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Isopropylidenemalononitrile in the Synthesis of 2-Amino-4,6,6-trimethylcyclohexa-2,4-diene-1,1,3-tricarbonitrile, 6-Amino-2-(4-methoxybenzoylmethylsulfanyl)-4,4-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile, and Fused 2-Aminopyrans according to Michael

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Abstract—Michael reactions of isopropylidenemalononitrile with cyanothioacetamide (in the presence of 4-methoxyphenacyl bromide), cyclohexane-1,3-dione, and 4-hydroxycoumarin, gave 6-amino-2-(4-methoxybenzoylmethylsulfanyl)-4,4-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile, 2-amino-4,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile, and 2-amino-4,4-dimethyl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]-chromene-3-carbonitrile, respectively. In the reaction of isopropylidenemalononitrile with cyanoacetamide, only dimerization product of the former, 2-amino-4,6,6-trimethylcyclohexa-2,4-diene-1,1,3-tricarbonitrile, was isolated. Its structure was proved by X-ray analysis.

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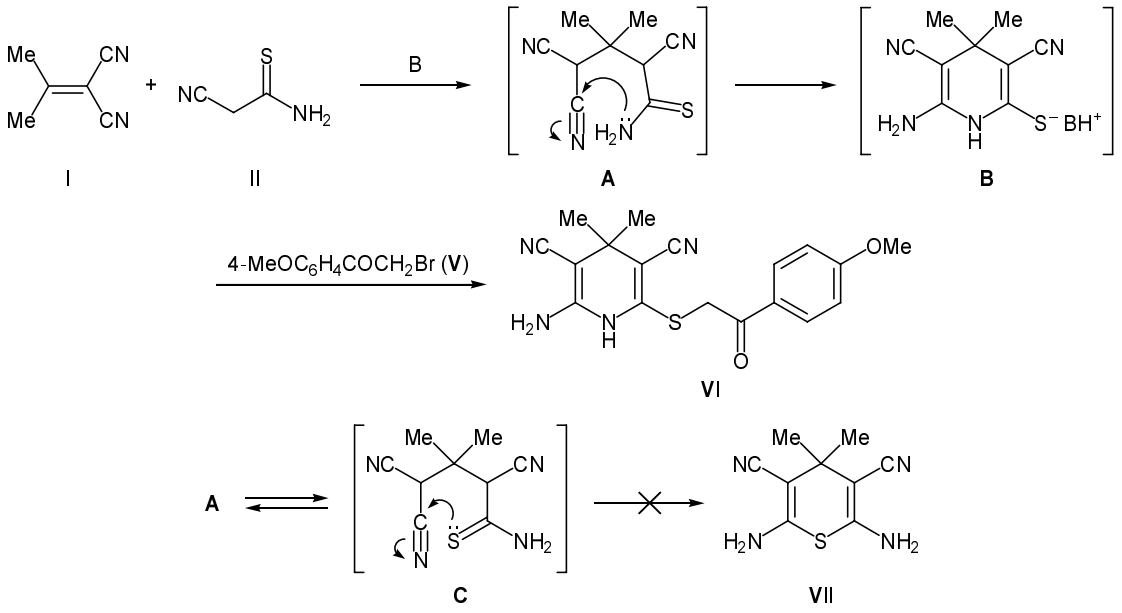
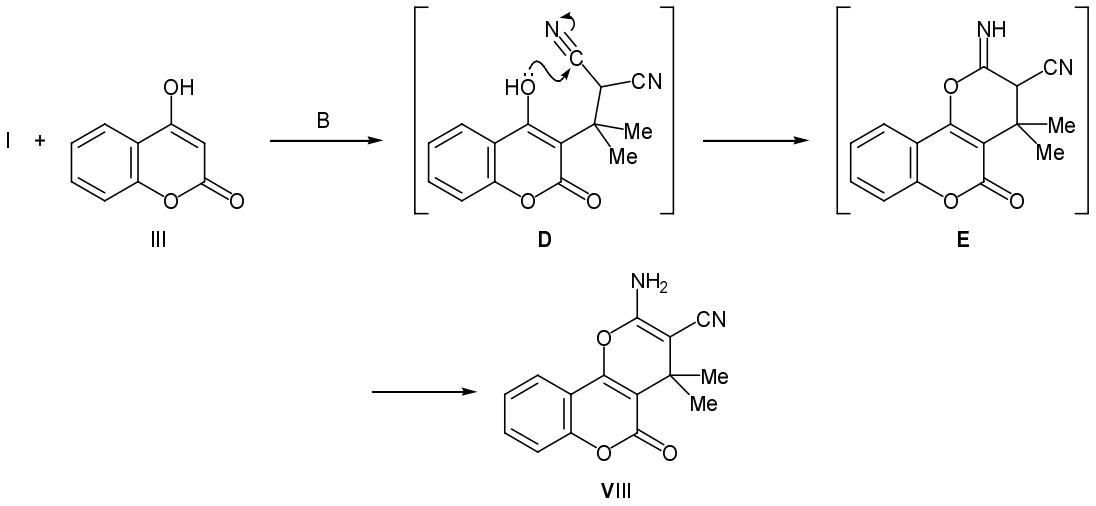
