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Synthesis of New Derivatives of 5-Alkyl-6-(2,6-dihalobenzyl)-2-(methylsulfanyl)pyrimidin-4(3*H*)-one and the Features of Their Oxidation

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Abstract—The synthesis and features of the regioselective S-monomethylation of new 5-alkyl-6-(arylmethyl)-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-ones were investigated, and also the character of the oxidative degradation of these compounds when treated with the system H_2O_2–AcOH.

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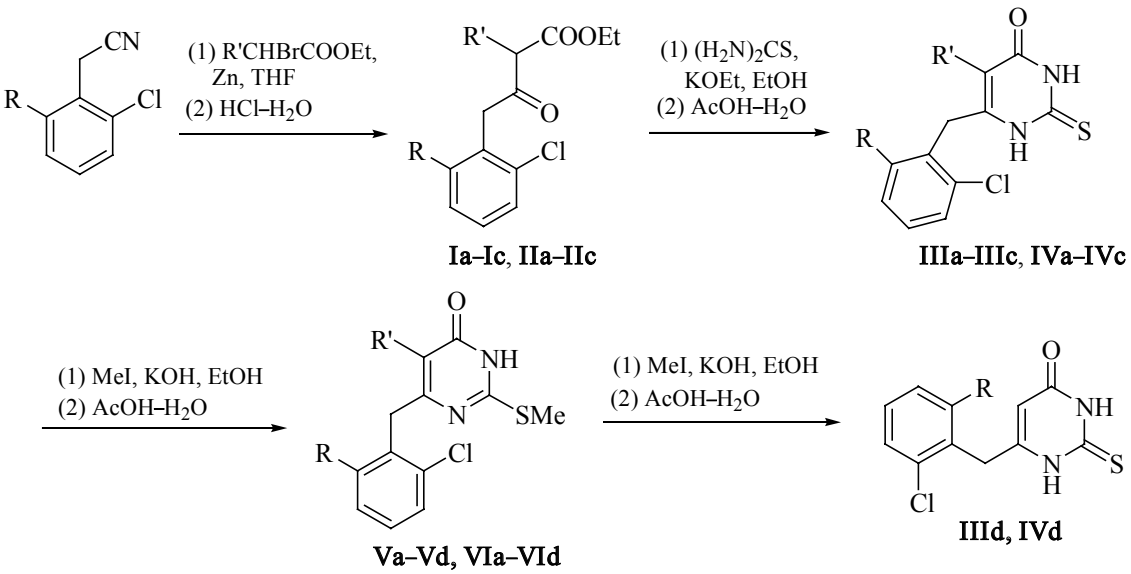
Many derivatives of 6-(arylmethyl)-2-(methylsulfanyl) pyrimidin-4(3*H*)-one are the key intermediates in the synthesis of highly active antiviral drugs [1–4]. In this connection we synthesized new derivatives of 5-alkyl-6-(2,6-dichlorobenzyl)-2-(methylsulfanyl)pyrimidin-4(3*H*)-one and 5-alkyl-6-(2-fluoro-6-chlorobenzyl)-2-(methylsulfanyl)pyrimidin-4(3*H*)-one and studied certain feature of their chemical behavior (Scheme 1).

We established that the yield of the condensation products of 3-oxoesters with thiourea decreased at the growth and branching of the alkyl substituent in the position *2* of the 3-oxoester molecule. Evidently this is due both to the steric influence of the alkyl group and to its positive inductive effect (reducing the CH-acidity of the 3-oxoester).

It was also shown that the reaction of the obtained 2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one derivatives with methyl iodide in 96% ethanol in the presence of

Scheme 1.



R = F (**I, IV, VI**), Cl (**II, III, V**); R' = Me (**a**), Et (**b**), *i*-Pr (**c**), H (**d**).

KOH proceeded relatively regioselectively giving virtually exclusively the products of the S-monomethylation even at the fivefold excess of the alkylating agent. The similar reaction carried out in anhydrous DMF in the presence of K_2CO_3 always resulted in complex mixtures of polyalkylated products. Thus in the reaction occurring in a protic solvent the 4-(arylmethyl)-6-oxo-1,6-dihydro-2-pyrimidinethiolate anion is surrounded with a tight solvate shell due to the existence of the hydrogen bonds. The destruction of this solvate shell evidently requires considerable energy consumption, therefore the reaction with methyl iodide proceeds prevailingly with the most nucleophilic tautomeric form, 4-(arylmethyl)-6-oxo-1,6-dihydro-2-pyrimidinethiolate anion. In the reaction in DMF medium the anion is surrounded with less tight solvate shell than in the case of lower alcohols, it is relatively weak, and the methyl iodide reacts both with the more nucleophilic 4-(arylmethyl)-6-oxo-1,6-dihydro-2-pyrimidinethiolate anion and with the other tautomeric forms of this anion where the negative charge is delocalized predominantly on one of the nitrogen atoms or on the oxygen atom. The high reactivity of the methyl iodide in this case compensates the difference in the nucleophilicity of these anions.

