

H. Namazi* [a], Y. R. Mirzaei, and H. Azamat

[a] Lab of Carbohydrates and Biopolymers, Faculty of Chemistry, University of Tabriz, Tabriz P.O. Box 51664, Iran
Received December 14, 2000

The compounds 5-ethoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**5**) and 5-ethoxycarbonyl-1-phenyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**1**) were prepared by the Biginelli condensation method and they converted to eight N-3 substituted dihydropyrimidines using NaH and various electrophiles (ClCO₂Et, TsCl, Ac₂O, AcCl and PhCOCl). Compound (**1**) was monobrominated at the C₆-methyl group using bromine solution. Reaction of the bromo derivative with amino nucleophiles such as methyl amine and cyclohexyl amine produced two pyrrolo-pyrimidine derivatives. All the compounds except 5-ethoxycarbonyl-1-phenyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4**) were purified by recrystallization methods. The structure of all the new compounds was confirmed using FT-ir, ¹H nmr, ¹³C nmr spectral and elemental analyses methods.

J. Heterocyclic Chem., **38**, 1051 (2001).

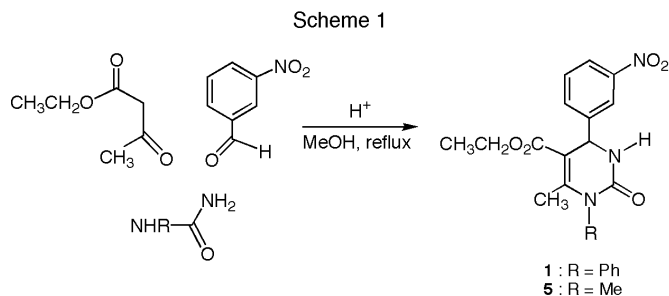
Introduction.

The first dihydropyrimidin (DHPM) compound was synthesized by Biginelli [1] in a one-pot condensation reaction from an aromatic aldehyde, ethyl acetoacetate and urea. Later this method was modified with applying acidic catalyst [2]. Because of the lower yields in these reactions, recently Atwal and coworkers [3,4] modified the condensation method. However, the Atwal modification is carried out in a two-pot process. Synthesis of this type compounds, which are known as Biginelli compounds [5], using solid phase and also with fluoros methods have been reported [6,7,8]. The DHPM derivatives show a diverse range of biological activities [4,5]. Before 1930, their derivatives have been applied for protecting wool against moths [5]. Some acted as antiviral agents against viruses of the trachoma group, and some as antibacterial or antitumor agents [5, 9,10]. An interesting characteristic of dihydropyrimidin compounds similar to the dihydropyridines (*e.g.*, Nifedipine) are calcium channel blockers and antihypertensive [10]. These compounds play the role of important media and tools in the field of cardiovascular medicine to survey the structure and function of calcium channel [11]. The existence of substitution especially carbonyl groups on the position N-3 lead to an increase in their stability and biological activity [12]. In order to examine the chemical reactivity of N-3, C-5 and C₆-methyl positions preparation of some new derivatives are reported here.

Results and Discussion.

In order to evaluate the chemical reactivity of N-3, C-5 and C₆-methyl the prerequisite DHPM compounds were prepared by means of Biginelli condensation using acidic catalyzed method. First, DHPMs having substitution on position N-1 using *N*-phenyl urea and *N*-methyl urea were prepared and the reaction route is shown in Scheme 1. In

another reaction urea and 4-isopropyl benzaldehyde are used to synthesize 5-ethoxycarbonyl-4-(4-isopropyl phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**10**). The yield of the reaction is maximized when the methanol was used and refluxed for 4-6 hours rather than using ethanol at 40 °C. This reaction has the advantages of producing precursor compounds in one-pot process with relatively high yields.

