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Synthesis of S- and O-alkanoic acid derivatives of 6-phenyl-2-sulfanyl-4(3*H*)-pyrimidinone

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Treatment of 6-phenyl-2-sulfanyl-4(3*H*)-pyrimidinone (**1**) with ethyl 2-bromopropanoate (butanoate) in methanol-sodium methoxide solution gave rise to formation of the corresponding 2-[(6-oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl)sulfanyl]alkanoic acid ethyl esters (**2a**, **b**). Alkylation of sodium salt of 2-methylsulfanyl-6-phenyl-4(3*H*)-pyrimidinone (**5**) with ethyl 2-bromopropanoate in dimethylformamide proceeded at the $O_{(4)}$-position of pyrimidine to give ethyl 2-{[2-(methylsulfanyl)-6-phenyl-4-pyrimidinyl]oxy}propanoate (**6**). Base-catalysed hydrolysis and reactions with hydrazine hydrate of the synthesized esters **2a**, **b** and **6** were studied.

Key words: 6-phenyl-2-sulfanyl-4(3*H*)-pyrimidinone, alkanoic acid esters, synthesis, hydrolysis, hydrazinolysis

INTRODUCTION

Pyrimidine derivatives are of considerable interest because of their practical use. We have reported already a number of S-, N- and O-alkyl derivatives of pyrimidine exhibiting a wide range of biological activity [1–5]. 6-Phenyl-2-sulfanyl-4(3*H*)-pyrimidinone, unlike its 6-methyl analogue, is not yet studied sufficiently. The miserly reports nevertheless have showed 6-phenyl-2-sulfanyl-4(3*H*)-pyrimidinone derivatives to have antibacterial [6] or anti-HIV-1 activity [7].

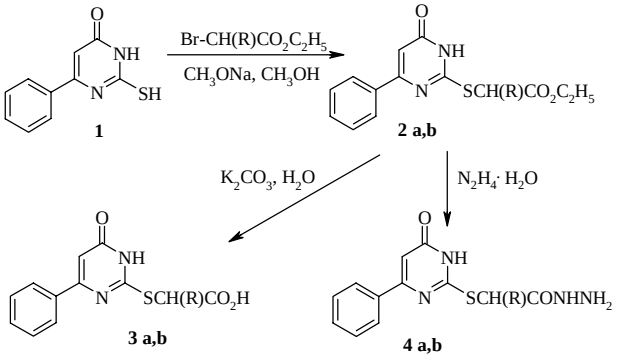
Continuing our interest in the synthesis of biologically active compounds, we report now on the S-propanoic (butanoic) and O-propanoic acid derivatives containing 6-phenyl-2-sulfanyl-4(3*H*)-pyrimidinone (**1**) moiety.

RESULTS AND DISCUSSION

Based on our previous study on the alkylation of different 2-sulfanylpyrimidines with ethyl bromoacetate [2, 8], we treated 6-phenyl-2-sulfanyl-4(3*H*)-pyrimidinone (**1**) with ethyl 2-bromopropanoate (or butanoate) in abs. methanol using sodium methoxide as a base.

The esters **2a**, **b** were obtained in high yields. In the ^{1}H NMR spectra of esters **2a**, **b** the characteristic signals of SCH group proton at 4.61–4.67 ppm, the corresponding alkyl group (attached to SCH) protons shifts at 1.72 and 1.26, 2.09 ppm as well as signals of ethyl group protons in the region of 1.16,

Scheme 1



R = CH_3 (a), C_2H_5 (b)

1.26 and 4.21 ppm were observed. The IR spectra showed absorption of ester C = O group at 1746, 1738 cm^{-1} and lactam C = O at 1652, 1649 cm^{-1}. Hydrolysis of esters **2a**, **b** with 5% potassium carbonate solution gave acids **3a**, **b**. ^{1}H NMR spectra of acids **3a**, **b** showed characteristic signals of hydroxy group protons at 12.89–12.12 ppm. The IR spectra displayed absorption bands of associating hydroxy groups in the region of 2680–2696 cm^{-1} characteristic for carboxylic acids and absorption of C = O group in the region of 1706–1708 cm^{-1}. The reaction of esters **2a**, **b** towards hydrazine hydrate was different. Hydrazide **4a** was synthesized in a 55% yield according to the earlier reported methods for hydrazide synthesis [2, 5, 8]. Hydrazide **4b** was obtained analogously but without using a solvent. In the ^{1}H NMR spectra of hydrazides **4a** and **4b,** splitting of the characteristic SCH group as well as ad-

