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SYNTHESIS OF AZOLES BASED ON N,N'-BIS(HYDRAZINOCARBONYL-ETHYL)-1,4-PHENYLENEDIAMINE

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N,N'-Bis[(1-methyl-3-oxobutylidene)hydrazinocarbonylethyl]-, N,N'-bis[(2,5-dimethylpyrrol-1-yl)carbamoylethyl]-, N,N'-bis(phenylureidocarbamoylethyl)-, N,N'-bis(phenylcarbamoyl)-, N,N'-bis(phenylureidocarbamoylethyl)-, and N,N'-bis[(4,5-dihydro-5-oxo-4-phenyl-1,2,4-triazol-3-yl)ethyl]-1,4-phenylenediamines, and their thio analogs were obtained by the condensation of N,N'-bis-(hydrazinocarbonylethyl)-1,4-phenylenediamine with 2,4-pentanedione, 2,5-hexanedione, phenyl isocyanates, or phenyl isothiocyanates (with subsequent treatment of the obtained semicarbazides with alkali), and carbon disulfide respectively.

Keywords: hydrazides, 1,3,4-oxadiazoles, pyrazoles, pyrroles, 1,2,4-triazoles, cyclization.

The chemical properties and biological activity of hydrazides and semicarbazides and also their heterocyclization products are of interest to many investigators. In particular, certain derivatives of semicarbazides exhibit antimicrobial activity [1, 2], and the triazole ring forms part of the structure of a series of antimicrobial drugs [3]. With the aim of producing derivatives of substituted β-amino acids, which frequently exhibit specific bioactivity [4-7], and continuing researches [8] into the synthesis of compounds each having two heterocycles in their structure in the present work the azoles were synthesized, starting from N,N'-bis-(hydrazinocarbonylethyl)-1,4-phenylenediamine.

The dihydrazide **2** was synthesized [9] by hydrazinolysis of N,N'-bis(methoxycarbonylethyl)-1,4-phenylenediamine and also by the action of hydrazine under mild conditions on N,N'-diacetyl-N,N'-bis-(methoxycarbonylethyl)-1,4-phenylenediamine, produced without isolation by the esterification of the diacid **1**. It is known [8] that derivatives of pyrazole are formed during the condensation of hydrazides with 2,4-pentanedione and dimethylpyrroles are formed in the reaction with 2,5-hexanedione. When the dihydrazide **2** is heated with acetylacetone in the presence of acetic or hydrochloric acids or without them tar formation is observed, and it is not possible to isolate the individual substances. At room temperature, however, the dihydrazone **3** is formed smoothly, but it was not possible to realize its cyclization to the pyrazole derivative **4**.

