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Synthesis and Reactivity of 3-(2,2-Dimethylhydrazono)-5-R-cyclopentane-1,1,2,2-tetracarbonitriles

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Abstract—A new method of the synthesis of 3-(2,2-dimethylhydrazono)-5-R-1,1,2,2-tetracarbonitriles via oxidation of 3-(2,2-dimethylhydrazino)-5-R-1,1,2,2- tetracarbonitriles with diluted nitric acid was developed. High reactivity of 3-(2,2-dimethylhydrazono)-5-R-1,1,2,2-tetracarbonitriles caused by the presence of ethyl-1,1,2,2-tetracarbonitrile and *N*,*N*-dimethylhydrazone moieties allowed obtaining 2-methyl-5-R-3,4-dihydro-2*H*-cyclopenta[*e*][1,2,4]triazine-6,6,7,7-tetracarbonitriles, 3-amino-4-(2,2-dimethylhydrazono)-6-methyl-1,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrrole-3a,6a-dicarbonitriles, and 3-(2,2-dimethylhydrazino)-5-methylcyclopent-2-ene-1,1,2-tricarbonitrile.

Keywords: oxidation, ethyl-1,1,2,2-tetracarbonitrile moiety, one-step methods, reverse hyperconjugation, antitumor activity

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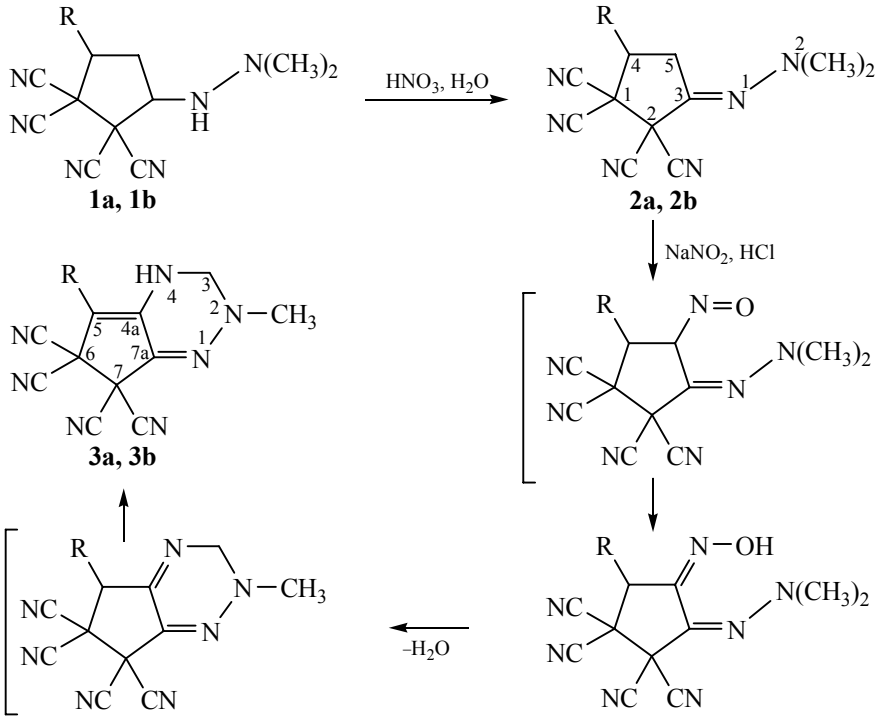
Development of new methods for the synthesis and study of reactivity of 3-(2,2-dialkylhydrazono)-5-R-cyclopentane-1,1,2,2-tetracarbonitriles and their derivatives are an urgent task, since they possess high antitumor activity [1] and have a unique combination of a closely spaced *N*,*N*-dimethylhydrazone and ethyl-1,1,2,2-tetracarbonitrile fragments in the ring. This unusual combination of the functional groups makes it possible to discover new reaction of 3-(2,2-dialkylhydrazono)-5-R-cyclopentane-1,1,2,2-tetracarbonitriles. Studies performed by the National Cancer Institute (USA) showed that among tetracyanoethylene-derived carbo- and heterocycles the compounds having ethyl-1,1,2,2-tetracarbonitrile fragment possess the highest antitumor activity [1, 2]. From a theoretical and practical point of view it is promising to study the reactivity of carbo- and heterocyclic compounds containing ethyl-1,1,2,2-tetracarbonitrile moiety, primarily 3-(2,2-dialkylhydrazono)-5-R-cyclopentane-1,1,2,2-tetracarbonitriles, because we believe that these compounds may be attributed to the group of alkylating agents and anticancer drugs (L01A) [3] by the nature of the action on the nucleophilic centers of the reagents and DNA biotargets. We believe that ethyl-1,1,2,2-tetra-carbonitrile group will alkylate readily the nucleophiles due to the close position and mutual activation of four nitrile moieties. In this combination their reciprocal activation effect is maximum.