We investigated the reaction of compounds **VIa**, **VIb**, and **VId** with hydrogen peroxide in acetic acid aiming at the probable preparation of the corresponding sulfones.

In this case in contrast to the other 2-(alkylsulfanyl)-4(3*H*)-pyrimidinones the oxidation of the substances under study with hydrogen peroxide in acetic acid did not allow the isolation of sulfones. The only separated reaction products were the corresponding uracils.

The probable reason of this phenomenon is the high mobility of the methylsulfonyl group and consequently the easy hydrolysis of the obtained sulfone (addition–elimination mechanism).

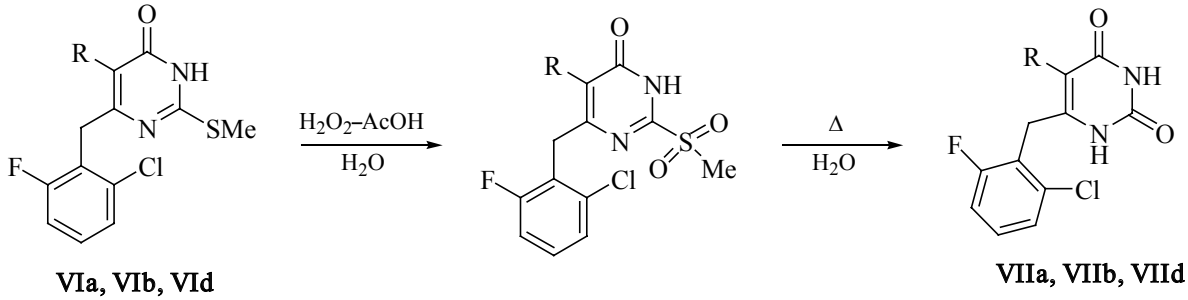
The data obtained allow a conclusion that the regioselectivity of the methylation of the 2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one derivatives depends to a high degree on the chemical character of the solvent, and the corresponding products are so prone to the solvolysis that it results in their hydrolytic cleavage in the reaction mixture.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian Mercury 300 BB at the operating frequency 300.73 MHz from solutions of compounds in DMSO-d_6, internal reference HMDS. Mass spectra were measured on a GC-MS instrument Varian MAT-111 in the mode of the direct admission of the sample into the ion source, ionizing electrons energy 70eV. Melting points were determined on Fisher–Johns heating block (Cole Palmer) at the heating rate 10 deg/min. The homogeneity of compounds obtained was proved by TLC on Alugram Nano-SIL G/UV_{254} plates, development under UV irradiation.

Ethyl 3-oxo-4-(2-fluoro-6-chlorophenyl)-2-ethylbutanoate (Ib). To a mixture of 140 ml of anhydrous THF and 12.8 g (0.196 mg-at) of zinc turnings was added several drops of ethyl 2-bromobutanoate, the mixture was boiled at stirring till the appearance of green color, 5.53 g (34.89 mmol) of 2-(2-fluoro-6-chlorophenyl)acetonitrile was charged, and dropwise was added 31.8 g (24 ml, 163.0 mmol) ethyl 2-bromobutanoate. The mixture was boiled at stirring for another 30 min, the solution was decanted, and THF was distilled off at a reduced pressure. To the residue 250 ml of toluene and 90 ml of 3 N HCl was poured, the mixture was stirred for 1.5 h at room temperature, the organic phase was separated, washed with water till neutral washings, dried with $MgSO_4$, concentrated at a reduces pressure, and the product was distilled in a

Scheme 2.



VIa, VIb, VId **VIIa, VIIb, VIId**

R = Me (**a**), Et (**b**), H (**d**).

vacuum. Yield 9.35 g (81%), bp 135–146°C (1 mm Hg). Found, %: C 59.04; H 5.22. $[M]^+$ 286. $C_{14}H_{16}ClFO_3$. Calculated, %: C 58.64; H 5.62. *M* 286.73.

Compounds **Ia, Ic, IIa–IIc** were similarly prepared.

Ethyl 2-methyl-3-oxo-4-(2-fluoro-6-chlorophenyl)-butanoate (Ia) was obtained using ethyl 2-bromo-propanoate. Yield 78%, bp 125–128°C (1 mm Hg). Found, %: C 57.04; H 5.12. $[M]^+$ 272. $C_{13}H_{14}ClFO_3$. Calculated, %: C 57.26; H 5.17. *M* 272.7.

Ethyl 2-isopropyl-3-oxo-4-(2-fluoro-6-chloro-phenyl)butanoate (Ic) was obtained using ethyl 2-bromo-3-methylbutanoate. Yield 63%, bp 147–157°C (1 mm Hg), mp 50–51.5°C (hexane). Found, %: C 60.04; H 5.89. $[M]^+$ 300. $C_{15}H_{18}ClFO_3$. Calculated, %: C 59.90; H 6.03. *M* 300.7.

Ethyl 2-methyl-3-oxo-4-(2,6-dichlorophenyl)butanoate (IIa) was obtained from 2-(2,6-dichlorophenyl) acetonitrile and ethyl 2-bromopropanoate. Yield 78%, bp 143–150°C (0.6 mm Hg), mp 98–99°C (hexane) {98–99°C (hexane) [5]}.

