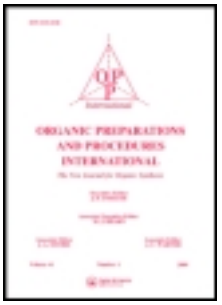

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SYNTHESIS AND CHARACTERIZATION OF PIPERAZINE-2,6-DIONES

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SYNTHESIS AND CHARACTERIZATION OF PIPERAZINE-2,6-DIONES

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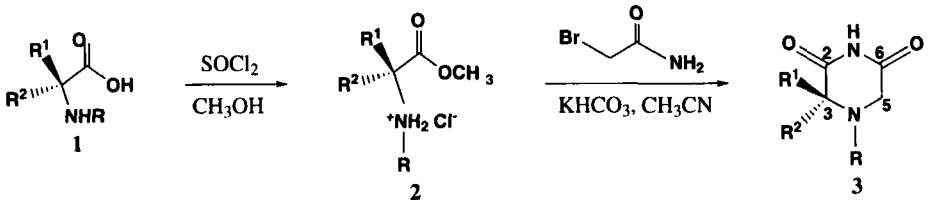
Piperazinediones also known as diketopiperazines, are the smallest cyclic peptides, as well as a common motif in several natural products with therapeutic properties.[1] It has been shown that *bis*diketopiperazines exhibit antitumor activity against Lewis lung carcinoma, sarcoma 180, L1210 leukemia, P388 leukemia, B16 myeloma, malignant lymphoma, C-26 colon, C-38 human colon and breast cancer.[2-8] They have also been used in clinical trial combination therapy.[9] Further investigations have been directed to establish the mechanism by which these drugs affect cell growth.[10-13] Piperazine-2,6-diones substituted at the 3 and 4 positions have shown hypolipidemic activity, the 3-substituted analogues being more active and clarify efficacious against both normal and induced hyperlipidemia in mice.[14]

Available methods for the preparation of piperazine-2,6-diones are scarce. They have been prepared from polypeptides,[15, 16] iminodiacetic acid and ammonium formate,[17] by reduction of 2,6-dibenzyloxypyrazine[18] and hydrolysis of 4-benzyl-2,6-bishydroxyiminopiperazine with hydrochloric acid.[19] Our current interest in piperazine-2,6-dione **3** derivatives of α-amino acids prompted us to develop a methodology to obtain them from α-amino acid methyl ester hydrochlorides **2** and 2-bromoacetamide. This paper describes a short, high yield synthesis and characterization of six new piperazine-2,6-diones **3b-g**, as well as the known piperazine-2,6-dione **3a** *via* 3+3 annulation. This method provides access to the surprisingly rare piperazine subtype derivatives, such as **3b-3f** which possess substituents at position 3. The structure of compound **3g** was further established by a single crystal X-ray diffraction study. The known α-amino acid methyl ester hydrochlorides **2a-g** were prepared by reaction of α-amino acids **1a-g** with thionyl chloride and methanol and were characterized by their ^{1}H NMR spectra.

Compounds **3a-3g** were obtained by the reaction of bromoacetamide with compounds **2a-2g** in the presence of potassium bicarbonate under reflux of acetonitrile. The ^{1}H NMR spectra of



1 2 3

a) $R = R^1 = R^2 = H$ b) $R = R^2 = H$, $R^1 = CH_3$ c) $R = R^1 = H$, $R^2 = CH_3$ d)[a] $R = R^2 = H$, $R^1 = CH_3CH_2$
e)[a] $R = R^2 = H$, $R^1 = CH_3CH_2CH_2CH_2CH_2CH_2$ f) $R = R^2 = H$, $R^1 = (CH_3)_2CHCH_2$
g)[b] $R = CH_3CO_2CH_2$, $R^1 = R^2 = H$
a) racemic mixture, b) $R = CH_2CO_2H$ for **1g**