Published data on the chemical properties of crotononitrile derivatives include their dimerization [1], Michael reactions as CH acids [2], and heterocyclizations with participation of the cyano group [3]. Their use as Michael acceptors was almost not studied [4]. In continuation of our studies on reactions of nucleophiles with α,β-unsaturated nitriles capable of undergoing dimerization [5], in the present work we examined Michael reactions of isopropylidenemalononitrile (**I**) as acceptor with the following CH acids: cyanothioacetamide (**II**), 4-hydroxycoumarin (**III**), and cyclohexane-1,3-dione (**IV**). The reaction of dinitrile **I** with cyanothioacetamide (**II**) in anhydrous ethanol at 20°C in the presence of equimolar amounts of *N*-methylmorpholine and 4-methoxyphenacyl bromide (**V**) led to the formation of 6-amino-2-(4-methoxybenzoylmethylsulfanyl)-4,4-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (**VI**) (Scheme 1). Presumably, primary Michael adduct **A** undergoes facile regioselective intramolecular heterocyclization to give salt **B**, and alkylation of the latter at the sulfur atom with α-bromo ketone **V** results in the formation of sulfide **VI**. Alkyl-(aryl, hetaryl)methylidenemalononitriles are known to react with cyanothioacetamide under analogous conditions to give the corresponding 4-alkyl-(aryl, hetaryl)-2,6-diamino-4*H*-thiopiran-3,5-dicarbonitriles [6]. Thus the Michael addition of activated alkene **I** to CH acid **II** gave no expected product **VII** which could be formed via heterocyclization of intermediate **C** (Scheme 1).