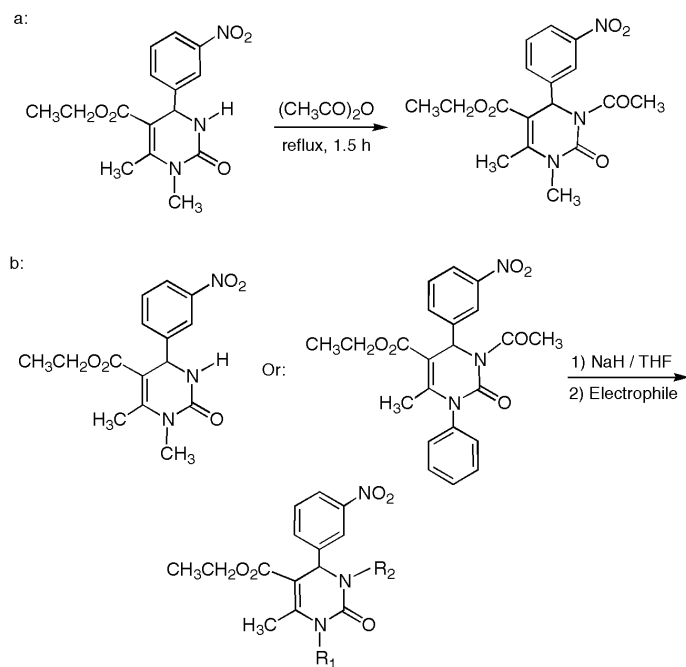


Different electrophiles such as CH₃COCl, (CH₃CO)₂O, TsCl, ClCO₂Et and PhCOCl were used to generate substituents *via* reaction at the N-3 position. For example, in the preparation of compound **5** acetic anhydride was used as the electrophile generating an acetyl group at the N-3 position (Scheme 2a). In other reactions, the N3-H proton was removed using NaH as a base and then was treated with electrophiles under argon atmosphere at -15 to -20 °C (Scheme 2b) [13-18].

In the IR spectrum the peak related to the N3-H stretching vibration in 3375 cm⁻¹ is not observed, which indicates that the substituent is at N3 position. The ¹H nmr spectra also support the substitution at the N3 position for all of these compounds.

The reactivity of the C-5 and C₆-methyl positions has also been examined. First, the methyl group on compound

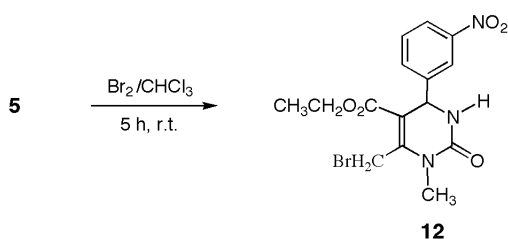
Scheme 2



Compound	2	3	4	7	8	9	11
R_1	Ph	Ph	Ph	Me	Me	Me	Ph
R_2	COCH_3	COPh	Ts	Ts	CO_2Et	COPh	CO_2Et

5 was brominated using bromine solution in chloroform to yield the bromomethyl pyrimidine (**12**) (Scheme 3). For monobromination, one equivalent of bromine was reacted with compound **5** [19,20,21].

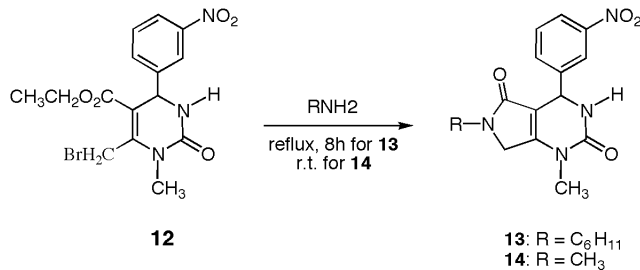
Scheme 3



The 6-bromomethyl pyrimidine **12** was converted to the pyrrolo[3,4-*d*]pyrimidones **13** and **14** by treatment with primary amines (Scheme 4). The omission of signals related to the ethyl group in the ^1H and ^{13}C NMR spectrum and also elemental analysis confirm the formation of compounds **13** and **14**. The yield of the reaction resulting in compound **14** was 35% higher than that of compound **13**. Presumably due to the fact that methyl amine is a much less bulky nucleophile than cyclohexyl amine. All synthesized compounds were purified by recrystallization in ethanol or a mixture of

ethanol and ethyl acetate. In the case of compound **4** column chromatography was applied for purification.

Scheme 4



EXPERIMENTAL

All the melting points were measured in open capillary tubes using Electrothermal 9100 apparatus and are uncorrected. The R_f of new compounds were carried out in ethylacetate and petroleum ether (3:2, v/v). IR spectra were obtained on a Shimadzu spectrophotometer. The ^1H nmr and ^{13}C nmr spectra were recorded on a GE NMR QE 300 MHz FT-NMR or Bruker FT-NMR 400 MHz and determined in deuteriochloroform and chemical shifts are expressed in ppm relative to internal Me_4Si . Microanalysis was performed on a Perkin Elmer C.H.N. Analyzer. Chemicals were purchased from the Aldrich (UK) or Merck Chemical Co. Ltd (Germany). The *N*-Phenyl urea was prepared by literature procedure [21].

