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SYNTHESIS AND PROPERTIES OF (6-METHYL-2-OXO-4-THIOXO-1,2,3,4-TETRAHYDRO-3-PYRIMIDINYL)ACETIC ACID METHYL ESTER

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On interacting of the methyl ester of (6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetic acid with the Lawesson's reagent the corresponding 4-thioxo derivative is synthesized. Its alkylation with methyl bromoacetate has been studied as has its interaction with N-nucleophiles, amines, and hydrazines.

Keywords: 3-alkylated 4-amino-substituted 2-pyrimidinones, 3-substituted 2-oxo-4-thioxo-1,2,3,4-tetrahydropyrimidines, pyrimido[6,1-*c*][1,2,4]triazine-3,6-diones, alkylation, thionation.

We previously reported the synthesis and study of the properties of 3-substituted pyrimidine-2,4-diones [1-3]. Thioxo derivatives of these compounds are as yet unknown, although the introduction of a sulfur atom at positions 2 or 4 of a pyrimidine ring should broaden the possibility of functionalizing these positions. On the other hand there are literature data on the biological activity of 4-pyrimidine-thiones [4,5].

The aim of the present investigation is to develop a procedure for converting the readily synthesized methyl ester of (6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetic acid (**1**) [6] into the corresponding 4-thioxo derivative **2** and to study its reaction with C-electrophile, such as methyl bromoacetate, and N-nucleophiles, amines, and hydrazines.

We chose the Lawesson's reagent, used widely in thionation reactions [7-9], particularly 3-alkyluracils [4, 10, 11], for the conversion of an oxo group into a thioxo group. On interacting methyl ester **1** with Lawesson's reagent in absolute toluene only the $C_{(4)}$=O group is thionated and compound **2** is formed. It was established that the yield depends not only on the molar ratio of compound **1** and Lawesson's reagent but also on the reaction duration. Compound **2** was obtained in the best yield at a molar ratio of compound **1** to Lawesson's reagent of 1 : 0.7 and boiling the reaction mixture for 2 h. At an equimolar reactant ratio and an increase in reaction time to 6 h no increased yield occurred. In all cases we isolated only the thionation product of one oxo group, i.e. compound **2**. In the IR spectrum of compound **2** there was no absorption band for $C_{(4)}$=O at 1634 cm^{-1}, characteristic for compound **1**, and in the ^{1}H NMR spectrum of compound **2** the signal of the proton at position 5 is displaced towards low field relative to the analogous signal of compound **1**, and is observed at 6.56 ppm (for **1** 5.65 ppm), which makes it possible to confirm that thionation occurred just at position 4 of the pyrimidine ring. In the ^{13}C NMR spectrum of compound **2** the signal of C-5 is also displaced by 14 ppm towards low field relative to the analogous signal of compound **1**, which confirms the structure of the thionation product.

On alkylating compound **2** with methyl bromoacetate we isolated only the product of S-alkylation, i.e. compound **3**, the yield of which depended on the reaction conditions. Stirring a solution of the components in

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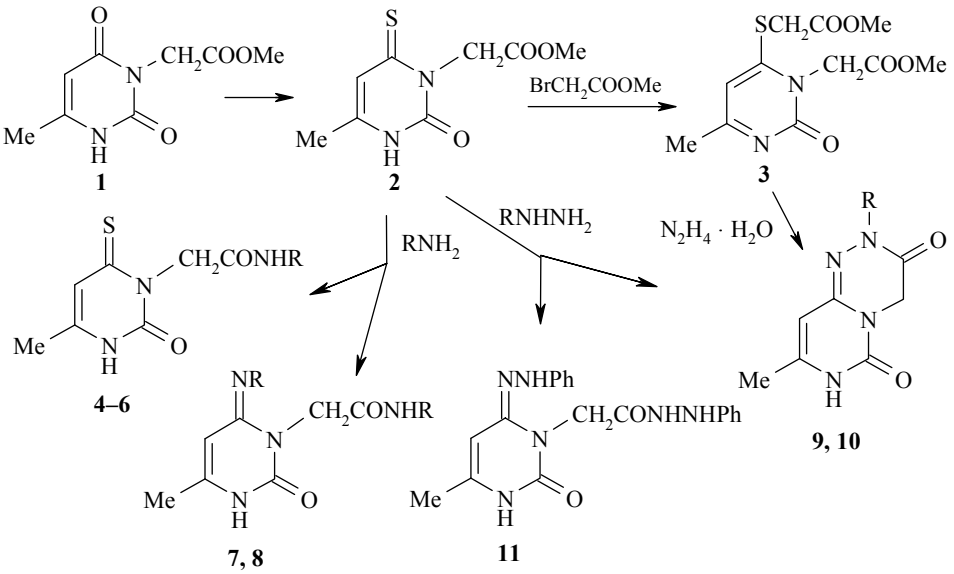
methanol in the presence of triethylamine at 35°C for 10 h led to the formation of ester **3** in 50% yield, however its isolation was hindered by the presence of triethylamine hydrobromide. Increasing the yield of compound **3** to 67% succeeded on carrying out the reaction in acetone in the presence of potassium carbonate.

