Monatshefte für Chemie 133, 173–181 (2002)

Monatshefte für Chemie
Chemical Monthly

Reactions of 5-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole-2-thione with Electrophiles

Romualdas Smicius, Virginija Jakubkiene, Milda M. Burbuliene, and **Povilas Vainilavicius***

Department of Organic Chemistry, Faculty of Chemistry, Vilnius University, LT-2006 Vilnius, Lithuania

Summary. Treatment of 5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole-2-thione with haloalkanes yielded oxadiazole S-alkyl derivatives, whereas its reaction with formaldehyde and amines resulted in formation of oxadiazole N(3)-aminomethyl derivatives. The alkylation of 2-alkylsulfanyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazoles with methyl bromoacetate proceeded at the N(1)-position of pyrimidine to give 2-alkylsulfanyl-5-(1-methoxycarbonylmethyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazoles, whereas aminomethylation, bromination, or nitration took place at position 5 of pyrimidine ring and afforded the corresponding 5-pyrimidine substituted derivatives.

Keywords. 5-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole-2-thione; Alkylation; Aminomethylation; Bromination; Nitration.

Introduction

5-Substituted 1,3,4-oxadiazole-2-thiones and their derivatives possess a wide range of biological properties. They have been found to influence CNS [1], effect tyrosinase inhibition [2] and some of them show bacteriostatic [3], antitubercular [4], anti-inflammatory [5], and pesticidal activity [6, 7]. To our knowledge, single representatives of 1,3,4-oxadiazole-2-thiones, particularly 5-pyrimidinyl substituted ones, exhibit anti-inflammatory [8] or pesticidal [9] activity, too.

However, N-alkylated oxopyrimidines with the 1,3,4-oxadiazole-2-thione moiety in the N-alkyl fragment have been studied insufficiently. These compounds may be considered as analogues of nucleosides. Therefore, valuable pharmacological properties may be expected. On the other hand they are of considerable interest in view of their chemistry because each of the rings – pyrimidine and oxadiazole – can take part in reactions with various reagents.

Recently we have reported the synthesis of 5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole-2-thione (**1**) [10]. In the present

* Corresponding author. E-mail: povilas.vainilavicius@chf.vu.lt

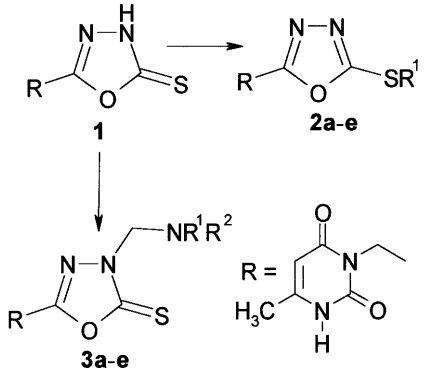
work we have studied reactions of **1** with different electrophiles in order to synthesize derivatives of potential pharmacological activity.

Results and Discussion

The alkylation reaction of the title compound **1** with iodomethane afforded **2a**. The best yield of **2a** was achieved when methanol and triethylamine were used as solvent and base, respectively.

Using different alkylating agents we synthesized a series of alkylated compounds **2b**–**e** by the same procedure. Theoretically, alkylation of **1** in the presence of a basic catalyst may occur either at the S or the N(3) atom of the oxadiazole ring or at the N(1) or O atom of the pyrimidine ring. The IR and ^{1}H NMR data inferred that in all cases formation of S-alkyl derivatives occured. In the IR spectra of **2a**–**e**, absorption bands of two C=O groups at 1634–1651 and 1678–1730 cm^{-1} and the absorption of an NH group in the region of 3156–3179 cm^{-1}, characteristic for the uracil ring [11, 12], were observed. No absorption of an N–C=S group at 1500 cm^{-1}, characteristic for 1,3,4-oxadiazole-2-thione [13], could be detected. In the ^{1}H NMR spectra of **2c**–**e**, the characteristic chemical shifts of SCH_2 protons were observed at 4.01–4.21 ppm.

