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Reaction of 4-Oxocyclohexane-1,1,2,2-tetracarbonitriles and 5-Hydroxy-7-oxo-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitriles with Amines

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Abstract — New methods have been developed for the synthesis of fused amino-substituted pyrrolidinones and dihydropyrrolones. 4-Oxocyclohexane-1,1,2,2-tetracarbonitriles react with ammonia, hydrazine, and hydroxylamine to give, respectively, 5-amino-, 5-hydrazino-, and 5-hydroxylamino-7-oxo-6-azabicyclo[3.2.1]-octane-1,2,2-tricarbonitriles, while with phenylhydrazine, semicarbazide, and thiosemicarbazide, 6-hydrazono-, 6-semicarbazono-, and 6-thiosemicarbazono-3-amino-1-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitriles are formed. The latter can also be obtained under analogous conditions from 5-hydroxy-7-oxo-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitriles. Reactions of 5-hydroxy-7-oxo-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitriles with diethylamine or triethylamine give 3-amino-1,6-dioxo-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitriles.

In the synthesis of amino derivatives of carbo- and heterocycles by cyclization of nitriles, the most important is preparation of amino-substituted nitrogen-containing heterocycles [1]. In the recent time, reactions involving transformations of amino and cyano groups are frequently used. A general preparative procedure for the synthesis of 2-amino-substituted five-membered heterocyclic compounds is based on the condensation of α-amino ketones with nitriles having an activated methylene group [2]. However, this method is not free from some essential disadvantages. α-Amino ketones used as starting compounds are unstable, and they tend to undergo self-condensation in the presence of bases; in addition, the yield of the final products is reduced due to the high temperature of the reaction medium. The synthesis of aminodihydropyrroles attracts considerable interest. These compounds are obtained from halogen-substituted nitriles [3–5], aminonitriles [6], and aminocarbonyl-containing nitriles [7–11]. Hydrolysis of phthalonitrile and its substituted derivatives by the action of bases leads to dihydroisoindoles [12].

We have developed a new method of synthesis of aminodihydropyrrole derivatives by reaction of 4-oxocyclohexane-1,1,2,2-tetracarbonitriles and 5-hydroxy-7-oxo-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitriles with amines. We previously reported on the synthesis of tetracyanocyclohexanones **I** by cycloaddition of tetracyanoethylene to α,β-unsaturated ketones [13, 14]. While studying the reactions of tetracyanocyclohexanones **I** with aqueous solutions of ammonia, hydrazine, and hydroxylamine, we have found that bicyclic compounds **IIa**–**IIh** are formed in high yields in 3–5 min. We believe that the reaction begins with addition of RNH_2 to the carbonyl group of **I**. The subsequent cyclization and decyclization processes involving OH···CN and $CONH_2$···C=NR interactions lead to formation of 5-aminotetrahydropyrrol-2-one derivatives **IIa**–**IIh** (Scheme 1).

The structure of compound **IIb** was proved by X-ray diffraction analysis (Fig. 1). The formation of bicyclic compounds **II** is analogous to the reaction of cyclohexanones **I** with water, which affords products **III** [14]. The latter are convenient reagents for the synthesis of aminodihydropyrroles. Treatment of compounds **III** with diethylamine or triethylamine in an anhydrous medium leads to opening of the pyrrole ring and formation of 1,2,2-tricyano-5-oxocyclohexanecarboxamides **IVa**, **IVb**, and **IVf**–**IVh**; their subsequent cyclization yields 3-amino-1,6-dioxo-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitriles **Va**–**Vh**; here, the conversion depends on the

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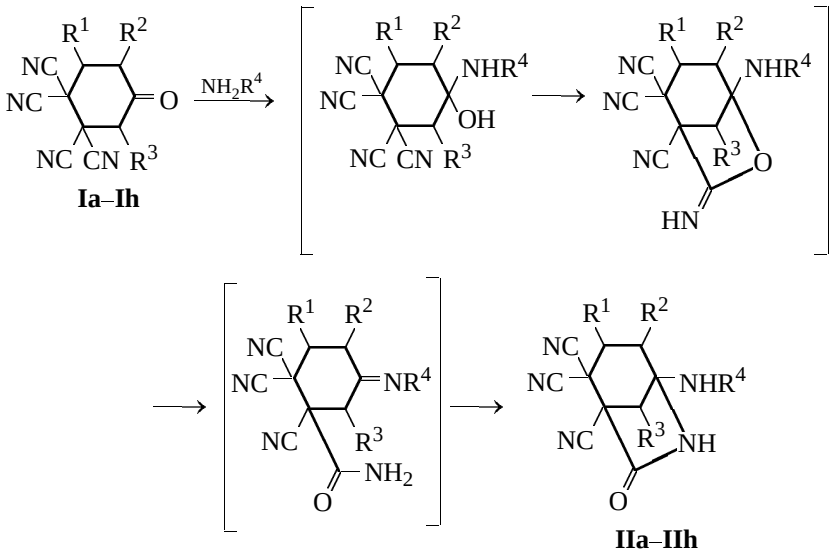
Scheme 1.



Ia–**Ih** **IIa**–**IIh**

R^1 = Ph, R^2 = C_3H_7, R^3 = R^4 = H (**a**); R^1 = Ph, R^2 = R^4 = H, R^3 = CH_3 (**b**); R^1 = Ph, R^2 = H, R^3 = CH_3, R^4 = NH_2 (**c**); R^1 = 4-$MeOC_6H_4$, R^2 = C_3H_7, R^3 = R^4 = H (**d**); R^1 = 4-$MeOC_6H_4$, R^2 = C_3H_7, R^3 = H, R^4 = NH_2 (**e**); R^1 = 4-$MeOC_6H_4$, R^2 = C_3H_7, R^3 = H, R^4 = OH (**f**); R^1 = Ph, R^2 = R^3 = CH_3, R^4 = H (**g**); R^1 = Ph, R^2 = R^3 = CH_3, R^4 = NH_2 (**h**).

temperature. The reaction with an equimolar amount of amine in alcohol at room temperature gives carboxamides **IVa**, **IVb**, and **IVf**–**IVh**. Heating of **IIIa**–**IIIh** with an equimolar amount of amine to 50–60°C in 2–5 min gives 55–75% of 3-amino-1,6-dioxo-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitriles **Va**–**Vh**. Similar results were obtained on dissolution of compounds **III** in diethyl- or triethylamine. In this case, dihydropyrroles **V** were formed in 5–10 min (Scheme 2).

