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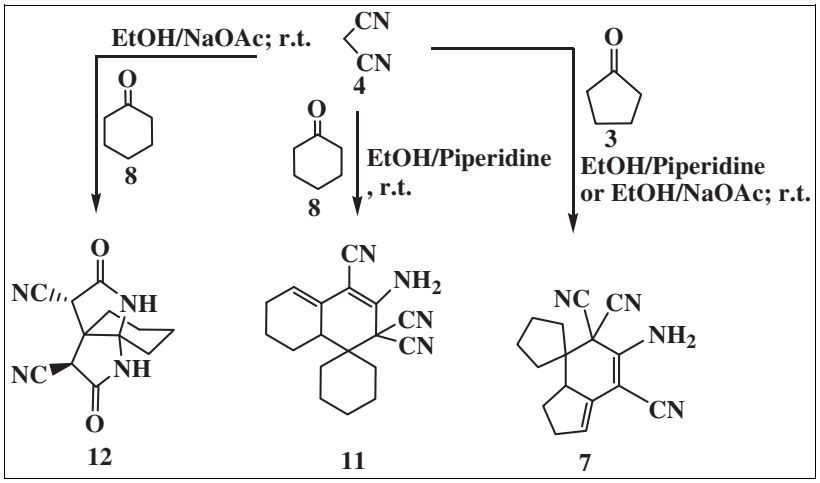
†This work is abstracted in part from the M.Sc. thesis of Mr. Mohamed T. Jaafar.
Received August 12, 2012
DOI 10.1002/jhet.1883
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



Cyclopentanone reacts with malononitrile catalyzed by piperidine or sodium acetate to afford under any case cyclopentylidenemalononitrile dimer: 5-aminospiro-[2,6,7,7a-tetrahydroindene-7,1′-cyclopentane]-4,6,6-tricarbonitrile (**7**) as the sole product. Contrary to this behavior, cyclohexanone reacts with malononitrile catalyzed by piperidine to afford the analogous cyclohexylidenemalononitrile dimer: 2-aminospiro-[3,4,5,6,7,4a-hexahydronaphthalene-4,1′-cyclohexane]-1,3,3-tricarbonitrile (**11**); whereas when the reaction is catalyzed by sodium acetate, it afforded 9,10-diaza-8,11-dioxo-tricyclo-[4.3.3.$0^{1,6}$]-dodecane-7,12-dicarbonitrile (**12**). The structures of these products were established on the basis of their elemental analysis and spectral data, and plausible mechanism has been postulated to account for their formation. X-ray crystallography was carried out as a further evidence for structures **7** and **12**.

INTRODUCTION

Pyridines and pyrido-fused derivatives are important heterocyclic compounds that find many pharmaceutical and agrochemical applications [1–5]. In the last two decades, we have been involved in a program aiming to develop new simple routes for the synthesis of heterocyclic compounds of biological interest [6–13]. In the context of this program, we have reported that 2-(1-arylehtylidene) malononitrile (**1**) undergoes dimerization upon reflux in ethanolic sodium ethoxide to afford 2-(3-cyano-6-methyl-4,6-diaryl-5,6-dihydro-1*H*-pyridin-2-ylidene)-malononitrile (**2**) (Scheme 1), and its structure was proven through X-ray crystallographic analysis, and a plausible mechanism was suggested for this transformation [14,15].

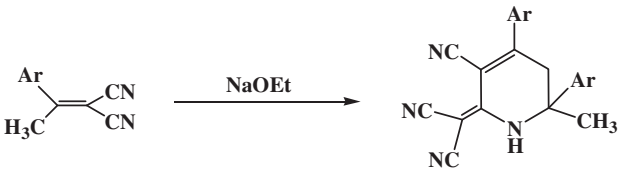
It seemed interesting to investigate the reaction of cycloalkylidenes of malononitrile (having methylene group instead of CH_3; neighboring the C═C) with sodium ethoxide and see if a dimer of similar structure will be obtained (Fig. 1).