The *Mannich* reaction of compound **1** with an equivalent amount of formaldehyde and the corresponding amine in methanol proceeded under formation of **3a**–**e**. Each of heterocyclic substructures of compound **1** can take place in this reaction. The formation of the oxadiazole N(3)-aminomethyl derivatives **3a**–**e** was



2	R^1
a	CH_3
b	n-C_3H_7
c	$CH_2CO_2CH_3$
d	$CH_2CO_2C_2H_5$
e	CH_2CONH_2

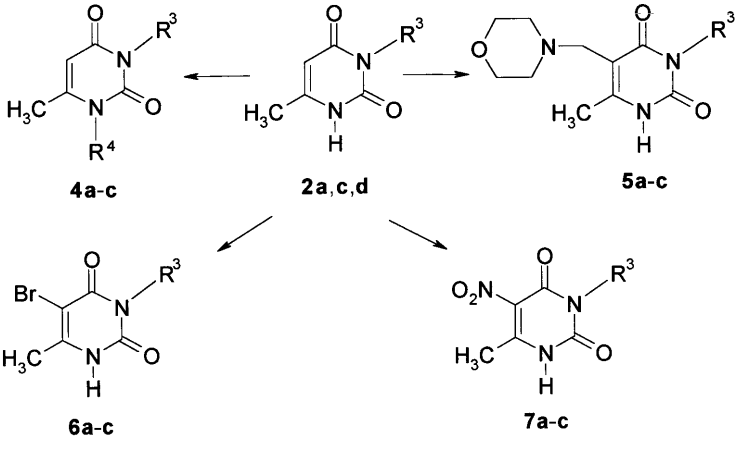
3	NR^1R^2
a	*n*-C_4H_9NH
b	$C_6H_5CH_2NH$
c	$HOCH_2CH_2NH$
d	
e	C_6H_5NH

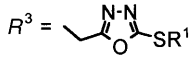
Scheme 1

proved by their IR and ^{1}H NMR data. In the IR spectra of **3a**–**e**, absorption bands of two C=O groups at 1638–1660 cm^{-1} and 1709–1726 cm^{-1} and the absorption of an NH group in the region of 3092–3184 cm^{-1}, characteristic for uracil derivatives, as well as the absorption of an N–C=S group at 1485–1507 cm^{-1}, characteristic for oxadiazole-2-thiones, were found. In the ^{1}H NMR spectra of compounds **3a**–**e** the chemical shifts of the protons at position 5 of the pyrimidine ring protons were found in the region of 5.51–5.61 ppm; the signals of the N(3)–CH_2N group protons of oxadiazole appeared at 4.62–4.91 ppm.

The results of alkylation and aminomethylation reactions of **1** discussed above show that the 1,3,4-oxadiazole moiety in compound **1** is more active in these reactions than pyrimidine. Therefore, in order to carry out electrophilic substitution reactions in the pyrimidine ring we used S-alkyl derivatives **2a**,**c**,**d** derived from compound **1**. Treatment of the sodium salts of **2a**,**c**,**d** with methyl bromoacetate led to the formation of pyrimidine N(1)-alkyl derivatives **4a**–**c**.

In the IR spectra of **4a**–**c** the absorption bands of two C=O groups, characteristic for uracil, were observed in the region of 1668 and 1711–1713 cm^{-1}, but no absorption of an NH group was found. In the ^{1}H NMR spectra of **4a**–**c** the characteristic shifts of N(1)–CH_2 and N(3)–CH_2 protons at 4.58–4.62 and 5.22–5.29 ppm were observed. The *Mannich* reaction of **2a**,**c**,**d** required stronger conditions than that of **1**. In this case, aminomethylation occured at position 5 of the pyrimidine ring under formation of **5a**–**c** as proved by their ^{1}H NMR spectra: the signal of the proton at position 5 of the pyrimidine ring vanished, whereas the signals of the C(5)–CH_2–N protons appeared in the region of 3.19–3.32 ppm. Bromination of **2a**,**c**,**d** with bromine in glacial acetic acid proceeded under



R^3 = 

R^4 = $CH_2CO_2CH_3$

4–7	R^1
a	CH_3
b	$CH_2CO_2CH_3$
c	$CH_2CO_2C_2H_5$

Scheme 2

formation of 5-bromo derivatives **6a**–**c**. Nitration of **2a**,**c**,**d** with a mixture of nitric and sulfuric acid afforded 5-nitro derivatives **7a**–**c**. In the ^{1}H NMR spectra of **6** and **7**, the signal of C(5)–H could not be observed. The IR spectra of **6a**–**c** are characterized by the absorption of C–Br in the region of 585–596 cm^{-1}, those of **7a**–**c** by the absorption band of the C–NO_2 group at 1512–1533 cm^{-1}.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were measured in nujol mull on a Perkin-Elmer FT spectrophotometer Spectrum BX II. ^{1}H NMR spectra were recorded with a Tesla BS 570 A (80 MHz) spectrometer using *TMS* as internal standard. The experimental values of microanalyses for compounds **1**–**7** agreed with the calculated ones.