Hydrazine and its derivatives, such as phenylhyd-

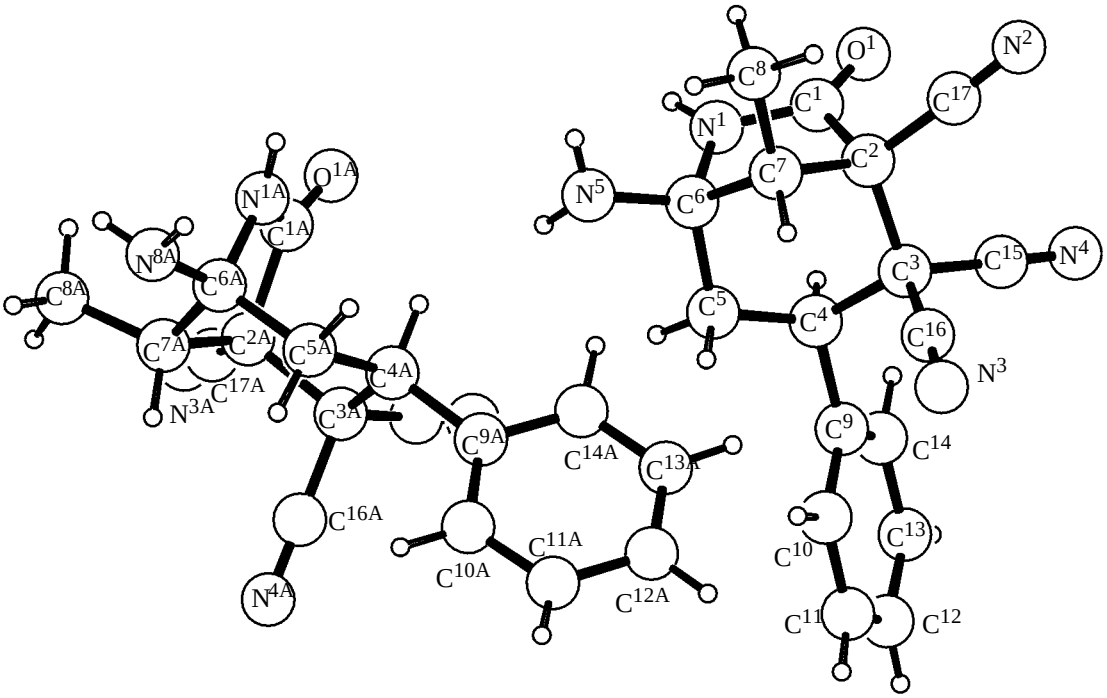
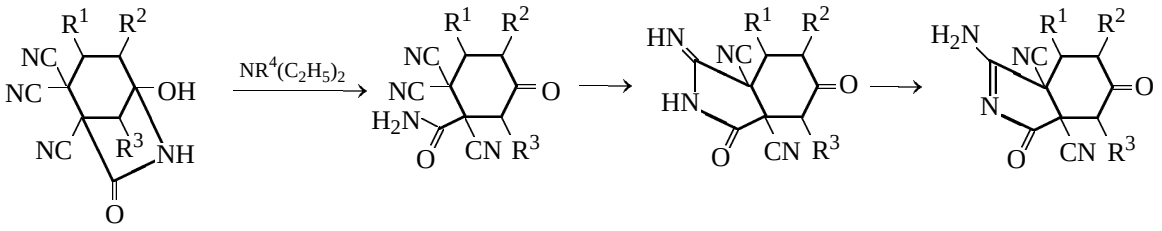


Fig. 1. Structure of the molecule of 5-amino-9-methyl-7-oxo-3-phenyl-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitrile (**IIb**) according to the X-ray diffraction data.

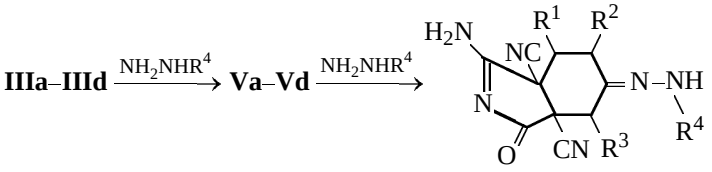
Scheme 2.



IIIa–IIIh **IVa, IVb, IVf–IVh** **Va–Vh**

R^1 = Ph, R^2 = C_3H_7, R^3 = H (**a**); R^1 = Ph, R^2 = H, R^3 = CH_3 (**b**); R^1 = 4-$MeOC_6H_4$, R^2 = C_3H_7, R^3 = H (**c**); R^1 = Ph, R^2 = R^3 = CH_3 (**d**); R^1 = 4-$MeOC_6H_4$, R^2 = R^3 = CH_3 (**e**); R^1 = Ph, R^2 = CH_3, R^3 = H (**f**); R^1 = $MeOC_6H_4$, R^2 = H, R^3 = CH_3 (**g**); R^1 = Ph, R^2 = R^3 = H (**h**); R^4 = H, C_2H_5.