It is known that 2-N-alkylamino-substituted pyrimidin-4-ones possess anti-inflammatory activity [12]. We studied the reaction of thione **2** with primary alkylamines, with hydrazine hydrate, and also with ethyl- and phenylhydrazines. Attempts to carry out the reaction of compound **2** with amines in methanol and dimethylformamide at room temperature or on boiling were not crowned with success. Subsequently the reaction of compound **2** with amines was carried out without solvent. Variation of the conditions of carrying out reactions of compound **2** with primary amines (temperature, time, and reactant ratio) enabled us to establish that the optimum ratio for the reactants **2** : amine is 1 : 3, temperature 50°C (R = Bu, Bn) or 80°C (R = *cyclo*-C_6H_{11}), and time 16 (R = Bu), 32 (R = cyclo-C_6H_{11}), or 24 h (R = Bn). As a result the yields of compounds **4-6** were 75, 69, and 75% respectively. On increasing the temperature to 135-140°C or increasing the reaction time the yields of the desired products were reduced and formed mixtures of compounds (for example **5** and **8**) or heavy resinification was observed. Reactions of compound **2** with hydrazines were carried out in methanol. Interaction of a fourfold excess of hydrazine hydrate with thione **2** for 6 h at room temperature led to the formation of pyrimido[6,1-*c*][1,2,4]triazine-3,6-dione (**9**) in high yield, which was successfully obtained after 0.5 h under the same conditions from diester **3**.



4, 7 R = *n*-Bu; **5, 8** R = *cyclo*-C_6H_{11}; **6** R = Bn; **9** R = H; **10** R = Et

Compound **2** reacts with ethyl- and phenylhydrazines with significantly more difficulty. The corresponding cyclization product **10** or the acyclic substitution product **11** were formed only on boiling compound **2** for 13 h with ethyl- or phenylhydrazine.

The structures of compounds **2-11** were confirmed by data of elemental analysis, IR, and ^{1}H and ^{13}C NMR spectra. We note that the evidence of the presence of the C=S group in compounds **2**, **4-6** is the presence in the ^{13}C NMR spectrum of a signal at 190.6-190.7 ppm, characteristic of precisely this group, while assignment of a particular absorption band to the C=S group in the IR spectrum is difficult.

Functionalization of position 4 of a 3-substituted 2,4-pyrimidinedione is therefore completely possible by the interaction of the corresponding 4-thioxo derivative both with N-nucleophiles and with electrophiles.

EXPERIMENTAL

A check on the progress of reactions and on the purity of compounds was effected on Alugram SIL G/UV 254 plates. The ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova instrument (300 and 75 MHz respectively) in $CDCl_3$ (compounds **1-3**) or DMSO-d_6 (compounds **4-11**), internal standard was TMS. The IR spectra were taken on a Perkin-Elmer Bx FT-IR spectrometer in KBr disks.

(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetic Acid Methyl Ester 1 was synthesized by the procedure of [6]. ^{13}C NMR spectrum, δ, ppm: 19.0 (CH_3); 41.3 (NCH_2); 52.7 (OCH_3); 100.3 (C-5); 151.1 (C-6); 153.2 (C-2); 162.9 (C-4); 168.6 (C=O).