By reaction of compound **I** with 4-hydroxycoumarin (**III**) as CH-acid component we obtained 2-amino-4,4-dimethyl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]-chromene-3-carbonitrile (**VIII**) (Scheme 2). The reaction scheme is likely to include intramolecular heterocyclization of Michael adduct **D** to imine **E** which is stabilized as prototropic tautomer **VIII**. Isopropylidenemalononitrile (**I**) reacted with cyclohexan-1,3-dione (**IV**) under analogous conditions to produce 2-amino-4,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**IX**) (Scheme 3). Presumably, the mechanism of its formation is analogous to that shown in Scheme 2. Fused 2-aminopyrans **VIII** and **IX** are promising intermediate product in the synthesis of compounds for protection of crops from damages caused by herbicides [7] and for suppression of cell proliferation [8].

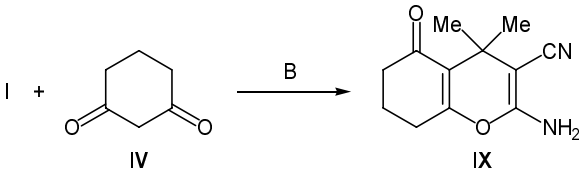
Scheme 1.



Scheme 2.



Scheme 3.

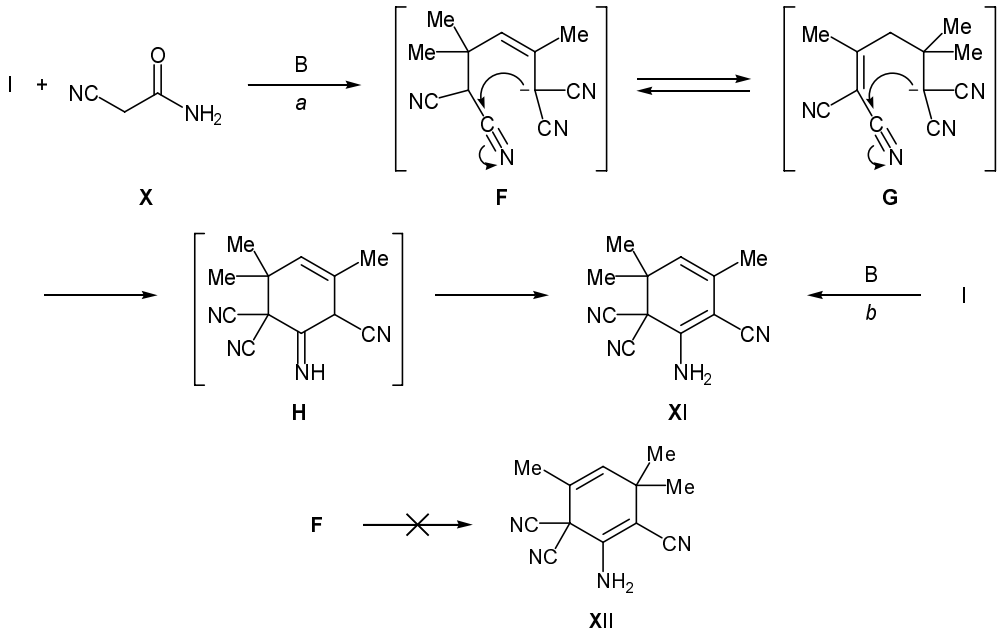


B = *N*-Methylmorpholine.

The structure of compounds **VI**, **VIII**, and **IX** is consistent with their physical properties and spectral parameters (see Experimental).

Cyanoacetamide (**X**) failed to react with isopropylidenemalononitrile (**I**) under the above conditions. From the reaction mixture we isolated 2-amino-4,6,6-trimethylcyclohexa-1,3-diene-1,1,3-tricarbonitrile (**XI**) (method *a*), which was obtained previously by dimerization of compound **I** in the presence of an organic base [9] (method *b*, Scheme 4). Compound **XI** was formed via dimerization of **I** according to the Michael addition pattern [10] to give adduct **F** or its tautomer

Scheme 4.



B = *N*-Methylmorpholine.

G. The subsequent intramolecular cyclization of these intermediates according to Thorpe–Ziegler [10] could give substituted 2-amino-4,4,6-trimethylcyclohexa-2,5-diene-1,1,3-tricarbonitrile (**XII**) or iminocyclohexene **H**. The latter is stabilized as enamine **XI** which can also be synthesized by treatment of **I** with a base (method *b*). Thus the dimerization of isopropylidenemalononitrile (**I**), following the Michael–Thorpe–Ziegler scheme, could lead to the formation of two isomeric products **XI** and **XII** which are difficult to distinguish on the basis of spectral data.

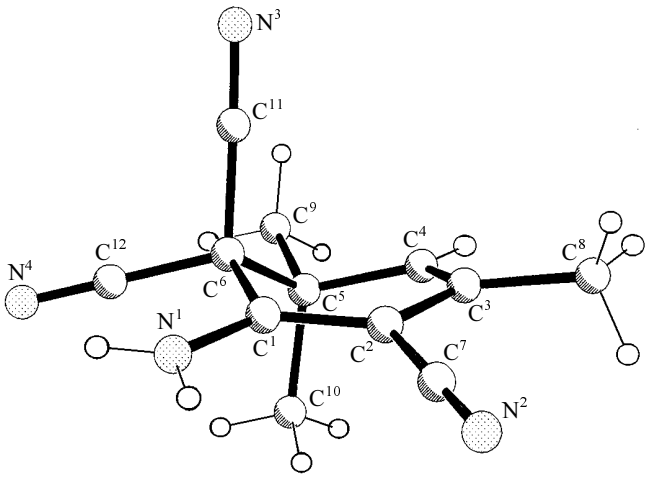


Fig. 1. Structure of the molecule of 2-amino-4,6,6-trimethylcyclohexa-2,4-diene-1,1,3-tricarbonitrile (**XI**) according to the X-ray diffraction data.