5-Ethoxycarbonyl-1-phenyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**1**).

A mixture of *N*-phenyl urea (1.36 g, 0.01 mole), 3-nitrobenzaldehyde (1.51 g, 0.01 mole), ethylacetoacetate (1.3 ml, 0.01 mole) and 15 ml of methanol containing 4 drops of concentrated hydrochloric acid was refluxed for 6 hour. The solution was allowed to stand at 0 °C for 4 hours and the resulting precipitate was recrystallized from ethanol to give compound **1**, yield, 1.96 g (52%), mp 168 °C (ethanol); ir (potassium bromide): 3375, 3080, 1710, 1680, 1530 and 1340 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.0 (t, $J = 7$ Hz, 3H); 2.0 (s, 3H); 4.2 (q, $J = 7$ Hz, 2H); 5.4 (d, $J = 3$ Hz, 1H); 6.7 (s, 1H); 7.3 (m, 8H); 8.1 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 165.0, 153.3, 150.0, 148.7, 145.6, 137.4, 32.4, 130.0, 128.7, 122.6, 121.5, 103.9, 60.43, 53.3, 18.3 and 14.3.

3-Acetyl-5-ethoxycarbonyl-1-phenyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**2**).

To a solution of **1** (1.14 g, 0.003 mole) in 12 ml dry THF, sodium hydride 60% (0.14 g, 0.035 mole) was added and the mixture was then stirred for 30 minutes at -20 °C under argon. Then, to the resulting mixture, acetyl chloride (0.25 ml, 0.033 mole) was added and stirred for 2 hours at room temperature. After extraction with ether and water the precipitate was recrystallized in ethanol (20 ml) and ethylacetate (2 ml) to yield, 0.27 g (21%) of compound **2**, $\text{R}_f = 0.51$; mp 169 °C (ethanol); ir (potassium bromide) 3100, 1710, 1680, 1530 and 1340 cm^{-1} ; ^1H nmr (deuteriochloroform, 400 MHz): δ 1.2 (t, $J = 7$ Hz, 3H); 2.1 (m, 6H); 4.2 (q, $J = 7$ Hz, 2H); 5.6 (s, 1H) and 7.1- 8.4 (m, 9H); ^{13}C nmr (deuteriochloroform, 400 MHz): δ 165.8, 153.6, 150.5,

148.8, 145.9, 137.5, 132.8, 130.0, 129.7, 129.0, 123.1, 122.0, 104.2, 60.9, 53.7, 31.2, 18.8 and 14.5.

Anal. Calcd. for C₂₂H₂₁N₃O₆: C, 62.41; H, 5.00; N, 9.92. Found: C, 62.82; H, 5.13; N, 9.97.

3-Benzoyl-5-ethoxycarbonyl-1-phenyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**3**).

This compound was prepared according to the procedure described for compound **2**, using benzoyl chloride (0.35 ml, 0.035 mole) instead of acetyl chloride. The yield of **3** was 0.77 g (53%), colorless, R_f = 0.88; mp 197 °C (ethanol); ir (Chloroform) 3075, 1698, 1637, 1536 and 1340 cm⁻¹; ¹H nmr (deuteriochloroform, 300 MHz): δ 1.3 (t, J = 7 Hz, 3H); 2.3 (s, 3H); 4.3 (q, J = 7 Hz, 2H); 6.6 (s, 1H) and 7.0-8.4 (m, 14H); ¹³C nmr (deuteriochloroform, 300 MHz): δ 171.3, 164.7, 151.3, 149.9, 148.4, 141.3, 136.2, 136.1, 134.9, 132.0, 129.5, 129.1, 128.7, 127.9, 122.1, 121.8, 109.0, 61.1, 53.6, 18.3 and 14.1.

Anal. Calcd. for C₂₇H₂₃N₃O₆: C, 66.80; H, 4.78; N, 8.66. Found: C, 66.48; H, 4.79; N, 8.73.

3-Tosyl-5-ethoxycarbonyl-1-phenyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**4**).