5-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole-2-thione (**1**; $C_8H_8N_4O_3S$)

1 was prepared according to Ref. [10].

5-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-methylsulfanyl-1,3,4-oxadiazole (**2a**; $C_9H_{10}N_4O_3S$)

Method A. To a mixture of **1** (1.2 g, 5 mmol) and KOH (0.28 g, 5 mmol) in 24 cm^3 H_2O, 0.32 cm^3 CH_3I (0.71 g, 5 mmol) were added dropwise, and the reaction mixture was stirred at 30°C for 5 h. The precipitate was filtered off and recrystallized from MeOH.

Yield: 0.81 g (64%); m.p.: 216–217°C; white crystals; IR: $\nu = 1168$ (C–O–C), 1645, 1722 (CO), 3175 (NH) cm^{-1}; ^{1}H NMR (*DMSO*–d_6): $\delta = 2.08$ (s, 3H, CH_3), 2.69 (s, 3H, SCH_3), 5.14 (s, 2H, NCH_2), 5.57 (s, 1H, CH), 11.08 (s, 1H, NH) ppm.

Method B. Triethylamine (0.7 cm^3, 0.51 g, 5 mmol) was used instead of KOH in the above procedure. Yield: 0.85 g (67%).

Method C. To a mixture of **1** (1.2 g, 5 mmol) and KOH (0.28 g, 5 mmol) in 24 cm^3 MeOH, 0.32 cm^3 CH_3I (0.71 g, 5 mmol) were added dropwise. The reaction mixture was stirred at 30°C for 1 h, then refluxed for 3 h, evaporated to 1/2 of its volume, and cooled. The precipitate was filtered off and recrystallized. Yield: 0.95 g (75%).

Method D. Triethylamine (0.7 cm^3, 0.51 g, 5 mmol) was used instead of KOH in the above procedure. Yield: 0.97 g (76%).

5-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-propylsulfanyl-1,3,4-oxadiazole (**2b**; $C_{11}H_{14}N_4O_3S$)

Compound **2b** was synthesized from **1** and 0.45 cm^3 1-bromopropane (0.62 g, 5 mmol) in analogy to procedure D for compound **2a** (reaction time: 6 h).

Yield: 1.06 g (75%); m.p.: 157–158°C (ethyl acetate); pale yellow crystals; IR: $\nu = 1163$ (C–O–C), 1641, 1709 (CO), 3161 (NH) cm^{-1}; ^{1}H NMR (*DMSO*–d_6): $\delta = 0.95$ (t, $J = 7$ Hz, 3H, CH_3), 1.68 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 3.19 (t, $J = 7$ Hz, 2H, SCH_2), 5.15 (s, 2H, NCH_2), 5.59 (s, 1H, CH), 11.32 (s, 1H, NH) ppm.

2-Methoxycarbonylmethylsulfanyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole (**2c**; $C_{11}H_{12}N_4O_5S$)

Compound **2c** was synthesized from **1** and 0.47 cm^3 methyl bromoacetate (0.77 g, 5 mmol) in analogy to procedure D for compound **2a**.

Yield: 1.12 g (72%); m.p.: 158.5–159.5°C (MeOH); pale yellow crystals; IR: $\nu = 1162$, 1192 (C–O–C), 1638, 1720, 1738 (CO), 3156 (NH) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.09$ (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 4.17 (s, 2H, SCH_2), 5.13 (s, 2H, NCH_2), 5.56 (s, 1H, CH), 11.37 (s, 1H, NH) ppm.

2-Ethoxycarbonylmethylsulfanyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole (**2d**; $C_{12}H_{14}N_4O_5S$)

Compound **2d** was synthesized from **1** and 0.56 cm^3 ethyl bromoacetate (0.84 g, 5 mmol) in analogy to procedure D for compound **2a**.

Yield: 1.12 g (69%); m.p.: 132–133°C (H_2O); white crystals; IR: $\nu = 1165$, 1193 (C–O–C), 1634, 1730, 1748 (CO), 3158 (NH) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 1.21$ (t, $J = 7$ Hz, 3H, CH_3), 2.10 (s, 3H, CH_3), 4.21 (s, 2H, SCH_2), 4.16 (q, $J = 7$ Hz, 2H, OCH_2), 5.16 (s, 2H, NCH_2), 5.59 (s, 1H, CH), 11.41 (s, 1H, NH) ppm.

2-Aminocarbonylmethylsulfanyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole (**2e**; $C_{10}H_{11}N_5O_4S$)

Compound **2e** was synthesized from **1** and iodoacetamide (0.93 g, 5 mmol) in analogy to procedure D for compound **2a**.

Yield: 1.05 g (71%); m.p. 259–260°C (H_2O); white crystals; IR: $\nu = 1172$ (C–O–C), 1651, 1678, 1721 (C=O), 3179 (NH) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.10$ (s, 3H, CH_3), 4.05 (s, 2H, SCH_2), 5.15 (s, 2H, NCH_2), 5.58 (s, 1H, CH), 7.33, 7.73 (2s, 2H, NH_2), 11.28 (s, 1H, NH) ppm.

3-Aminomethyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazol-2-thiones **3a–e**; *general procedure*

A mixture of **1** (0.6 g, 2.5 mmol), 0.22 cm^3 32% formaldehyde (0.23 g, 2.5 mmol), and 2.5 mmol of the corresponding amine in 15 cm^3 MeOH was stirred at 40°C for 4 h and cooled. The solid was filtered off and recrystallized to give **3a–e**.

3-Butylaminomethyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazol-2-thione (**3a**; $C_{13}H_{19}N_5O_3S$)

Yield: 0.68 g (84%); m.p.: 227–228.5°C (MeOH); white crystals; IR: $\nu = 1141$ (C–O–C), 1505 (CS), 1638, 1715 (CO), 3175 (NH) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 0.92$ (m, 3H, CH_3), 1.44 (m, 4H, CH_2CH_2), 2.10 (s, 3H, CH_3), 3.58 (m, 2H, NCH_2), 4.63 (s, 2H, NCH_2N), 5.27 (s, 2H, NCH_2), 5.54 (s, 1H, CH), 11.27 (s, 1H, NH) ppm.

3-Benzylaminomethyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazol-2-thione (**3b**; $C_{16}H_{17}N_5O_3S$)

Yield: 0.71 g (79%); m.p.: 218–220°C (MeOH); pale yellow crystals; IR: $\nu = 1194$ (C–O–C), 1505 (CS), 1648, 1726 (CO), 3092 (NH) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.08$ (s, 3H, CH_3), 4.62 (s, 2H, NCH_2N), 4.80 (s, 2H, NCH_2), 5.16 (s, 2H, NCH_2), 5.53 (s, 1H, CH), 7.37 (m, 5H, C_6H_5), 11.27 (s, 1H, NH) ppm.

3-(2-Hydroxyethanaminomethyl)-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazol-2-thione (**3c**; $C_{11}H_{15}N_5O_4S$)

Yield: 0.63 g (80%); m.p.: 200–202°C (MeOH); yellow crystals; IR: $\nu = 1180$ (C–O–C), 1485 (CS), 1655, 1718 (CO), 3180 (NH) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.09$ (s, 3H, CH_3), 3.66

(m, 4H, NCH_2CH_2O), 4.69 (s, 2H, NCH_2N), 5.41 (s, 2H, NCH_2), 5.61 (s, 1H, CH), 11.42 (s, 1H, NH) ppm.

5-(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-3-morpholinomethyl-1,3,4-oxadiazol-2-thione (**3d**; $C_{13}H_{17}N_5O_4S$)

Yield: 0.68 g (80%); m.p.: 166–167°C (MeOH); pale yellow crystals; IR: $\nu = 1151$ (C–O–C), 1507 (CS), 1654, 1709 (CO), 3184 (NH) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.13$ (s, 3H, CH_3), 2.74 (m, 4H, $N(CH_2)_2$), 3.66 (m, 4H, $O(CH_2)_2$), 4.91 (s, 2H, NCH_2N), 5.11 (s, 2H, NCH_2), 5.51 (s, 1H, CH), 11.18 (s, 1H, NH) ppm.

3-Anilinomethyl-5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazol-2-thione (**3e**; $C_{15}H_{15}N_5O_3S$)

Yield: 0.68 g (79%); m.p.: 183–185°C (2-PrOH:H_2O = 6:1); yellow crystals; IR: $\nu = 1153$ (C–O–C), 1495 (CS), 1660, 1724 (CO), 3092 (NH) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.10$ (s, 3H, CH_3), 4.71 (s, 2H, NCH_2N), 5.55 (s, 1H, CH), 5.75 (s, 2H, NCH_2), 7.50 (m, 5H, C_6H_5), 11.31 (s, 1H, NH) ppm.