Therefore, the structure of the isolated product was determined by X-ray analysis. The results showed that the dimerization gives structure **XI** (Fig. 1, see table). The six-membered ring in molecule **XI** is not planar; the C^1, C^2, C^3, and C^6 atoms lie in one plane within 0.021 Å, while the C^4 and C^5 atoms deviate from that plane by 0.360 and 0.854 Å, respectively. In keeping with the modified Cremer–Pople parameters [11], the six-membered ring adopts a *half-boat* conformation (S = 0.44, θ = 48.25, ψ = 29.41). Orientation of the amino group N^1H_2 is quite favorable for conjugation between the lone electron pair on the nitrogen with the C^1=C^2 π-bond: the sum of the bond angles on the N^1 atom is 360°, and the amino hydrogen atoms (H^{11} and H^{12}) reside exactly in the plane formed by the N^1, C^1, C^2, and C^6 atoms. The C^1–N^1 bond is shortened to 1.332(2) Å, while the C^1=C^2 bond is extended against the standard lengths of single N_{sp^2}–C_{sp^2} and double C=C bonds (1.43–1.45 and 1.32–1.33Å, respectively [12, 13]). The interatomic distance C^2–C^3 [1.464(2) Å] approaches that typical of standard length of a single C_{sp^2}–C_{sp^2} bond (1.47 Å [12, 13]). The torsion angle $C^1C^2C^3C^4$ is 14.1(3)°.

Molecules **XI** in crystal (Figs. 2, 3) are linked to centrosymmetric dimers via intermolecular hydrogen bonds N^1–H···$N^{2'}$. Weaker N^1–H···$N^{3'}$ bonds give rise to "columns" along the crystallographic *a* axis. The principal parameters of the hydrogen bonds are as

follows: $N^1\cdots N^{2'}$ 3.032(2), N^1–H^{12} 0.91(2), $N^{2'}\cdots H^{12}$ 2.14(2) Å, $\angle N^1H^{12}N^{2'}$ 167(2)°; $N^1\cdots N^{3'}$ 3.144(2), N^1–H^{11} 0.85(2), $H^{12}\cdots N^{3'}$ 2.47(2) Å, $\angle N^1H^{11}N^{3'}$ 136(2)°.

EXPERIMENTAL

The IR spectra were recorded on an IKS-40 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were obtained on Bruker WP-100SY (100 MHz; compound **VIII**), Varian Gemini-200 (199.975 MHz; **VI**), Bruker WM-250 (250.13 MHz; **IX**), and Varian VXR-300 spectrometers (300 MHz; **XI**); DMSO-d_6 was used as solvent, and tetramethylsilane, as internal reference. The mass spectrum (electron impact, 70 eV) of compound **XI** was recorded on a Kratos MS-890 instrument with direct sample admission into the ion source. The melting points were determined on a Kofler melting point apparatus. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; spots were visualized under UV light or by treatment with iodine vapor.

The X-ray diffraction data for a single crystal of compound **XI** were acquired at room temperature on an Enraf–Nonius CAD-4 automatic four-circle diffractometer (λMoK_α irradiation, graphite monochromator, $\omega/2\theta$ scanning, θ_{max} 24.1°, spherical segment $0 \le h \le 8$, $0 \le k \le 12$, $-16 \le l \le 16$). The unit cell parameters and orientation matrix of a single crystal of **XI** (0.28×0.45×0.47 mm) were determined from 22 reflections with $11 < \theta < 13°$. Total of 1983 reflections were measured, 1825 of which were independent (averaging factor R = 0.0147). Monoclinic crystal system: a = 7.259(1), b = 11.007(2), c = 14.653(3) Å; β = 99.02(2)°, V = 1156.3(4) Å^3; Z = 4; d_{calc} = 1.219 g/cm^3; μ = 0.077 mm^{-1}; $F(000)$ = 448; space group $P2_1/n$ (no. 14). The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix anisotropic approximation using SHELXS and SHELXL93 programs [14, 15]; 1387 reflections with $I > 2\sigma(I)$ were used in the refinement {193 refined parameters, 7.19 reflections per parameter; weight scheme $\omega = 1/[\sigma^2(Fo^2) + (0.0522P)^2 + 0.1561P]$, where $P = (Fo^2 + 2Fc^2)/3$; ratio of the maximal (middle) shift to the error in the last cycle 0.010 (0.001)}. A correction for anomalous scattering was introduced; absorption by the crystal was not taken into account. All hydrogen atoms were visualized objectively, and their positions were refined in isotropic approximation. The final divergence factors were $R_1(F)$ = 0.0383 and $R_W(F^2)$ = 0.0897; GOF 1.000. The residual electron density from the Fourier difference synthesis after the last iteration cycle was 0.11 and –0.14 e/Å^3. All calculations were performed using a PC. The coordinates of atoms are available from the authors.