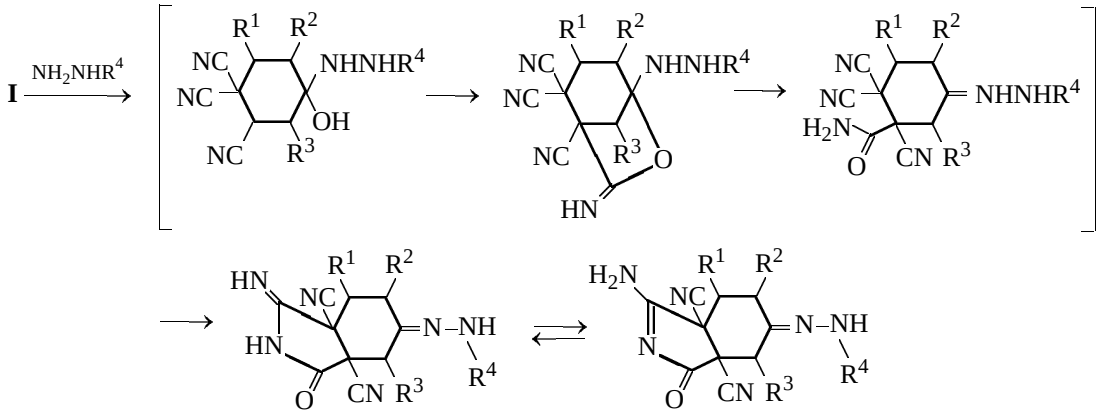
Scheme 3.



VIa–VId

R^1 = Ph, R^2 = C_3H_7, R^3 = H, R^4 = $CONH_2$ (**a**); R^1 = R^4 = Ph, R^2 = H, R^3 = CH_3 (**b**); R^1 = 4-$MeOC_6H_4$, R^2 = C_3H_7, R^3 = H, R^4 = $CSNH_2$ (**c**); R^1 = R^4 = Ph , R^2 = R^3 = CH_3 (**d**).

Scheme 4.



VIa–VIi

R^1 = Ph, R^2 = C_3H_7, R^3 = H, R^4 = $CONH_2$ (**a**); R^1 = R^4 = Ph, R^2 = H, R^3 = CH_3 (**b**); R^1 = 4-$MeOC_6H_4$, R^2 = C_3H_7, R^3 = H, R^4 = $CSNH_2$ (**c**); R^1 = R^4 = Ph, R^2 = R^3 = CH_3 (**d**); R^1 = 4-$MeOC_6H_4$, R^2 = C_3H_7, R^3 = H, R^4 = H (**e**); R^1 = R^4 = Ph, R^2 = C_3H_7, R^3 = H (**f**); R^1 = 4-$MeOC_6H_4$, R^2 = C_3H_7, R^3 = H, R^4 = $CONH_2$ (**g**); R^1 = Ph, R^2 = R^4 = H, R^3 = CH_3 (**h**); R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = *i*-C_3H_7, R^4 = $CONH_2$ (**i**).

razine, semicarbazide, and thiosemicarbazide, promote further transformations. By heating compounds **IIIa**–**IIId** in a boiling aqueous–alcoholic solution of hydrazine in the presence of acetic acid (reaction time 2–3 h) we obtained hydrazones **VIa**–**VId** (Scheme 3). Scheme 3 was proved by the synthesis of compounds **VIa**–**VId** from **Va**–**Vd** by the action of the corresponding hydrazine derivatives. In addition, hydrazones and semicarbazones **VIa**–**VIi** were obtained by heating cyclohexanones **I** with hydrazine, phenylhydrazine, semicarbazide, and thiosemicarbazide in boiling aqueous alcohol for 5–10 min (Scheme 4).

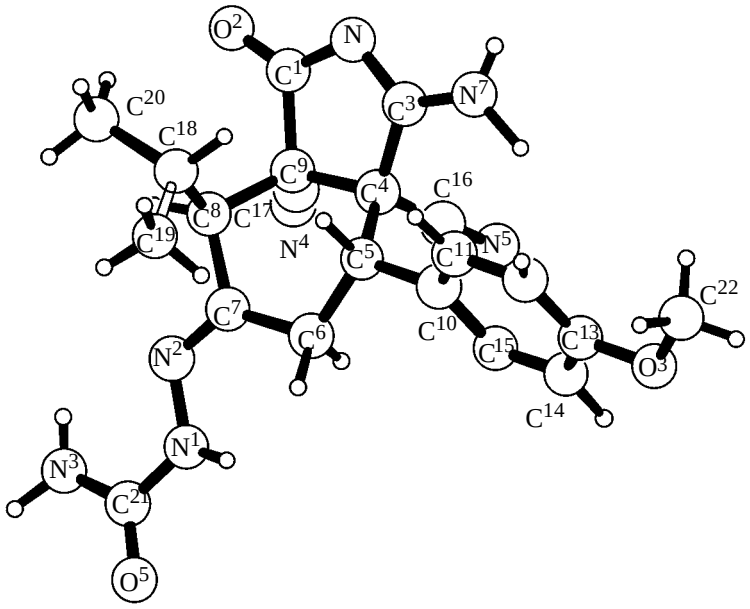


Fig. 2. Structure of the molecule of 3-amino-1-oxo-6-semicarbazono-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (**VIi**) according to the X-ray diffraction data.

In the absence of water (using anhydrous alcohol), we also succeeded in synthesizing hydrazones **VIa**–**VIi** from cyclohexanones **I**. Therefore, we believe that the process begins with addition of hydrazine molecule at the carbonyl group. The structure of hydrazone **VIi** was proved by X-ray diffraction (Fig. 2).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument from samples dispersed in mineral oil. The ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz) in DMSO-d_6. The molecular weight were determined from the mass spectra which were run on a Finnigan-MAT Incos-50 mass spectrometer (70 eV). The unit cell parameters of compounds **IIb** and **VIi** and reflection intensities were measured on a Siemens-P3/PC four-circle diffractometer (λMoK_α irradiation, graphite monochromator, $\theta/2\theta$ scanning). The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates.