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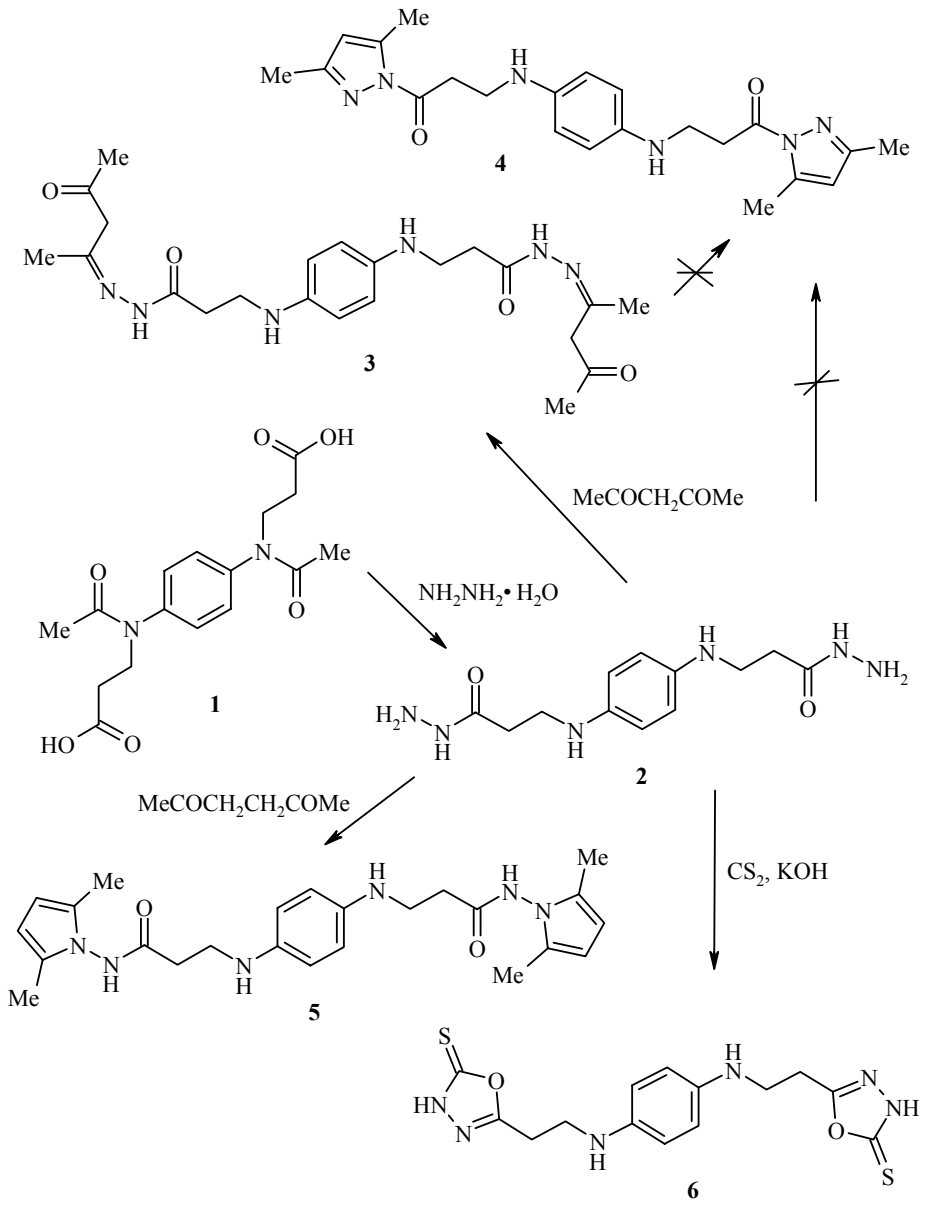
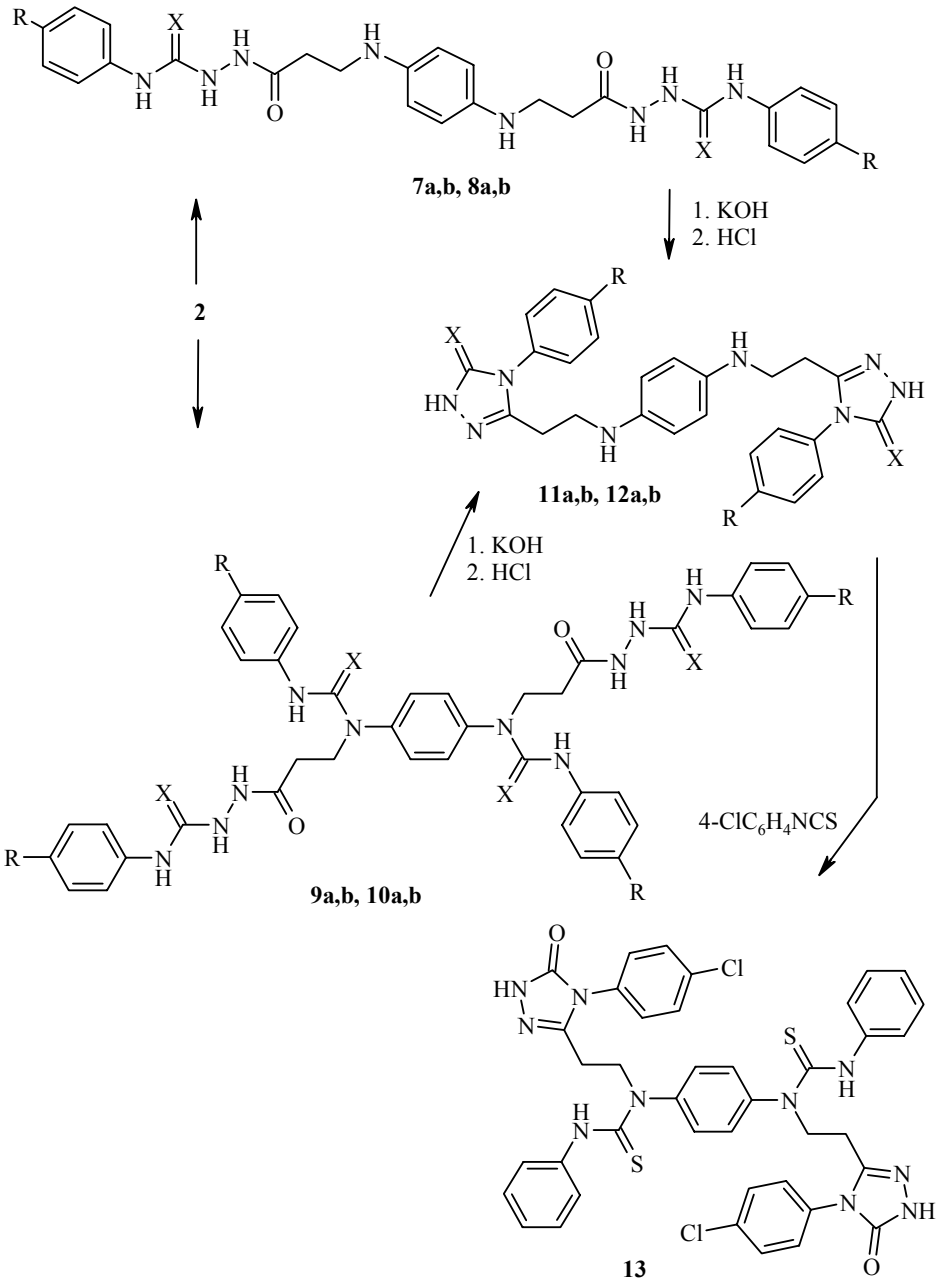