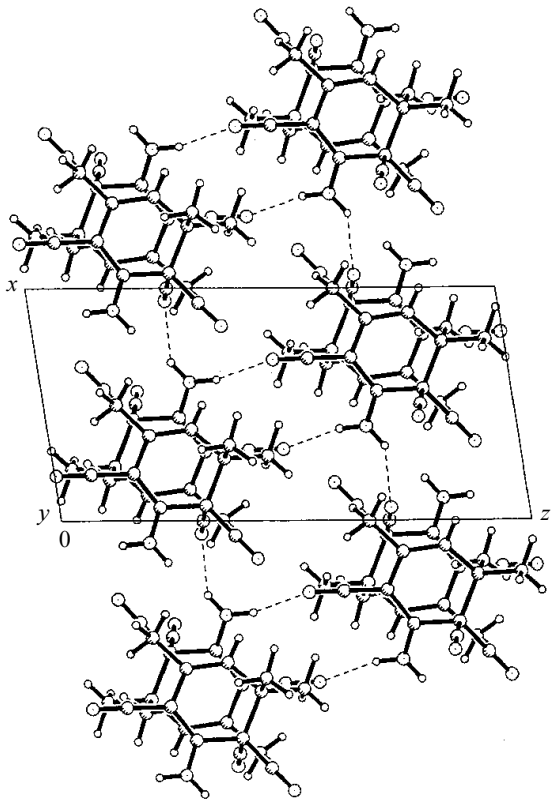


Fig. 2. Fragment of the crystal packing of compound **XI** along the crystallographic x axis. Hydrogen bonds are shown with dashed lines.

6-Amino-2-(4-methoxybenzoylmethylsulfanyl)-4,4-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile

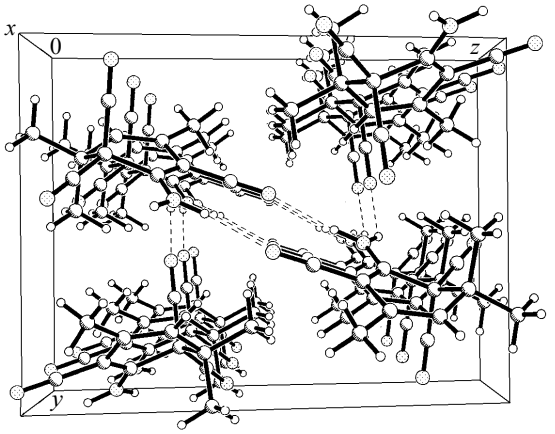


Fig. 3. Projection of the crystal packing of compound **XI** onto the xz plane. Hydrogen bonds are shown with dashed lines.

Principal bond lengths *d* and bond angles ω in the molecule of 2-amino-4,6,6-trimethylcyclohexa-2,4-diene-1,1,3-tricarbonitrile (**XI**)

Bond	*d*, Å	Angle	ω, deg
C^1–N^1	1.332(2)	$N^1C^1C^2$	126.3(2)
C^1–C^2	1.359(2)	$N^1C^1C^6$	117.6(2)
C^1–C^6	1.539(2)	$C^2C^1C^6$	116.2(2)
C^2–C^3	1.464(2)	$C^1C^2C^3$	122.09(14)
C^3–C^4	1.331(2)	$C^4C^3C^2$	119.3(2)
C^4–C^5	1.510(2)	$C^3C^4C^5$	122.1(2)
C^5–C^6	1.563(2)	$C^4C^5C^6$	106.37(14)
N^1–H^{11}	0.85(2)	$C^1C^6C^5$	111.04(13)
N^1–H^{12}	0.91(2)	$C^1N^1H^{11}$	121.1(13)
		$C^1N^1H^{12}$	120.7(12)
		$H^{11}N^1H^{12}$	118(2).

(VI). *N*-Methylmorpholine, 1.10 ml (10 mmol), was added at 20°C to a suspension of 1.00 g (10 mmol) of cyanothioacetamide (**II**) in 25 ml of anhydrous ethanol, the mixture was stirred for 10 min until it became homogeneous, 1.06 g (10 mmol) of isopropylidenemalononitrile (**I**) was added, and the mixture was stirred for 5 min. 4-Methoxyphenacyl bromide (**VI**), 2.29 g (10 mmol), was then added, and the mixture was stirred for 1 h and diluted with an equal volume of water. The precipitate was filtered off and washed in succession with water, ethanol, and hexane. Yield 2.76 g (78%), white powder, mp 233–235°C (from EtOH). IR spectrum, ν, cm^{-1}: 1640 (δNH_2); 1728 (C=O); 2180, 2193 (C≡N); 3210, 3354, 3422 (NH_2). ^{1}H NMR spectrum, δ, ppm: 1.23 s (6H, Me), 3.84 s (3H, MeO), 4.45 s (2H, CH_2), 5.41 br.s (2H, NH_2), 6.99 d and 7.87 d (2H each, C_6H_4, J = 8.83 Hz), 9.01 br.s (1H, NH). Found, %: C 60.84; H 4.95; N 15.66. $C_{18}H_{18}N_4O_2S$. Calculated, %: C 61.74; H 5.12; N 15.81.

