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Fatty Acid Hydrazides in Heterocyclic Synthesis: Synthesis of 1,2-Diazepine and Pyridazine Derivatives

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ABSTRACT: *1,2-Diazepinone derivatives* **6a–d, 8a,b,** *and* **10a–c** *were synthesized from the reaction of olefines carrying EWG as ethoxymethylene malononitrile, ethoxymethylene cyanoacetate, and tetracyanoethylene with* **1a–f** *respectively. Also, 5-alkyl-6-oxotetrahydropyridazine-4,4-dicarboxylate derivatives* **12a–c** *were afforded via the reaction of* **1d–f** *with diethyl ethoxymethylene malonate.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:259–264, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20294

INTRODUCTION

During the last century, the production and utilization of oils, fats, and their derivatives have grown both in volume and diversity in the industrial field [1,2]. There has been a competition between oleochemicals and petrochemicals. More recently, some fatty acid derivatives have shown insecticidal and antimicrobial properties [3].

RESULTS AND DISCUSSION

In connection with our ongoing work [4–7] aimed at the synthesis of heterocycles and the study of the reactivity of nucleophiles toward olefine derivatives as electron-deficient alkenes, we investigated the reaction of fatty acid hydrazides with ethoxymethylene malononitrile, ethoxymethylene cyanoacetate, tetracyanoethylene and diethyl ethoxymethylene malonate.

Treatment of caproic, caprylic, capric and lauric acid hydrazides **1a–d**, respectively, with ethoxymethylene malononitrile **2** in refluxing ethanol afforded an unexpected product. The reaction may be assumed to proceed via the Michael addition of **1** to **2** with the elimination of ethanol. The resulting adduct undergoes in situ cyclization by nucleophilic attack of CO*NH* on a cyano group to give a six-membered ring which on aromatization gives *N*-amino-2-pyridone **3**. However, as previously reported in [8], the characterization of the isolated product disagrees with the characterization of *N*-amino-2-aminopyridone (Scheme 1).

As a representative example, 6-butyl-5-imino-7-oxo-5,6-dihydro-7*H*-1,2-diazepine-4-carbonitrile **6a**, in its IR spectra the band 1700 cm^{-1} can be assigned to the carbonyl group and the absence of amino group signal in the ^1H NMR spectrum (in the region of δ 5–6 ppm which is normally expected) with the appearance of two singlets at δ 9.5 ppm corresponding to CH and NH acidic (exchangeable with D_2O). Moreover, the ^{13}C NMR spectra of the isolated product revealed a signal at δ 171 ppm attributed to a carbonyl group and does not belong to the carbonyl of *N*-amino 2-pyridone, normally seen in