The IR spectrum of the hydrazone **3** contains absorption bands for the amide and ketone carbonyl groups at 1638 and 1625 cm^{-1}, while the two nonequivalent methyl groups appear in the ^1H NMR spectrum at 1.77 and 1.99 ppm. The reaction of the dihydrazide **2** with 2,5-hexanedione takes place readily, and the derivative **5** is isolated from the reaction mixture with a yield of 75%. The ^1H NMR spectrum of compound **5** contains signals for the methylene groups. The signals for the protons of the four methyl groups of the pyrrole ring appear in the form of a singlet at 1.99 ppm, while the signals for the protons of the methine groups of the pyrrole ring give a singlet at 5.64 ppm. In the IR spectrum the carbonyl groups absorb at 1664 cm^{-1}. The bis derivative of 2-thioxo-1,3,4-oxadiazole **6** was synthesized by boiling an alkaline solution of carbon disulfide in alcohol with the hydrazide **2** followed by acidification of the obtained solution of the potassium salt of the hydrazinecarbodithioate derivative with hydrochloric acid. In the ^{13}C NMR spectrum of compound **6** the sp^2-hybridized carbon atoms of the C=N and C=S groups appear at 162.75 and 177.70 ppm respectively.

In order to obtain azoles containing phenyl substituents the hydrazide **2** was reacted with phenyl isocyanates, and the diphenylcarbamoyl **7** or tetraphenylcarbamoyl **9** derivatives were obtained depending on the ratio of the reactants. In the reaction of the dihydrazide with phenyl isothiocyanates the corresponding thio analogs **8** and **10** were obtained.