RESULTS AND DISCUSSION

For this purpose, cyclopentylidenemalononitrile (**5**) was needed (Scheme 2). This compound was reported to be obtained via Knoevenagel condensation between cyclopentanone (**3**) and malononitrile (**4**) in the presence of sodium acetate at RT, as yellow crystals of mp 83–85°C [16,17].

In our hands, the reaction of cyclopentanone (**3**) with malononitrile (**4**) in ethanol catalyzed by sodium acetate or piperidine at RT has afforded colorless crystalline product with mp 195°C. The mass spectrum of this product revealed a base peak at $m/z = 264$ that is twice of the molecular weight of **5** ($m/z = 132$) (Scheme 2); denoting a dimer of **5**. The IR spectrum of this product showed absorption band at $\nu_{max} = 3404$, 3326, and 2221 cm^{-1} attributable to amino and cyano groups, respectively. The ^{1}H-NMR spectrum of this product revealed a multiplet at $\delta = 1.34$–2.40 ppm integrated for 12 protons and a triplet at $\delta = 3.0$ ppm integrated for 1H and a triplet

Scheme 1. Dimerization of 2(1-arylethylidene)-malononitrile.



1 2

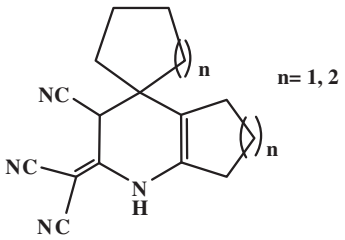


Figure 1. The structure of the initially expected dimers.

at $\delta = 5.50$ ppm assignable to an olefinic proton in addition to a D_2O-exchangeable signal (2H) appeared at $\delta = 7.52$ ppm.

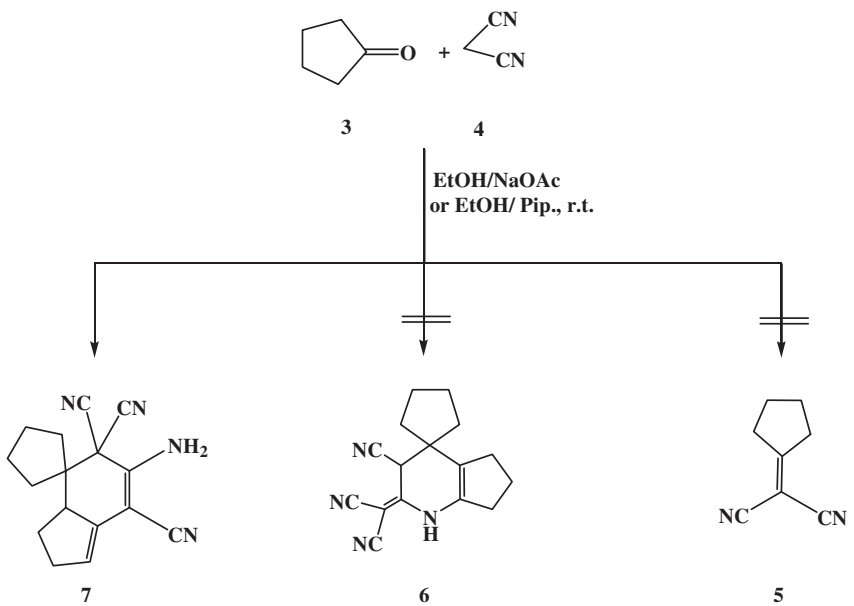
These spectral data are not applicable completely to our expected dimer structure **6** shown in Scheme 2; Figure 1 ($n = 1$). Therefore, an X-ray crystallography [18,19] seemed necessary to verify the actual structure of this dimer for which structure **7** was assigned (Fig. 2).

A plausible mechanism for the formation of this cyclopentylidenemalononitrile dimer is outlined in Scheme 3 and involves the initial Knoevenagel condensation of cyclopentanone (**3**) with malononitrile (**4**) to afford **5** that *in situ* undergoes proton elimination to afford A that undergoes electron shift to give the keneteneimine B. This latter undergoes electrocyclic addition to another molecule of **5** to afford C that gains a proton to give the imine D. The imine D then undergoes a 1,5-H shift to afford our product **7** (Scheme 3) [20].

