Polish J. Chem., **76**, 557–563 (2002)

Reactions of 5-(2-Dimethylamino-6-methyl-4--pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione with Carbon Electrophiles

by M.M. Burbuliene[1], E. Udrenaite[1], P. Gaidelis[2] and P. Vainilavicius[1*]

[1]*Faculty of Chemistry, Vilnius University, Naugarduko 24, LT-2006, Vilnius, Lithuania*
[2]*Faculty of Medicine, Vilnius University, M.K. Čiurlionio 21, LT-2009, Vilnius, Lithuania*

(Received October 9th, 2001; revised manuscript January 14th, 2002)

From 2,4-dichloro-6-methylpyrimidine (**1**) *via* esters **2** and **3**, (2-dimethylamino-6-methyl-4-pyrimidinylsulfanyl)acethydrazide (**4**) was synthesized. The latter under treatment either with carbon disulfide in the presence of a base or with potassium O-ethylxanthate in ethanol yielded 5-(2-dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione (**5**). Alkylation of **5** afforded S-alkyl derivatives **6a**,**b**, whereas aminomethylation, acylation or cyanoethylation gave $N_{(3)}$-substituted derivatives **7**–**9**. Compounds were tested for their anti-inflammatory activity.

Key words: 1,3,4-oxadiazole-2-thiones, anti-inflammatory activity

Derivatives of 5-substituted 1,3,4-oxadiazole-2-thione exhibit a wide spectrum of biological activity: antimicrobial or tuberculostatic [1,2], tyrosinase inhibition [3], anti-inflammatory [4–6] and insecticidal [7,8]. On the other hand, 5-substituted 1,3,4-oxadiazole-2-thiones are interesting in view of their chemistry. Being ambident anions in alkali medium 5-substituted 1,3,4-oxadiazole-2-thiones show diverse reactivity towards electrophilic reagents, *i.e.*, they are able to form either S- or $N_{(3)}$-substituted compounds [1,9].

Taking this into account and continuing our earlier research [9], we have synthesized 5-(2-dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione (**5**) and investigated its reactions with carbon electrophiles.

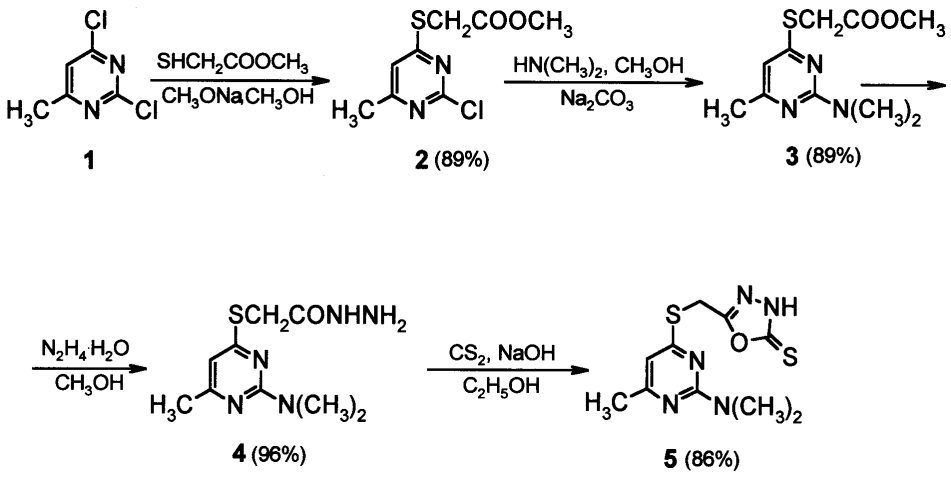
RESULTS AND DISCUSSION

The starting 2,4-dichloro-6-methylpyrimidine (**1**) is readily synthesized from 6-methyluracil [10]. By the reaction of **1** with sodium salt of methyl mercaptoacetate the methyl (2-chloro-6-methyl-4-pyrimidinylsulfanyl)acetate (**2**) was obtained. The isomeric methyl (4-chloro-6-methyl-2-pyrimidinylsulfanyl)acetate was not formed in this reaction. Structure assignment was made, due to the different physical data of latter [11]. Under treatment of **2** with methanolic solution of dimethylamine methyl

*Author for correspondence.