7, 9, 11 X = O; **8, 10, 12** X = S; **7–12 a** R = H, **b** R = Cl

The oxotriazoles **11** and triazolethiones **12** were isolated by heating the phenylsemicarbazides **7** and phenylthiosemicarbazides **8** with alkali and acidifying the reaction mixture. The cyclization of N,N'-bis-(phenylcarbamoyl)-N,N'-bis(phenylureidocarbamoylethyl)-1,4-phenylenediamines **9** under the same conditions

is accompanied by removal of the phenylcarbamoyl group, and the same compounds **11** are produced. Similar reactions occur when the thio derivatives **10** are heated, and under the same conditions give the phenyl-substituted triazoles **12**. The action of 4-chlorophenyl thioisocyanate on the triazole **12b** in methanol gave N,N'-bis{[4,5-dihydro-5-oxo-4-(4-chlorophenyl)-1,2,4-triazol-3-yl]ethyl}-N,N'-diphenylthiocarbamoyl-1,4-phenylenediamine (**13**). The direction of thiocarbamoylation of compound (**12b**) is confirmed by the absence of a signal for the hydrogen of the amine groups adjacent to the phenylene radical in the ^{1}H NMR spectrum.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 instrument (300 and 75 MHz respectively) in DMSO-d_6 with TMS as internal standard. The IR spectra were recorded on a Perkin-Elmer Spectrum Bx FT-IR spectrometer in tablets with KBr. The mass spectra were recorded on a Waters/Micromass ZQ 2000 instrument; chemoionization (ACPI$^+$, 20 eV). Elemental analysis was performed on an Exeter Analytical CE-440 Elemental instrument. The reaction and the purity of the obtained compounds were monitored by TLC on Silufol 254 and Silufol UV-254 plates.

N,N'-Bis(hydrazinocarbonylethyl)-1,4-phenylenediamine (2). A. Sulfuric acid (1 ml) was added to a solution of N,N'-diacetyl-N,N'-bis(ethoxycarbonyl)-1,4-phenylenediamine (**1**) (2 g, 6 mmol) in methanol (20 ml), and the mixture boiled for 24 h. The reaction mixture was cooled, sodium carbonate was added, and the mixture was filtered. The liquid fractions were distilled, hydrazine hydrate (0.6 g, 12 mmol) was added, and the mixture was left at room temperature for 48 h. The crystals were filtered off and washed with diethyl ether. The yield was 0.85 g (43%); mp 186.9-187.6°C (from 2-propanol).

B. From N,N'-bis(methoxycarbonylethyl)-1,4-phenylenediamine (5 g, 20 mmol) according to [9] obtained 4.5 g (90%) of compound **2**; mp 188-189°C. IR spectrum, ν, cm^{-1}: 3126-3308 (NH, NH_2), 3031 (CH Ar), 2838-2946 (CH aliph.), 1643 (CO), 815 (*p*-substituted benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (4H, t, *J* = 7.0, CH_2CO); 3.14 (4H, t, *J* = 7.0, NHC$\underline{H}_2$); 4.20 (4H, br. s, NH_2); 4.70 (2H, br. s, NH); 6.45 (4H, s, H Ar); 9.03 (2H, s, N$\underline{H}NH_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 281 $[M + H]^+$ (100).