2-Amino-4,4-dimethyl-5-oxo-4*H*,5*H*-pyrano-[3,2-*c*]chromene-3-carbonitrile (VIII). *N*-Methylmorpholine, 1.10 ml (10 mmol), was added to a mixture of 1.06 g (10 mmol) of isopropylidenemalononitrile (**I**) and 1.62 g (10 mmol) of 4-hydroxycoumarin (**III**) in 20 ml of anhydrous ethanol. The mixture was stirred for 15 min and was left to stand for 24 h. The precipitate was filtered off and washed with ethanol and hexane. Yield 1.61 g (60%), white powder, mp 210–211°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 1650 (δNH_2), 1680 (C=O), 2194 (C≡N), 3242–3410 (NH_2). ^{1}H NMR spectrum, δ, ppm: 1.51 s (6H, Me), 7.06 br.s (2H, NH_2), 7.33–7.52 m (2H, H_{arom}), 7.61 d.d (1H, H_{arom}, J = 7.88 Hz), 7.82 d.d (1H, H_{arom}, J = 7.76 Hz). Found, %: C 66.97; H 4.38; N 10.28. $C_{15}H_{12}N_2O_3$. Calculated, %: C 67.16; H 4.51; N 10.44.

2-Amino-4,4-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (IX) was synthesized as described above for compound **VIII** using 1.12 g (10 mmol) of cyclohexane-1,3-dione (**IV**) instead of 4-hydroxycoumarin (**III**). Yield 1.77 g (81%), colorless crystals, mp 191–193°C (from *i*-PrOH), sublimes at 160°C. IR spectrum, ν, cm^{-1}: 1639 (δNH_2); 1677 (C=O); 2187 (C≡N); 3210, 3300, 3412 (NH_2). ^{1}H NMR spectrum, δ, ppm: 1.34 s (6H, Me), 1.72–2.01 m (2H, C^7H_2), 2.30 t (2H, C^6H_2, J = 6.09 Hz), 2.46 t (2H, C^8H_2, J = 6.12 Hz), 6.61 br.s (2H, NH_2). Found, %: C 65.87; H 6.29; N 12.68. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.04; H 6.47; N 12.84.

2-Amino-4,6,6-trimethylcyclohexa-2,4-diene-1,1,3-tricarbonitrile (XI). *a*. *N*-Methylmorpholine, 1.10 ml (10 mmol), was added at 20°C to a suspension of 0.84 g (10 mmol) of cyanoacetamide (**X**) in 25 ml of anhydrous ethanol. The mixture was stirred for 15 min until it became homogeneous, 1.06 g (10 mmol) of isopropylidenemalononitrile (**I**) was added, and the mixture was stirred for 5 min and was left to stand for 24 h. The precipitate was filtered off and washed with ethanol and hexane. Yield 0.85 g (40%), yellow crystals, mp 158–160°C (from BuOH); published data [9]: mp 168–170°C. IR spectrum, ν, cm^{-1}: 1648 (δNH_2); 2195 (C≡N); 3200, 3311, 3425 (NH_2). ^{1}H NMR spectrum, δ, ppm: 1.31 s (6H, Me), 1.88 s (3H, Me), 5.09 s (1H, CH), 7.50 br.s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 213 (4) $[M + 1]^+$, 212 (38) $[M]^+$, 197 (95) $[M - Me]^+$, 182 (32) $[M - 2Me]^+$, 170 (39), 144 (90), 77 (19), 65 (24), 51 (27), 39 (100). Found, %: C 67.81; H 5.84; N 26.35. $C_{12}H_{12}N_4$. Calculated, %: C 67.90; H 5.70; N 26.40.

b. *N*-Methylmorpholine, 0.11 ml (1 mmol), was added at 20°C to a solution of 1.06 g (10 mmol) of isopropylidenemalononitrile (**I**) in 25 ml of anhydrous ethanol. The mixture was stirred for 15 min and was left to stand for 24 h. The precipitate was filtered off and washed with ethanol and hexane. Yield 48%. The product was identical in the melting point, IR spectrum, and TLC data to a sample of **XI** prepared as described above in *a*.

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