2-Alkylsulfanyl-5-(1-methoxycarbonylmethyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazoles **4a–c**; *general procedure*

A solution of 2.5 mmol of compound **2a**, **2b**, or **2c** and sodium methoxide (0.135 g, 2.5 mmol) in 10 cm^3 MeOH (in the case of **2c**: sodium ethoxide (0.17 g, 2.5 mmol) in 10 cm^3 abs. EtOH) was refluxed for 5 min, evaporated to dryness *in vacuo*, and dried to constant weight. The salt obtained was suspended in 10 cm^3 of dry dioxane, and 0.24 cm^3 methyl bromoacetate (0.38 g, 2.5 mmol) were added. The reaction mixture was stirred at reflux for 6 h. The inorganic salt was filtered off and washed with 6 cm^3 of dry dioxane. The filtrates were combined and evaporated to dryness *in vacuo*. The residue was washed with 10 cm^3 diethyl ether, decanted, and dissolved in 15 cm^3 $CHCl_3$. The obtained solution was washed with 5% KOH (2×25 cm^3) and H_2O (2×25 cm^3). The organic extract was dried over $CaCl_2$ and concentrated. The crude product was purified by column chromatography on silica gel (63–210 µm, Aldrich) using acetone:$CHCl_3$ = 1:2 as eluent (column diameter: 1 cm, column length 30 cm). TLC (silufol UV 254 (Kavalier, Czech Republic), acetone:$CHCl_3$ = 1:2): **4a**: $R_f = 0.4$, **4b**,**c**: $R_f = 0.5$.

5-(1-Methoxycarbonylmethyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-methylsulfanyl-1,3,4-oxadiazole (**4a**; $C_{12}H_{14}N_4O_5S$)

Yield: 0.65 g (80%); yellowish glassy paste; IR: $\nu = 1167$, 1218 (C–O–C), 1668, 1713, 1753 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.16$ (s, 3H, CH_3), 2.65 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 4.58 (s, 2H, NCH_2), 5.24 (s, 2H, NCH_2), 5.69 (s, 1H, CH) ppm.

5-(1-Methoxycarbonylmethyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-methoxycarbonylmethylsulfanyl-1,3,4-oxadiazole (**4b**; $C_{14}H_{16}N_4O_7S$)

Yield: 0.57 g (59%); greenish glassy paste; IR: $\nu = 1160$, 1216 (C–O–C), 1668, 1711, 1749 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.20$ (s, 3H, CH_3), 3.78 (s, 6H, 2 OCH_3), 4.03 (s, 2H, SCH_2), 4.62 (s, 2H, NCH_2), 5.29 (s, 2H, NCH_2), 5.71 (s, 1H, CH) ppm.

2-Ethoxycarbonylmethylsulfanyl-5-(1-methoxycarbonylmethyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole (**4c**; $C_{15}H_{18}N_4O_7S$)

Yield: 0.64 g (64%); yellowish glassy paste; IR: $\nu = 1153$, 1218 (C–O–C), 1668, 1713, 1748 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.20$ (t, $J = 7$ Hz, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3),

4.05 (q, $J = 7$ Hz, 2H, OCH_2), 4.18 (s, 2H, SCH_2), 4.61 (s, 2H, NCH_2), 5.22 (s, 2H, NCH_2), 5.63 (s, 1H, CH) ppm.

2-Alkylsulfanyl-5-(6-methyl-5-morpholinomethyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazoles **5a–c**; *general procedure*

A mixture of 2.5 mmol of compound **2a**, **2c**, or **2d**, 0.22 cm^3 32% formaldehyde (0.23 g, 2.5 mmol), and 0.22 cm^3 morpholine (0.22 g, 2.5 mmol) in 15 cm^3 EtOH (in the case of **2c**, MeOH was used) was refluxed for 16 h (**2c**: 26 h), evaporated to 1/2 of its volume, and cooled. The solid was filtered off and recrystallized.

