm: 5.75 (2H, s, CH_2); 7.50-7.58 (3H, m, Ph); 8.11-8.20 (2H, m, Ph); 11.72 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 53.9 (CH_2); 127.4, 128.2, 129.9, 131.3 (Ph); 165.8 (CN_4); 167.3 (COOH). Found, %: C 53.08; H 4.28; N 27.54. $C_9H_8N_4O_2$. Calculated, %: C 52.94; H 3.95; N 27.44.

5-Phenyltetrazol-2-ylpropanoic Acid (5b). Nitrile **2b** (12.6 g, 0.063 mol) was added to 70% H_2SO_4 (50 ml). The mixture was stirred for 3 h with heating (85°C) and added to water (500 ml). The precipitate was filtered off and recrystallized from 50% ethanol. Obtained 7.6 g (55%) of acid **5b**; mp 127-128°C (mp 128°C [16] and 128-129°C [14]). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 3.23 (2H, t, *J* = 6.6, $\underline{CH_2}COOH$); 5.00 (2H, t, *J* = 6.6, $\underline{CH_2}CH_2COOH$); 7.50-7.58 (3H, m, Ph); 8.08-8.17 (2H, m, Ph); 11.11 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 33.2 ($\underline{C}H_2COOH$); 49.6 ($\underline{C}H_2CH_2COOH$); 127.3, 128.6, 129.9, 131.1 (Ph); 165.4 (CN_4); 171.5 (COOH). Found, %: C 55.26; H 4.86; N 25.97. $C_{10}H_{10}N_4O_2$. Calculated, %: C 55.04; H 4.62; N 25.68.

5-Phenyltetrazol-2-ylbutanoic Acid (5c). Nitrile **2c** (5.9 g, 0.028 mol) was added to solution of NaOH (3.3 g, 0.084 mol) in water (50 ml). The mixture obtained was heated with stirring for 7 h, then added to water (400 ml) and acidified with HCl to pH ~2. The precipitate was filtered out and recrystallized from 50% ethanol. Obtained 6.1 g (94%) of acid **5c**; mp 86°C (mp 81°C [16]). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.34 (2H, q, *J* = 6.8, $\underline{CH_2}CH_2COOH$); 2.50 (2H, t, *J* = 7.1, $\underline{CH_2}COOH$); 4.84 (2H, t, *J* = 6.8, $\underline{CH_2}CH_2CH_2CN$); 7.50-7.58 (3H, m, Ph); 8.09-8.18 (2H, m, Ph); 10.75 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 25.3 ($\underline{C}H_2COOH$); 30.7 ($\underline{C}H_2CH_2COOH$); 53.0 ($\underline{C}H_2CH_2CH_2COOH$); 127.4, 128.7, 129.9, 131.1 (Ph); 165.6 (CN_4); 173.7 (COOH). Found, %: C 56.50; H 5.64; N 23.93. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

5-Phenyl-2-(tetrazol-5-ylmethyl)tetrazole (6a) was obtained by the procedure [8]; mp 145°C. ^{1}H NMR spectrum, ppm: 6.51 (2H, s, CH_2); 7.48-7.56 (3H, m, Ph); 8.06-8.15 (2H, m, Ph); 14.69 (1H, br. s, CN_4H). ^{13}C NMR spectrum, δ, ppm: 47.2 (CH_2); 127.4, 127.9, 129.8, 131.4 (Ph); 154.4 (CN_4H); 166.1 ($Ph\underline{C}N_4$). Found, %: C 47.43; H 3.67; N 49.41. $C_9H_8N_8$. Calculated, %: C 47.37; H 3.53; N 49.10.

1-(5-Phenyltetrazol-2-yl)-2-(tetrazol-5-yl)ethane (6b). Nitrile **2b** (10.0 g, 0.05 mol), NaN_3 (3.6 g, 0.055 mol), Me_2NH_2Cl (4.5 g, 0.055 mol), and DMF (70 ml) were stirred for 3 h at 90-95°C. NaCl precipitate formed was filtered off, DMF was distilled off, the residue was dissolved in water (50 ml) and acidified with HCl to pH ~2. The precipitate was filtered off and recrystallized from 50% ethanol. Obtained 10.7 g (88%) of tetrazole **6b**; mp 153°C. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 3.87 (2H, t, *J* = 6.8, $\underline{CH_2}CN_4H$); 5.27 (2H, t, *J* = 6.8, $\underline{CH_2}CH_2CN_4H$); 7.49-7.57 (3H, m, Ph); 8.03-8.13 (2H, m, Ph); 15.13 (1H, br. s, CN_4H). ^{13}C NMR spectrum, δ, ppm: 24.4 ($\underline{C}H_2CN_4H$); 51.3 ($\underline{C}H_2CH_2CN_4H$); 127.3, 128.3, 129.8, 131.2 (Ph); 154.6 (CN_4H); 165.6 ($Ph\underline{C}N_4$). Found, %: C 49.05; H 4.29; N 46.55. $C_{10}H_{10}N_8$. Calculated, %: C 49.58; H 4.16; N 46.26.

1-(5-Phenyltetrazol-2-yl)-3-(tetrazol-5-yl)propane (6c) was obtained similarly to tetrazole **6b** from nitrile **2c** (held for 33 h at 110°C). Yield 75%; mp 146°C. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.63 (2H, q, *J* = 7.1, $\underline{CH_2}CH_2CN_4H$); 3.17 (2H, t, *J* = 7.7, $\underline{CH_2}CN_4H$); 4.93 (2H, t, *J* = 7.0, $\underline{CH_2}CH_2CH_2CN_4H$); 7.49-7.57 (3H, m, Ph); 8.07-8.16 (2H, m, Ph); 14.97 (1H, br. s, CN_4H). ^{13}C NMR spectrum, δ, ppm: 21.1. ($\underline{C}H_2CN_4H$); 27.5 ($\underline{C}H_2CH_2CN_4H$); 52.8 ($\underline{C}H_2CH_2CH_2CN_4H$); 127.3, 128.5, 129.8, 131.1 (Ph); 156.2 (CN_4H); 165.6 ($PhCN_4$). Found, %: C 51.79; H 4.87; N 43.90. $C_{11}H_{12}N_8$. Calculated, %: C 51.56; H 4.72; N 43.72.

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