We developed a new method of the synthesis of 3-(2,2-dialkylhydrazono)-5-R-cyclopentane-1,1,2,2-tetracarbonitriles **2a** and **2b** via the oxidation of 3-(2,2-dialkylhydrazino)-5-R-cyclopentane-1,1,2,2-tetracarbonitriles **1a** and **1b** with diluted nitric acid. Compared with the known methods for their preparation [4] the new method is easier and allows to obtain the target compounds in a higher yield.

It was found that among the leader compounds with a high antitumor activity [1] 3-(2,2-dialkylhydrazono)-5-R-cyclopentane-1,1,2,2-tetracarbonitriles have the highest reactivity. We used these compounds to obtain 1-dimethylamino-4-methyl-6-oxopiperidine-2,2,3,3-tetracarbonitriles [4] and 2,5-dimethyl-3,4-dihydro-2*H*-cyclopenta[*e*][1,2,4]triazine-6,6,7,7-tetracarbonitriles **3a** and **3b**. The reaction proceeded in one step (Scheme 1).

Compound **3a** we obtained earlier in 33% yield [5] by heating 3-(2,2-dimethyl-1-nitrosohydrazino)-5-methyl-

Scheme 1.



R = CH_3 (**a**), C_6H_5 (**b**).

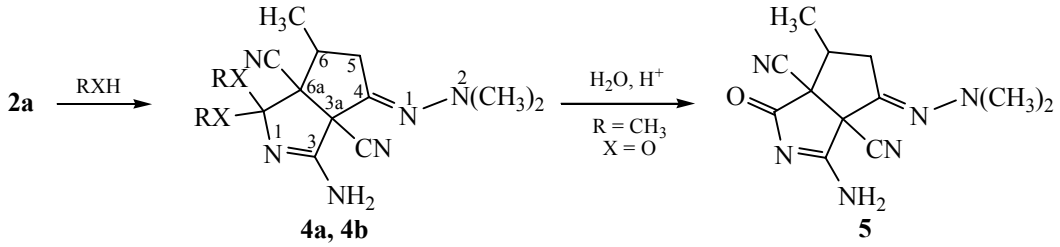
1,1,2,2-tetracarbonitrile in 2-propanol in the presence of hydrochloric acid.

In the ^{13}C NMR spectra of hydrazones **2a** and **2b** the signals of C=N moiety were shifted upfield (125–127 ppm) compared with the standard values (≈150–160 ppm) for the non-conjugated systems [6]. We think that in this case $p(N^2)$–$\pi(C^3{=}N^1)$ conjugation took place. However, as reported earlier, the p–π-conjugation does not occur in ketone alkylhydrazones series [7]. Then the question arose, which factors in the hydrazone moiety cause the conjugation between the lone electron pair of N^2 atom and $C^3{=}N^1$ π-bond?

It is known that electron-withdrawing groups like CF_3, $C(CF_3)_3$, $C(CN)_3$ due to the effect of reverse hyperconjugation [8, 9] cause polarization of not only neighboring σ-bonds, but also of the π-bond. Obviously, in the molecules of cyano-containing hydrazone cyclopentanes **2a** and **2b** the highly acceptor fragment $C(CN)_2C(CN)_2$ causes shifting the electron density from N^1 and N^2 atoms of hydrazone moiety to the C^3 carbon, which could explain the upfield shift of the signals of $C^3{=}N^1$ group (125–127 ppm).