5-(6-Methyl-5-morpholinomethyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-methylsulfanyl-1,3,4-oxadiazole (**5a**; $C_{14}H_{19}N_5O_4S$)

Yield: 0.62 g (70%); m.p.: 184–185°C (EtOH); white crystals; IR: $\nu = 1159$ (C–O–C), 1648, 1720 (CO) cm^{-1}; ^{1}H NMR (*DMSO*–d_6): $\delta = 2.20$ (s, 3H, CH_3), 2.31 (m, 4H, $N(CH_2)_2$), 2.68 (s, 3H, SCH_3), 3.19 (s, 2H, NCH_2), 3.52 (m, 4H, $O(CH_2)_2$), 5.16 (s, 2H, NCH_2), 11,15 (s, 1H, NH) ppm.

2-Methoxycarbonylmethylsulfanyl-5-(6-methyl-5-morpholinomethyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole (**5b**; $C_{16}H_{21}N_5O_6S$)

Yield: 0.6 g (58%); m.p.: 135–136°C (MeOH); pale yellow crystals; IR: $\nu = 1152$, 1206 (C–O–C), 1639, 1714, 1747 (CO) cm^{-1}; ^{1}H NMR (*DMSO*–d_6): $\delta = 2.21$ (s, 3H, CH_3), 2.31 (m, 4H, $N(CH_2)_2$), 3.20 (s, 2H, NCH_2), 3.53 (m, 4H, $O(CH_2)_2$), 3.68 (s, 3H, OCH_3), 4.20 (s, 2H, SCH_2), 5.17 (s, 2H, NCH_2), 11.04 (s, 1H, NH) ppm.

2-Ethoxycarbonylmethylsulfanyl-5-(6-methyl-5-morpholinomethyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole (**5c**; $C_{17}H_{23}N_5O_6S$)

Yield: 0.57 g (54%); m.p.: 163–164°C (EtOH); white crystals, IR: $\nu = 1164$, 1208 (C–O–C), 1652, 1719, 1732 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$:*DMSO*–$d_6 = 2{:}1$): $\delta = 1.28$ (t, $J = 7$ Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.46 (m, 4H, $N(CH_2)_2$), 3.32 (s, 2H, NCH_2), 3.66 (m, 4H, $O(CH_2)_2$), 4.04 (s, 2H, SCH_2), 4.19 (q, $J = 7$ Hz, 2H, OCH_2), 5.31 (s, 2H, NCH_2), 11.09 (s, 1H, NH) ppm.

2-Alkylsulfanyl-5-(5-bromo-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazoles **6a–c**; *general procedure*

To a suspension of 2.5 mmol of compound **2a**, **2c**, or **2d** in 4 cm^3 glacial acetic acid, 0.14 cm^3 Br_2 (0.44 g, 2.75 mmol) were added dropwise. After stirring at 20°C for 40 min the reaction mixture was quenched with a solution of 1.5 g $Na_2S_2O_7$ and 0.5 g NaOH in 20 cm^3 H_2O cooled to 10°C. The precipitate was filtered off, washed with H_2O, and recrystallized.

5-(5-Bromo-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-methylsulfanyl-1,3,4-oxadiazole (**6a**; $C_9H_9BrN_4O_3S$)

Yield: 0.54 g (65%); m.p.: 219.5–220°C (MeOH); white crystals; IR: $\nu = 585$ (C–Br), 1165 (C–O–C), 1658, 1720 (CO) cm^{-1}; ^{1}H NMR (*DMSO*–d_6): $\delta = 2.29$ (s, 3H, CH_3), 2.70 (s, 3H, SCH_3), 5.21 (s, 2H, NCH_2), 11.90 (s, 1H, NH) ppm.

5-(5-Bromo-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-methoxycarbonylmethylsulfanyl-1,3,4-oxadiazole (**6b**; $C_{11}H_{11}BrN_4O_5S$)

Yield: 0.66 g (68%); m.p.: 197–198°C (CH_3COCH_3:$H_2O = 3:1$); pale yellow crystals; IR: $\nu = 596$ (C–Br), 1161, 1202 (C–O–C), 1655, 1711, 1737 (CO) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.29$ (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.20 (s, 2H, SCH_2), 5.20 (s, 2H, NCH_2), 11.30 (s, 1H, NH) ppm.