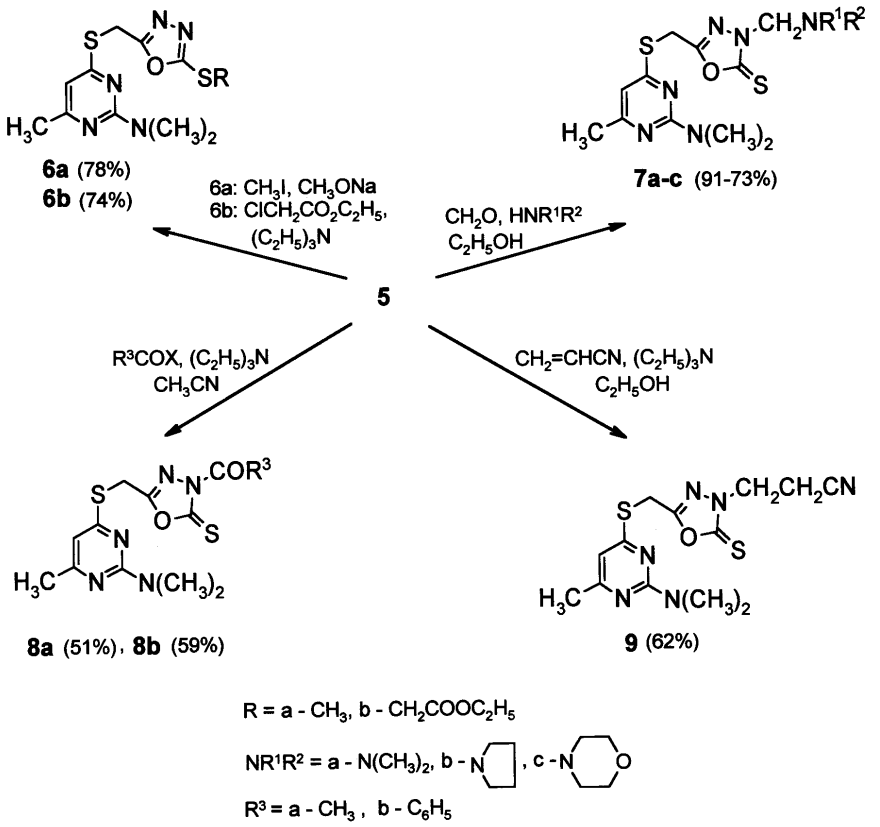
(2-dimethylamino-6-methyl-4-pyrimidinylsulfanyl)acetate (**3**) was obtained. Ester **3** reacted with hydrazine hydrate to form hydrazide **4**. The 1,3,4-oxadiazole-2-thione **5** was prepared by the reaction of hydrazide **4** either with carbon disulfide in the presence of base (*method A*) or with potassium O-ethylxanthate (*method B*) in ethanol. Both methods gave similar yields. The thione form of compound **5** in solid state was confirmed by IR spectra, where the absorption bands of NH (3020 cm^{-1}) and C=S (1338 cm^{-1}) groups were observed, but absorption of SH group in the region of 2500–2600 cm^{-1} was absent.

Scheme 1



Compound **5** was alkylated with iodomethane or ethyl chloroacetate to give **6a** and **6b**, respectively. Sodium methoxide (or ethoxide) was used as a base. When triethylamine was used instead of sodium ethoxide, the yield of **6b** was higher (Scheme 2). Under treatment of **5** with formaldehyde and amines in ethanol aminomethyl derivatives **7** were obtained. Compounds **8** were synthesized by the reaction of 1,3,4-oxadiazole-2-thione **5** with acetic anhydride or benzoyl chloride. The best yields were achieved, when acetonitrile as a solvent and triethylamine as a base were used. Refluxing of 1,3,4-oxadiazole-2-thione **5** with an excess of acrylonitrile in ethanol solution in the presence of triethylamine gave cyanoethyl derivative **9**. In the reaction of 1,3,4-oxadiazole-2-thione **5** with electrophilic reagents the formation of S-derivatives as well as $N_{(3)}$-derivatives (or mixture of both) is possible. Under the reaction conditions, used in our experiments, formation of mixtures was not observed. The structure of compounds **6–9** was proved by IR, ^{1}H and ^{13}C NMR spectra. IR spectra of compounds **7–9** show the characteristic for $N_{(3)}$-substituted derivatives absorption band at 1318–1346 cm^{-1} (C=S), the same absorption is observed in 1,3,4-oxadiazole-2-thione **5**. This absorption band was not observed in IR spectra of