To study the influence of electron-withdrawing properties of ethyl-1,1,2,2-tetracarbonitrile fragment on

Scheme 2.



R = CH_3, X = O (**4a**); R = C_4H_9, X = S (**4b**).

C=NN$(CH_3)_2$ bond and $p(N^2)$–$\pi(C^3{=}N^1)$-conjugation, we synthesized compounds **4** and **5** whose molecules contained C=NN$(CH_3)_2$ fragment bearing groups with electron acceptor properties less pronounced compared to hydrazones **2** (Scheme 2).

The transformations **2a**→**4a**,**4b** catalyzed with morpholine occured within seconds (TLC), which indicates the singularity of these reactions. We believe that the compounds having the highest antitumor activity and containing ethane-1,1,2,2-tetracarbonitrile fragment [1, 3] react with the nucleophilic centers of the DNA of tumor cells in a similar manner. Nitriles have been known to interact with nucleophiles under rigid conditions like prolonged heating of a mixture of a nitrile, a nucleophile, and a catalyst [10].

The signals of C^4 atom in ^{13}C NMR spectra of compounds **4** and **5** lied in the standard range (≈150–155 ppm). In **4** and **5**, there were no shift in the electronic environment N^2N^1→C^4 compared to hydrazones **2a** and **2b**. This was confirmed by ^{13}C NMR and UV spectroscopy. Relative violation of $p(N^2)$–$\pi(C^4{=}N^1)$ conjugation in the molecule of **4a** was detected by comparison of its electronic spectra with those of compounds **2a**.

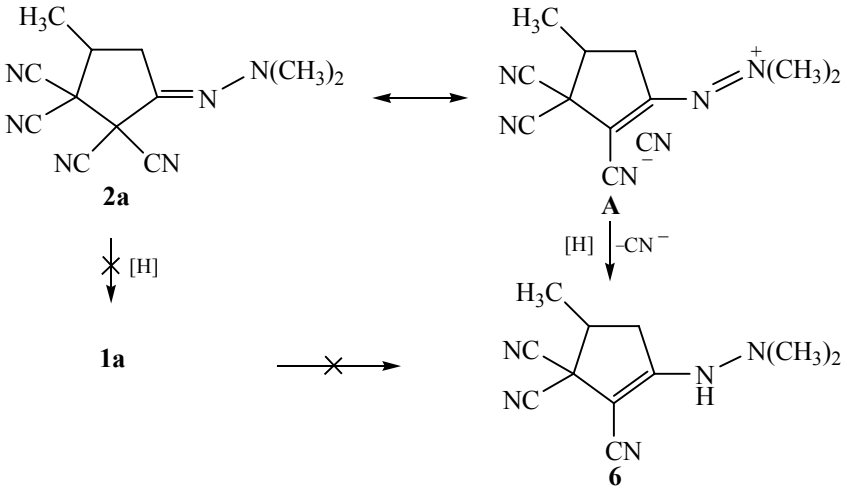
For hydrazone **2a** the absorption maximum was observed in the region of 270 nm (ε = 10200). In UV spectrum of **4a** (λ_{max} = 265 nm, ε = 3500) a blue shift was observed in comparison with the spectrum of compound **2a**. It can be suggested that a disruption of $p(N^2)$–$\pi(C^4{=}N^1)$ conjugation in the hydrazone fragment of **4a** compared to the same $p(N^2)$–$\pi(C^3{=}N^1)$ conjugation in **2a** is due to steric factors. To solve this question, we carried out a comparison of the UV spectra of compounds **2a** and **4a** with that of cyclopentanone dimethylhydrazone. It was synthesized from cyclopentanone and unsymmetrical dimethylhydrazone according to standard procedures [11]. Cyclopentanone dimethylhydrazone has no antitumor activity [3]. The absorption maximum corresponding to the n→π-transition for cyclopenta-none dimethylhydrazone was observed at 268 nm, the extinction coefficient equaled 1370. Thus, by ^{13}C NMR and UV spectroscopy data, in the case of cyclo-pentanone dimethylhydrazone, compounds **4a**, **4b**, and **5** $p(N^2)$–$\pi(C^3{=}N^1)$ the conjugation was not observed in contrast to compound **2a**. We can state that this is not due to steric factors and depends on the acceptor properties of the substituents or the number of nitrile groups in the α,β-positions relative to C=NN$(CH_3)_2$ fragment.