5-Amino-7-oxo-3-phenyl-4-propyl-6-azabicyclo-[3.2.1]octane-1,2,2-tricarbonitrile (IIa). Tetracyanocyclohexanone **Ia**, 0.005 mol, was added under continuous stirring to 10 ml of a 20% ammonia solution. The mixture was stirred for 3–5 min (the mixture remained heterogeneous), and the precipitate was filtered off, washed with water, 2-propanol, and diethyl ether, dried in air, and recrystallized from 2-propanol. Yield 95%, mp 223–224°C. IR spectrum, ν, cm^{-1}: 3435, 3335, 3225 (NH_2); 2270 (C–N); 1710 (C=O); 1645 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.26 s (1H, NHCO), 7.54 t (2H, *m*-H), 7.48 m (3H, *o*-H, *p*-H), 3.10 d (1H, PhC*H*), 2.88 d (1H, CH_2), 2.56 d (1H, CH_2), 2.50 s (2H, NH_2), 2.33 m (1H, C*H*Pr), 1.45–0.9 m (4H, $CH_2CH_2CH_3$), 0.63 t (3H, CH_3). Found, %: C 68.36; H 5.71; N 20.94. M^+ 333. $C_{19}H_{19}N_5O$. Calculated, %: C 68.45; H 5.74; N 21.01.

Compounds **IIb**–**IIh** were synthesized and purified in a similar way. In the synthesis of **IIc**, **IIe**, and **IIh**, 20% aqueous hydrazine was used instead of ammonia, and in the synthesis of **IIf**, 20% aqueous hydroxylamine.

5-Amino-8-methyl-7-oxo-3-phenyl-6-azabicyclo-[3.2.1]octane-1,2,2-tricarbonitrile (IIb). Yield 95%, mp 238–239°C. IR spectrum, ν, cm^{-1}: 3415, 3300, 3210 (NH_2); 2265 (C–N); 1710 (C=O); 1645 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.9 s (1H, NHCO), 7.57 t (2H, *m*-H), 7.47 m (3H, *o*-H, *p*-H), 3.53 d.d (1H, PhC*H*), 2.61 q (1H, MeCH), 2.57 s (2H, NH_2), 2.47 t (1H, $CHCH_2$), 2.08 d.d (1H, $CHCH_2$), 1.27 d (3H, CH_3). Found, %: C 66.92; H 5.01; N 22.94. M^+ 305. $C_{17}H_{15}N_5O$. Calculated, %: C 66.87; H 4.95; N 22.94.

5-Hydrazino-8-methyl-7-oxo-3-phenyl-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitrile (IIc). Yield 74%, mp 212–214°C. IR spectrum, ν, cm^{-1}: 3460–3200 (NH_2); 2270 (C–N); 1710 (C=O); 1655 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.02 s (1H, NHCO), 7.56 t (2H, *m*-H), 7.49 m (3H, *o*-H, *p*-H),

3.69 t (1H, NH), 3.58 d (2H, NH_2), 3.54 d.d (1H, PhC*H*), 2.68 q (1H, MeC*H*), 2.49 t (1H, CHCH_2), 2.1 d.d (1H, CHCH_2), 1.24 d (3H, CH_3). Found, %: C 63.80; H 5.09; N 26.31. M^+ 320. $C_{17}H_{16}N_6O$. Calculated, %: C 63.74; H 5.03; N 26.23.

5-Amino-3-(4-methoxyphenyl)-7-oxo-4-propyl-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitrile (IId). Yield 93%, mp 226–227°C (decomp.). IR spectrum, ν, cm^{-1}: 3410, 3350, 3220 (NH_2); 2275 (C–N); 1710 (C=O); 1645 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.3 s (1H, NHCO), 7.5 d (2H, *o*-H), 7.04 d (2H, *m*-H), 3.8 s (3H, CH_3O), 3.1 d (1H, ArC*H*), 2.89 d (1H, CH_2), 2.58 d (1H, CH_2), 2.60 s (2H, NH_2), 2.34 m (1H, C*H*Pr), 1.45–0.9 m (4H, CH_2CH_2CH_3), 0.61 t (3H, CH_3). Found, %: C 66.17; H 5.79; N 19.33. M^+ 363. $C_{20}H_{21}N_5O_2$. Calculated, %: C 66.10; H 5.82; N 19.27.

5-Hydrazino-3-(4-methoxyphenyl)-7-oxo-4-propyl-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitrile (IIe). Yield 81%, mp 238–239°C (decomp.). IR spectrum, ν, cm^{-1}: 3480–3200 (NH_2); 2270 (C–N); 1715 (C=O); 1645 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.21 s (1H, NHCO), 7.54 d (2H, *o*-H), 7.11 d (2H, *m*-H), 3.82 t (1H, NH), 3.61 d (2H, NH_2), 3.82 s (3H, CH_3O), 3.14 d (1H, ArC*H*), 2.89 d (1H, CH_2), 2.62 d (1H, CH_2), 2.31 m (1H, C*H*Pr), 1.4–0.9 m (4H, CH_2CH_2CH_3), 0.63 t (3H, CH_3). Found, %: C 63.47; H 5.90; N 22.22. M^+ 378. $C_{20}H_{22}N_6O_2$. Calculated, %: C 63.48; H 5.86; N 22.21.

5-Hydroxylamino-3-(4-methoxyphenyl)-7-oxo-4-propyl-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitrile (IIf). Yield 62%, mp 241–242°C (decomp.). IR spectrum, ν, cm^{-1}: 3500–3250 (NH_2); 2275 (C–N); 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.05 s (1H, NHCO), 7.55 d (2H, *o*-H), 7.14 d (2H, *m*-H), 4.92 d (1H, OH), 3.89 d (1H, NH), 3.82 s (3H, CH_3O), 3.13 d (1H, ArC*H*), 2.84 d (1H, CH_2), 2.67 d (1H, CH_2), 2.36 m (1H, C*H*Pr), 1.4–1.0 m (4H, CH_2CH_2CH_3), 0.68 t (3H, CH_3). Found, %: C 63.29; H 5.61; N 18.53. M^+ 379. $C_{20}H_{21}N_5O_3$. Calculated, %: C 63.31; H 5.58; N 18.46.