On the other hand, we have prepared cyclopentylidenemalononitrile (**5**) via the condensation of **3** and **4** according to literature method [21]. Leaving compound **5** in ethanol with piperidine or sodium acetate as catalyst at RT overnight, we could obtain the same dimer **7** as shown by the melting points and TLC analysis.

It seemed interesting to investigate the reaction of cyclohexanone (**8**) with malononitrile (**4**) under the same reaction conditions to see if the condensation product **9** or our expected dimer **10** (Fig. 1; $n = 2$) or an analogous dimer (structure **11**; Scheme 4) will be obtained. However, in contrast to the behavior of cyclopentanone (**3**) with malononitrile (**4**), the product of the reaction of cyclohexanone (**8**) with malononitrile (**4**) was found to depend on the catalyst used. Thus, cyclohexanone (**8**) reacts with **4** in ethanol at RT catalyzed by piperidine to afford a yellow crystalline product of mp 173°C. The mass spectrum of this product revealed a base peak at $m/z = 292$ that corresponds to a dimer of cyclohexylidenemalononitrile (**9**) ($m/z = 146$). Two possible structures can be assumed for this dimer: either our initially expected dimer **10** (Fig. 1, $n = 2$) or structure **11** (analogous to the dimer **7**). The IR and ^{1}H-NMR spectra of this product were in complete agreement with structure **11** that was assigned for this dimer (cf. Experimental; Scheme 4). The reaction of cyclohexanone (**8**) with malononitrile (**4**) in ethanol catalyzed by piperidine to afford the

Scheme 2. The reaction of cyclopentanone with malononitrile.



3 4

7 6 5

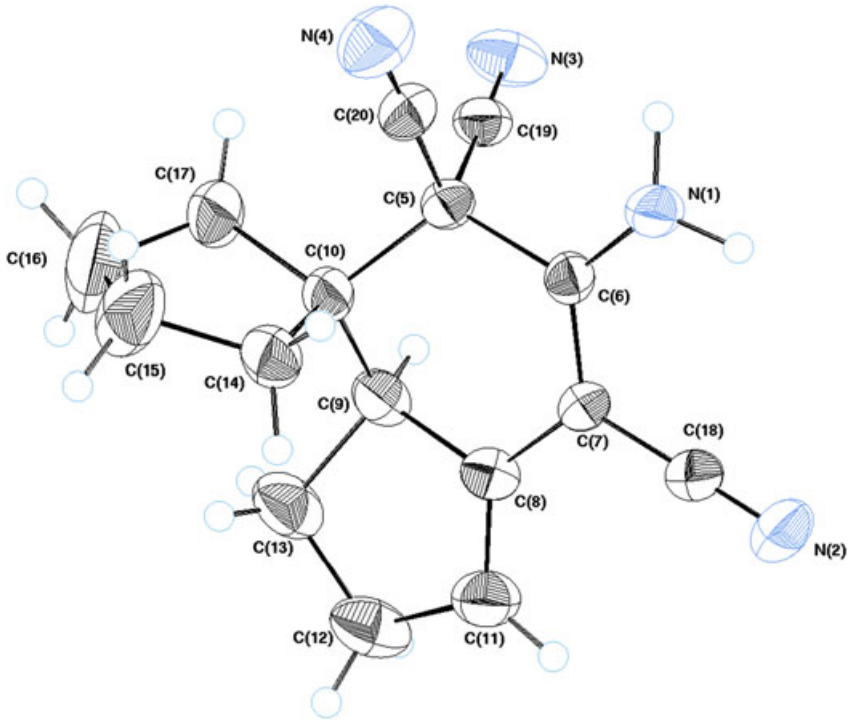
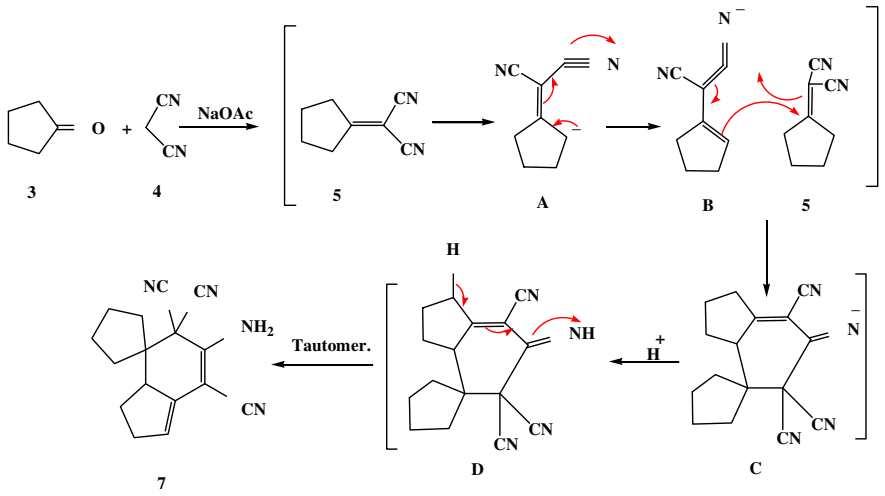