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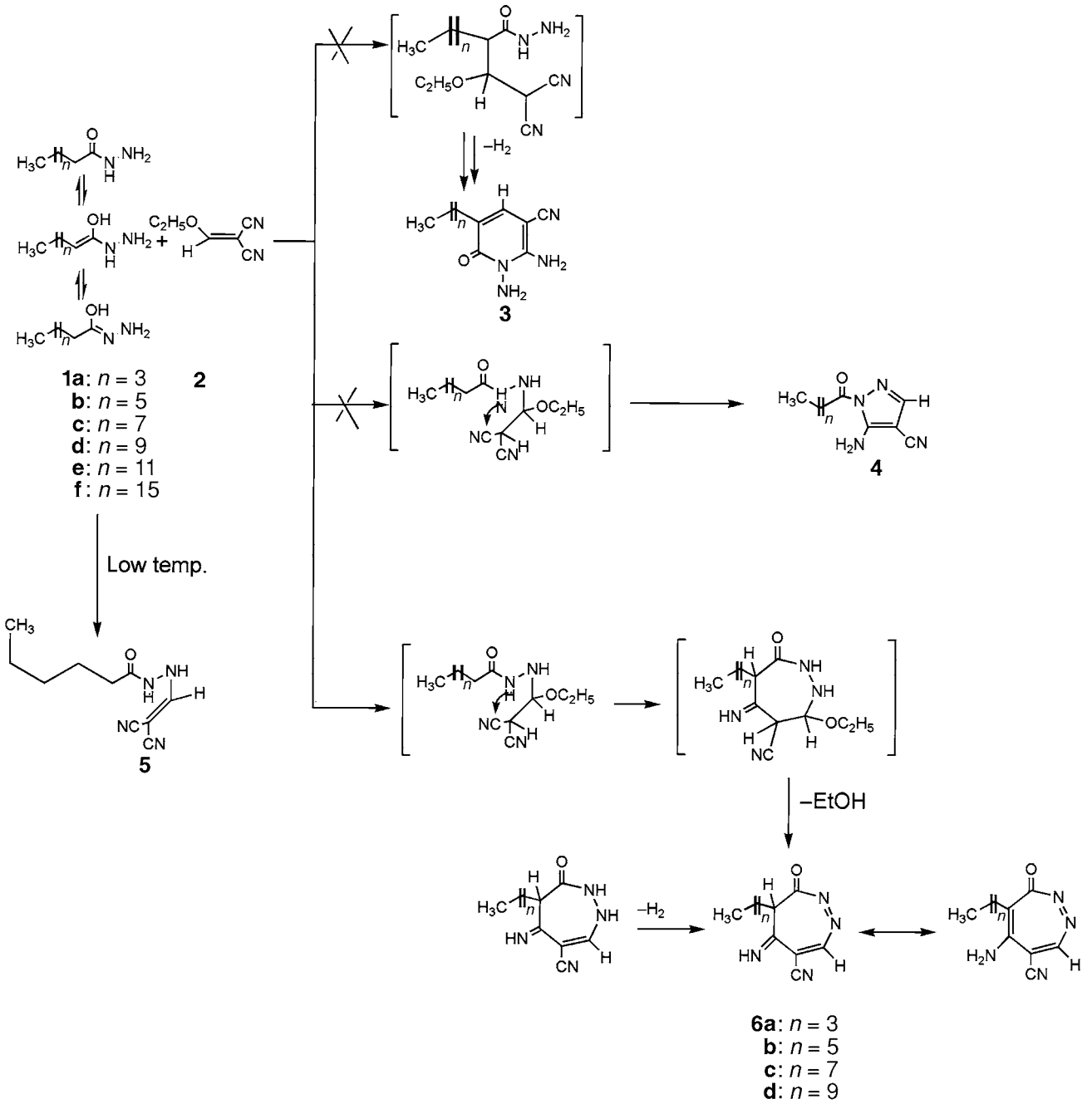
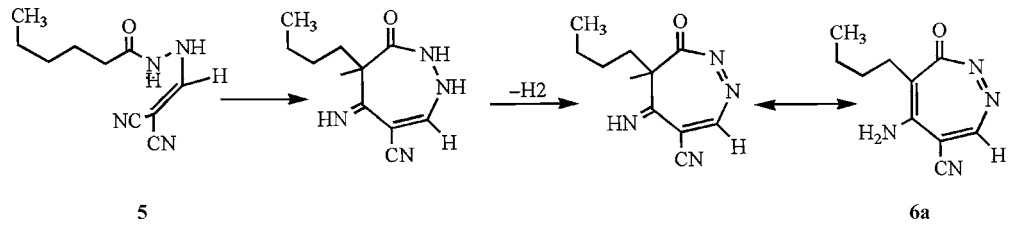


SCHEME 1

δ 155–160 ppm [9]. Also, the postulation of the formation of *N*-pyrazolyl derivative **4** can be eliminated because ^{13}C NMR spectrum that had shown *N-CO* [10] in the region of 140–155 ppm was absent in the ^{13}C NMR spectrum of **6a** (Scheme 1).

The cyclization to seven-membered diazeapine ring is possible and must be favored by the nucleophilic character of CH_2—CO that acts as carbon acid [11] in the presence of base with respect to the CONH group. We assumed that the reaction was initiated first by a nucleophilic substitution forming enaminone derivative *N′*-(2,2-dicyanovinyl) hexanohydrazide **5** as an intermediate that could be isolated at ambient temperature.