5-Amino-4,8-dimethyl-7-oxo-3-phenyl-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitrile (IIg). Yield 92%, mp 221–222°C (decomp.). IR spectrum, ν, cm^{-1}: 3420, 3340, 3225 (NH_2); 2270 (C–N); 1710 (C=O); 1645 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.18 s (1H, NHCO), 7.2–7.1 m (5H, Ph), 2.99 d (1H, PhC*H*), 2.7 q (1H, C*H*CH_3), 2.4 m [1H, C*H*(CH_3)CH·Ph], 2.37 s (2H, NH_2), 1.28 d (3H, CHCH_3), 0.79 d [3H, CH(CH_3)CHPh]. Found, %: C 67.77; H 5.32; N 21.84. M^+ 319. $C_{18}H_{17}N_5O$. Calculated, %: C 67.70; H 5.37; N 21.93.

5-Hydrazino-4,8-dimethyl-7-oxo-3-phenyl-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitrile (IIh). Yield 75%, mp 234–235°C (decomp.). IR spectrum, ν, cm^{-1}: 3450–3180 (NH_2); 2270 (C–N); 1710 (C=O); 1655 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.18 s (1H, NHCO), 7.2–7.1 m (5H, Ph), 3.88 t (1H, NH), 3.59 d (2H, NH_2), 3.02 d (1H, PhCH), 2.76 q (1H, CHCH_3), 2.45 m [1H, C*H*(CH_3)CHPh], 1.24 d (3H, CHCH_3), 0.73 d [3H, CH(CH_3)CHPh]. Found, %: C 64.67; H 5.42; N 25.08. M^+ 334. $C_{18}H_{18}N_6O$. Calculated, %: C 64.66; H 5.43; N 25.13.

1,2,2-Tricyano-5-oxo-3-phenyl-4-propylcyclohexanecarboxamide (IVa). Compound **IIIa**, 0.01 mol, was added to a solution of 0.01 mol of diethyl- or triethylamine in 20 ml of anhydrous ethanol, and the mixture was stirred at room temperature until it became homogeneous. After 10–15 min, a solid precipitated and was filtered off and washed with alcohol. Yield 57%, mp 184–185°C. IR spectrum, ν, cm^{-1}: 3405, 3260 (NH_2); 2270 (C–N); 1720, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.69 m (3H, *m*-H, *p*-H), 7.4 d (2H, *o*-H), 6.63 s (1H, $CONH_2$), 6.44 s (1H, $CONH_2$), 3.53 d (1H, C*H*Ph), 2.81 d (1H, CH_2), 2.48 d (1H, CH_2), 2.34 m (1H, C*H*Pr), 1.46–0.9 m (4H, CH_2CH_2CH_3), 0.68 t (3H, CH_3). Found, %: C 68.39; H 5.47; N 16.66. M^+ 334. $C_{19}H_{18}N_4O_2$. Calculated, %: C 68.25; N 5.43; N 16.76.

Compounds **IVb** and **IVf**–**IVh** were synthesized in a similar way.

1,2,2-Tricyano-6-methyl-5-oxo-3-phenylcyclohexanecarboxamide (IVc). Yield 49%, mp 174–175°C. IR spectrum, ν, cm^{-1}: 3385, 3290 (NH_2); 2270 (C–N); 1725, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.6 m (5H, Ph), 6.6 s (1H, $CONH_2$), 6.55 s (1H, $CONH_2$), 4.02 d. d (1H, C*H*Ph), 3.98 q (1H, COC*H*Me), 3.58 t (1H, $COCH_2$), 2.74 d.d (1H, $COCH_2$), 1.21 d (3H, CHCH_3). Found, %: C 66.55; H 4.64; N 17.21. M^+ 306. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.66; N 4.61; N 17.29.

1,2,2-Tricyano-4-methyl-5-oxo-3-phenylcyclohexanecarboxamide (IVf). Yield 46%, mp 174–175°C. IR spectrum, ν, cm^{-1}: 3385, 3290 (NH_2); 2270 (C–N); 1725, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.5–7.7 m (5H, Ph), 6.11 s (2H, $CONH_2$), 4.32 d (1H, C*H*Ph), 4.07 m (1H, C*H*Me), 3.7 d (1H, $COCH_2$), 2.87 d (1H, $COCH_2$), 0.96 d (3H, CH_3). Found, %: C 66.55; H 4.64; N 17.21. M^+ 306. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.71; H 4.65; N 17.19.

1,2,2-Tricyano-3-(4-methoxyphenyl)-6-methyl-5-oxocyclohexanecarboxamide (IVg). Yield 41%, mp 169– 170°C. IR spectrum, ν, cm^{-1}: 3400, 3295 (NH_2);

2265 (C–N); 1720, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.56 d (2H, *o*-H), 7.11 d (2H, *m*-H), 6.6 s (2H, $CONH_2$), 4.21 d.d (1H, C*H*Ar), 4.01 q (H, C*H*CH_3), 3.84 s (3H, OCH_3), 3.56 t (1H, CH_2CO), 2.79 d.d (1H, CH_2CO), 0.98 d (3H, C*H*$_3$). Found, %: C 64.22; H 4.70; N 16.58. M^+ 336. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.13; H 4.77; N 16.69.

1,2,2-Tricyano-5-oxo-3-phenylcyclohexanecarboxamide (IVh). Yield 57%, mp 195–196°C (decomp.). IR spectrum, ν, cm^{-1}: 3395, 3280 (NH_2); 2270 (C–N); 1730, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.68 m (3H, *m*-H, *p*-H), 7.51 d (2H, *o*-H), 6.51 s (1H, $CONH_2$), 6.48 s (1H, $CONH_2$), 3.66 d.d (1H, C*H*Ph), 3.01 d (1H, CH_2CCN), 2.71 t (1H, CHC*H*$_2$), 2.68 d (1H, CH_2CCN), 2.17 d.d (1H, CHC*H*$_2$). Found, %: C 65.85; H 4.23; N 19.06. M^+ 292. $C_{16}H_{12}N_4O_2$. Calculated, %: C 65.75; H 4.14; N 19.17.