Figure 2. X-ray crystallography of compound **7** [18,19].

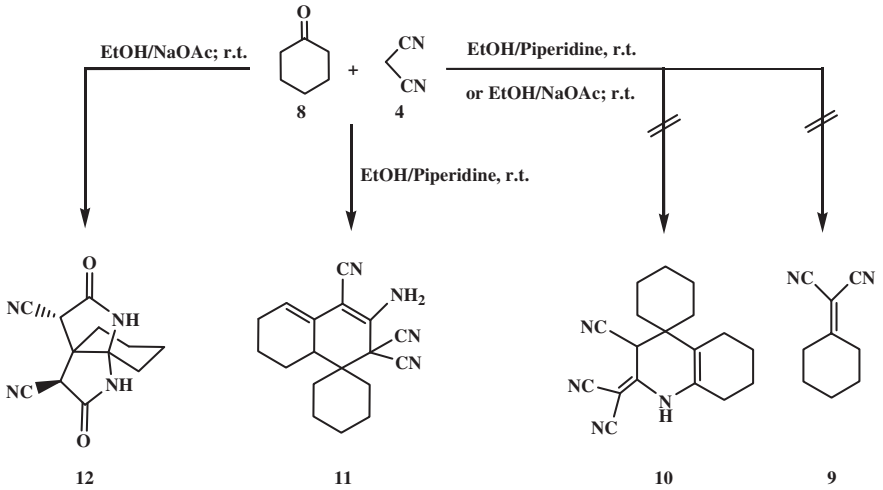
Scheme 3. Mechanism for the formation of the dimer 7.



dimer **11** apparently followed the same route analogous to the formation of the dimer **7** as depicted in Scheme 3.

When the reaction of **8** with **4** was carried out in ethanol in the presence of sodium acetate at RT, a white crystalline product of mp 289°C was obtained (Scheme 4). The IR spectrum of this last product showed absorption bands at $\nu_{max} = 3330.5$, 3269.7, 2257.3, and 1723 cm^{-1} presumably because of NH, CN, and CO groups, respectively. The ^{1}H-NMR spectrum revealed the presence of a multiplet signals at $\delta = 1.05$–2.47 (8H) that can be assigned to the methylene groups of the cyclohexane ring and a singlet signal (1H) at $\delta = 4.57$ ppm integrated to one CH proton and another singlet at 4.80 ppm (1H). In addition, a D_2O-exchangeable signal appeared at $\delta = 9.20$ ppm. The mass spectrum of this product revealed a base peak at $m/z = 244$. This mass value as well as the spectral data (cf. Experimental) are not applicable to either the condensation product **9** (MW 146) or to our expected dimer **10** (Fig. 1; $n = 2$) (MW 292), or the dimer structure **11** or any of its tautomers (MW 292). Considering the mass spectrum and the data of the elemental analysis of this product, we could calculate a molecular formula

Scheme 4. The reaction of cyclohexanone with malononitrile.