The structure of **5** was established by the presence of two CN groups in its IR spectrum at 2223 and 2230 cm^{-1}, CO at 1700 cm^{-1}. and the absence of NH_2. Its ^{1}H NMR spectrum revealed two singlets at



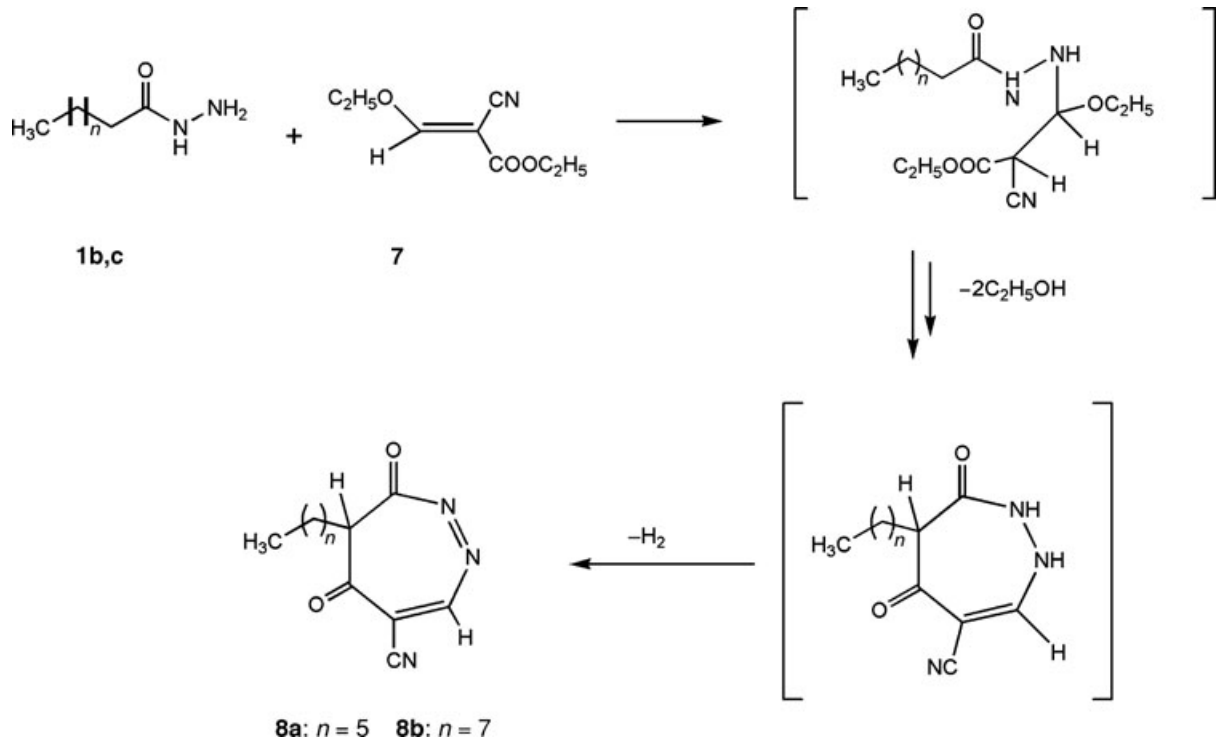
SCHEME 2

δ 9.5 and 9.6 ppm corresponding to CH and NH (exchangeable with D_2O) as the characteristic signals for this structure and the absence of NH_2. Refluxing of this intermediate in ethanol afforded **6a** as a result of intranucleophilic attack by CH_2—CO at the cyano group (Scheme 2).

Similarly, the reaction of ethoxymethylene cyanoacetate **7** toward **1b,c** under the same experimental conditions afforded 6-alkyl-5,7-dioxo-5,6-dihydro-7*H*-1,2-diazepine-4-carbonitrile **8a,b** (Scheme 3).

An interaction of **1b–d** with tetracyanoethylene **9** took place with the elimination of HCN followed by an interanucleophilic attack of CH_2CO affording 6-alkyl-5-amino-7-oxo-6,7-dihydro-1*H*-1,2-diazepine-3,4-dicarbonitrile derivatives **10a–c**. The reaction took place in ice bath due to high reactivity of tetracyanoethylene (Scheme 4).