N,N'-Bis[(1-methyl-3-oxobutylidene)hydrazinocarbonylethyl]-1,4-phenylenediamine (3). Acetylacetone (1.6 g, 16 mmol) was added dropwise to a solution of the dihydrazide **2** (1.5 g, 5.4 mmol) in methanol (20 ml). The mixture was stirred at 20°C for 24 h. The crystals that separated were filtered off and washed with ether. The yield was 1.61 g (68%); mp 172-173°C (mixture of DMF and water). IR spectrum, ν, cm^{-1}: 3384 (NH), 3312 (NH), 3034 (CH Ar), 2922-2952 (CH aliph.), 1638 (CO), 1625 (CO), 841 (*p*-substituted benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.77 (6H, s, CH_3); 1.96 (6H, s, CH_3); 2.74 (4H, t, *J* = 7.0, CH_2CO); 3.18 (4H, t, *J* = 7.0, $NHCH_2$); 3.35 (4H, s, CH_2C); 4.74 (2H, br. s, NH); 6.25 (2H, s, NHN=); 6.47 (4H, s, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 467 $[M + Na]^+$ (100). Found, %: C 59.85; H 7.40; N 19.01. $C_{22}H_{32}N_6O_4$. Calculated, %: C 59.44; H 7.26; N 18.91.

N,N'-Bis[(2,5-dimethylpyrrol-1-yl)carbamoylethyl]-1,4-phenylenediamine (5). A mixture of dihydrazide **2** (1 g, 3.6 mmol), 2-propanol (50 ml), 2,5-hexanedione (1 ml, 8 mmol), and acetic acid (1 ml) was boiled for 3 h. The mixture was cooled, and the crystals that separated were filtered off. The yield was 1.17 g (75%); mp 222-223°C (DMSO). IR spectrum, ν, cm^{-1}: 3354 (NH), 3266 (NH), 3027 (CH Ar), 2836-2977 (CH aliph.), 1664 (CO), 804 (*p*-substituted benzene). ^{1}H NMR spectrum, δ, ppm: 1.99 (12H, s, CH_3); 2.52-2.54 (4H, m, CH_2CO); 3.27-3.31 (4H, m, NHC$\underline{H}_2$); 4.84 (2H, br. s, NH); 5.64 (4H, s, CH); 6.52 (4H, s, H Ar); 10.62 (2H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 437 $[M + H]^+$ (100). Found, %: C 65.76; H 7.34; N 18.99. $C_{24}H_{32}N_6O_2$. Calculated, %: C 66.03; H 7.39; N 19.25.

N,N'-Bis[(2-thioxo-2,3-dihydro-1,3,4-oxadiazol-5-yl)ethyl]-1,4-phenylenediamine (6). To a solution of KOH (1.68 g, 30 mmol) in ethanol (50 ml) we added dropwise CS_2 (2.28 g, 30 mmol). The mixture was stirred at room temperature for 15 min, a solution of dihydrazide **2** (2.8 g, 10 mmol) in ethanol (20 ml) was

added, and the mixture was boiled with stirring for 24 h. The liquid fractions were distilled, the remaining mass was dissolved in water, and HCl was added to pH 5. The crystals that separated were filtered off and washed with ether. The yield was 1.02 g (28%); mp 351-352°C (ethanol). IR spectrum, ν, cm^{-1}: 3185 (NH), 3072 (CH Ar), 2869 (CH aliph.), 1623 (C=N), 1163 (C=S), 818 (*p*-substituted benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.93 (4H, t, *J* = 6.5, CH_2CN); 3.33 (4H, t, *J* = 6.5, $C\underline{H_2}NH$); 6.50 (4H, s, H Ar); 8.56-9.50 (4H, m, NH). ^{13}C NMR spectrum, δ, ppm: 25.42; 40.50; 114.19; 139.55; 162.75; 177.70. Mass spectrum, *m*/*z* (I_{rel}, %): 365 $[M + H]^+$ (70). Found, %: C 46.33; H 4.65; N 23.32. $C_{14}H_{16}N_6O_2S_2$. Calculated, %: C 46.14; H 4.43; N 23.06.