$C_{12}H_{12}N_4O_2$. This formula indicated that one molecule of cyclohexanone and two molecules of malononitrile are involved in the reaction with one molecule of oxygen and elimination of one molecule of water. X-ray crystallographic analysis [23,24] of this product seemed necessary to verify the correct structure that was shown to be **12** as depicted in Scheme 4 and Figure 3.

It should be stated that the same compound has been previously reported as a patent [24] and was obtained in two steps: from cyclohexan-1,2-dione with cyanoacetamide in dichloromethane for 9 h to obtain firstly compound **18** (Scheme 5; mp 169°C) and secondly to allow this latter compound **18** to react with malononitrile in methanol in the presence of sodium methoxide for 3 h standing at temperature below 5°C to give **12**.

However, this is the first time this compound is obtained from cyclohexanone (**8**) and malononitrile (**4**). A plausible mechanism to the formation of this compound from **8** and **4** seemingly involves an autoxidation process. Autoxidation is a free radical chain process, and free radicals can be produced purposefully by the decomposition of a radical initiator, such as benzoyl peroxide. In some cases, initiation occurs by a process that is not well understood but is thought to be the spontaneous reaction of oxygen with a material with readily abstractable hydrogen, for example, the allylic aero-auto oxidation of limonene to produce mainly carveol and carvone (Fig. 4) [25–29].

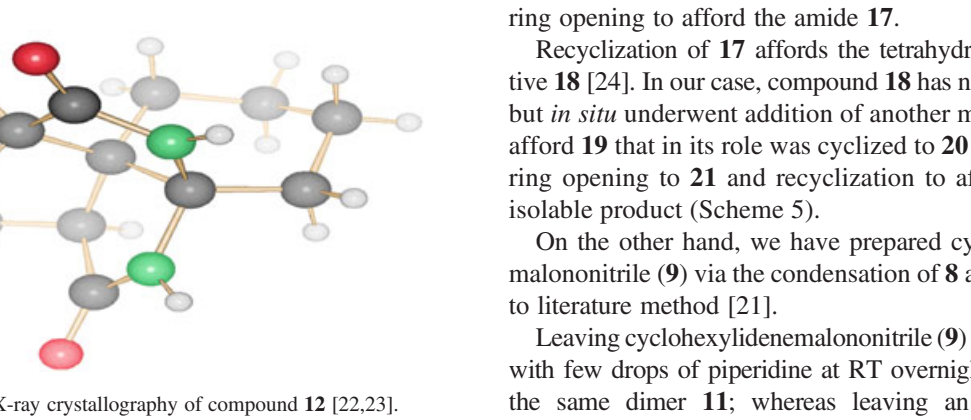


Figure 3. X-ray crystallography of compound **12** [22,23].

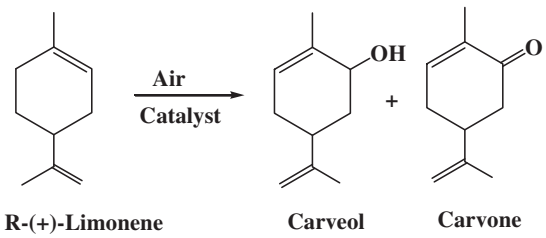


Figure 4. Auto air oxidation of Limonine.