compounds **3a-3c**, **3f** and **3g** exhibited a single signal assigned to the methylene protons of the CH_2CONH moiety, while those of **3d** and **3e** exhibited an AB system. Moreover, they showed signals characteristic for the imidic protons in the range between δ 10.70 and 11.15 and for the amine protons between δ 2.92 and 3.19 (except for **3g**). The ^{15}N NMR spectra exhibited two signals due to the imidic and amine nitrogen atoms. The signals for the amine nitrogen atom in compounds **3b** to **3f** and **3g** are deshielded due to β- and α-effects, respectively.[20] Table 1 shows the ^1H and ^{15}N spectra data for compounds **3a-g**. The ^{13}C NMR spectra exhibited the expected signals for compounds **3a** to **3g**. The assignments of C_3 and C_5 in **3b-3f**, C_7, C_8 and C_{10} in **3e**, C_8 in **3f**, as well as C_5 and C_7 in **3g**, were obtained by ^{13}C-^1H HETCOR techniques. The assignments of C_2 and C_6 in compounds **3b-3f**, as well as C_2 and C_8 in **3g** were obtained from their ^{13}C-^1H COLOC spectra. Table 2 shows spectra data for compounds **3a-g**. The IR spectra of compounds **3a-g** show the absorption band characteristic of the RCONHCOR group in the range between 1640-1700 cm^{-1}. The 70 eV EI mass spectra of compound **3a-g** exhibit the molecular ion. The fragment ions of m/z = 43, m/z = 57, m/z = 57, m/z = 71, m/z = 70, m/z = 56 and m/z = 42 correspond to the base peak for compound **3a-g**, respectively.

Suitable crystals of **3g** for X-ray analysis were obtained from acetonitrile/chloroform, the molecular structure and crystallographic numbering is shown in figure 1. The molecular structure shows the following intermolecular contacts: $C{=}O_1.....H_{1a}$ 2.016, $C{=}O_2.....H_{7b}$ 2.471, $C{=}O_3.....H_{5b}$ 2.558, $C{=}O_3.....H_{9c}$ 2.622 and $C{=}O_4.....H_{5a}$, 2.655 Å, which are significantly shorter than the sum of the van der Waals radii for the oxygen and hydrogen atoms (2.70Å).[21] In addition the following intramolecular contacts were observed between $C{=}O_1.....H_{1a}$ 2.403, $C{=}O_1.....H_{3b}$ 2.557, $C{=}O_2....H_{1a}$ 2.415, $C{=}O_2.....H_{5a}$ 2.535, $C{=}O_3.....H_{3a}$ 2.443, $C{=}O_3.....H_{5b}$ 2.535, $C{=}O_3.....H_{9b}$ 2.592, $C{=}O_3.....H_{9c}$, 2.626, $C\text{-}O_4.....H_{7a}$ 2.507, $C\text{-}O_4.....H_{7b}$ 2.543, $C\text{-}O_4.....H_{9a}$ 1.980 $C\text{-}O_4.....H_{9b}$ 1.980, $C\text{-}O_4.....H_{9c}$ 1.983, $C\text{-}N_4....H_{3a}$ 1.998, $C\text{-}N_4.....H_{3b}$ 1.994, $C\text{-}N_4....H_{5a}$ 1.98, $C\text{-}N_4.....H_{5b}$ 1.986, $C\text{-}N_4.....H_{7a}$ 1.975 and $C\text{-}N_4.....H_{7b}$ 1.978Å (sum of the van der Waals radii for N-H is 2.75Å).[21] In general the bond distances are within the expected values and relevant distances are: $O_1\text{-}C_2$ 1.217(3), $O_2\text{-}C_6$ 1.205(3), $O_3\text{-}C_8$ 1.197(3), $O_4\text{-}C_8$ 1.333(3), $N_1\text{-}C_2$ 1.370(3) and $N_1\text{-}C_6$ 1.387(3) Å. The torsion angles for the $H_{1a}\text{-}N_1\text{-}C_2\text{-}O_1$, $H_{1a}\text{-}N_1\text{-}C_2\text{-}C_3$, $H_{1a}\text{-}N_1\text{-}C_6\text{-}O_2$, $H_{1a}\text{-}N_1\text{-}C_6\text{-}C_5$, $C_2\text{-}N_1\text{-}C_6\text{-}C_5$, $C_6\text{-}N_1\text{-}C_2\text{-}C_3$, $C_6\text{-}N_1\text{-}C_2\text{-}O_1$ and $C_2\text{-}N_1\text{-}C_6\text{-}O_2$ fragments are -5.98°, 177.70°, 4.51°, -177.43°, 2.86°, -2.59°, -173.73°, and 175.19°, respectively evidencing that this part of the ring is almost planar due to the resonance effect of the imide