Hence, ethyl-1,1,2,2-tetracarbonitrile fragment in compounds **2a** and **2b** has a direct impact on the $p(N^2)$–$\pi(C^3{=}N^1)$ conjugation. A greater degree of $p(N^2)$–$\pi(C^3{=}N^1)$ conjugation of compounds **2a** and **2b** in comparison with **4a** and cyclopentanone dimethylhydrazone as well as unusual δ_C values of compounds **2** can probably be attributed to $\sigma(C^2{-}C^3)$–$p(N^1)$- and $\sigma(C^2{-}CN)$–$\pi(C^3{=}N^1)$ interactions, i.e. by reverse hyperconjugation effect.

The investigation of reactivity of compounds **2a** and **2b** confirmed this conclusion. The quartenization of hydrazones **2a** and **2b** with alkyl halides (CH_3I, C_2H_5Br) and dimethyl sulfate did not occur as well as the protonation of N^1 and N^2 atoms with mineral acids. These facts indicate considerable delocalization of the unshared electron pairs of the nitrogen atoms in the hydrazone fragment of compounds **2a** and **2b** in comparison with ordinary hydrazones, which react with alkylating agents and acids to form the corresponding salts [12, 13]. In accordance with the suggested $\sigma(C^2{-}CN)$–$\pi(C^3{=}N^1)$ interaction, the decyanation of hydrazone 2a took place by the action of some reducing agents to form cyclopentene **6**. Since σ–π-interaction in hydrazone **2a** implied the formation of a boundary structure **A**, it probably facilitated the formation of the final product **6**. In the reaction **6**→**2a** the formation of hydrazine **1a** did not occur (TLC). Furthermore, if one of the first stages of the process is the reduction of the C=N bond to CH–NH, then cyclopentene **6** could be synthesized by the reaction of cyclopentane **1a** with the same reagents. However, cyclopentene **6** was not formed from **1a** (Scheme 3).

Hence, compared with the known methods of the synthesis of 3-(2,2-dimethylhydrazono)-5-R-1,1,2,2-tetracarbonitriles the oxidation of 3-(2,2-dimethyl-hydazino)-5-R-1,1,2,2-tetracarbonitriles is more convenient for their preparation, since the desired products are formed in higher yields, the process occurs within a few minutes, and the oxidizer, nitric acid, can be regenerated. 3-(2,2-Dimethylhydrazono)-5-R-1,1,2,2-tetracarbonitriles are promising synthons allowing to obtain polyfunctional carbo- and heterocyclic compounds by one-stage reaction. 3-(2,2-Dimethylhydrazono)-5-R-1,1,2,2-tetracarbonitriles possess unusual properties like reverse hyperconjugation effect and unique activation of two nitrile groups in ethyl-1,1,2,2-tetracarbonitrile fragment allowing them to ineract easily and readily with nucleophiles. We believe that the study of the properties of carbo- and heterocyclic compounds containing ethyl-1,1,2,2-

Scheme 3.



tetracarbonitrile fragment among polycarbonitriles is the most relevant, due to the fact that this fragment is probably a new pharmacophore of alkylating action.

EXPERIMENTAL

The reaction progress and compounds purity were monitored by thin layer chromatography (TLC) using Silufol UV-254 plates, developing with UV irradiation, iodine vapor, or heating. IR spectra (mineral oil) were recorded on an UR-20 instrument. ^{13}C NMR spectra (CD_3CN) were taken on a spectrometer Varian VXR-300 (75 MHz). ^{1}H NMR spectra (DMSO-d_6) were registered on a Bruker AM-300 instrument operating at 300 MHz. Mass spectra were recorded on a Finnigan 50 mat.incos instrument (EI, 70 eV). UV spectra of the solu-tions in CH_3CN were obtained on a SF-26 instrument.