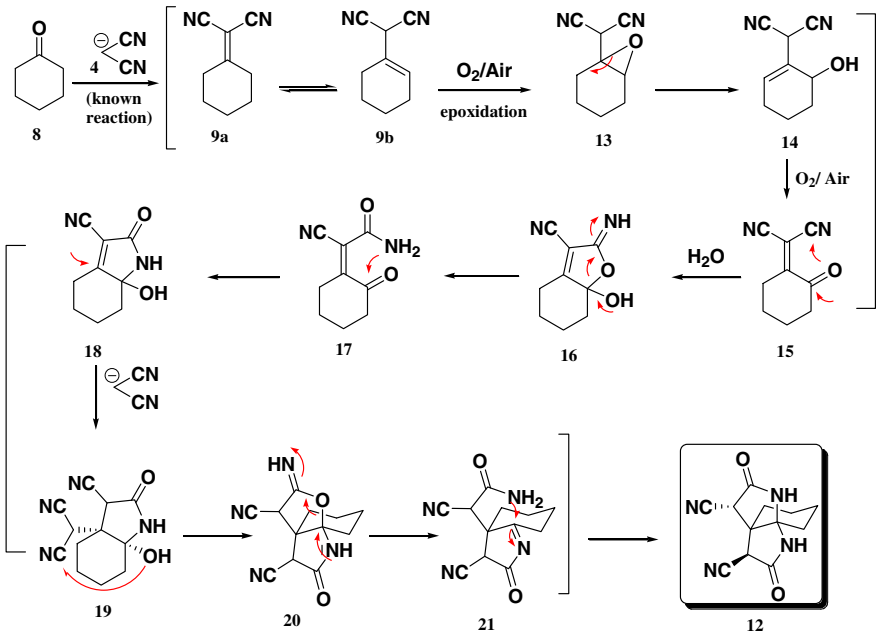
Accordingly, the suggested mechanism as depicted in Scheme 5 involving firstly the Knövenagel condensation of **8** and **4** to afford **9a/9b**. This latter undergoes allylic epoxidation to afford **13** that undergoes the small ring opening to afford **14** that is further autoxidized to afford **15**. Water attacks the carbonyl group of **15** with simultaneous attack of the resulting OH on one of the cyano groups to afford the intermediate **16** that *in situ* undergoes ring opening to afford the amide **17**.

Recyclization of **17** affords the tetrahydroindole derivative **18** [24]. In our case, compound **18** has not been isolated but *in situ* underwent addition of another molecule of **4** to afford **19** that in its role was cyclized to **20** that undergoes ring opening to **21** and recyclization to afford **12** as the isolable product (Scheme 5).

On the other hand, we have prepared cyclohexylidenemalononitrile (**9**) via the condensation of **8** and **4** according to literature method [21].

Leaving cyclohexylidenemalononitrile (**9**) alone in ethanol with few drops of piperidine at RT overnight, we obtained the same dimer **11**; whereas leaving an equimolecular

Scheme 5. Mechanism for the formation of compound 12.



mixture of compound **9** and **4** in ethanol with sodium acetate at RT overnight, we could obtain the same compound **12**. The identity in each case was deduced from matching the melting points and TLC analysis.

As a further proof to this suggested mechanism, cyclohexanone (**8**) was left with malononitrile (**4**) (1:2) in ethanol and sodium acetate under argon atmosphere at RT overnight, and we could only obtain the condensation product **9** in low yield, whereas the majority of the reactants remained unreacted, which means that air–oxygen is essential in the formation of **12**. This low yield of the condensation product can be rationalized on the basis that in the presence of air–oxygen, the condensation product undergoes oxidation and thus eliminated from the reaction sphere that enhances further condensation to take place.

EXPERIMENTAL

Melting points were measured on a digital Electrothermal 9100 apparatus (Kleinfeld, Gehrden, Germany) and are uncorrected. FTIR spectra (KBr) were obtained on a Nicolet 205 spectrophotometer (Nicolet, Madison, WI, USA). ^{1}H-NMR spectra were obtained on a Bruker AC 300 P- 300 MHz (Bruker, Rheinstetten, Germany) in DMSO-d_6 if not mentioned otherwise. Chemical shifts are expressed in δ values. Mass spectra were recorded with a Hewlett Packard Esquire-LC (LC/MS; Hewlett Packard, Palo Alto, CA, USA) at 70 eV. Elemental analyses were carried out at the Microanalysis Center at Cairo University, Giza, Egypt. X-ray crystallography of compound **7** was carried out at National Research Center, Dokki, Giza, Egypt; and X-ray crystallography of compound **12** was carried out at Technical University of Dresden, Germany.