As a continuation of these results, treatment each of lauric, myristic, palmitic, and stearic acid hydrazide **1d–f** with diethyl ethoxy methylene malonate afforded β-enaminones as an intermediate, followed by nucleophilic addition of CH_2 to a double bond forming pyridazine derivatives. The cyclization to seven-membered ring is less favored because of less reactivity of CH_2 toward the ester group (Scheme 5). The ^{1}H NMR spectrum of isolated product revealed the presence of an ester group and $CH_{2\,ring}$. The ^{13}C NMR spectrum of **12b** revealed signals at δ 167.9 and 165.5 ppm corresponding to CO_{ester} and δ 159.2 ppm corresponding to *C*O (cyclic amide).



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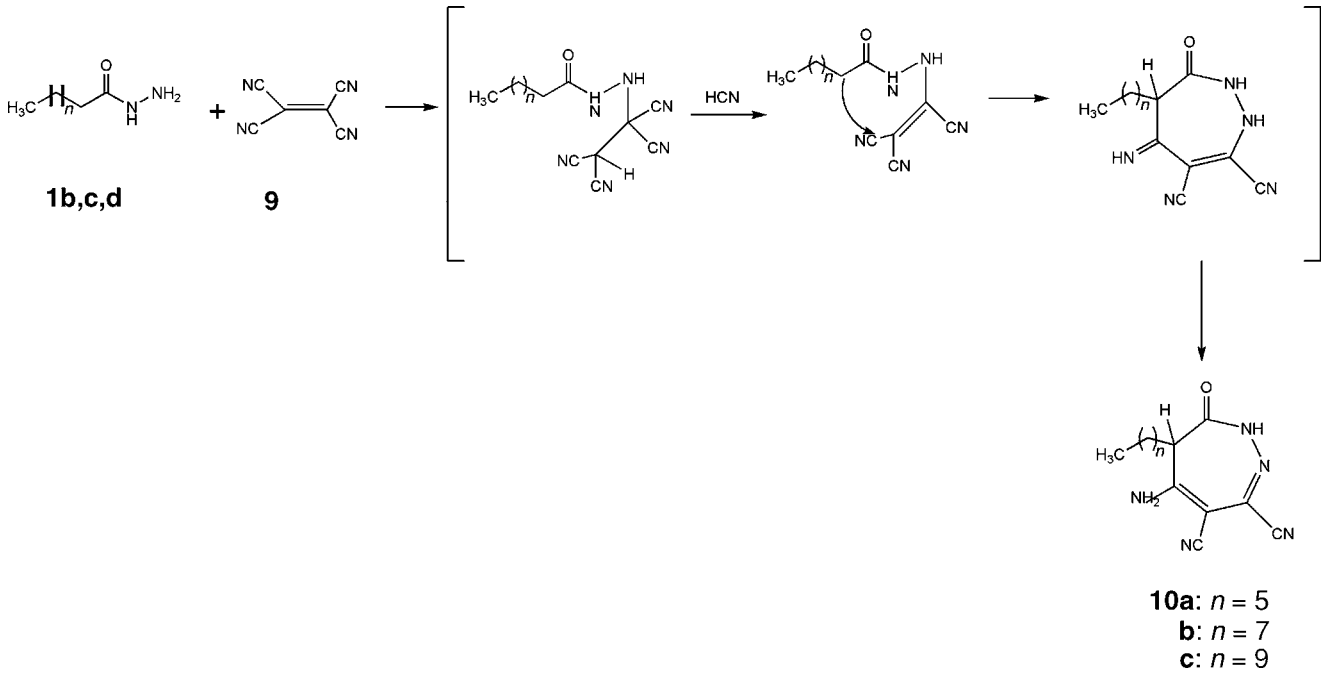