To the solution of **1** (1.14 g, 0.003 mole) in 15 ml dry THF, sodium hydride 60% (0.14 g, 0.035 mole) was added and stirred for 20 minutes at -15 °C then *p*-toluenesulfonyl chloride (0.57 g, 0.003 mole) was added and mixture was stirred for 1 hour at room temperature. The product was purified by column chromatography on silicagel 100 with dichloromethane/ethylacetate (100:4, v/v) and then was recrystallized in ethanol to yield, 0.91 g (57%), of colorless crystals, R_f = 0.86; mp 177 °C (ethanol); ir (chloroform) 3087, 1703, 1638, 1531 and 1353 cm⁻¹; ¹H nmr (deuteriochloroform, 300 MHz): δ 1.3 (t, J = 7 Hz, 3H); 2.1 (s, 3H); 2.3 (s, 3H); 4.3 (q, J = 7 Hz, 2H); 6.7 (s, 1H) and 7.0-8.3 (m, 13H); ¹³C nmr (deuteriochloroform, 300 MHz): δ 164.0, 153.0, 149.0, 148.0, 145.0, 141.0, 136.8, 133.1, 129.7, 129.4, 129.1, 128.9, 123.1, 121.6, 108.4, 61.0, 54.3, 21.0, 18.1 and 14.2.

Anal. Calcd. for C₂₇H₂₅N₃O₇S: C, 60.55; H, 4.70; N, 8.66. Found: C, 60.32; H, 4.69; N, 8.73.

5-Ethoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**5**).

This compound was obtained in an analogous way to compound **1** starting from *N*-methyl urea and refluxing for 4 hour. The yield of **5** was 1.90 g (59.5%), colorless crystals, R_f = 0.29; mp 148 °C; ir (potassium bromide) 3250, 1710, 1670, 1525 and 1340 cm⁻¹.

3-Acetyl-5-ethoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**6**).

A solution of compound **5** (0.96 g, 0.003 mole) in acetic anhydride was heated under reflux for 1.5 hour. The solution was cooled to the room temperature and a precipitate was formed that was recrystallized in ethanol to yield, 0.49 g (45%), compound **6** as colorless crystals, R_f = 0.62; mp 149 °C (ethanol); ir (chloroform) 3083, 1698, 1637, 1531 and 1347 cm⁻¹; ¹H nmr (deuteriochloroform, 300 MHz): δ 1.2 (t, J = 7 Hz, 3H); 2.5 (s, 3H); 2.6 (s, 3H); 3.2 (s, 3H); 4.2 (q, J = 7 Hz, 2H); 6.7 (s, 1H) and 7.4-8.2 (m, 4H); ¹³C nmr (deuteriochloroform, 300 MHz): δ 171.7, 164.7, 152.0, 149.7, 148.4, 141.3, 133.7, 129.6, 122.9, 121.4, 107.9, 61.0, 50.7, 31.3, 25.8, 16.1 and 14.1.

Anal. Calcd. for C₁₇H₁₉N₃O₆: C, 56.51; H, 5.30; N, 11.63. Found: C, 56.51; H, 5.29; N, 11.84.

3-Tosyl-5-ethoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**7**).

This compound was prepared according to the procedure described for compound **4**, starting with 5-ethoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**5**) instead of compound **1**. The yield of **7** was 0.83 g (58.5%), colorless, R_f = 0.68; mp 186 °C (ethanol); ir (chloroform) 3076, 1697, 1635, 1532 and 1351 cm⁻¹; ¹H nmr (deuteriochloroform, 300 MHz): δ 1.3 (t, J = 7 Hz, 3H); 2.3 (s, 3H); 2.5 (s, 3H); 3.1 (s, 3H); 4.2 (q, J = 7 Hz, 2H); 6.6 (s, 1H) and 7.1-8.2 (m, 8H); ¹³C nmr (deuteriochloroform, 300 MHz): δ 64.4, 149.9, 149.4, 148.2, 145.1, 141.7, 135.2, 132.6, 129.6, 128.9, 123.0, 121.6, 107.2, 61.0, 55.5, 31.0, 21.5, 16.2 and 14.1.

Anal. Calcd. for C₂₂H₂₃N₃O₇S: C, 55.81; H, 4.90; N, 8.87. Found: C, 56.04; H, 4.98; N, 8.89.

3,5-Diethoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**8**).