(6-Methyl-2-oxo-4-thioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetic Acid Methyl Ester (2). Lawesson's reagent (2.83 g, 7 mmol) was added to a solution of compound **1** (1.98 g, 10 mmol) in absolute toluene (15 ml). The reaction mixture was boiled for 2 h and filtered hot. The filtrate was cooled to room temperature, and after 2 h the precipitated solid was filtered off, washed with toluene, dried, and recrystallized from water. Yield 1.72 g (80%); mp 159-160°C. IR spectrum, ν, cm^{-1}: 1694, 1753 (C=O). 3086 (NH). ^1H NMR spectrum, δ, ppm: 2.15 (3H, s, CH_3); 3.81 (3H, s, OCH_3); 5.25 (2H, s, NCH_2); 6.56 (1H, s, CH); 10.78 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 18.5 (CH_3); 47.4 (NCH_2); 52.9 (OCH_3); 114.3 (C-5); 145.1 (C-6); 151.2 (C-2); 167.9 (C=O); 190.6 (C=S). Found, %: C 45.28; H 4.70; N 13.25. $C_8H_{10}N_2O_3S$. Calculated, %: C 44.85; H 4.70; N 13.08.

(3-Methoxycarbonylmethyl-6-methyl-2-oxo-2,3-dihydro-4-pyrimidinylthio)acetic Acid (3). Methyl bromoacetate (0.84 g, 0.51 ml, 5.5 mmol) was added dropwise to a suspension of compound **2** (1.07 g, 5 mmol) and K_2CO_3 (0.69 g, 5 mmol) in acetone (15 ml). The reaction mixture was stirred at room temperature for 3 h, heated to boiling, and filtered hot. The filtrate was evaporated to half volume and cooled. The precipitated solid was filtered off, washed with acetone, and recrystallized from 2-propanol. Yield 0.96 g (67%); mp 137-138°C. IR spectrum, ν, cm^{-1}: 1664, 1734, 1760 (C=O). ^1H NMR spectrum, δ, ppm: 2.38 (3H, s, CH_3); 3.79 (3H, s, OCH_3); 3.82 (2H, s, SCH_2); 3.83 (3H, s, OCH_3); 4.93 (2H, s, NCH_2); 6.13 (1H, s, CH). ^{13}C NMR spectrum: 25.9 (CH_3); 35.0 (SCH_2); 47.3 (NCH_2); 53.1, 53.7 ($2OCH_3$); 102.3 (C-5); 156.3 (C-6); 159.3 (C-4); 167.3, 167.4 (2C=O); 174.4 (C-2). Found, %: C 46.58; H 4.80; N 9.47. $C_{11}H_{14}N_2O_5S$. Calculated, %: C 46.15; H 4.93; N 9.78.

Synthesis of Acetamides 4-6 (General Method). A mixture of compound **2** (0.43 g, 2 mmol) and the appropriate amine (6 mmol) was stirred in an atmosphere of argon at 50°C (R = Bu, 16 h; R = Bn, 24 h) or 80°C (R = cyclo-C_6H_{11}, 32 h), until disappearance of thione 2 from the reaction mixture (according to TLC). The mixture was cooled to room temperature, triturated with water (5 ml), the mixture was acidified with HCl to pH 2, the precipitate filtered off, washed with water, and recrystallized from methanol–water.

N-Butyl(6-methyl-2-oxo-4-thioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetamide (4). Mp 208-210°C. IR spectrum, ν, cm^{-1}: 1662, 1729 (C=O); 3092, 3448 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, J = 7.1, CH_3); 1.20-1.45 (4H, m, $2CH_2$); 2.06 (3H, s, CH_3); 3.05 (2H, q, J = 5.8, $NHC\underline{H}_2$); 4.92 (2H, s, NCH_2); 6.42 (1H, s, CH); 8.01 (1H, t, J = 5.8, $N\underline{H}CH_2$); 11.86 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 14.4, 18.3 ($2CH_3$); 20.2, 31.9, 38.9 ($3CH_2$); 48.7 (NCH_2); 112.5 (C-5); 147.9 (C-6); 150.2 (C-2); 166.1 (C=O); 190.7 (C=S). Found, %: C 52.07; H 6.41; N 16.15. $C_{11}H_{17}N_3O_2S$. Calculated, %: C 51.74; H 6.71; N 16.46.