3-(2,2-Dimethylhydrazono)-5-R-cyclopentane-1,1,2,2-tetracarbonitriles (2a, 2b). To a suspension of 10 mmol of cyclopentane **1a** or **1b** in 50 mL of water was added 20 mL of nitric acid (55–65%). The mixture was heated to 45–50°C with stirring for 5–10 min (TLC monitoring). After the reaction completed, the mixture was cooled with cold water, diluted with 50 mL of water. The precipitate was filtered off, washed with 100 mL of water, and recrystallized from 2-propanol.

3-(2,2-Dimethylhydrazono)-5-methyl-cyclopentane-1,1,2,2-tetracarbonitrile (2a). Yield 1.8 g (75%), white crystals, mp 105–106°C.

3-(2,2-Dimethylhydrazono)-5-phenyl-cyclopentane-1,1,2,2-tetracarbonitrile (2b). Yield 1.9 g (63%), white crystals, mp 156–157°C.

Samples of compounds **2a** and **2b** obtained by us and by procedure described in [4] showed no melting points depression when mixed. Elemental analysis, IR, ^{13}C NMR spectroscopy and mass spectrometry data were consistent with the previously published data [4].

2-Methyl-5-R-3,4-dihydro-2*H*-cyclopenta[*e*]-[1,2,4]-triazine-6,6,7,7-carbonitriles (3a, 3b). To a solution of 10 mmol of compound **2a** or **2b** in 50 mL of methanol–water mixture (4 : 1) was added 15 mmol (1.56 g) of 35% hydrochloric acid. After cooling to 0–5°C, 15 mmol (5.175 g) of 20% aqueous sodium nitrite solution was added dropwise to the mixture with stirring. The reaction mixture was heated to reflux for 1 min, cooled and diluted with 50 mL of water. The precipitate was filtered off, washed with water, and recrystallized from 2-propanol.

2,5-Dimethyl-3,4-dihydro-2*H*-cyclopenta[*e*][1,2,4]-triazine-6,6,7,7-tetracarbonitrile (3a). Yield 1.33 g (53%), pel yellow crystals, mp 160°C (decomp.). IR spectrum, ν, cm^{-1}: 3370 (NH), 2260 (CN), 1672 (C=C), 1600 (C=NN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.92 s (3H, CH_3), 2.97 s (3H, CH_3N), 4.01 d (2H, $NH\underline{CH_2}$, $^{3}J_{HH}$ 2.44 Hz), 7.49 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 58.44 (C^3), 110.84 (C^{4a}), 135.00 (C^5), 51.75 (C^6), 48.05 (C^7), 126.97 (C^{7a}), 109.25 (CN), 110.23 (CN), 111.01 (CN), 111.19 (CN). Mass spectrum, *m*/*z* (I_{rel}, %): 251 [M^+].

Found, %: C 57.44; H 3.45; N 39.10. $C_{12}H_9N_7$. Calculated, %: C 57.37; H 3.61; N 39.02.

2-Methyl-5-phenyl-3,4-dihydro-2*H*-cyclopenta[*e*]-[1,2,4]triazine-6,6,7,7-tetracarbonitrile (3b). Yield 1.41 g (45%), pale yellow crystals, mp 170°C (decomp.). IR spectrum, ν, cm^{-1}: 3372 (NH), 2262 (CN), 1670 (C=C), 1615 (C=NN). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.10 s (3H, CH_3N), 4.10 d (2H, $NH\underline{CH_2}$, $^3J_{HH}$ 2.93 Hz), 6.23 br.s (1H, NH), 7.56 m (5H, C_6H_5). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 58.11 (C^3), 99.09 (C^{4a}), 133.00 (C^5), 45.00 (C^6), 48.97 (C^7), 129.94 (C^{7a}), 109.11 (CN), 109.38 (CN), 110.67 (CN), 111.34 (CN). Mass spectrum, *m*/*z* (I_{rel}, %): 313 [M^+]. Found, %: C 65.24; H 3.43; N 31.20. $C_{17}H_{11}N_7$. Calculated, %: C 65.17; H 3.54; N 31.29.