Compound **8** was prepared according to the procedure described above for **2** starting from **5** and using ethylchloroformate (0.34 ml, 0.035 mole). The yield of **8** was 0.61 g (51%), pale yellow crystals, R_f = 0.50; mp 128 °C (ethanol); ir (chloroform) 3085, 1716, 1637, 1531 and 1355 cm⁻¹; ¹H nmr (deuteriochloroform, 300 MHz): δ 1.3 (t, J = 7 Hz, 3H); 1.4 (t, J = 7 Hz, 3H); 2.6 (s, 3H); 3.2 (s, 3H); 4.3 (q, J = 7 Hz, 2H); 4.4 (q, J = 7 Hz, 2H); 6.4 (s, 1H) and 7.3-8.2 (m, 4H); ¹³C nmr (deuteriochloroform 300 MHz): δ 164.7, 153.5, 150.0, 149.8, 148.6, 141.4, 132.4, 129.5, 123.2, 121.5, 107.8, 60.9, 53.7, 31.2, 16.2 and 14.1.

Anal. Calcd. for C₁₈H₂₁N₃O₇: C, 55.24; H, 5.41; N, 10.74. Found: C, 55.30; H, 5.50; N, 10.81.

3-Benzoyl-5-ethoxycarbonyl-1,6-dimethyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**9**).

Compound **9** was obtained in an analogous way as **3** starting from **5** instead of **1**. The yield of **9** was 1.00 g (78%), pale yellow crystals, R_f = 0.69; mp 181 °C (ethanol); ir (chloroform) 3077, 1691, 1635, 1529 and 1342 cm⁻¹; ¹H nmr (deuteriochloroform, 300 MHz): δ: 1.3 (t, J = 7 Hz, 3H); 2.6 (s, 3H); 3.1 (s, 3H); 4.2 (q, J = 7 Hz, 2H); 6.4 (s, 1H) and 7.2-8.2 (m, 9H); ¹³C nmr (deuteriochloroform, 300 MHz): δ 171.3, 164.7, 152.0, 149.9, 148.3, 144.1, 141.1, 134.9, 131.8, 129.6, 128.1, 123.7, 121.6, 108.6, 61.0, 53.1, 31.2, 16.4 and 14.1.

Anal. Calcd. for C₂₂H₂₁N₃O₆: C, 62.41; H, 5.00; N, 9.92. Found: C, 62.41; H, 5.01; N, 9.96.

5-Ethoxycarbonyl-4-(4-isopropylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**10**).

This compound was obtained in an analogous way from **1** starting from urea and 4-isopropyl benzaldehyde. The yield of **10** was 0.80 g (26.5%), colorless crystals, R_f = 0.40; mp 162 °C (ethanol); ir (chloroform) 3235, 3110, 1702 and 1644 cm⁻¹; ¹H nmr (deuteriochloroform, 300 MHz): δ 1.2 (m, 9H); 2.3 (s, 3H); 2.8 (hep., J = 7 Hz, 1H); 4 (q, J = 7 Hz, 2H); 5.3 (d, J = 3 Hz, 1H); 6.1 (s, 1H); 7.2 (m, 4H) and 8.7 (m, 1H); ¹³C nmr (deuteriochloroform 300 MHz): δ 165.7, 153.9, 148.4, 146.3, 141.1, 126.4, 101.4, 59.9, 55.2, 33.7, 23.8, 18.5 and 14.1.

Anal. Calcd. for C₁₇H₂₂N₂O₃: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.62; H, 7.39; N, 9.28.

3,5-Diethoxycarbonyl-1-phenyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**11**).

Compound **11** was prepared according to the procedure described above for **8**, starting with **1**. The crystals thus obtained were recrystallized in ethanol/ethylacetate (10:1, v/v) to yield 0.74 g (54.4%), yellow crystals, $R_f = 0.78$; mp 119 °C (ethanol); ir (potassium bromide) 3070, 1720, 1641, 1529 and 1340 cm^{-1} ; ^1H nmr (deuteriochloroform, 300 MHz): δ 1.2 (t, $J = 7$ Hz, 3H); 1.3 (t, $J = 7$ Hz, 3H); 2.2 (s, 3H); 4.2 (q, $J = 7$ Hz, 2H); 4.4 (q, $J = 7$ Hz, 2H); 6.6 (s, 1H) and 7.2-8.4 (m, 9H); ^{13}C nmr (deuteriochloroform, 300 MHz): δ 164.0, 153.0, 151.0, 150.0, 149.0, 141.0, 136.8, 133.1, 129.7, 129.4, 128.9, 123.1, 121.6, 108.4, 61.0, 54.3, 18.1 and 14.2.