5-Aminospiro-[2,6,7,7a-tetrahydroindene-7,1′-cyclopentane]-4,6,6-tricarbonitrile (7). Anhydrous sodium acetate (0.01 mol) or piperidine (1 mL) was added to a mixture of cyclopentanone (**3**) (0.01 mol) and malononitrile (**4**) (0.01 mol) in 50 mL of absolute ethanol. The reaction mixture was stirred at 25°C for 2 h, diluted with water, and acidified to pH 3–4 with hydrochloric acid. The solid so formed was filtered off, washed with water, and crystallized from dimethylformamide to afford **7** as yellow crystals, yield (60%), mp 195°C; ν_{max}/cm^{-1} (KBr) 3404 and 3326 (NH_2), 2221 (CN). δ_H = 1.34–2.40 (m, 12H, 6CH_2), 3.0 (t, 1H), 5.50 (t, 1H, =CH), 7.52 (s, 2H, NH_2). MS: *m/z* = 264. *Anal.* Calcd for $C_{16}H_{16}N_4$ (264.33): C, 72.70; H, 6.10; N, 21.20. Found: C, 72.50; H, 6.28; N, 21.43%.

X-ray crystallographic data using Altomare & Mackay [19] program to solve structure. The X-ray diffraction measurement λ = 0.71073 Å; Crystal data for compound **7**; colorless needles $C_{16}H_{16}N_4$, M_r = 264.332 g × mol^{-1}; crystal system, space group: Triclinic, unit cell dimensions: a = 6.4719(2) Å, b = 8.9917(3) Å, c = 12.0148(4) Å, α = 93.5341(14)°, β = 91.8453(13)°, γ = 92.230(2)°; volume: 696.90(4) Å^3; T = 298 K; Z = 2; calculated density: 1.260 mg m^{-3}; absorption coefficient: μ = 0.08 mm^{-1}; reflection 2199 measured, θ_{max} = 27.51°; R_{int} = 0.019, data collection Kappa CCD with graphite monochromator.

2-Aminospiro-[3,4,5,6,7,4a-hexahydronaphthalene-4,1′-cyclohexane]-1,3,3-tricarbonitrile (11). Piperidine (1 mL) was added to a mixture of cyclohexanone (**8**) (0.01 mol) and malononitrile (**4**) (0.01 mol) in 50 mL of absolute ethanol. The reaction mixture was stirred at 25°C for 2 h, then left at RT overnight, diluted with water, and acidified to pH 3–4 with hydrochloric acid. The solid so formed was filtered off, washed with water, and crystallized from dimethylformamide to afford **11** as pale yellow crystals, yield (61%), mp 173°C. ν_{max}/cm^{-1} (KBr): 3438.5 and 3349.7 (NH_2), 2214.8 (CN) cm^{-1}. δ_H = 1.36–2.05 (m, 17H, cyclohexane + cyclohexene protons), 5.62 (t, 1H, =CH), 9.20 (s, 2H, NH_2). MS: *m/z* = 292 (25%). *Anal.* Calcd for $C_{18}H_{20}N_4$ (292.39): C, 73.94; H, 6.89; N, 19.16. Found: C, 73.90; H, 6.92; N, 19.30.

9,10-Diaza-8,11-dioxo-tricyclo-[4.3.3.0^{1,6}]-dodecane-7,12-dicarbonitrile (12). Anhydrous sodium acetate (0.01 mol) was added to a mixture of cyclohexanone (**8**) (0.01 mol) and malononitrile (**4**) (0.02 mol) in 50 mL of absolute ethanol. The reaction mixture was stirred at 25°C for 2 h, then left to stand at RT overnight. To the reaction mixture was added cold water (10 mL) and neutralized with drops of concentrated HCl The solid so formed was filtered off, washed with cold water, and recrystallized from dimethylformamide to afford compound **12** as white crystals, yield (65%), mp 289°C; ν_{max}/cm^{-1} (KBr) 3330.5 and 3269.7 (NH), 2257.3 (CN), 1723 (CO) cm^{-1}. $\delta_H = 1.05–2.47$ (m, 8H, $4CH_2$), 4.57 (s, 1H), 4.80 (s, 1H), 9.20 (s, 2H, 2NH).MS: *m/z* = 244 (26%). *Anal.* Calcd for $C_{12}H_{12}N_4O_2$ (244.25): C, 59.01; H, 4.95; N, 22.94. Found: C, 59.19; H, 4.76; N, 22.70%.