Scheme 2



S-substituted derivatives **6**. Structure assignment of compounds **6–9** to S- or $N_{(3)}$-derivatives also was made by chemical shifts of methylene group protons in the 1,3,4-oxadiazole ring, *e.g.*, S-CH_2 group protons of S-alkyl derivative **6b** resonate at 4.03 ppm, whereas N-CH_2 signals of $N_{(3)}$-derivatives **7** appear in the down field region (4.85–5.05 ppm). The main information of S- or $N_{(3)}$- structure of compounds **6–9**, however, is based on ^{13}C NMR spectra. Chemical shifts of $C_{(2)}$ signals of the 1,3,4-oxadiazole ring are observed in two rather narrow ranges. The chemical shift of $C_{(2)}$, characteristic for S-substituted derivatives **6**, appear at 166.6–168.8 ppm, while the analogue $C_{(2)}$ shift, characteristic for $N_{(3)}$-derivatives **7–9**, is observed at 176.0–179.8 ppm. The chemical shift of $C_{(2)}$ of 1,3,4-oxadiazole-2-thione **5** falls under the same region, what confirms compound **5** to be in the thione form in solutions, as well as in solid state. It is noticeable, that in compounds **6**, **7** with side-chain methylene group, there is a marked difference between meanings of chemical shifts of corresponding C atoms of methylene. Thus, in the ^{13}C NMR spectra signal of C atom of S-CH_2 group in S-alkyl derivative **6b** is shifted up-field (35.0 ppm) in comparison with that of N-CH_2 group in $N_{(3)}$-derivatives **7,** where chemical shifts are observed at

66.9–71.8 ppm. Compounds **3**–**6**, **7a**, **7c**, **8b** and **9** were tested for their anti-inflammatory activity. The data of activity and acute toxicity are summarized in Table 1. Anti-inflammatory activity of compounds **6b**, **7a**, **7c** and **8b** is similar to that of acetylsalicylic acid and less than that of ibuprofen. 5-(2-Dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione (**5**) was found to be twice more active than ibuprofen. It will be observed, that S-alkylation, N-aminomethylation, N-acylation and N-cyanoethylation of 1,3,4-oxadiazole-2-thione **5** decreased anti-inflammatory activity. The tests of acute toxicity (LD_{50}) showed that all the compounds are less toxic than the standards.

Table 1. Anti-inflammatory activity (50 mg/kg p.o.) and acute toxicity (LD_{50}) data for compounds **3–9**.

Compound	0.1 ml of 1% carrageenin solution		0.1 ml of 5% bentonite suspension		LD_{50} (mg/kg)
	Cross-section of rat paw (relative units)	Inhibition of rat paw oedema (%) over control	Cross-section of rat paw (relative units)	Inhibition of rat paw oedema (%) over control	
Control	96.2	–	95.4	–	–
3	82.0	14.7	95.3	0	
4	80.1	16.7	92.1	3.4	
5	48.3	49.7	45.3	52.5	1874 (1563–2245)
6a	89.6	6.8	80.4	15.7	
6b	74.8	22.2	71.5	25.0	1063 (911–1344)
7a	74.2	22.8	61.6	35.4	>1500
7c	74.0	23.0	73.7	22.7	>1500
8b	70.3	26.9	68.3	28.4	>1500
9	82.3	14.4	72.5	24	1366 (1212–1478)
Acetylsalicylic acid	77.2	19.8	74.7	21.6	1216
Ibuprofen	59.7	38.0	75.6	20.7	500

EXPERIMENTAL

M.p.'s were determined in open capillaries and are uncorrected. IR spectra were measured on a Spectrum BX FT-IR (Perkin-Elmer) in Nujol, ^{13}C and ^{1}H-NMR spectra were recorded on a BS-587A (80 MHz, Tesla) in $CDCl_3$ with TMS as an internal standard. Chemical shifts (δ) are reported in ppm, coupling constants (*J*) are given in Hz. The reactions were monitored by TLC on silica gel coated Al plates (KAVALIER). Elemental analyses were perfromed at the Microanalysis Laboratory of the Department of Organic Chemistry of Vilnius University.