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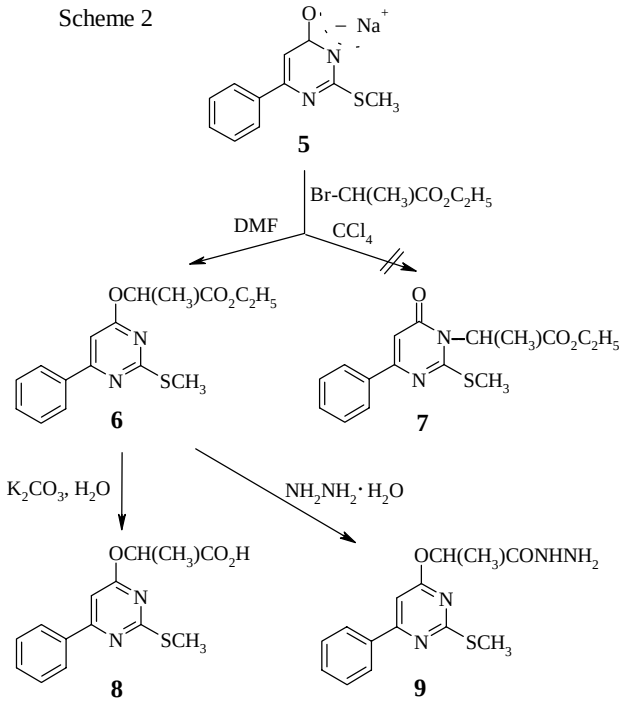
Scheme 2



jacent alkyl group protons was observed, and the signals of ethoxy group protons were absent. The IR spectra of hydrazides **4a**, **b,** besides the absorption bands of NH group in the region 3424–3302 cm^{-1} display three absorption bands characteristic of hydrazides [9]: 1674–1681 cm^{-1} (amide I), 1535–1538 cm^{-1} (amide II) and 1268–1236 cm^{-1} (amide III).

Alkylation of sodium salt 2-methylsulfanyl-6-phenyl-4(3*H*)-pyrimidinone (**5**) in principle is possible either at $N_{(3)}$- or O-position of pyrimidine ring with the formation of different compounds i.e. either N- (**7**) or O-isomer (**6**) or mixture of both

With reference to our earlier experience on regioselective alkylation of ambident 2-alkylsulfanyl-4-pyrimidinones with ethyl bromoacetate [10], we have used for alkylation of sodium salt **5** two aprotic solvents – nonpolar tetrachloromethane and dipolar dimethylformamide. However, alkylation of **5** with ethyl bromopropanoate using tetrachloromethane as a solvent did not proceed at $N_{(3)}$-atom. Steric obstruction seems likely, while alkylation in dimethylformamide was regioselective to form O-substituted ester **6** in a 78% yield. Interestingly, ^{1}H NMR showed a characteristic group OCH proton shifted downfield by 0.76 ppm as compared to that of S-substituted ester **2a** and the CH proton of the 5th position of pyrimidine ring shifted by 0.47 ppm upfield as compared to that of **2a**. Ester **6** was resistant to base-catalysed hydrolysis conditions applied for esters **2a**, **b** (5% potassium carbonate solution at reflux). Formation of 2-[(2-methylsulfanyl-6-phenyl-4-pyrimidinyl)oxy]propanoic acid (**8**) was achieved using 25% potassium hydroxide solution. Hydrazide **9** was obtained as reported earlier [2, 5, 8]. The IR and ^{1}H NMR spectra of ester **6**, acid **8** and hydrazide **9** displayed signals analogous to those of ester **2a**, acid **3a** and hydrazide **4a**.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were measured on a Spectrum BX FT-IR (Perkin-Elmer) in Nujol, ^{1}H-NMR spectra were recorded on a Unity Varian Inova (300 MHz) spectrophotometer with TMS as an internal standard. Chemical shifts (δ) are reported in ppm. All reactions and purity of the synthesized compounds were monitored by TLC on a Silica gel 60 aluminium plates with a fluorescent indicator UV_{254} (Merck). Elemental analyses were performed at the Microanalysis Laboratory of the Department of Organic Chemistry Faculty of Chemistry of Vilnius University.