N,N'-Bis(phenylureidocarbamoylethyl)-1,4-phenylenediamine (7a). A mixture of dihydrazide **2** (1.5 g, 5 mmol), phenyl isocyanate (1.5 g, 13 mmol), and methanol (10 ml) was kept at room temperature for 24 h, and the crystals that formed were filtered off. The yield was 1.1 g (40%); mp 155-156°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (4H, t, *J* = 7.0, CH_2CO); 3.15 (4H, t, *J* = 7.0, $NHC\underline{H_2}$); 4.26 (2H, br. s, ArNH); 6.46 (4H, s, H Ar); 6.93-7.01 (2H, m, H Ar'); 7.22-7.28 (3H, m, H Ar'); 7.44-7.50 (5H, m, H Ar'); 8.04 (2H, s, NH); 8.72 (2H, s, NH); 9.04 (2H, s, NHAr). Mass spectrum, *m*/*z* (I_{rel}, %): 519 $[M + H]^+$ (80). Found, %: C 60.68; H 5.40; N 21.99. $C_{26}H_{30}N_8O_4$. Calculated, %: C 60.22; H 5.83; N 21.61.

N,N'-Bis[(4-chlorophenyl)ureidocarbamoylethyl]-1,4-phenylenediamine (7b). From dihydrazide **2** (0.5 g, 1.8 mmol) and 4-chlorophenyl isocyanate (0.65 g. 4 mmol) by analogy with **7a** we obtained 0.38 g (38%) of compound **7b**; mp 144-145°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.43 (4H, t, *J* = 6.6, CH_2CO); 3.21 (4H, t, *J* = 6.6, $NHC\underline{H_2}$); 4.72 (2H, br. s, ArNH); 6.51 (4H, s, H Ar); 7.29-7.51 (8H, m, H Ar'); 8.13 (2H, d, *J* = 10.0, $NHN\underline{H}CO$); 8.89 (2H, d, *J* = 10.0, $N\underline{H}NHCO$); 9.78 (2H, s, ArNH). Mass spectrum, *m*/*z* (I_{rel}, %): 588 $[M + H]^+$ (50). Found, %: C 53.68; H 4.40; N 19.31. $C_{26}H_{28}Cl_2N_8O_4$. Calculated, %: C 53.16; H 4.80; N 19.07.

N,N'-Bis(phenylthioureidocarbamoylethyl)-1,4-phenylenediamine (8a). From dihydrazide **2** (1 g, 3.6 mmol) and phenyl isothiocyanate (1.2 g, 9 mmol) by analogy with compound **7a** we obtained compound **8a** with a yield of 1.40 g (71%); mp 165-166°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.67 (4H, t, *J* = 6.6, CH_2CO); 3.33-3.36 (4H, m, $NHC\underline{H_2}$); 4.36 (2H, t, *J* = 6.6, ArNH); 6.55-7.53 (14H, m, H Ar + H Ar'); 9.63 (4H, bs, NHNHCS); 10.02 (2H, br. s, NHAr). Mass spectrum, *m*/*z* (I_{rel}, %): 552 $[M + H]^+$ (100). Found, %: C 56.98; H 5.40; N 20.21. $C_{26}H_{30}N_8O_2S_2$. Calculated, %: C 56.71; H 5.49; N 20.35.

N,N'-Bis(phenylcarbamoyl)-N,N'-bis(phenylureidocarbamoylethyl)-1,4-phenylenediamine (9a). A mixture of dihydrazide **2** (1 g, 3 mmol) and phenyl isocyanate (2.1 ml, 18 mmol) in methanol (20 ml) was kept at room temperature for 24 h. The crystals that separated were filtered off and washed with methanol. The yield was 0.6 g (22%); mp 170-171°C (mixture of DMF and water). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.52-2.57 (4H, m, CH_2CO); 3.98 (4H, t, *J* = 7.2, $NHCH_2$); 6.94-7.01 (4H, m, H Ar'); 7.22-7.28 (8H, m, H Ar'); 7.45-7.47 (8H, m, H Ar'); 7.50 (4H, s, H Ar); 7.87 (2H, br. s, $NHN\underline{H}CO$); 8.06 (2H, br. s, $N\underline{H}NHCO$); 8.76 (2H, s, NHAr); 9.83 (2H, s, NHAr). Mass spectrum, *m*/*z* (I_{rel}, %): 758 $[M + H]^+$ (50). Found, %: C 63.98; H 5.30; N 18.31. $C_{40}H_{40}N_{10}O_6$. Calculated, %: C 63.48; H 5.33; N 18.51.