The starting compounds (6-methyluracil and methyl mercaptoacetate) were purchased from Aldrich, the other – from Aldrich or Merck and were used without further purification.

Methyl (2-chloro-6-methyl-4-pyrimidinylsulfanyl)acetate (2). To a mixture of 2,4-dichloro-6-methylpyrimidine (**1**) (10 mmol, 1.63 g) in abs. CH_3OH (15 ml) a solution of sodium methoxide (10 mmol, 0.23 g of sodium dissolved in 30 ml abs. CH_3OH) and methyl mercaptoacetate (10 mmol, 1.06 g) was added dropwise at 18–20°C. The reaction mixture was stirred at room temperature for 1 h and filtered off. Filtrate was evaporated, the residue recrystallized from hexane. Yield 2.07 g (89%), m.p. 56–57°C. Anal. calcd. for $C_8H_9ClN_2O_2S$ (232.69): C, 41.29; H, 3.90; N, 12.04%. Found: C, 41.33; H, 3.84; N, 11.96%. ^{1}H NMR: 2.43 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.98 (s, 2H, SCH_2), 7.02 (s, 1H, CH-5).

Methyl (2-dimethylamino-6-methyl-4-pyrimidinylsulfanyl)acetate (3). A mixture of **2** (10 mmol, 2.33 g) and Na_2CO_3 (30 mmol, 3.18 g) in CH_3OH (40 ml) was cooled to 2–5°C and then the solution of dimethylamine (35 mmol, 1.6 g) in methanol (10 ml) was added dropwise. The mixture was stirred at the same temperature for 1 h, then allowed to warm to room temperature. The inorganic salt was filtered off, the filtrate was concentrated *in vacuo* and the residue was recrystallized from hexane. Yield 2.14 g (89%), m.p. 72–73°C. Anal. calcd. for $C_{10}H_{15}N_3O_2S$ (241.31): C, 49.77; H, 6.27; N, 17.41%. Found: C, 50.08; H, 6.37; N, 17.78%. ^{1}H NMR: 2.25 (s, 3H, CH_3), 3.14 (s, 6H, $N(CH_3)_2$), 3.73 (s, 2H, OCH_3), 3.89 (s, 2H, SCH_2), 6.29 (s, 1H, CH-5). IR (cm^{-1}): 1742 (C=O).

(2-Dimethylamino-6-methyl-4-pyrimidinylsulfanyl)acethydrazide (**4**). A mixture of 85% hydrazine hydrate (40 mmol, 2.0 g) and ester **3** (10 mmol, 2.41 g) in C_2H_5OH (10 ml) was left to stand at 18–20°C for a day. The solid was filtered off, washed with ether-ethanol (2:1), dried and recrystallized from water. Yield 2.32 g (96%), m.p. 157–158°C. Anal. calcd. for $C_9H_{15}N_5OS$ (241.32): C, 44.79; H, 6.27; N, 29.02%. Found: C, 44.44; H, 5.96; N, 29.10%. ^{1}H NMR: 2.27 (s, 3H, CH_3), 3.19 (s, 6H, $N(CH_3)_2$), 3.80 (s, 4H, SCH_2+NH_2), 6.32 (s, 1H, CH-5), 8.32 (s, 1H, NH). IR (cm^{-1}): 3255 (NH), 1649 (C=O).

5-(2-Dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione (5).

Method A. A mixture of hydrazide **4** (10 mmol, 2.41 g) and sodium O-ethylxanthate (10 mmol, 1.60 g) in C_2H_5OH (50 ml) was heated at refluxed for 8 h. After the solvent was evaporated *in vacuo* the residue was dissolved in ice-cold water and acidified carefully with 20% HCl to pH 5–6. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol. Yield 2.46 g (87%), m.p. 202–203°C. Anal. calcd. for $C_{10}H_{13}N_5OS_2$ (283.38): C, 42.39; H, 4.62; N, 24.71%. Found: C, 41.99; H, 4.34; N, 24.72%. ^{1}H NMR: 2.22 (s, 3H, CH_3), 3.14 (s, 6H, $N(CH_3)_2$), 4.40 (s, 2H, SCH_2), 6.27 (s, 1H, CH-5), 8.02 (s, 1H, NH). IR (cm^{-1}): 3020 (NH), 1623 (C=N), 1552 (C=C), 1338 (C=S), 1220, 1020 (C-O-C). ^{13}C NMR: 21.6 (SCH_2), 23.2 (CH_3), 36.2 [$N(CH_3)_2$], 104.5 (C-5 pyrimidine), 160.3 (C-5 oxadiazole), 160.4 (C-2 pyrimidine), 164.2 (C-6 pyrimidine), 165.1 (C-4 pyrimidine), 177.6 (C-2 oxadiazole).