TABLE 1. Yields, ^1H and ^{15}N NMR Data for Compounds **3**

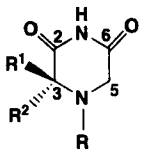
Cmpd	Yield	^1H NMR Data(δ)[a]					^{15}N NMR Data
	(%)	H_1	H_5	R	R^1	R^2	NH, NR
3a	39	10.8 (s)	3.38 (s)	H_4: 3.07 (br)	H_3: 3.38 (s)	H_3: 3.38 (s)	NH: -208.98 NR: -363.53
3b	63	10.70 (s)	3.43 (s)	H_4: 3.04 (br)	H_7: 1.20 (d, J = 7.0)	H_3:3.39 (q, J = 7.0)	NH:-210.85 NR: -348.88
3c	59	10.78 (s)	3.42 (s)	H_4: 3.19 (br)	H_3: 3.40 (q, J = 7.0)	H_7: 1.20 (d, J = 7.0)	NH: -210.81 NR: -348.75
3d	51	10.76 (s)	H_A: 3.42 (d, J = 17.6) H_B: 3.39 (d, J = 17.6)	H_4: 2.97 (br)	H_{7A}: 1.83 (ddq, J = 14.16, J = 7.3, J = 4.2) H_{7B}: 1.58 (ddq, J = 14.16, J = 8.2, J = 7.3) H_8: 0.91 (t, J = 7.3)	H_3: 3.20 (dd, J = 8.2, J = 4.2)	NH: -210.81 NR: -348.75
3e	50	10.75 (s)	H_A: 3.41 (d, J = 17.8) H_B: 3.38 (d, J = 17.8)	H_4: 2.94 (br)	H_{7A}: 1.72-181, (m) H_{7B}: 1.42-1.51 (m) H_{8-11}: 1.25- 1.42 (m) H_{12}: 0.86 (t, J = 6.8)	H_3: 3.25 (dd, J = 8.4, J = 4.0)	NH: -210.17 NR: -352.75
3f[b]	55	10.74 (s)	3.40 (s)	H_4: 2.92 (br)	H_{7A}: 1.59 (ddd, J = 13.9, J = 9.5, J = 4.7) H_{7B}: 1.40 (ddd, J = 13.9, J = 9.5 J = 4.7) H_8: 1.80 (ddd, J = 6.6, J = 9.5, J = 4.7) H_9: 0.90 (d, J = 6.6) H_{10}: 0.86 (d, J = 6.6)	H_3: 3.42 (dd, J = 9.5, J = 4.4)	NH: -210.11 NR: -352.79
3g	88	11.15 (s)	3.47 (s)	H_7: 3.47 (s) H_9: 3.62 (s)	H_3: 3.47 (s)	H_3: 3.47 (s)	NH: -209.93 NR: -358.35

a) In DMSO-d_6. b) H_9 and H_{10} chemical shifts can be interchanged.

group. The torsion angles for the N_1-C_6-C_5-N_4 (-25.87°), N_1-C_2-C_3-N_4 (25.47°), O_1-C_2-C_3-N_4 (157.97°) and O_2-C_6-C_5-N_4 (-156.97°) fragments show that N_4 is out of the main plane of the cyclic system and it is pointing upward. Moreover, the torsion angles for the C_9-O_4-C_8-O_3, O_3-C_8-C_7-N_4 and

O_4-C_8-C_7-N_4 fragments are 4.02°, 2.37° and -177.12°, respectively and the planarity of this part of the molecule can be attributed to intramolecular interactions between $C{=}O_3$.....H_{3a} and $C{=}O_4$.....H_{7a}.

TABLE 2. ^{13}C NMR Data of Compounds **3**[a]



3a R = R^1 = R^2 = H **3b** R = R^2 = H, R^1 = $^7CH_3$

3c R = R^1 = H, R^2 = $^7CH_3$ **3d** R = R^2 = H, R^1 = $^8CH_3{}^7CH_2$

3e R = R^2 = H, R^1 = $^{12}CH_3{}^{11}CH_2{}^{10}CH_2{}^9CH_2{}^8CH_2{}^7CH_2$

3f R = R^2 = H, R^1 = $(^{9,10}CH_3)_2{}^8CH^7CH_2$ **3g** R = $^9CH_3{}^8CO_2{}^7CH_2$, R^1 = R^2 = H

Cmpd	C_2	C_3	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}
3a	173.09	48.16	48.16	173.09						
3b	175.24	52.16	48.26	173.48	15.64					
3c	175.32	52.68	48.31	173.58	15.68					
3d	174.76	57.98	47.49	173.40	22.48	10.34				
3e	175.05	56.73	47.78	173.45	29.32	28.59	25.37	31.25	22.11	13.98
3f	175.46	54.96	47.48	173.42	38.20	23.98	21.32[b]	23.27[b]		
3g	170.24	54.28	54.28	170.24	54.86	170.08	51.50			