3-Amino-1,6-dioxo-4-phenyl-5-propyl-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (Va). *a*. Compound **IIIa**, 0.01 mol, was added to a solution of 0.01 mol of diethyl- or triethylamine in 20 ml of anhydrous ethanol, and the mixture was stirred for 5 min at 50°C. The solution was cooled, and the precipitate was filtered off and washed with alcohol. Yield 64%.

b. Compound **IIIa**, 0.01 mol, was dissolved at room temperature in 10 ml of diethylamine or triethylamine. After 5–10 min, a solid precipitated and was filtered off, washed with water and diethyl ether, and recrystallized from dioxane. Yield 73%, mp 222–224°C (decomp.). IR spectrum, ν, cm^{-1}: 3350, 3265 (NH_2); 2265 (C–N); 1710, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.73 s (1H, =NH), 7.92 s (1H, NH), 7.44 m (3H, *m*-H, *p*-H), 7.37 d (2H, *o*-H), 3.79 d (1H, C*H*Ph), 3.64 d (1H, CH_2), 2.87 d (1H, CH_2), 2.85 m (1H, CHPr), 1.3–1.0 m (4H, CH_2CH_2CH$_3$), 0.64 t (3H, CH_2 C*H*$_3$). Found, %: C 68.32; H 5.48; N 16.67. M^+ 334. $C_{19}H_{18}N_4O_2$. Calculated, %: C 68.25; N 5.43; N 16.76.

Compounds **Vb**–**Vh** were synthesized and purified in a similar way.

3-Amino-7-methyl-1,6-dioxo-4-phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (Vb). Yield 55% (*a*), 75% (*b*), mp 210–211°C (decomp.). IR spectrum, ν, cm^{-1}: 3365, 3265 (NH_2); 2270 (C–N); 1720, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.79 s (1H, =NH), 8.0 s (1H, NH), 7.7–7.6 m (5H, Ph), 4.02 t (1H, C*H*Ph), 3.88 q (1H, C*H*Me), 3.74 t (1H, CH_2), 2.88 d.d (1H, CH_2), 1.26 d (3H, CHC*H*$_3$). Found, %: C 66.56; H 4.67; N 18.28. M^+ 306. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.66; H 4.61; N 18.29.

3-Amino-4-(4-methoxyphenyl)-1,6-dioxo-5-propyl-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (Vc). Yield 67% (*a*), 82% (*b*), mp 222–224°C (decomp.). IR spectrum, ν, cm^{-1}: 3345, 3260 (NH_2); 2275 (C–N); 1710, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.88 s (1H, =NH), 8.07 s (1H, NH), 7.59 d (2H, *o*-H), 7.22 d (2H, *m*-H), 3.87 d (1H, C*H*Ar), 3.84 s (3H, OCH_3), 3.78 d (1H, $COCH_2$), 3.2 d (1H, $COCH_2$), 3.01 d.d (1H, C*H*Pr), 1.4–1.1 m (4H, CH_2CH_2CH$_3$), 0.72 t (3H, $CH_2CH_2CH_3$). Found, %: C 66.01; H 5.59; N 15.45. M^+ 364. $C_{20}H_{20}N_4O_3$. Calculated, %: C 65.92; H 5.53; N 15.38.

3-Amino-4-(4-methoxyphenyl)-5,7-dimethyl-1,6-dioxo-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (Vd). Yield 69% (*a*), 84% (*b*), mp 216–217°C (decomp.). IR spectrum, ν, cm^{-1}: 3365, 3270 (NH_2); 2275 (C–N); 1720, 1700 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.85 s (1H, =NH), 8.26 s (1H, NH), 7.35–42 m (5H, Ph), 3.79 d.d (1H, C*H*Ph), 3.12 q (1H, C*H*Me), 2.96 m (1H, PhCHC*H*CH$_3$), 1.38 d (3H, CHC*H*$_3$), 1.11 d (3H, CHC*H*$_3$). Found, %: C 67.54; H 5.13; N 17.66. M^+ 320. $C_{18}H_{16}N_4O_2$. Calculated, %: C 67.49; H 5.03; N 17.49.

3-Amino-4-(4-methoxyphenyl)-4,7-dimethyl-1,6-dioxo-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (Ve). Yield 71% (*a*), 82% (*b*), mp 138–139°C. IR spectrum, ν, cm^{-1}: 3360, 3275 (NH_2); 2265 (C–N); 1720, 1705 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.94 s (1H, NH), 8.16 s (1H, NH), 7.51 d (2H, *o*-H), 7.12 d (2H, *m*-H), 3.86 s (3H, CH_3O), 3.84 d.d (1H, C*H*Ar), 3.12 q (1H, C*H*Me), 2.92 m (1H, ArCHCHCH$_3$), 1.44 d (3H, CHC*H*$_3$), 1.13 d (3H, CHC*H*$_3$). Found, %: C 65.03; H 5.13; N 16.06. M^+ 350. $C_{19}H_{18}N_4O_3$. Calculated, %: C 65.13; H 5.18; N 15.99.

3-Amino-5-methyl-1,6-dioxo-4-phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (Vf). Yield 62% (*a*), 79% (*b*), mp 210–211°C (decomp.). IR spectrum, ν, cm^{-1}: 3360, 3265 (NH_2); 2270 (C–N); 1720, 1705 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.86 s (1H, NH), 8.03 s (1H, NH), 7.7–7.6 m (5H, Ph), 4.14 d (1H, C*H*Ph), 3.92 m (1H, C*H*Me), 3.68 d (1H, CH_2), 2.8 d (1H, CH_2), 1.14 d (3H, CHC*H*$_3$). Found, %: C 66.59; H 4.63; N 18.26. M^+ 306. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.66; H 4.61; N 18.29.