Method B. A solution of hydrazide **4** (10 mmol, 2.41 g), KOH (10 mmol, 0.56 g) and carbon disulfide (15 mmol, 1.14 g) in C_2H_5OH (50 ml) was heated at reflux for 6 h. The compound **5** was isolated as described in *method A*. Yield 2.43 g (86%).

5-(2-Dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-2-methylsulfanyl-1,3,4-oxadiazole (6a). To a mixture of compound **5** (10 mmol, 2.83 g) and sodium methoxide [prepared from sodium (10 mmol, 0.23 g) dissolved in CH_3OH (30 ml)] iodomethane (10 mmol, 1.42 g) was added dropwise. The reaction mixture was stirred at room temperature for 30 min. The formed solid was filtered off and recrystallized from hexane. Yield 2.32 g (78%), m.p. 110–111°C. Anal. calcd. for $C_{11}H_{15}N_5OS_2$ (297.40): C, 44.43; H, 5.08; N, 23.55%. Found: C, 44.70; H, 5.12; N, 23.43%. ^{1}H NMR: 2.25 (s, 3H, CH_3), 2.68. (s, 3H, SCH_3), 3.17 (s, 6H, $N(CH_3)_2$), 4.55 (s, 2H, SCH_2), 6.27 (s, 1H, CH-5). IR (cm^{-1}): 1592 (C=N), 1556 (C=C), 1224, 1021 (C-O-C). ^{13}C NMR: 15.0 (SCH_3), 22.5 (SCH_2), 24.7 (CH_3), 37.6 [$N(CH_3)_2$], 106.0 (C-5 pyrimidine), 160.7 (C-2 pyrimidine), 161.9 (C-5 oxadiazole), 165.7 (C-4 pyrimidine), 165.8 (C-6 pyrimidine), 166.4 (C-2 oxadiazole).

5-(2-Dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-2-(ethoxycarbonylmethylsulfanyl)--1,3,4-oxadiazole (6b).

Method A. To a mixture of 1,3,4-oxadiazole-2-thione **5** (2 mmol, 0.567 g) and triethylamine (2 mmol, 0.202 g) in anhydrous C_2H_5OH (10 ml) ethyl chloroacetate (2.1 mmol, 0.257 g) was added dropwise. The reaction mixture was stirred at room temperature for 30 min. The formed solid was filtered off and recrystallized from cyclohexane. Yield 0.55 g (74%), m.p. 92–93°C. Anal. calcd. for $C_{14}H_{19}N_5O_3S_2$ (369.47): C, 45.51; H, 5.18; N, 18.96%. Found: C, 45.32; H, 5.04; N, 19.16%. ^{1}H NMR: 1.28 (t J = 6 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.17 (s, 6H, $N(CH_3)_2$), 4.03 (s, 2H, SCH_2), 4.18 (q J = 6 Hz, 2H, CH_2), 4.57 (s, 2H, SCH_2), 6.27 (s, 1H, CH-5). IR (cm^{-1}): 1737 (C=O), 1554 (C=N), 1227, 1197, 1022 (C–O–C). ^{13}C NMR: 14.7 ($OCH_2\underline{C}H_3$), 22.7 (SCH_2), 24.4 (CH_3), 35.0 ($S\underline{C}H_2CO$), 37.8 [$N(CH_3)_2$], 63.0 ($O\underline{C}H_2CH_3$), 106.1 (C-5 pyrimidine), 160.2 (C-2 pyrimidine), 161.9 (C-5 oxadiazole), 166.3 (C-4 pyrimidine), 166.5 (C-6 pyrimidine), 168.8 (C-2 oxadiazole), 170.1 (CO).