5-(5-Bromo-6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-ethoxycarbonylmethylsulfanyl-1,3,4-oxadiazole (**6c**; $C_{12}H_{13}BrN_4O_5S$)

Yield: 0.58 g (57%); m.p.: 143–144°C (ethyl acetate); pale yellow crystals; IR: $\nu = 592$ (C–Br), 1162, 1195 (C–O–C), 1655, 1714, 1725 (CO) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 1.20$ (t, $J = 7$ Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.10 (q, $J = 7$ Hz, 2H, OCH_2), 4.21 (s, 2H, SCH_2), 5.21 (s, 2H, NCH_2), 11.42 (s, 1H, NH) ppm.

2-Alkylsulfanyl-5-(6-methyl-5-nitro-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazoles **7a–c**; *general procedure*

To a suspension of 2.5 mmol of compound **2a**, **2c**, or **2d** in 2 cm^3 of conc. H_2SO_4, 0.22 cm^3 58% HNO_3 (0.3 g, 2.75 mmol) were added. The reaction mixture was stirred for 30 min at 20°C and poured onto 20 g of ice. The precipitate was filtered off, washed with H_2O, and recrystallized.

5-(6-Methyl-5-nitro-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-2-methylsulfanyl-1,3,4-oxadiazole (**7a**; $C_9H_9N_5O_5S$)

Yield: 0.33 g (44%); m.p.: 182–183°C (ethyl acetate); pale yellow crystals; IR: $\nu = 1187$ (C–O–C), 1512 (C–NO_2), 1679, 1737 (C=O) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.35$ (s, 3H, CH_3), 2.68 (s, 3H, SCH_3), 5.18 (s, 2H, NCH_2), 12.90 (s, 1H, NH) ppm.

2-Methoxycarbonylmethylsulfanyl-5-(6-methyl-5-nitro-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole (**7b**; $C_{11}H_{11}N_5O_7S$)

Yield: 0.46 g (51%); m.p.: 166–167°C (CH_3COCH_3); yellow crystals; IR: $\nu = 1165$, 1192 (C–O–C), 1533 (C–NO_2), 1681, 1732, 1747 (C=O) cm^{-1}; ^1H NMR (*DMSO*–d_6): $\delta = 2.40$ (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.24 (s, 2H, SCH_2), 5.24 (s, 2H, NCH_2), 12.95 (s, 1H, NH).

2-Ethoxycarbonylmethylsulfanyl-5-(6-methyl-5-nitro-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-methyl-1,3,4-oxadiazole (**7c**; $C_{12}H_{13}N_5O_7S$)

Yield: 0.4 g (43%); m.p.: 69–71°C (H_2O); yellow crystals; IR: $\nu = 1179$, 1213 (C–O–C), 1529 (C–NO_2), 1676, 1731, 1743 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.27$ (t, $J = 7$ Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.09 (s, 2H, SCH_2), 4.15 (q, $J = 7$ Hz, 2H, OCH_2), 5.26 (s, 2H, NCH_2), 12.60 (s, 1H, NH) ppm.

References

[1] El-Ansary SL, Sarhan TZ, Aly EI, Soliman GA (1993) Bull Fac Pharm **31**: 203
[2] Yamamoto S (1993) JP 05124948; (1993) CA **119**: 146370
[3] Ghattas AG, El-Sherief HA, Abdelrahman AE, Mahmoud (1982) Pharmazie **37**: 410
[4] Pancechowska-Ksepko D, Foks H, Landowska E, Janowiec M, Zwolska-Kwiek Z (1986) Acta Pol Pharm **43**: 116

[5] Boschelli DH, Connor DT, Kostlan CR, Kramer JB, Mullican MD, Sircar JC (1991) EP 449211; (1992) CA **116**: 6570
[6] Dutta MM, Kataky JCS (1992) J Indian Chem Soc **69**: 107
[7] Bettarini F, Capuzzi L, LaPorta P, Massimini S, Caprioli V (1993) EP 533276; (1993) CA **119**: 49400
[8] Belliotti TR, Connar DT, Kostlan CR (1992) WO 9213844; (1993) CA **118**: 6990
[9] Eckhardt W, Beriger E, Zondler H (1990) EP 371925; (1990) CA **113**: 191385
[10] Vainilavicius P, Smicius R, Jakubkiene V, Tumkevicius S, Monatsh Chem (to be published)
[11] Angell CL (1961) J Chem Soc 504
[12] Wittenburg E (1966) Chem Ber **99**: 2380
[13] Charistos DA, Vagenas GV, Tzavellas LC, Tsoleridis CA, Rodios NA (1994) J Heterocycl Chem **31**: 1593

Received May 9, 2001. Accepted (revised) August 17, 2001