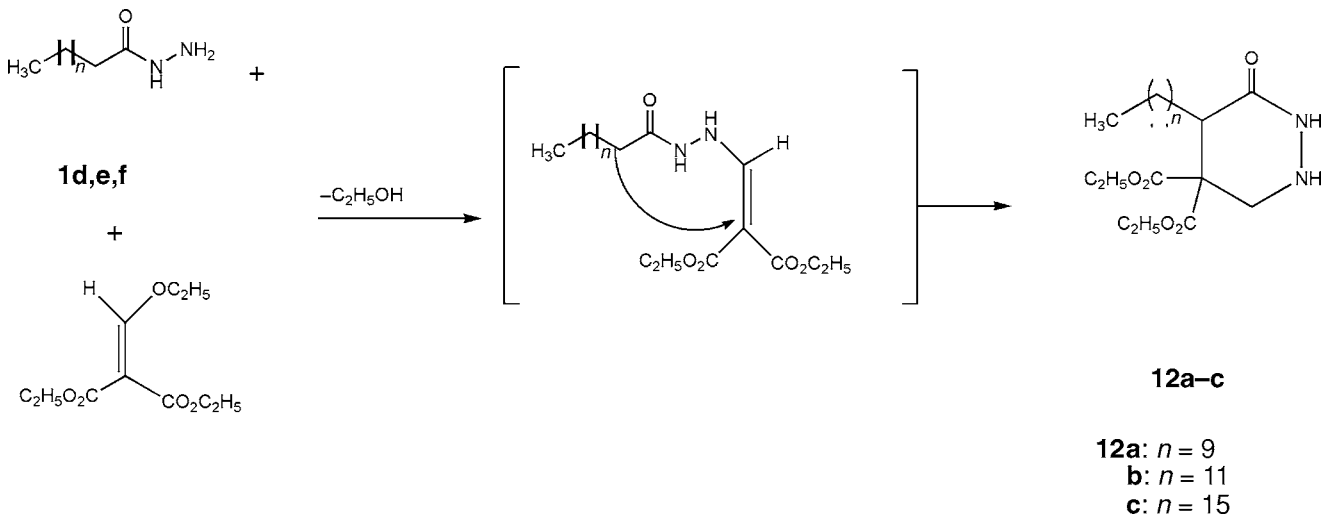
SCHEME 4

EXPERIMENTAL

Melting points are uncorrected and were recorded on Electrothermal A 9000 Series digital melting point apparatus. Microanalyses were performed by the Central Services Laboratory NRC. (Satisfactory microanalysis was obtained: C ± 0.40; H ± 0.27; N ± 0.30). IR spectra were recorded on Carlzeise spectrophotometer model "UR 10" using KBr. ^{1}H NMR and ^{13}C NMR spectra were determined on Varian Gemini 200 MHz using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Finnigan SSQ 7000 mass spectrometer. Silica gel with fluorescent indicator 254 nm on aluminum cards (layer thickness 0.2 mm with a package of 20 cards) was used for thin layer chromatography (TLC) . Chloroform–methanol was used as an eluting system in thin layer chromatography.

Synthesis of N′-(2,2-Dicyanovinyl) Hexanohydrazide **5**

Malononitrile (0.02 mol) was added to a solution of fatty acid hydrazide **1a** (0.01 mol) in 20 mL dry benzene and ethoxymethylene. The reaction mixture



SCHEME 5

was stirred in ice bath for 4 h and monitored by TLC. The solid that separated was collected, washed with diethyl ether, filtered, washed with cold ethanol and dried to afford **5**. 55%, mp 71–72°C, IR (γ/cm^{-1}) 3330 (NH), 2223 and 2230 (CN), 1700 (CO); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.8 (t, 3H, CH_3), 1.2–1.3 (m, 4H, 2× CH_2), 1.8 (m, 2H, CH_2), 2.1 (t, 2H, CH_2), 8.5 (s, 1H, CH) , 9.6 (br s, 1H, NH exchangeable with D_2O). Anal Calcd for $C_{10}H_{14}N_4O$: req. C, 61.22; H, 7.14; N, 28.57. Found C, 61.45; H, 7.48; N, 28.97.