Method B. To a mixture of compound **5** (10 mmol, 2.83 g) and sodium ethoxide [prepared from sodium (10 mmol, 0.23 g) dissolved in anhydrous C_2H_5OH (40 ml)] ethyl chloroacetate (10 mmol, 1.23 g) was added dropwise. The reaction mixture was refluxed for 1 h, then filtered. The filtrate was concentrated *in vacuo* to a small volume (~10 ml) and cooled. The solid was filtered off and recrystallized from cyclohexane. Yield 2.4 g (65%).

3-Dialkylaminomethyl-5-(2-dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione (7a–c) (General procedure). To a suspension of compound **5** (5 mmol, 1.415 g) and triethylamine (5 mmol, 0.51 g) in C_2H_5OH (30 ml) corresponding amine (5 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 1 h, then the solid was filtered off. After evaporation of the solvent *in vacuo* to a half of volume the additional amount of product was obtained. The solids were combined, dried and recrystallized from cyclohexane (**7a**, **7c**) or hexane (**7b**).

3-Dimethylaminomethyl-5-(2-dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione (7a): Yield 91%, m.p. 115–116°C. Anal. calcd. for $C_{13}H_{20}N_6OS_2$ (340.47): C, 45.86; H, 5.92; N, 24.68%. Found: C, 45.64; H, 5.97; N, 24.94%. ^{1}H NMR: 2.22 (s, 3H, CH_3), 2.35 (s, 6H, $CH_2N(\underline{C}H_3)_2$), 3.19 (s, 6H, $N(CH_3)_2$), 4.45 (s, 2H, SCH_2), 4.85 (s, 2H, NCH_2), 6.32 (s, 1H, CH-5). IR (cm^{-1}): 1616 (C=N), 1571, 1543 (C=C), 1330 (C=S), 1225, 1025 (C-O-C). ^{13}C NMR: 23.0 (SCH_2), 24.6 (CH_3), 37.5 ($N(CH_3)_2$-2 pyrimidine), 42.9 ($CH_2N(\underline{C}H_3)_2$), 71.7 ($NCH_2$), 106.0 (C-5 pyrimidine), 160.0 (C-5 oxadiazole), 161.8 (C-2 pyrimidine), 165.0 (C-6 pyrimidine), 166.7 (C-4 pyrimidine), 179.8 (C-2 oxadiazole).

5-(2-Dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-3-pyrrolidinomethyl-1,3,4-oxadiazole-2-thione (7b): Yield 78%, m.p. 99–100°C. Anal. calcd. for $C_{15}H_{22}N_6OS_2$ (366.51): C, 49.20; H, 6.05; N, 22.92%. Found: C, 48.93; H, 6.04; N, 23.05%. ^{1}H NMR: 1.69 (m, 4H, $(CH_2)_2$), 2.25 (s, 3H, CH_3), 2.79 (m, 4H, $N(CH_2)_2$), 3.16 (s, 6H, $N(CH_3)_2$), 4.37 (s, 2H, SCH_2), 6.28 (s, 1H, CH-5); 5.05 (s, 2H, NCH_2). IR (cm^{-1}): 1616 (C=N), 1551 (C=C), 1346 (C=S), 1221, 1037 (C–O–C). ^{13}C NMR: 23.0 (SCH_2), 24.6 (CH_3), 24.6 ($2CH_2$ pyrrolidine), 37.5 ($N(CH_3)_2$), 50.6 ($N(CH_2)_2$ pyrrolidine), 66.9 (NCH_2), 106.1 (C-5 pyrimidine), 160.0 (C-5 oxadiazole), 161.8 (C-2 pyrimidine), 165.1 (C-6 pyrimidine), 166.7 (C-4 pyrimidine), 179.0 (C-2 oxadiazole).