N,N'-Bis[(4-chorophenyl)carbamoyl]-N,N'-bis[(4-chlorophenyl)ureidocarbamoylethyl]-1,4-phenylenediamine (9b). From dihydrazide **2** (0.5 g, 1.8 mmol) and 4-chlorophenyl isocyanate (1.5 g, 10 mmol) in methanol (10 ml) by analogy with the synthesis of compound **9a** we obtained 0.25 g (16%) of compound **9b**; mp 211-212°C (mixture of DMF and water). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.52-2.56 (4H, m, CH_2CO); 3.97 (4H, t, *J* = 6.3, $NHC\underline{H_2}$); 7.28-7.34 (8H, m, H Ar'); 7.47-7.50 (12H, m, H Ar + H Ar'); 7.96 (2H, br. s, $NHN\underline{H}CO$); 8.13 (2H, br. s, $N\underline{H}NHCO$); 8.86 (2H, s, NHAr); 9.83 (2H, s, NHAr). Mass spectrum, *m*/*z* (I_{rel}, %): 895 $[M + H]^+$ (50). Found, %: C 53.98; H 4.40; N 15.31. $C_{40}H_{36}Cl_4N_{10}O_6$. Calculated, %: C 53.70; H 4.06; N 15.66.

N,N'-Bis(phenylthiocarbamoyl)-N,N'-bis(phenylthioureidocarbamoylethyl)-1,4-phenylenediamine (10a). From dihydrazide **2** (1 g, 3.6 mmol) and phenyl isocyanate (3 g, 22 mmol) in methanol (20 ml) after stirring the reaction mixture at room temperature for 24 h by analogy with compound **9a** we obtained 1.15 g (39%) of compound **10a**; mp 157-158°C (mixture of DMF and water). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.52-2.57 (4H, m, CH_2CO); 3.98 (4H, t, *J* = 6.9, $NHC\underline{H_2}$); 6.94-7.01 (4H, m, H Ar'); 7.25 (8H, t, *J* = 7.5,

H Ar'); 7.46 (8H, d, J = 7.5, H Ar'); 7.51 (4H, s, H Ar); 7.86 (2H, br. s, NHNHCO); 8.05 (2H, br. s, NHNHCO); 8.73 (2H, s, NHAr); 9.83 (2H, s, NHAr). Mass spectrum, m/z (I_{rel}, %): 822 $[M + H]^+$ (60). Found, %: C 58.98; H 4.44; N 17.31. $C_{40}H_{40}N_{10}O_2S_4$. Calculated, %: C 58.51; H 4.91; N 17.06.

N,N'-Bis[(5-oxo-4-phenyl-4,5-dihydro-1,2,4-triazol-3-yl)ethyl]-1,4-phenylenediamine (11a). A. Compound **7a** (0.55 g, 1 mmol) was boiled in 10% KOH (15 ml) for 4 h. The mixture was cooled, 18% HCl was added to pH 4, and the precipitate that separated was filtered off, washed with water, and crystallized from a 1:10 mixture of DMF and water. We obtained 0.25 g (49%) of compound **11a**; mp 195-196°C.

B. Compound **9a** (0.75 g, 1 mmol) was boiled in 15 ml of a 10% solution of KOH for 4 h. The product was isolated by analogy with method A. The yield was 0.32 g (67%); mp 197-198°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.60 (4H, t, J = 7.3, $NHCH_2C\underline{H_2}$); 3.08 (4H, t, J = 7.3, $NHC\underline{H_2}$); 4.85 (2H, br. s, ArNH); 6.19 (4H, s, H Ar); 7.40–7.58 (10H, m, H Ar'); 11.72 (2H, s, NHN). Mass spectrum, m/z (I_{rel}, %): 505 [M + Na] (50). Found, %: C 64.98; H 5.50; N 23.31. $C_{26}H_{26}N_8O_2$. Calculated, %: C 64.72; H 5.43; N 23.22.