3-Amino-4-(4-methoxyphenyl)-7-methyl-1,6-dioxo-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-

dicarbonitrile (Vg). Yield 74% (*a*), 64% (*b*), mp 164–165°C. IR spectrum, ν, cm^{-1}: 3365, 3265 (NH_2); 2270 (C–N); 1720, 1700 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.71 s (1H, NH), 8.13 s (1H, NH), 7.43 d (2H, *o*-H), 7.06 d (2H, *m*-H), 3.95 d.d (1H, C*H*Ar), 3.89 q (1H, C*H*Me), 3.66 t (1H, CH_2), 2.97 d.d (1H, CH_2), 1.36 d (3H, CHCH_3). Found, %: C 64.41; H 4.68; N 16.59. M^+ 336. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.28; H 4.79; N 16.66.

3-Amino-1,6-dioxo-4-phenyl-3a,4,5,6,7,7a-hexahydro-*1*H-isoindole-3a,7a-dicarbonitrile (Vh). Yield 70% (*a*), 73% (*b*), mp 202–203°C (decomp.). IR spectrum, ν, cm^{-1}: 3385, 3290 (NH_2); 2270 (C–N); 1725, 1700 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.95 s (1H, NH), 8.05 s (1H, NH), 7.7–7.6 m (5H, Ph), 3.94 d.d (1H, C*H*Ph), 3.09 d.d (1H, CH_2CCN), 2.79 t (1H, CHCH_2), 2.64 d. d (1H, CH_2CCN), 2.3 d.d (1H, CHCH_2). Found, %: C 65.85; H 4.23; N 19.06. M^+ 292. $C_{16}H_{12}N_4O_2$. Calculated, %: C 65.75; H 4.14; N 19.17.

3-Amino-1-oxo-4-phenyl-5-propyl-6-semicarbazono-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VIa). *a*. A solution of 0.02 mol of semicarbazide in 10 ml of ethanol and 1–2 ml of acetic acid was added to 0.01 mol of compound **IIIa** in 10 ml of ethanol. The mixture was heated for 2–3 h under reflux until the reaction was complete (TLC) and cooled, and the precipitate was filtered off and washed with water and 2-propanol. Yield 67%.

b. A solution of 0.02 mol of semicarbazide in 10 ml of ethanol and 1–2 ml of glacial acetic acid was added to 0.01 mol of compound Va in 10 ml of ethanol. The mixture was heated for 1–2 h under reflux (TLC) and cooled, and the precipitate was filtered off and washed with water and 2-propanol.

c. A solution of 0.02 mol of semicarbazide in a mixture of 10 ml of ethanol, 20 ml of water, and 1–2 ml of acetic acid was added to 0.01 mol of compound **Ia** in 10 ml of ethanol. The mixture was heated for 5–10 min until the reaction was complete (TLC), cooled, and diluted with 20 ml of water, and the precipitate was filtered off, washed with water and 2-propanol, and recrystallized from 2-propanol. Yield 75%, mp 276–278°C (decomp.). IR spectrum, ν, cm^{-1}: 3540–3210 (NH); 2270 (C–N); 1710 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.79 s (1H, =NH), 9.24 s (1H, N*H*CONH_2), 7.68 s (1H, NH), 7.4–7.2 m (5H, Ph), 6.24 s (1H, CONH_2), 4.06 d (1H, C*H*Ph), 3.74 d (1H, $COCH_2$), 3.26 d (1H, $COCH_2$), 3.01 d.d (1H, C*H*Pr), 1.6–1.3 m (4H, CH_2CH_2CH_3), 0.87 t (3H, $CH_2CH_2CH_3$). Found, %: C 65.85; H 4.23; N 19.06. M^+ 391. $C_{20}H_{21}N_7O_2$. Calculated, %: C 61.37; H 5.41; N 25.05.

Compounds **VIb**–**VIi** were synthesized and purified in a similar way.

3-Amino-7-methyl-1-oxo-4-phenyl-6-phenylhydrazono-3a,4,5,6,7,7a-hexahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VIb). Yield 53% (*a*), 94% (*b*), 79% (*c*); mp 285–286°C (decomp.). IR spectrum, ν, cm^{-1}: 3500– 3250 (NH); 2275 (C–N); 1715 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.61 s (1H, =NH), 8.11 s (1H, NHCO), 7.5 m (5H, Ph), 7.3 m (3H, *m*-H, *p*-H), 7.2 d (2H, *o*-H), 6.23 s (1H, NHPh), 4.45 t (1H, CHPh), 3.43 d (1H, CH_2), 3.31 m (1H, CHMe), 2.81 d (1H, CH_2), 1.4 s (3H, CH_3). Found, %: C 69.66; H 4.98; N 21.16. M^+ 391. $C_{20}H_{21}N_7O_2$. Calculated, %: C 69.68; H 5.08; N 21.20.

3-Amino-4-(4-methoxyphenyl)-1-oxo-5-propyl-6-thiosemicarbazono-4,5,6,7-tetrahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VIc). Yield 65% (*a*), 84% (*b*), 81% (*c*); mp 293–294°C (decomp.). IR spectrum, ν, cm^{-1}: 3500–3200 (NH); 2270 (C–N); 1715 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.79 s (1H, =NH), 9.11 s [1H, N*H*C(S)NH_2], 7.78 s (1H, NH), 7.51 d (2H, *o*-H), 7.29 d (2H, *m*-H), 6.13 s [1H, C(S)NH_2], 4.02 d (1H, C*H*Ar), 3.86 s (3H, OCH_3), 3.74 d (1H, $COCH_2$), 3.21 d (1H, $COCH_2$), 3.13 d.d (1H, C*H*Pr), 1.6–1.3 m (4H, CH_2CH_2CH_3), 0.89 t (3H, $CH_2CH_2CH_3$). Found, %: C 57.59; H 5.34; N 22.46. M^+ 437. $C_{21}H_{23}N_7O_2S$. Calculated, %: C 57.65; H 5.30; N 22.41.