5-(2-Dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-3-morpholinomethyl-1,3,4-oxadiazole-2-thione (7c): Yield 73%, m.p. 132–133°C. Anal. calcd. for $C_{15}H_{22}N_6O_2S_2$ (382.51): C, 47.10; H, 5.8; N, 21.97%. Found: C, 47.51; H, 5.83; N, 21.88%. ^{1}H NMR: 2.25 (s, 3H, CH_3), 2.70 (m, 4H, $O(CH_2)_2$), 3.16 (s, 6H, $N(CH_3)_2$), 3.65 (m, 4H, $N(CH_2)_2$), 4.38 (s, 2H, SCH_2), 4.92 (s, 2H, NCH_2), 6.28 (s, 1H, CH-5). IR (cm^{-1}): 1622 (C=N), 1551 (C=C), 1342 (C=S), 1226, 1039 (C–O–C). ^{13}C NMR: 22.9 (SCH_2), 24.7 (CH_3), 37.6 ($N(CH_3)_2$), 51.1 ($N(CH_2)_2$ morpholine), 67.3 ($O(CH_2)_2$ morpholine), 70.8 (NCH_2), 106.1 (C-5 pyrimidine), 160.1 (C-5 oxadiazole), 161.8 (C-2 pyrimidine), 164.9 (C-6 pyrimidine), 166.7 (C-4 pyrimidine), 179.2 (C-2 oxadiazole).

3-Acetyl-5-(2-dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione (8a). To a solution of 1,3,4-oxadiazole-2-thione **5** (5 mmol, 1.415 g) and triethylamine (5 mmol, 0.51 g) in dry acetonitrile (50 ml) acetic anhydride (5.2 mmol, 0.57 g) was added dropwise at 5–8°C. The stirred reaction mixture was allowed to warm to room temperature and then maintained at this temperature for 0.5 h. The solid was filtered off and recrystallized from ethanol. Yield 0.83 g (51%), m.p. 160–162°C. Anal. calcd. for $C_{12}H_{15}N_5O_2S_2$ (325.42): C, 44.29; H, 4.65; N, 21.52%. Found: C, 44.60; H, 4.57; N, 21.67%. ^{1}H NMR: 2.26 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.18 (s, 6H, $N(CH_3)_2$), 4.38 (s, 2H, SCH_2), 6.28 (s, 1H, CH-5). IR (cm^{-1}): 1764 (C=O), 1646 (C=N), 1559 (C=C), 1337 (C=S), 1220, 1036 (C–O–C). ^{13}C NMR: 22.8 (SCH_2), 24.6 (CH_3), 24.9 ($CO\underline{C}H_3$), 37.6 ($N(CH_3)_2$), 105.9 (C-5 pyrimidine), 159.8 (C-5 oxadiazole), 161.8 (C-2 pyrimidine), 164.8 (C-6 pyrimidine), 167.0 (C-4 pyrimidine), 168.2 (NCO), 176.0 (C-2 oxadiazole).

3-Benzoyl-5-(2-dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl-1,3,4-oxadiazole-2-thiione (8b). Compound **8b** was synthesized as described for **8a**. Benzoyl chloride (0.005 mol, 0.73 g) was added dropwise at 18–20°C. Yield 1.14 g (59%), m.p. 135–136°C (from ethanol). Anal. calcd. for $C_{17}H_{17}N_5O_2S_2$ (387.49): C, 52.70; H, 4.42; N, 18.07%. Found: C, 52.91; H, 4.42; N, 18.11%. ^{1}H NMR: 2.33 (s, 3H, CH_3), 3.16 (s, 6H, $N(CH_3)_2$), 4.45 (s, 2H, SCH_2), 6.34 (s, 1H, CH-5); 7.70 (m, 5H, C_6H_5). IR (cm^{-1}): 1731 (C=O), 1641 (C=N), 1598, 1559 (C=C), 1323 (C=S), 1208, 1026 (C–O–C). ^{13}C NMR: 22.9 (SCH_2), 24.7 (CH_3), 37.5 ($N(CH_3)_2$), 106.1 (C-5 pyrimidine), 128.8, 131.4, 134.4 (C_6H_5), 159.2 (C-5 oxadiazole), 161.8 (C-2 pyrimidine), 164.8 (C-6 pyrimidine), 166.9 (C-4 pyrimidine), 168.3 (3-NCO), 176.3 (C-2 oxadiazole).

3-Cyanoethyl-5-(2-dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione (9). A mixture of 1,3,4-oxadiazole-2-thione **5** (2 mmol, 0.567 g), triethylamine (10 mmol, 1.01 g) and acrylonitrile (20 mmol, 1.06 g) in anhydrous C_2H_5OH (10 ml) was heated at reflux for 5 h. The solvent was removed *in vacuo* and the solid residue was recrystallized from ethanol. Yield 0.42 g (62%), m.p.