6-Alkyl-5-imino-7-oxo-5,6-dihydro-7H-1,2-diazepine-4-carbonitrile **6a–d** *and 6-Alkyl-5,7-dioxo-2,5,6,7-tetrahydro-1H-1,2-diazepine-4-carbonitrile* **8a,b**

General Procedure. Malononitrile (0.02 mol) was added to a solution of the appropriate fatty acid hydrazide **1a–d** (0.01 mol) in 20 mL absolute ethanol and ethoxymethylene. The reaction mixture was refluxed in the presence of DBU as a catalyst for 4 h and monitored by TLC. The solid that separated was collected by filtration and recrystallized from *n*-hexane.

6-Butyl-5-imino-7-oxo-5,6-dihydro-7H-1,2-diazepine-4-carbonitrile **6a**. 75%, mp 111–112°C; IR γ (cm^{-1}): 3330 (NH), 2984 (CH aliphatic), 2223 (CN), 1700 (CO), 1630 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.8 (t, 3H, CH_3), 1.2–1.3 (m, 4H, 2× CH_2), 2.1 (t, 2H, CH_2), 2.8 (t, 1H, H-6), 9.5 (s, 1H, H-3), 9.6 (br, 1H, NH exchangeable with D_2O); ^{3}C NMR (DMSO-d_6): δ 171 (*C*-7), 154.2 (*C*-3), 144.2 (*C*-5), 116.4 (*CN*), 110.4 (*C*-4), 34.2 (*C*-6), 28.9, 25.2, 21.8, 14.1 ppm C-aliphatic chain; MS *m/z* (%): 204 (M^+, 6%), 172 (18%), 130 (77%) 99 (100%). Anal. Calcd for $C_{10}H_{12}N_4O$: req. C, 58.81; H, 5.92; N, 27.43. Found C, 58.65, H, 5.98, N, 27.67.

6-Hexyl-5-imino-7-oxo-5,6-dihydro-7H-1,2-diazepine-6-carbonitrile **6b**. 80%, mp 124–125°C: IR γ (cm^{-1}): 3310 (NH), 2989 (CH-aliphatic), 2240 (CN), 1720 (CO), 1600 (C=NH bending), ^{1}H NMR (DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), 1.3–1.5 (m, 10H, $5CH_{2,aliphatic}$), 2.4 (m, 1H, H-6), 8.8 (s, 1H, H-3), 9.6 (br s, 1H, NH exchangeable with D_2O). Anal Calcd for $C_{12}H_{16}N_4O$ (232.28): req. C, 62.05; H, 6.94; N, 24.12. Found C, 62.29; H, 7.16; N, 24.31.

5-Imino-6-octyl-7-oxo-5,6-dihydro-7H-1,2-diazepine-4-carbonitrile **6c**. 80%, mp 141–145°C; IR γ (cm^{-1}): 3320 (NH), 2225 (CN), 1730 (CO), 1600 (NH bending), ^{1}H NMR (DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), 1.3–1.7 (m, 14H, 7CH_2), 2.6 (t, 1H, H-6), 8.4 (1s, 1H, H-3), 9.1 (s, 1H, NH exchangeable with D_2O). Anal Calcd for $C_{14}H_{20}N_4O$ (260.33): req. C, 64.59; H, 7.74; N, 21.52. Found C, 64.69; H, 7.86; N, 21.61.

6-Decyl-5-imino-7-oxo-5,6-dihydro-7H-1,2-diazepine-4-carbonitrile **6d**. 69%, mp 138–139°C; IR γ (cm^{-1}): 3430 (NH), 2237 (CN), 1727 (CO), 1560 (NH bending); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.8 (t, 3H, CH_3), 1.2–1.6 (m, 18H, 9CH_2), 2.9 (t, 1H, H-6), 7.9 (s, 1H, H-3), 8.9 (s, 1H, NH exchangeable with D_2O). Anal Calcd for $C_{16}H_{24}N_4O$ (288.39): req. C, 66.64; H, 8.39; N, 19.43. Found C, 66.89; H, 8.76; N, 19.61.