3-Amino-5,7-dimethyl-1-oxo-4-phenyl-6-phenylhydrazono-4,5,6,7-tetrahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VId). Yield 44% (*a*), 81% (*b*), 62% (*c*); mp 272–273°C (decomp.). IR spectrum, ν, cm^{-1}: 3470–3180 (NH); 2270 (C–N); 1710 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.58 s (1H, =NH), 8.24 s (1H, NHCO), 7.45–7.35 m (5H, Ph), 7.27 m (3H, *m*-H, *p*-H), 7.17 d (2H, *o*-H), 6.12 s (1H, N*H*Ph), 3.88 d.d (1H, C*H*Ar), 3.16 q (1H, C*H*Me), 2.88 m (1H, ArCHC*H*CH_3), 1.34 d (3H, CHCH_3), 1.12 d (3H, CHCH_3). Found, %: C 70.31; H 5.51; N 20.51. M^+ 410. $C_{24}H_{22}N_6O$. Calculated, %: C 70.23; H 5.40; N 20.47.

3-Amino-6-hydrazono-4-(4-methoxyphenyl)-1-oxo-5-propyl-4,5,6,7-tetrahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VIe). Yield 74% (*c*), mp 222–223°C (decomp.). IR spectrum, ν, cm^{-1}: 3475–3365, 3210 (NH); 2275 (C–N); 1710 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.73 s (1H, =NH), 8.16 s (1H, NH), 7.64 d (2H, *o*-H), 7.35 d (2H, *m*-H), 6.12 s (2H, =NNH_2), 3.98 d (1H, C*H*Ar), 3.84 s (3H, OCH_3), 3.82 d (1H, $COCH_2$), 3.12 d (1H, $COCH_2$), 3.08 d.d (1H, C*H*Pr), 1.6–1.3 m (4H, CH_2CH_2CH_3), 0.84 t (3H, $CH_2CH_2CH_3$). Found, %: C 63.59; H 5.87;

N 22.28. M^+ 378. $C_{20}H_{22}N_6O_2$. Calculated, %: C 63.48; H 5.86; N 22.21.

3-Amino-1-oxo-4-phenyl-6-phenylhydrazono-5-propyl-4,5,6,7-tetrahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VIf). Yield 69% (*c*), mp 244–245°C (decomp.). IR spectrum, ν, cm^{-1}: 3450–3210 (NH); 2270 (C–N); 1710 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.62 s (1H, =NH), 8.12 s (1H, NH), 7.54 m (8H, C_6H_5, *m*-H, *p*-H), 7.41 d (2H, *o*-H), 6.54 s (1H, N*H*Ph), 4.25 d (1H, C*H*Ph), 3.6 d (1H, CH_2), 2.95 m (1H, C*H*Pr), 2.82 d (1H, CH_2), 1.6–1.3 m (4H, $CH_2CH_2CH_3$), 0.78 t (3H, $CH_2CH_2CH_3$). Found, %: C 70.71; H 5.76; N 19.91. M^+ 424. $C_{25}H_{24}N_6O$. Calculated, %: C 70.73; H 5.70; N 19.80.

3-Amino-4-(4-methoxyphenyl)-1-oxo-5-propyl-6-semicarbazono-4,5,6,7-tetrahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VIg). Yield 73% (*c*), mp 265–266°C (decomp.). IR spectrum, ν, cm^{-1}: 3510–3250 (NH); 2270 (C–N); 1710 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.76 s (1H, =NH), 9.31 s (1H, N*H*$CONH_2$), 7.76 s (1H, NH), 7.53 d (2H, *o*-H), 7.25 d (2H, *m*-H), 6.2 s (1H, $CONH_2$), 4.0 d (1H, C*H*Ar), 3.85 s (3H, OCH_3), 3.79 d (1H, $COCH_2$), 3.22 d (1H, $COCH_2$), 3.1 d.d (1H, C*H*Pr), 1.6–1.35 m (4H, $CH_2CH_2CH_3$), 0.91 t (3H, $CH_2CH_2CH_3$). Found, %: C 59.98; H 5.47; N 23.35. M^+ 421. $C_{21}H_{23}N_7O_3$. Calculated, %: C 59.85; H 5.50; N 23.26.

3-Amino-6-hydrazono-7-methyl-1-oxo-4-phenyl-4,5,6,7-tetrahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VIh). Yield 79% (*c*), mp 251–252°C (decomp.). IR spectrum, ν, cm^{-1}: 3460–3275 (NH); 2270 (C–N); 1710 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.52 s (2H, NH_2), 7.51 m (3H, *m*-H, *p*-H), 7.38 d (2H, *o*-H), 6.04 s (2H, $=NNH_2$), 4.34 t (1H, C*H*Ph), 3.23 m (1H, C*H*Me), 3.12 d (1H, CH_2), 2.81 d (1H, CH_2), 1.3 s (3H, CH3). Found, %: C 63.79; H 5.08; N 26.29. M^+ 320. $C_{17}H_{16}N_6O$. Calculated, %: C 63.74; H 5.03; N 26.23.

3-Amino-7-isopropyl-4-(4-methoxyphenyl)-1-oxo-6-semicarbazono-4,5,6,7-tetrahydro-1*H*-isoindole-3a,7a-dicarbonitrile (VIi). Yield 74% (*c*), mp 245–246°C (decomp.). IR spectrum, ν, cm^{-1}: 3490–3245 (NH); 2275 (C–N); 1715 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.8 s (1H, =NH), 9.28 s (1H, N*H*$CONH_2$), 7.7 s (1H, NH), 7.48 d (2H, *o*-H), 7.0 d (2H, *m*-H), 6.22 s (1H, $CONH_2$), 3.82 s (3H, OCH_3), 3.60 m (1H, C*H*Ar), 3.01 d.d (1H, CH_2), 2.98 d (1H, CHCO), 2.69 d.d (1H, CH_2), 2.07 m (1H, C*H*Me_2), 1.2 t (3H, CH_3), 0.82 t (3H, CH_3). Found, %: C 59.85; H 5.47; N 23.28. M^+ 421. $C_{21}H_{23}N_7O_3$. Calculated, %: C 59.85; H 5.50; N 23.26.

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