Anal. Calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_7$: C, 60.92; H, 5.11; N, 9.27. Found: C, 61.01; H, 5.15; N, 9.36.

6-Bromomethyl-5-ethoxycarbonyl-1-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**12**).

To the solution of compound **5** (3.19 g, 0.01 mole) in chloroform (20 ml) was added at ambient temperature a solution of bromine (0.52 ml, 0.01 mole) in chloroform (12 ml) dropwise and the resulting solution was stirred for 4 hour. The resulting mixture was treated with a solution of sodium hydrogen carbonate (50 ml, 0.12 M) followed by isopropyl alcohol. Recrystallization in ethanol with 2% ethyl acetate and compound **12** was obtained, yield 3.25 g (84%), pale yellow crystals, $R_f = 0.37$; mp 168 °C (ethanol); ir (potassium bromide) 3200, 3100, 1710, 1610, 1530 and 1340 cm^{-1} ; ^1H nmr (deuteriochloroform, 400 MHz): δ 0.5 (t, $J = 7$ Hz, 3H); 2.6 (s, 3H); 3.0 (s, 2H); 3.4 (q, $J = 7$ Hz, 2H); 4.8 (d, $J = 3$ Hz, 1H); 6.4 (s, 1H) and 6.8-7.4 (m, 4H); ^{13}C nmr (deuteriochloroform, 300 MHz): δ 163.9, 153.5, 148.1, 148.0, 144.2, 131.7, 129.5, 122.6, 121.3, 104.5, 60.8, 52.8, 28.9, 23.3 and 13.6.

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_5\text{Br}$: C, 45.24; H, 4.05; N, 10.55. Found: C, 45.04; H, 4.16; N, 10.47.

6-Cyclohexyl-1-methyl-4-(3-nitrophenyl)-3,4,6,7-tetrahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,5(1*H*)-dione (**13**).

Compound **12** (1.19 g, 0.003 mole) was treated with cyclohexylamine (0.29 ml, 0.0035 mole) and was heated under reflux for 8 hour. The obtained precipitate was filtered, washed with a solution of sodium hydrogen carbonate (20 ml, 0.1 M) and the crystals thus obtained were recrystallized in ethanol/petroleum ether (1:1, v/v) to yield 0.4 g (36%), pale yellow crystals, $R_f = 0.12$; mp 211 °C (ethanol); ir (potassium bromide) 3250, 3100, 1710, 1610, 1530 and 1300 cm^{-1} ; ^1H nmr (deuteriochloroform, 400 MHz): δ 1.3 (m, 6H); 1.7 (m, 4H); 2.1 (s, 1H); 3.1 (s, 3H); 4.0 (s, 2H); 5.6 (s, 1H); 6.2 (s, 1H) and 7.5-8.3 (m, 4H); ^{13}C nmr (deuteriochloroform, 300 MHz): δ 168.1, 152.9, 150.7, 148.9, 144.3, 133.5, 130.0, 123.4, 121.9, 105.2, 54.1, 50.5, 44.3, 31.9, 30.0, 25.9 and 25.8.

Anal. Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_4$: C, 61.61; H, 5.99; N, 15.31. Found: C, 61.27; H, 6.23; N, 14.27.

1,6-Dimethyl-4-(3-nitrophenyl)-3,4,6,7-tetrahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,5(1*H*)-dione (**14**).

Compound **14** was obtained in an analogous way as **13** by using 35% solution of methylamine. The yield of **14** was 0.48 g (53%), yellow crystals, $R_f = 0.27$; mp 249 °C (ethanol); ir (potas-

sium bromide) 3250, 3100, 1700, 1640, 1520 and 1340 cm^{-1} ; ^1H nmr (deuteriochloroform, 400 MHz): δ 2.2 (s, 3H); 3.2 (s, 3H); 2.1 (s, 1H); 4.1 (s, 2H); 5.6 (s, 1H); 6.0 (s, 1H) and 7.4-8.4 (m, 4H); ^{13}C nmr (deuteriochloroform 300 MHz): δ 168.0, 152.7, 150.4, 148.0, 144.2, 133.4, 130.0, 123.6, 121.9, 105.0, 54.3, 49.8, 30.1 and 29.2.

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.52; H, 4.73; N, 18.42.

Acknowledgments.

The authors are grateful to the members of graduate studies committee and research council of Tabriz University for the financial support.

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* Correspondence to: H. Namazi, E-mail: hnamazi2001@yahoo.com

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