6-Hexyl-5,7-dioxo-5,6-dihydro-7H-1,2-diazepine-4-carbonitrile **8a**. 60%, mp 108–109°C; IR γ (cm^{-1}) 3391 (NH), 2233 (CN), 1710 (CO), 1624 (NH bending), ^{1}H NMR (DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), 1.2–1.9 (m, 10H, 5CH_2), 3.3(t, 1H, CH-6), 7.9 (s, 1H, H-3); MS *m/z* (%): 206 (M^+—HCN, 10%), 158 (100%), 127 (90%). Anal Calcd for $C_{12}H_{15}N_3O_2$: req. C, 61.79; H, 6.48; N, 18.01. Found C, 61.58; H, 6.76; N, 18.35.

6-Octyl-5,7-dioxo-5,6-dihydro-7H-1,2-diazepine-4-carbonitrile **8b**. 65%, mp 127–129°C; IR γ (cm^{-1}): 3455 (NH), 2230 (CN), 1708 (CO), 1617 (NH bending), ^{1}H NMR (DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), δ 1.2–1.6 (m, 12H, 6CH_2), 2.1 (m, 2H, CH_2), 2.9 (t, 1H, CH-6), 8.7 (1s, 1H, H-3). Anal Calcd for $C_{14}H_{19}N_3O_2$ (261.32): req. C, 64.35; H, 7.33; N, 16.08. Found C, 64.58; H, 7.61; N, 16.25.

5-Amino-6-alkyl-7-oxo-6,7-dihydro-1H-1,2-diazepine-3,4-dicarbonitrile **10a–c**

General Procedure. Tetracyanoethylene (0.02 mol) was added to a solution of appropriate fatty acid hydrazide **1b–d** (0.01 mol) in 20 mL absolute ethanol. The reaction mixture was stirred for 3 h untill it cooled and monitored by TLC. The solid that separated was collected by filtration and recrystallized from ethanol.

5-Amino-6-hexyl-7-oxo-6,7-dihydro-1H-1,2-diazepine-3,4-dicarbonitrile **10a**. 60%, mp 137–139°C; IR γ (cm^{-1}): 3455 (NH), 2211 (CN), 1690 (CO), 1600 (NH bending); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.88 (t, 3H, CH_3), 1.1–1.4 (m, 10H, 5CH_2), 2.3 (t, 1H, H-6), 6.9–7.2 (br, 2H, NH_2, exchangeable with D_2O), 8.2 (s, 1H, NH, exchangeable with D_2O); MS *m/z* (%): 259 (M^+, 1%), 185 (10%), 133 (15%), 127 (100%). Anal Calcd for $C_{13}H_{17}N_5O$ (259.31): req. C, 60.21; H, 6.61; N, 27.01. Found C, 60.58; H, 6.76; N, 27.35.

5-Amino-6-octyl-7-oxo-6,7-dihydro-1H-1,2-diazepine-3,4-dicarbonitrile **10b**. 72%, mp 149–150°C; IR γ (cm^{-1}): 3430 (NH), 2237 (CN), 1727 (CO), 1560 (NH bending), ^{1}H NMR (DMSO-d_6) δ (ppm): 0.9 (t, 3H, CH_3), 1.1–1.4 (m, 14H, $7CH_2$), 2.7 (m, 1H, H-6), 7.2 (br, 2H, NH_2, exchangeable with D_2O), 8.1 (s, 1H, NH, exchangeable with D_2O). Anal Calcd for $C_{15}H_{21}N_5O$ (287.31): req. C, 62.71; H, 7.31; N,24.39. Found C, 62.58; H, 7.66; N, 24.15.

5-Amino-6-decyl-7-oxo-6,7-dihydro-1H-1,2-diazepine-3,4-dicarbonitrile **10c**. 85%, mp 164–165°C; IR γ (cm^{-1}): 3419 (NH_2), 2235 (CN), 1743 (CO), 1630 (NH bending); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.8 (t, 3H, CH_3), 1.2–1.6 (m, 18H, $9CH_2$), 2.2 (t, 1H, H-6), 2.7 (m, 1H, H-6), 8.3 (br, 2H, NH_2, exchangeable with D_2O); MS *m/z* (%): 316 (M^{+1}, 58%), 231 (10%), 183 (100%). Anal Calcd for $C_{17}H_{25}N_5O$ (315.41): req. C, 64.73; H, 7.99; N, 22.20. Found C, 64.98; H, 7.76; N, 22.35.