3-Amino-4-(2,2-dimethylhydrazono)-6-methyl-1,1-dimethoxy-1,3a,4,5,6,6a-hexahydrocyclopenta[*c*]-pyrrole-3a,6a-dicarbonitrile (4a). To a mixture of 2.4 g (10 mmol) of compound **2a** and 30 mL of methanol were added 3–4 drops of morpholine. The reaction mixture was cooled to 0–5°C. The precipitate was filtered off, washed with 10 mL of 2-propanol–hexane mixture (2 : 1), and recrystallized from 2-propanol. Yield 1.55 g (51%), white crystals, ppm 154–155°C (decomp.). IR spectrum, ν, cm^{-1}: 3420 br (NH_2), 2260 (CN), 1685 (C=N), 1600 (C=NN). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 118.50 (C^1), 159.09 (C^3), 62.75 (C^{3a}), 150.16 (C^4), 37.40 (C^5), 50.43 (C^6), 61.86 (C^{6a}), 114.62 (CN), 115.23 (CN). Mass spectrum, *m*/*z* (I_{rel}, %): 304 [M^+]. Found, %: C 55.30; H 6.71; N 27.53. $C_{14}H_{20}N_6O_2$. Calculated, %: C 55.25; H 6.62; N 27.61.

3-Amino-1,1-bis(butylthio)-4-(2,2-dimethylhydrazono)-6-methyl-1,3a,4,5,6,6a-hexahydrocyclopenta-[*c*]pyrrole-3a,6a-dicarbonitrile (4b). To a mixture of 2.4 g (10 mmol) of compound **2a** and 30 mL of 1,4-dioxane were added 3–4 drops of morpholine and a solution of 2.7 g (0.03 mol) of butanethiol in 20 mL of dioxane with stirring. The reaction mixture was kept at room temperature for 15–20 min, and then diluted with 60 mL of water. The precipitate was filtered off, washed with 2-propanol–water mixture (1 : 1), and recrystallized from 2-propanol. Yield 1.47 g (35%), yellow crystals, mp 149–150°C (decomp.). IR spectrum, ν, cm^{-1}: 3420 br (NH_2), 2255 (CN), 1680 (C=N), 1620 (C=NN). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 95.33 (C^1), 158.85 (C^3), 65.96 (C^{3a}), 155.45 (C^4), 35.40 (C^5), 37.05 (C^6), 62.64 (C^{6a}), 115.45 (CN), 116.61 (CN). Mass spectrum, *m*/*z* (I_{rel}, %): 420 [M^+]. Found, %: C 57.07; H 7.61; N 19.99; S 15.33. $C_{20}H_{32}N_6S_2$. Calculated, %: C 57.11; H 7.67; N 19.98; S 15.24.

3-Amino-4-(2,2-dimethylhydrazono)-6-methyl-1-oxo-1,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrrole-3a,6a-dicarbonitrile (5). To a suspension of 3.04 g (10 mmol) of compound **4a** in 30 mL of 2-propanol–water mixture (1 : 1) was added 1 mL of diluted sulfuric acid (8–10%). The reaction mixture was refluxed for 1 min. After cooling to 0–5°C the precipitate formed was filtered off, washed with 20 mL of water, and recrystallized from 2-propanol. Yield 1.99 g (77%), white crystals, mp 210°C (decomp.). IR spectrum, ν, cm^{-1}: 3450 br (NH_2), 2258 (CN), 1710 (C=O), 1620 (C=NN). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 170.00 (C^1), 162.20 (C^3), 68.03 (C^{3a}), 153.49 (C^4), 37.60 (C^5), 40.15 (C^6), 63.71 (C^{6a}), 117.42 (CN), 117.71 (CN). Mass spectrum, *m*/*z* (I_{rel}, %): 258 [M^+]. Found, %: C 55.86; H 5.41; N 32.50. $C_{12}H_{14}N_6O$. Calculated, %: C 55.80; H 5.46; N 32.54.