6-Phenyl-2-sulfanyl-4(3*H*)-pyrimidinone (**1**) and 2-methylsulfanyl-6-phenyl-4(3*H*)-pyrimidinone (**5**) were synthesized according to the procedures reported in reference [6].

2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl) sulfanyl]alkanoic acid ethyl esters (2a, b)

A solution of sodium methoxide (10 mmol, 0.23 g of sodium dissolved in 20 ml of methanol) and 6-phenyl-2-sulfanyl-4(3*H*)-pyrimidinone (**1**) (10 mmol, 2.04 g) in 40 ml of methanol was treated dropwise with the corresponding 2-bromoalkanoic acid ethyl ester (10 mmol). The reaction mixture was heated at reflux for 3 h and cooled to room temperature. The precipitate formed was filtered off and recrystallized from isopropanol.

Ethyl 2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl)sulfanyl]propanoate (2a): yield 72%, m.p. 190–191 °C. ^{1}H NMR ($CDCl_3$): 1.26 (t, J = 7.4 Hz, 3H, $OCH_2\mathit{CH_3}$), 1.72 (d, J = 7.4 Hz, 3H, CH_3), 4.21 (q, J = 7.4 Hz, 2H, OCH_2), 4.67 (q, J = 7.4 Hz, 1H, SCH), 6.73 (s, 1H, CH-5), 7.49, 7.99 (2 m, 5H, C_6H_5), 13.18 (s br, 1H, NH). IR (ν, cm^{-1}): 3454 (NH), 1746, 1652 (CO). Found, %: C, 59.46; H, 4.96; N, 9.40. Calculated for $C_{15}H_{16}N_2O_3S$ (304.36): C, 59.19; H, 5.30; N, 9.20%.

Ethyl 2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl)sulfanyl]butanoate (2b): yield 96%, m.p. 173–174 °C. ^{1}H NMR ($CDCl_3$): 1.16 (t, J = 7.5 Hz, 3H, $OCH_2\mathit{CH_3}$), 1.26 (t, J = 7.2 Hz, 3H, $CH_2\mathit{CH_3}$), 2.09 (m, 2H, $\mathit{CH_2}CH_3$), 4.21 (m, 2H, OCH_2), 4.61 (t, J = 7.4 Hz, 1H, SCH), 6.72 (s, 1H, CH-5), 7.49, 8.00 (2 m, 5H, C_6H_5), 12.79 (s br, 1H, NH). IR (ν, cm^{-1}): 3448 (NH), 1738, 1649 (CO). Found, %: C, 60.51; H, 5.68; N, 8.96. Calculated for $C_{16}H_{18}N_2O_3S$ (318.39): C, 60.36; H, 5.70; N, 8.80%.

2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl)sulfanyl]alkanoic acids (3a, b)

A solution of 5% potassium carbonate (10 ml) and each of ester **2a**, **b** (1.6 mmol) was heated at reflux for 8 h. After cooling the solution was filtered and acidified with conc. hydrochloric acid. The precipitate formed was filtered off, washed with water and recrystallized from methanol–water mixture.

2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl)sulfanyl]propanoic acid (3a): yield 84%, m.p. 228–229 °C. ^{1}H NMR (DMSO-d_6): 1.58 (d, J = 7.5 Hz, 3H, CH_3), 4.50 (q, J = 7.5 Hz, 1H, SCH), 6.75 (s, 1H, CH-5), 7.50, 8.10 (2 m, 5H, C_6H_5), 12.92 (s br, 2H, NH, COOH). IR (ν, cm^{-1}): 3429 (NH), 2696 (OH associated), 1708, 1637 (CO). Found, %: C, 56.44; H, 4.43; N, 9.94. Calculated for $C_{13}H_{12}N_2O_3S$ (276.31): C, 56.51; H, 4.38; N, 10.14%.