Diethyl 5-alkyl-6-oxotetrahydropyridazine-4,4(1H)-dicarboxylate **12a–c**

Ethoxymethylene diethylmalonate (0.02 mol) was added to a solution of the fatty acid hydrazide **1d–f** (0.01 mol) in 20 mL absolute ethanol. The reaction mixture was refluxed for 4 h and monitored by TLC. The solid that separated was collected, filtered, washed with ethanol, and dried to afford **12a–c**.

Diethyl 5-decyl-6-oxohexahydropyridazine-4,4(1H)-dicarboxylate **12a**. 75%, mp 154–155°C; IR γ (cm^{-1}): 3300 (NH), 2985 ($CH_{aliphatic}$), 1737 (CO), 1589 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.8 (m, 3H, CH_3), 0.9–1.5 (m, 24H, $9CH_{2+}$, $2CH_{3\,ester}$), 2.2 (m, 2H, CH_2), 3.3 (m, 1H, CH-5 pyridazine), 4.1 (m, 4H, $2CH_{2\,ester}$), 7.8 (br, 1H, 1NH, exchangeable with D_2O), 10.2 (br, 1H, NH, exchangeable with D_2O). Anal Calcd for $C_{20}H_{36}N_2O_5$ (384.51): req. C, 62.47; H, 9.44; N, 7.29. Found C, 62.78; H, 9.67; N, 7.41.

Diethyl 5-dodecyl-6-oxohexahydropyridazine-4,4(1H)-dicarboxylate **12b**. 69%, mp 168–170°C; IR γ (cm^{-1}): 3300 (NH), 2990 (CH aliphatic), 1735 (CO): ^{1}H NMR (DMSO-d_6) δ (ppm): 0.8 (m, 3H, CH_3), 1.2–1.7 (m, 26H, $10CH_{2+}$, $2CH_{3\,ester}$), 1.8 (m, 2H, CH_2), 2.1 (m, 2H, CH_2), 3.2 (s, 1H, CH-5), 4.1 (m, 4H, $2CH_{2\,ester}$), 7.7 (br, 1H, exchangeable with D_2O), 10.1 (br, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 167.9 and 165.5 ($2CO_{ester}$), 159.2 (*C*-6), 60.3 and 60 ($2CH_{2\,ester}$), 35.2 (C-5), 33.9 (C-3) and 31.9 (C-4), 29.9, 29.4, 29.3, 29.2, 28.8 ($CH_{2\,aliphatic\,chain}$), 14.2 and 14.01 ($CH_{3\,ester}$ and $CH_{3\,aliphatic\,chain}$); MS *m/z*(%): 413 (M^+, 90%), 366 (60%), 157 (100%). Anal Calcd for $C_{22}H_{40}N_2O_5$ (412.56): req. C, 64.05; H, 9.77; N, 6.79. Found C, 64.38; H, 9.54; N, 7.41.

Diethyl 5-hexadecyl-6-oxotetrahydropyridazine-4,4(1H)-dicarboxylate **12c**. 65%, mp 138–140°C; IR γ (cm^{-1}): 3300 (NH), 1740 (CO), 1590 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.8 (m, 3H, CH_3), 1.2–1.7 (m, 36H, $15CH_{2+}$, $2CH_{3\,ester}$), 2.1 (m, 2H, CH_2), 3.3 (m, 1H, CH-5 pyridazine), 4.2 (m, 4H, $2CH_{2\,ester}$), 7.8 (br, 1H, NH, exchangeable with D_2O), 10.2 (br, 1H, NH, exchangeable with D_2O); MS *m/z* (%) 468 (M^+, 25%), 423 (20%), 157 (100%). Anal Calcd for $C_{26}H_{48}N_2O_5$ (468.67): req. C, 66.63; H, 10.32; N, 5.98. Found C, 66.48; H, 10.58; N, 5.71.

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