X-ray crystallographic data: colorless crystals, $C_{12}H_{12}N_4O_2$ ($M_r = 244.26\ g \times mol^{-1}$), monoclinic, space group P-2_1/c (No. 14), $a = 7.505(1)$ Å, $b = 12.221(4)$ Å, $c = 14.400(1)$ Å, $\alpha[^O] = 90.00$, $\beta[^O] = 121.60(1)$, $\gamma[^O] = 90.00$; $V[Å^3] = 1124.9(4)$, $Z = 4$, $D_{calcd} = 1.442\ g \times cm^{-3}$, $F(000) = 512\ e$, $\mu = 0.103\ mm^{-1}$; the final difference Fourier $\rho = 0.28(-0.25)\ e\ Å^{-3}$.Crystal dimensions = 0.17 × 0.13 × 0.09 nm. Maximum resolution [sin θ/λ] = 0.64 $Å^{-1}$/ 99.9%. Data were collected at $T[°C] = -75(2)$, with graphite monochromator with Mo Kα radiation ($\lambda = 0.71073$ Å) using the CCD data collection and SADABS absorption correction method; minimum 98.3%; maximum 99.1%.. Total independent reflections are 24470 were counted with observed reflections 1840. $R_{av} = 0.051$. The final $R = 0.045$ and $R_W^2 = 0.098$.

Synthesis of the cycloalkylidene malononitrile derivatives 5 and 9. Cyclopentylidenemalononitrile (**5**) and cyclohexylidenemalononitrile (**9**) were prepared by condensing cyclopentanone (**3**) or cyclohexanone (**8**) with malononitrile (**4**) according to the reported literature method [21].

Alternative synthesis of 7 and 11. Piperidine (1 mL) was added to a solution of either cyclopentylidenemalononitrile (**5**) (0.01 mol); or cyclohexylidenemalononitrile (**9**) (0.01 mol) in 30 mL of absolute ethanol. The reaction mixture was stirred at 25°C for 2 h then left at RT overnight. The precipitated solid so formed was filtered off, washed with water, and crystallized from dimethylformamide to afford **7** and **11**, respectively.

Alternative synthesis of 12. Anhydrous sodium acetate (0.01 mol) was added to a mixture of cyclohexylidenemalononitrile (**9**) (0.01 mol) and malononitrile (**4**) (0.01 mol) dissolved in 30 mL of absolute ethanol followed by two drops of water. The reaction mixture was stirred at 25°C for 2 h then left to stand at RT overnight. The solid product so formed was filtered off, washed with cold water, and recrystallized from dimethylformamide to afford compound **12**.

The reaction of cyclohexanone (8) and malononitrile (4) in absence of oxygen. To a mixture of cyclohexanone (**8**) (0.01 mol) and malononitrile (**4**) (0.02 mol) in ethanol (30 mL) was added sodium acetate (0.01 mol), and argon gas was streamed in the flask that was then closed and left at RT overnight. To this reaction, mixture was added cold water (10 mL) and neutralized with few drops of concentrated HCl, and after extraction with ether, we have obtained the condensation product **9** (yield 30%); identical to that obtained according to the reported literature method [21].

Acknowledgment. F. M. Abdelrazek thanks the Alexander von Humboldt-Foundation (Germany) for the continuous support through granting short research fellowships whenever applied for.

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[18] Crystallographic data (excluding structure factors) for the structure of compound **7** reported in this paper has been deposited with the Cambridge Crystallographic Data Centre under the number CCDC-854371. Copies of the data can be obtained free of charge from the Director on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44-01223-336033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk.).

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[22] Crystallographic data (excluding structure factors) for the structure **12** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-890175. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax.: (internat.) + 441223/336-033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk.).

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