3-(2,2-Dimethylhydrazino)-5-methylcyclopent-2-ene-1,1,2-tricarbonitrile (6). *a*. To a solution of 10 mmol (2.4 g) of compound **2a** in 100 mL of methanol–water mixture (4 : 1) were added 1.96 g (30 mmol) of zinc powder and 5.4 g (90 mmol) of acetic acid. The reaction mixture was refluxed for 10–15 min. After the reaction completed (monitoring by TLC), insoluble impurities were separated. Then methanol was distilled off, the resulting precipitate was filtered off and washed with 2-propanol–water mixture (1 : 2). Yield 0.95 g (44%), pale yellow crystals, mp 119–120°C (decomp.). IR spectrum, ν, cm^{-1}: 3245 (NH), 2260 (CN), 2200 (CN, conjug.) 1630 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.51 d (3H, $\underline{CH_3}CH$, $^3J_{HH}$ 7.02 Hz), 3.05 s [6H, $(CH_3)_2N$)], 2.73 m (1H, 4-H), 3.26 m (1H, 4-H), 3.49 m (1H, 5-H), 4.05 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 49.17 (C^1), 65.45 (C^2), 161.06 (C^3), 36.21 (C^4), 42.43 (C^5), 15.68 ($CH\underline{CH_3}$), 113.97 (CN), 115.48 (CN), 116.26 (CN). Mass spectrum, *m*/*z* (I_{rel}, %): 215 [M^+]. Found, %: C 61.30; H 6.15; N 32.50. $C_{11}H_{13}N_5$. Calculated, %: C 61.38; H 6.09; N 32.53.

b. To a suspension of 10 mmol (2.4 g) of compound **2a** in 50 mL of 1,4-dioxane was added 10 mmol (0.38 g) of $NaBH_4$. The mixture was stirred for 30 min, diluted with 100 mL of water, neutralized to pH = 7.0 with 10% acetic acid solution, and extracted with diethyl ether (2 × 50 mL). The combined ether extracts were washed with water (3 × 50 mL), dried with calcined magnesium sulfate, and evaporated. The

residue was dissolved in 30 mL of ether and diluted with 40 mL of hexane. The separated precipitate was filtered off. Yield 0.495 g (23%), mp 119–120°C (decomp.). Samples obtained by procedures *a* and *b* showed no melting points depression when mixed. IR and mass spectral data of two samples were identical.

X-Ray diffraction study of compounds 2a. The crystals are monoclinic, $C_{12}H_{12}N_6$, M 240.28, space group $P2_1/n$; parameters of unit cell at 153(2) K: a = 7.721(2), b = 10.287(2), c = 16.814(3) Å, β = 100.94(1)°, V = 1311.2(5) Å^3, Z = 4, d_{calc} = 1.217 g cm^{-3}, $F(000)$ = 504, μ = 0.080 mm^{-1}.

The unit cell parameters and intensity of 2529 reflections (2334 independent reflections, R_{int} = 0.019) were measured on a four-circle automatic diffractometer Siemens P3/PC [λ(MoK_α)-irradiation, graphite monochromator, φ- and ω-scanning, 2θ = 52°). The structure was determined by the direct method and refined by full matrix least squares method with respect to F^2 in an anisotropic approximation for non-hydrogen atoms. Positions of the hydrogen atoms were geometrically calculated and refined using fixed positional parameters of a *rider* model and isotropic parameters $U_{iso}(H) = 1.5U_{eq}(C)$ for CH_3-groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for other groups. The final divergence factors: R_1 = 0.041 for 1744 independent reflections with $I \geq 2\sigma(I)$ and wR_2 = 0.100 for all independent reflections, S 1.010. The maximum and minimum residual electron density peaks were 0.18 and –0.14 e/Å^3, respectively. Tables of atomic coordinates, bond lengths, bond and torsion angles, and anisotropic thermal parameters for compound **2a** were deposited in the Cambridge Structural Database (CCDC 1,410,359).

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