2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl)sulfanyl]butanoic acid (3b): yield 87%, m.p. 230–231 °C. ^{1}H NMR (DMSO-d_6): 1.05 (t, J = 7.5 Hz, 3H, $CH_2\mathit{CH_3}$), 1.96 (m, 2H, $\mathit{CH_2}CH_3$), 4.47 (t, J = 6.9 Hz, 1H, SCH), 6.75 (s, 1H, CH-5), 7.50, 8.10 (2 m, 5H, C_6H_5), 12.89 (s br, 2H, NH, COOH). IR (ν, cm^{-1}): 3430 (NH), 2680 (OH associated), 1706, 1645 (CO). Found, %: C, 57.65; H, 4.43; N, 9.26. Calculated for $C_{14}H_{14}N_2O_3S$ (290.34): C, 57.92; H, 4.86; N, 9.65%.

2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl)sulfanyl]propanohydrazide (4a)

To a solution of ester **2a** (1.6 mmol, 0.49 g) in 7 ml of ethanol hydrazine hydrate (6.4 mmol, 0.32 g) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The solid formed was filtered off, washed with water, dried and recrystallized from isopropanol. Yield 0.26 g (55%), m. p. 250–252 °C.

^{1}H NMR (DMSO-d_6): 1.57 (d, J = 7.1 Hz, 3H, CH_3), 4.62 (q, J = 7.1 Hz, 1H, SCH), 6.74 (s, 1H, CH-5), 7.52, 8.12 (2 m, 5H, C_6H_5), 9.51 (s br, 1H, NH). IR (ν, cm^{-1}): 3424, 3338 (NH), 1674 (amide I), 1652 (CO), 1538 (amide II), 1268 (amide III). Found, %: C, 53.50; H, 4.91; N, 19.48. Calculated for $C_{13}H_{14}N_4O_2S$ (290.34): C, 53.78; H, 4.86; N, 19.30%.

2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl)sulfanyl]butanohydrazide (4b)

Suspension of ester **2b** (1.6 mmol, 0.51 g) and hydrazine hydrate (6.4 mmol, 0.32 g) was stirred at 50 °C for 1 h, then left at room temperature for 2 days. The precipitate was filtered off, washed with methanol-ether solution, dried and recrystallized from isopropanol. Yield 0.27 g (56%), m. p. >320 °C. ^{1}H NMR (DMSO-d_6): 0.98 (t, J = 7.3 Hz, 3H, CH_3), 1.95 (m, 2H, CH_2), 4.50 (t, J = 7.3 Hz, 1H, SCH), 6.74 (s, 1H, CH-5), 7.53, 8.12 (2 m, 5H, C_6H_5), 9.53 (s, 1H, NH). IR (ν, cm^{-1}): 3302 (NH), 1681 (amide I), 1660 (CO), 1535 (amide II), 1286 (amide III). Found, %: C, 55.78; H, 5.50; N, 17.90. Calculated for $C_{14}H_{16}N_4O_2S$ (304.37): C, 55.28; H, 5.30; N, 18.41%.

Ethyl 2-[(2-methylsulfanyl-6-phenyl-4-pyrimidinyl)oxy]propanoate (6)

A mixture of pyrimidinone **1** (10 mmol, 2.04 g) and sodium methoxide (10 mmol, 0.23 g of sodium dissolved in 20 ml of methanol) was refluxed for 5 min and methanol was distilled under reduced pressure to give remainder **5** which was dried at 80 °C. A suspension of dry sodium salt **5** in 20 ml of dimethylformamide was treated dropwise with ethyl 2-bromopropanoate (0.014 mol, 2.53 g, 1.8 ml). The reaction mixture then was heated at reflux for 1 h, filtered off and distilled under reduced pressure. The residue was extracted with ether (3 × 30 ml). The extracts were washed with water and dried under sodium sulfate. After the solvent was removed, the residue was recrystallized from hexane to give ester **6**. Yield 2.49 g (78%), m. p. 240 °C. ^{1}H NMR ($CDCl_3$): 1.31 (t, J = 7.1 Hz, 3H, $OCH_2\mathit{CH_3}$), 1.67 (d, J = 7.1 Hz, 3H, CH_3), 2.59 (s, 3H, SCH_3), 4.26 (q, J = 7.1 Hz, 2H, OCH_2), 5.43 (q, J = 7.1 Hz, 1H, OCH), 6.29 (s, 1H, CH-5), 7.50, 8.07 (2 m, 6H, NH + C_6H_5). IR (ν, cm^{-1}): 1745 (CO). Found, %: C, 60.61; H, 5.63; N, 8.94. Calculated for $C_{16}H_{18}N_2O_3S$ (318.39): C, 60.36; H, 5.70; N, 8.80%.