a) In DMSO-d_6. b) Assignments can be interchanged

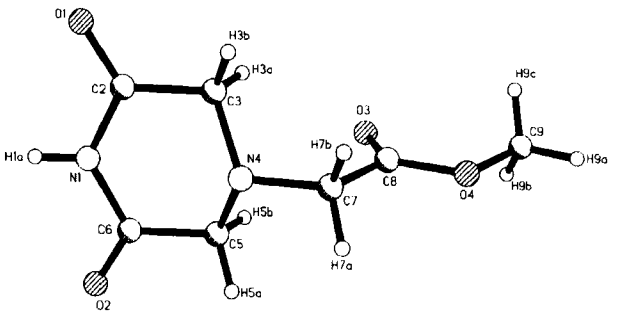


Fig. 1 Ortep Drawing of Compound **3g**

EXPERIMENTAL SECTION

NMR spectra were recorded on Jeol GLX-270, Jeol Eclipse 400 and Bruker Avance 300-DPX spectrometers. All ^1H and ^{13}C resonances are reported relative to TMS and ^{15}N to neat $MeNO_2$, DMSO-d_6 was used as solvent. Mass spectra were obtained with a Hewlett-Packard 5994-A instrument, infrared spectra were recorded as KBr pellets on a Perkin-Elmer 16F PC FT-IR spectrometer. Melting points were taken in open capillary tubes on a Gallenkamp MFB-595 apparatus and are uncorrected. The single crystal X-ray study was performed on a CAD4 ENRAF NONIUS diffractometer. Reagents were purchased from Aldrich Co.

Compound **3g**, $C_7H_{10}N_2O_4$ (MW=186.17), crystallized in the space group Pbcn, orthorhombic, colorless rectangular crystals, size: 0.3 x 0.2 x 0.2 mm^3, a = 12.337(2), b = 7.3380 (10), c = 18.777(4)Å, V = 1699.9(5)$Å^3$. Lattice constants were determined from least squares refinement on diffractometer angles for 24 automatically centered reflections; ρ 1.455 Mg/m^3, Z = 8, μ = 0.120 mm^{-1}, F (000) = 784. Data collection: monitoring of check reflections showed no signs of decay. A total of 1492 reflections was measured ($2>\theta>26°$), 1492 were independent and of these 990 were considered observed [$Fo>4.0\sigma(Fo)$]. Absorption correction was not necessary. Solution and refinement: direct methods, all non-hydrogen atoms refined anisotropically, all hydrogen were located by difference Fourier maps and refined with an overall isotropic thermal parameter, R = 0.0423, Rw = 0.1091, w = $1/\sigma^2$, GOOF = 1.028, parameter to data ratio 1:12.6, largest residual electron density peak/hole in the final difference map: 0.181/-0.220 e/$Å^3$. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[22] The data reduction was performed by JANA 98.[23] All calculations were carried out on a VAX 4000 computer using the SHELX 93 (Sheldrick G. M.) program package.[24]

The procedure outlined below is general for the preparation of α-amino acid methyl ester hydrochlorides **2a-2g**.

Synthesis of Glycine Methyl Ester Hydrochloride (2a).- General Procedure.- To a suspension of 1.0 g (13.33 mmol) of glycine **1a** in 100 mL of methanol was added at room temperature 0.97 mL (13.13 mmol) of thionyl chloride in a 250 mL flask. The mixture was refluxed 8 h with stirring. After being cooled to room temperature the solvent was evaporated under vacuum. The residue was washed three times with methylene chloride to yield 1.62 g (97%) of compound **2a** as a white solid, mp 173-175° (dec.), *Lit.*[25] mp 175° (dec.) ^{1}H NMR (DMSO-d_6): δ 8.76 (br, 3H), 3.74 (s, 2H), 3.70 (s, 3H).