N,N'-Bis{[4-(4-chlorophenyl)-5-oxo-4,5-dihydro-1,2,4-triazol-3-yl]ethyl}-1,4-phenylenediamine (11b). A. From compound **7b** (0.7 g, 1.2 mmol) by boiling in 10% KOH (20 ml) by analogy with compound **11a** we obtained 0.22 g (33%) of compound **11b**; mp 187-188°C (mixture of DMF and water).

B. From compound (**9b**) (0.67 g, 0.75 mmol) by analogy with method B we obtained 0.22 g (52%) of compound **11b**; mp 188-189°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.61 (4H, t, J = 7.4, $NHCH_2C\underline{H_2}$); 3.09 (4H, t, J = 7.4, $NHC\underline{H_2}$); 4.86 (2H, br. s, ArNH); 6.19 (4H, s, H Ar); 7.47 (4H, d, J = 8.6, H Ar'); 7.60 (4H, d, J = 8.6, H Ar'); 11.75 (2H, s, NHN). Mass spectrum, m/z (I_{rel}, %): 552 $[M + H]^+$ (60). Found, %: C 56.60; H 4.40; N 20.31. $C_{26}H_{24}Cl_2N_8O_2$. Calculated, %: C 56.63; H 4.39; N 20.32.

N,N'-Bis[(4-phenyl-5-thioxo-4,5-dihydro-1,2,4-triazol-3-yl)ethyl]-1,4-phenylenediamine (12a). A. From compound **8a** (0.55, 1.2 mmol) by boiling in 10 ml of 10% KOH for 3 h by analogy with compound **11a** we obtained 0.27 g (53%) of compound **12a**; mp 219-220°C (mixture of DMF and water).

B. From compound **10a** (1 g, 1.2 mmol) by boiling for 4 h in 10% KOH (20 ml) by analogy with compound **11a** we obtained 0.58 g (92%) of compound **12a**; mp 219-220°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.63 (4H, t, J = 7.0, $NHCH_2C\underline{H_2}$); 3.11 (4H, t, J = 7.0, $NHC\underline{H_2}$); 4.88 (2H, br. s, ArNH); 6.17 (4H, br. s, H Ar); 7.42-7.58 (10H, m, H Ar'); 13.67 (2H, s, NHN). Mass spectrum, m/z (I_{rel}, %): 516 $[M + H]^+$ (50). Found, %: C 60.75; H 5.40; N 21.31. $C_{26}H_{26}N_8S_2$. Calculated, %: C 60.68; H 5.09; N 21.77.

N,N'-Bis{[4-(4-chlorophenyl)-5-oxo-4,5-dihydro-1,2,4-triazol-3-yl]ethyl}-N,N'-bis(phenylthiocarbamoyl)-1,4-phenylenediamine (13). A mixture of triazole **11b** (0.2 g, 40 mmol), phenyl isothiocyanate (0.2 g, 1.5 mmol), and methanol (5 ml) was kept at 20°C for 24 h. The crystals that separated were filtered off and washed with ethanol. The yield was 0.21 g (70%); mp 245-246°C (mixture of DMF and water). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.90 (4H, t, J = 7.3, $NHCH_2C\underline{H_2}$); 4.31 (4H, t, J = 7.3, $NC\underline{H_2}$); 7.14-7.59 (22H, m, H Ar + H Ar'); 8.37 (2H, s, NHAr); 11.80 (2H, s, NHN). Mass spectrum, m/z (I_{rel}, %): 823 $[M + H]^+$ (50). Found, %: C 58.60; H 4.40; N 17.31. $C_{40}H_{34}Cl_2O_2S_2$. Calculated, %: C 58.46; H 4.17; N 17.04.

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