2-[(2-Methylsulfanyl-6-phenyl-4-pyrimidinyl)oxy]propanoic acid (8)

A solution of 25% potassium hydroxide (10 ml) and ester **7** (0.51 g, 1.6 mmol) was heated at reflux for 6 h. After cooling the solution was filtered and acidified with diluted hydrochloric acid. The precipitate formed was filtered off, washed with water and recrystallized from methanol–water mixture. Yield 0.23 g (59%), m. p. 125–126 °C. ^{1}H NMR (CF_3COOD): 2.00 (d, J = 7.0 Hz, 3H, CH_3), 2.91 (s, 3H, SCH_3), 5.91 (q, J = 7.0 Hz, 1H, OCH), 7.29 (s, 1H, CH-5), 7.78, 7.91 (2 m, 5H, C_6H_5). IR (ν, cm^{-1}): 3563 (OH), 2627 (OH associated), 1724 (CO). Found, %: C, 58.01; H, 5.05; N, 9.84. Calculated for $C_{14}H_{14}N_2O_3S$ (290.34): C, 57.92; H, 4.86; N, 9.65%.

2-[(2-Methylsulfanyl)-6-phenyl-4-pyrimidinyl)oxy]propanohydrazide (9)

To a solution of ester **6** (3 mmol, 0.8 g) in 10 ml of ethanol hydrazine hydrate (12 mmol, 0.6 g) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The solid formed was filtered off, washed with water, dried and recrystallized from isopropanol. Yield 0.5 g (53%), m. p. 150–151 °C. ^{1}H NMR (CF_3COOD): 2.66 (d, J = 7.1 Hz, 3H, CH_3), 3.58 (s, 3H, SCH_3), 6.96 (q, J = 7.1

Hz, 1H, OCH), 8.01 (s, 1H, CH-5), 8.43, 8.55 (2 m, 5H, C_6H_5). IR (ν, cm^{-1}): 3279 (NH), 1667 (amide I), 1541 (amide II), 1297 (amide III). Found, %: C, 55.19; H, 5.63; N, 18.44. Calculated for $C_{14}H_{16}N_4O_2S$ (318.39): C, 55.06; H, 5.61; N, 18.35%.

CONCLUSIONS

1. 2-[(6-Oxo-4-phenyl-1,6-dihydro-2-pyrimidinyl) sulfanyl]alkanoic acid ethyl esters were obtained under treatment of 6-phenyl-2-sulfanyl-4(3*H*)-pyrimidinone with ethyl 2-bromopropanoate (butanoate) in methanol in the presence of sodium methoxide. Alkylation of sodium salt of 2-methylsulfanyl-6-phenyl-4(3*H*)-pyrimidinone with ethyl 2-bromopropanoate in dimethylformamide gave rise to ethyl 2-{[2-(methylsulfanyl)-6-phenyl-4-pyrimidinyl]oxy}propanoate formation.

2. Esters were converted to alkanoic acids under base-catalysed hydrolysis and reacted with hydrazine hydrate to give hydrazides.

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6-FENIL-2-SULFANIL-4(3*H*)-PIRIMIDINONO S- IR O-ALKANO RÛGÐÈIØ DARINIØ SINTEZË

Santrauka

Veikiant 6-fenil-2-sulfanil-4(3*H*)-pirimidinonà 2-brom-propano (butano) rûgðèiø etilesteriais metanolio ir natrio metoksido tirpale susintetinti 2-[(4-fenil-6-okso-1,6-dihidro-2-pirimidinil)sulfanil]propano (butano) rûgðèiø etilesteriai. Alkilinant 6-fenil-2-metilsulfanil-4(3*H*)-pirimidinono natrio druskà etil-2-brompropanoatu dimetilformamide susidarë etil-[(6-fenil-2-metilsulfanil-4-pirimidinil)oksi]propanoatas. Atliekant esteriø ðarminæ hidrolizæ, susintetintos atitinkamos rûgðtys, o reakcijose su hidrazinhidratu susidarë hidrazidai.