Synthesis of L-Alanine Methyl Ester Hydrochloride (2b).- The reaction of 1.0 g (11.24 mmol) of L-alanine **1b** with 0.83 mL (11.24 mmol) of thionyl chloride in 100 mL of methanol gave 1.53 g (98%) of compound **2b** as a white solid, mp 109-111°, *Lit.*[26] mp 109-111°. ^{1}H NMR (D_2O): δ 4.20 (q, 1H), 3.82 (s, 3H), 1.54 (d, 3H)

Synthesis of D-Alanine Methyl Ester Hydrochloride (2c).- The reaction of 1.0 g (11.24 mmol) of D-alanine **1c** with 0.83 mL (11.24 mmol) of thionyl chloride in 100 mL of methanol gave 1.52 g (97%) of compound **2c** as a white solid, mp 108-111°, *Lit.*[26] mp 109 -110°. ^{1}H NMR (DMSO-d_6): δ 8.75 (s, 3H), 4.01 (q, 1H), 3.70 (s, 3H), 1.41 (d, 3H).

Synthesis of DL-2-Aminobutyl Methyl Ester Hydrochloride (2d).- The reaction of 1.0 g (9.71 mmol) of DL-2-aminobutyric acid **1d** with 0.71 mL (9.71 mmol) of thionyl chloride in 100 mL of methanol gave 1.45 g (98.7%) of compound **2d** as a white solid, mp 123-125°, *Lit.*[27] mp 116-117° (Me_2CO).^{1}H NMR (DMSO-d_6): δ 8.76 (s, 3H), 3.91 (t, 1H), 3.71 (s, 3H), 1.84 (quint, 2H), 0.89 (t, 3H).

Synthesis of DL-2-Aminooctyl Methyl Ester Hydrochloride (2e).- The reaction of 1.0 g (6.29 mmol) of DL-2-aminooctanoic acid **1e** with 0.46 mL (6.29 mmol) of thionyl chloride in 100 mL of methanol gave 1.3 g (98.7%) of compouund **2e** as a white solid, mp 83-85°, *Lit.*[28] mp 76-77°. ^{1}H NMR

(DMSO-d_6): δ 8.71 (s, 3H), 3.92 (t, 1H), 3.71 (s, 3H), 1.76-1.81 (m, 2H), 1.33-1.39 (m, 1H), 1.19-1.28 (m, 8H), 0.84 (t, 3H).

Synthesis of L-Leucine Methyl Ester Hydrochloride (2f).- The reaction of 1.0 g (7.63 mmol) of L-leucine **1f** with 0.56 mL (7.63 mmol) of thionyl chloride in 100 mL of methanol, gave 1.3 g (97%) of compound **2f** as a white solid, mp 148-150° (dec.), *Lit.*[29] mp 150-151° (dec).^{1}H NMR (DMSO-d_6): δ 8.78 (s, 3H), 3.78 (s, 1H), 3.71 (s, 3H), 1.57-1.84 (m, 3H), 0.83 (d, 6H).

Synthesis of Dimethyliminodiacetate Hydrochloride (2g).- The reaction of 1.0 g (7.53 mmol) of iminodiacetic acid **1g** with 1.10 mL (15.06 mmol) of thionyl chloride in 100 mL of methanol for 12 h, gave 1.46g (98%) of compound **2g** as a white solid, mp 171-173° (dec.), *Lit.*[30] mp 177-178° (dec).^{1}H NMR (DMSO-d_6): δ 10.16 (s, 2H, 4.02 (s, 4H), 3.75 (s, 6H).

The procedure outlined below is general for the preparation of piperazine-2,6-diones **3a-g**.

Synthesis of Piperazin-2,6-dione (3a). General Procedure.- To a stirred suspension of 1.0 g (7.97 mmol) of compound **2a** and 1.99 g (19.93 mmol) of potassium bicarbonate in 60 mL de acetonitrile was added 1.1 g (7.97 mmol) of 2-bromoacetamide at room temperature. The reaction mixture was refluxed for 8 h. After being cooled to room temperature, the mixture was filtered and the solvent was evaporated under reduced pressure to give a solid which was washed with chloroform and acetone to give 0.37 g (40%) of **3a** as a white solid, mp 176-180° (dec.), *Lit.*[18] mp 165-170° (dec.) sealed tube. IR: 3440, 3298, 2932, 2900, 1694 cm^{-1}(KBr). MS: m/z (%) = 114 (M^+, 14), 70 (1), 57 (1), 56 (1), 43 (100), 42 (50).