130–132°C. Anal. calcd. for $C_{13}H_{16}N_6OS_2$ (336.44): C, 46.41; H, 4.79; N, 24.98%. Found: C, 46.71; H, 4.78; N, 24.8%. ^{1}H NMR: 2.25 (s, 3H, CH_3), 2.90 (t J = 6 Hz, 2H, CH_2), 3.17 (s, 6H, $N(CH_3)_2$), 4.31 (s, 2H, SCH_2), 4.40 (t J = 6 Hz, 2H, NCH_2), 6.27 (s, 1H, CH-5). IR (cm^{-1}): 2254 (CN), 1624 (C=N), 1552 (C=C), 1318 (C=S), 1223, 1022 (C–O–C). ^{13}C NMR: 16.4 ($\underline{C}H_2CN$), 22.7 (SCH_2), 24.5 (CH_3), 37.5 ($N(CH_3)_2$), 45.0 (NCH_2), 105.9 (C-5 pyrimidine), 116.3 (CN), 160.9 (C-5 oxadiazole), 161.7 (C-2 pyrimidine), 164.6 (C-6 pyrimidine), 166.7 (C-4 pyrimidine), 177.2 (C-2 oxadiazole).

Anti-inflammatory activity of the synthesized compounds. For anti-inflammatory activity tests adult male Wistar strain rats were used. Each experiment was made with five groups of rats, 10 animals each. All test compounds and the reference drugs were suspended in 0.5% carboxymethylcellulose solution and administered orally. Carrageenin-induced hind paw oedema in rats was produced by the method of Winter *et al*. [12]. Hind paw volume was measured with an electronic onkograph immediately before and 1, 2, 3 and 5 h after the carrageenin injection. The results were compared with those of control rats. Bentonite-induced hind paw oedema was studied as described in [13]. The data were evaluated statistically using Student's t-test. A level of $p < 0.05$ was adopted as the test of significance. The tests of acute toxicity of the compounds were done on male BALB/C strain mice [14].

REFERENCES

1. Pancechowska-Ksepko D., Foks H., Landowska E., Janowiec H. and Zwolska-Kwiek Z., *Acta Pol. Pharm*., **43**, 116 (1986).
2. Krasovsky A.N., Bulgakov A.K., Andrushko A.P., Krasovsky I.A., Djachenko A.M., Bokun A.A., Kravchenko N.A. and Demchenko A.M., *Khim.-Pharm. Zh*., **34**, 13 (2000).
3. Yamamoto S., Jap. Pat. 05124948; *C.A*., **119**, 146370 (1993).
4. Bochelli D.H., Connor D.T., Kostlan C.R., Kramer J.B., Mullican M.D. and Sircar J.Ch., EP Pat. 449211; *C.A*., **116**, 6570 (1992).
5. Bellioti T.R., Connor D.T. and Kostlan C.R., WO Pat. 9213844; *C.A*., **118**, 6990 (1993).
6. Song I., Connor D.T., Sercel A.D., Soreson R.J., Doubledoy R., Unangst P.C., Roth B.D., Beylin V.G., Gilbersten R.B., Chan K., Schrier D., Guglieta A., Bornemeier D. and Dyer R.D., *J. Med. Chem*., **42**, 1161 (1999).
7. Eckhardt W., Beriger E. and Zondler H., EP Pat. 371925; *C.A*., **113**, 191385 (1990).
8. Bettarini F., Capuzzi L., La Porta P., Massimini S. and Caprioli V., EP Pat. 533276; *C.A*., **119**, 49400 (1993).
9. Mekuškiene G., Vainilavičius P., Hetzheim A. and Šematovič R., *Khim. Geterotsikl. Soedin*., **5**, 700 (1993).
10. Matsukawa T. and Ohta B., *J. Pharm. Soc. Jap*., **70**, 134 (1950).
11. Vainilavicius P.J., Burbuliene M.-M.V., Rocka V.-S.M. and Lauciuviene N.-D.I., *Khim.- Pharm. Zh*., **16**, 931 (1982).
12. Winter C.A., Risley E.A. and Nuss G.W., *Proc. Soc. Exp. Biol. Med*., **3**, 544 (1962).
13. Marek J., *Pharmazie***, 36**, 46 (1981).
14. Litchfield J.T. and Wilkoxon F., *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).