N-Cyclohexyl(6-methyl-2-oxo-4-thioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetamide (5). Mp 226-228°C. IR spectrum, ν, cm^{-1}: 1657, 1702 (C=O); 3095, 3280 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.05-1.35 (6H, m, $3CH_2$); 1.5-1.8 (4H, m, $2CH_2$); 2.06 (3H, s, CH_3); 4.91 (2H, s, NCH_2); 6.41 (1H, s, CH); 7.93 (1H, d, J = 8, NH); 11.8 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 18.3 (CH_3); 25.2, 25.9, 33.1 ($3CH_2$); 48.4 (NHCH), 48.6 (NCH_2); 112.4 (C-5); 147.9 (C-6); 150.2 (C-2); 165.2 (C=O); 190.7 (C=S). Found, %: C 55.07; H 7.13; N 14.60. $C_{13}H_{19}N_3O_2S$. Calculated, %: C 55.49; H 6.81; N 14.93.

N-Benzyl(6-methyl-2-oxo-4-thioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetamide (6). Mp 238-240°C. IR spectrum, ν, cm^{-1}: 1655, 1709 (C=O); 3259, 3442 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.07 (3H, s, CH_3); 4.31 (2H, d, J = 5.8, CH_2); 5.02 (2H, s, NCH_2); 6.45 (1H, s, CH); 7.19-7.42 (5H, m, C_6H_5); 8.59 (1H, t, J = 5.3,

N<u>H</u>CH_2); 11.84 (1H, br s, NH). ^{13}C NMR spectrum, δ, ppm: 18.3 (CH_3); 42.7, 48.8 (2NCH_2); 112.5 (C-5); 127.5, 127.8, 128.9, 139.9 (C_6H_5); 148.1 (C-6); 150.3 (C-2); 166.6 (C=O); 190.7 (C=S). Found, %: C 58.27; H 5.34; N 14.24. $C_{14}H_{15}N_3O_2S$. Calculated, %: C 58.11; H 5.23; N 14.52.

N-Cyclohexyl(6-methyl-2-oxo-4-thioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetamide (5) and N-Cyclohexyl(6-methyl-4-cyclohexylamino-2-oxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetamide (8). A mixture of compound **2** (0.43 g, 2 mmol) and cyclohexylamine (0.6 g, 0.69 ml, 6 mmole) was heated on a sand bath at 130-140°C in an argon atmosphere for 3.5 h. The reaction mixture was cooled to room temperature and triturated with a mixture (5 ml) of methanol–water, 1 : 1. The solid was filtered off, washed with methanol, and recrystallized from methanol. Compound **8** (0.27 g, 39%) was obtained. Mp 240-242°C. IR spectrum, ν, cm^{-1}: 1641, 1681 (C=O), 3211, 3283 (NH). ^{1}H NMR spectrum, δ, ppm: 1.1-1.69 (20H, m, 10CH_2); 1.97 (3H, s, CH_3); 4.36 (2H, s, NCH_2); 5.58 (1H, s, CH); 7.7 (1H, s, NH); 10.15 (1H, s, NH). Found, %: C 66.24; H 8.77; N 16.45. $C_{19}H_{30}N_4O_2$. Calculated, %: C 65.87; H 8.73; N 16.17.

Adding methanol (2 ml) to the obtained filtrate precipitated compound **5** (0.21 g, 38%).

N-Butyl(4-butylimino-6-methyl-2-oxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-acetamide (7). A mixture of compound **2** (0.43 g, 2 mmol) and butylamine (11 or 20 mmol) was boiled in an argon atmosphere for 6 or 13 h respectively. The reaction mixture was cooled to room temperature, the precipitated solid filtered off, washed with water, and recrystallized from methanol–water. The yield of compound **7** was 36 or 27% respectively. Mp 172-174°C. IR spectrum, ν, cm^{-1}: 1664, 1702 (C=O); 3097, 3302 (NH). ^{1}H NMR spectrum, δ, ppm: 0.9-0.95 (6H, m, 2CH_3); 1.3-1.4 (8H, m, 4CH_2); 1.99 (3H, s, CH_3); 3.03-3.09 (4H, m, 2NHC<u>H</u>$_2$); 4.4 (2H, s, NCH_2); 5.58 (1H, s, CH); 7.83 (1H, br. s, NH); 10.23 (1H, br. s, NH). Found, %: C 61.28; H 9.03; N 19.32. $C_{15}H_{26}N_4O_2$. Calculated, %: C 61.20; H 8.90; N 19.03.