Synthesis of (3S)-Methylpiperazine-2,6-dione (3b).- The reaction of 1.0 g (7.17 mmol) of **2b** with 0.99 g (7.17 mmol) of 2-bromoacetamide and 1.80 g (17.97 mmol) of $KHCO_3$, gave 0.59 g (64%) of **3b**, as a white solid, mp 149-151°C. IR: 3444, 3298, 2938, 2854, 1700, 1640 cm^{-1} (KBr). MS: m/z (%) = 128 (M^+, 12), 129 (2), 113 (2), 85 (14), 70 (3), 57 (100), 56 (50), 43 (6), 42 (19).

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 47.10; H, 6.22; N, 21.84

Synthesis of (3R)-Methylpiperazine-2,6-dione (3c).- The reaction of 1.0 g (7.17) mmol) of **2c** with 0.99 g (7.17 mmol) of 2-bromoacetamide and 1.80 g (17.93 mmol) of $KHCO_3$, gave 0.56 g (61 %) of **3c**, as a white solid, mp 149-151°C. IR: 3426, 3298, 2938, 2852, 1698, 1642 cm^{-1} (KBr). MS: m/z (%) = 128 (M^+, 16), 129 (2), 113 (3), 85 (20), 70 (4), 57 (100), 56 (50), 43 (5), 42 (21).

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 47.10; H, 6.21; N, 21.60

Synthesis of 3-Ethylpiperazine-2,6-dione (3d).- The reaction of 1.0 g (6.51 mmol) of **2d** with 0.89 g (6.51 mmol) of 2-bromoacetamide and 1.63 g (16.28 mmol) of $KHCO_3$, gave 0.51 g (55 %) of **3d**, as a white solid, mp 94-96°C. IR: 3428, 3304, 2936, 2862, 1696, 1642 cm^{-1} (KBr). MS: m/z (%): 142 (M^+, 19), 143 (2), 114 (9), 113 (29), 86 (2), 85 (25), 71(100), 70 (46), 57 (8), 56 (69), 43 (10), 42 (50).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.70. Found: C, 50.90, H, 7.01; N, 19.82

Synthesis of 3-Hexylpiperazine-2,6-dione (3e).- The reaction of 1.0 g (4.77 mmol) of **2e** with 0.66 g (4.77 mmol) of 2-bromoacetamide and 1.19 g (11.93 mmol) of $KHCO_3$, gave 0.49 g (52%) of **3e** as a white solid, mp 107-109° C. IR: 3430, 3310, 3242, 2956, 2870, 1698, 1644 cm^{-1} (KBr). MS: m/z (%)

= 198 (M^+, 8), 199 (2), 114 (11), 113 (39), 86 (2), 85 (37), 71 (8), 70 (100), 57 (55), 56 (58), 43 (18), 42 (30).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.12. Found: C, 61.0, H, 9.1; N, 14.06

Synthesis of (3S)-(2-Methylpropyl)piperazine-2,6-dione (3f).- The reaction of 1.0 g (5.51 mmol) of compound **2f** with 0.76 g (5.51 mmol) of 2-bromoacetamide and 1.38 g (13.78 mmol) of $KHCO_3$, gave 0.49 g (52%) of **3f** as a white solid, mp 116-118° C. IR (KBr, cm^{-1}) 3426, 3290, 3166, 2958, 2926, 2856 1690. MS: m/z = 170 (M^+, 5), 171 (2), 114 (17), 113 (32), 86 (2), 85 (26), 71 (1), 70 (9), 57 (21), 56 (100), 43 (11), 42 (26).

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.45. Found: C, 56.65, H, 9.81; N, 16.29

Synthesis of 4(carboxylmethyl methyl ester)piperazine-2,6-dione (3g).- The reaction of 1.0 g (5.06 mmol) of compound **2g** with 0.70 g (5.06 mmol) of 2-bromoacetamide and 1.27 g (12.65 mmol) of $KHCO_3$, gave 0.85 g (90%) of **3g**, as a white solid, mp 116-117° C. IR 3446, 3306, 3184, 2930, 2858, 1734, 1698 cm^{-1} (KBr). MS: m/z (%) = 186 (M^+, 9), 187 (1), 127 (53), 99 (16), 71 (72), 43 (13), 42 (100). *Anal.* Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.04. Found: C, 45.23; H, 5.2; N, 14.86

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