8-Methyl-3,4,6,7-tetrahydro-2H-pyrimido[6,1-*c*][1,2,4]triazine-3,6-dione (9). Hydrazine hydrate (0.4 g, 0.39 ml: 8 mmol) was added to a solution of compound **2** or **3** (2 mmol) in absolute methanol (3 ml), and the mixture was stirred at room temperature for 6 or 0.5 h respectively. The precipitated solid was filtered off, washed with water, and recrystallized from DMSO–water. The yield of compound **9** was 67 or 63% respectively. Mp >300°C. IR spectrum, ν, cm^{-1}: 1678, 1698 (C=O); 3078, 3203 (NH). ^{1}H NMR spectrum, δ, ppm: 1.89 (3H, s, CH_3); 4.11 (2H, s, NCH_2); 5.33 (1H, s, CH); 10.26, 10.45 (2H, 2s, 2NH). ^{13}C NMR spectrum, δ, ppm: 18.4 (CH_3); 43.5 (NCH_2); 96.4 (C-9); 139.7 (C-8); 142.4 (C-10); 150.5 (C-6); 160.1 (C-3). Found, %: C 46.68; H 4.34; N 31.01. $C_7H_8N_4O_2$. Calculated, %: C 46.67; H 4.48; N 31.10.

2-Ethyl-8-methyl-3,4,6,7-tetrahydro-2H-pyrimido[6,1-*c*][1,2,4]triazine-3,6-dione (10) and N^2-Phenyl(6-methyl-2-oxo-4-phenylhydrazono-1,2,3,4-tetrahydro-3-pyrimidinyl)acethydrazide (11). Ethyl- or phenylhydrazine (8 mmol) was added to a solution of compound **2** (0.43 g, 2 mmol) in absolute methanol (2 ml). The reaction mixture was boiled in an argon atmosphere for 13 h, and cooled to room temperature. The precipitated solid was filtered off, washed with methanol, and recrystallized from a DMF–water mixture (for compound **10**) or 2-propanol (**11**).

Compound 10. Yield 0.27 g (64%), mp 226-228°C. IR spectrum, ν, cm^{-1}: 1655, 1712 (C=O); 3092, 3207 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.11 (3H, t, J = 7.2, CH_3); 1.92 (3H, s, CH_3); 3.58 (2H, q, *J* = 7.2, CH_2); 4.18 (2H, s, NCH_2); 5.41 (1H, s, CH); 10.39 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.4, 18.4 (2CH_3); 42.6, 43.5 (2NCH_2); 96.1 (C-9); 140.4 (C-8); 143.1 (C-10); 150.2 (C-6); 157.5 (C-3). Found, %: C 52.24; H 5.76; N 26.93. $C_9H_{12}N_4O_2$. Calculated, %: C 51.92; H 5.81; N 26.91.

Compound 11 Yield 0.44 g (61%), mp 217-219°C. IR spectrum, ν, cm^{-1}: 1660, 1697 (C=O); 3293 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.0 (3H, s, CH_3); 4.58 (2H, s, NCH_2); 5.93 (1H, s, CH); 6.6-7.2 (10H, m, 2C_6H_5); 7.69 (1H, d, *J* = 2.2, NH); 8.35 (1H, s, NH); 9.85 (1H, d, *J* = 2.2, NH); 10.2 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 19.1 (CH_3); 42.6 (NCH_2); 90.7 (C-5); 112.8, 113.0, 117.7, 118.9, 129.1, 129.3, 129.7, 143.4, 148.5, 149.9, 151.6 (C-2); 168.3 (C=O). Found, %: C 62.33; H 5.67; N 22.87. $C_{19}H_{20}N_6O_2$. Calculated, %: C 62.63; H 5.53; N 23.06.

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