Ethyl 3-oxo-4-(2,6-dichlorophenyl)-2-ethylbutanoate (IIb) was obtained from 2-(2,6-dichlorophenyl) acetonitrile and ethyl 2-bromobutanoate. Yield 65%, bp 148–153°C (0.5 mm Hg). Found, %: C 55.04; H 5.22. $[M]^+$ 303. $C_{14}H_{16}Cl_2O_3$. Calculated, %: C 55.46; H 5.32. *M* 303.2.

Ethyl 2-isopropyl-3-oxo-4-(2,6-dichlorophenyl)butanoate (IIc) was obtained from 2-(2,6-dichlorophenyl) acetonitrile and ethyl 2-bromo-3-methylpropanoate. Yield 62%, bp 158–164°C (0.6 mm Hg), mp 66–68°C (hexane). Found, %: C 56.41; H 5.62. $[M]^+$ 317. $C_{15}H_{18}Cl_2O_3$. Calculated, %: C 56.80; H 5.72. *M* 317.2.

5-Isopropyl-2-thioxo-6-(2,6-dichlorobenzyl)-2,3-dihydropyrimidin-4(1*H*)-one (IIIc). A mixture of 3.4 g (10.7 mmol) of compound **IIc**, 5.4 g (64.1 mmol) of potassium ethoxide, and 3.3 g (43.4 mmol) of thiourea in anhydrous ethanol was boiled for 96 h, the solvent was removed in a vacuum, the residue was dissolved in water and filtered. The filtrate was acidified with acetic acid to pH 5–6, the separated precipitate was filtered off, washed with 10 ml of 96% ethanol, 30 ml of ether, dried, and recrystallized. Yield 1.1 g (31%), mp 266.5–267.5°C (acetonitrile) {262–264°C (96% ethanol) [1]}.

Compounds **IIIa, IIIb, IVa–IVd** were similarly obtained.

5-Methyl-2-thioxo-6-(2,6-dichlorobenzyl)-2,3-dihydropyrimidin-4(1*H*)-one (IIIa) was obtained from compound **IIa**. Yield 79%, mp 268–270°C (96% ethanol) {258–260°C (96% ethanol) [5]}.

5-Ethyl-2-thioxo-6-(2,6-dichlorobenzyl)-2,3-dihydropyrimidin-4(1*H*)-one (IIIb) was obtained from compound **IIb**. Yield 81%, mp 272–274°C (acetonitrile) {270–271°C (96% ethanol) [1]}.

2-Thioxo-6-(2,6-dichlorobenzyl)-2,3-dihydropyrimidin-4(1*H*)-one (IIId) was obtained by procedure [6]. Yield 84%, mp 318–321°C (acetic acid).

5-Methyl-2-thioxo-6-(2-fluoro-6-chlorobenzyl)-2,3-dihydropyrimidin-4(1*H*)-one (IVa) was obtained from compound **Ia**. Yield 84%, mp 253°C (decomp., 96% ethanol) {253–254°C (96% ethanol) [1]}.

5-Ethyl-2-thioxo-6-(2-fluoro-6-chlorobenzyl)-2,3-dihydropyrimidin-4(1*H*)-one (IVb) was obtained from compound **Ib**. Yield 31%, mp 228–230°C (acetonitrile) {228–230°C (acetonitrile) [1]}.

5-Isopropyl-2-thioxo-6-(2-fluoro-6-chloro-benzyl)-2,3-dihydropyrimidin-4(1*H*)-one (IVc) was obtained from compound **Ic**. Yield 32%, mp 240–242°C (acetonitrile) {240–242°C (96% ethanol) [1]}.

2-Thioxo-6-(2-fluoro-6-chlorobenzyl)-2,3-dihydropyrimidin-4(1*H*)-one (IVd) was obtained by procedure [6]. Yield 78%, mp 268–270.5°C (acetic acid).

2-(Methylsulfanyl)-6-(2,6-dichlorobenzyl)-5-ethylpyrimidin-4(3*H*)-one (Vb). To a solution of 84.8 mg (1.4 mmol) of KOH in 25 ml of 96% ethanol was added 400 mg (1.27 mmol) of compound **IIIb**, the mixture was stirred till dissolution, and 0.4 ml (6.35 mmol) of methyl iodide was added, and then the mixture was stirred for another 1 h. Then it was diluted with 70 ml of water, acidified with acetic acid till pH 5, the precipitate was filtered off, dried till constant weight, and recrystallized. Yield 276 mg (66%), mp 246–249°C (96% ethanol–DMF). Found, %: C 51.05; H 4.22; N 8.81. $[M]^+$ 329. $C_{14}H_{14}Cl_2N_2OS$. Calculated, %: C 51.07; H 4.29; N 8.51. *M* 329.2.

Compounds **Va, Vc, Vd, VIa–VId** were similarly obtained.

5-Methyl-2-(methylsulfanyl)-6-(2,6-dichlorobenzyl)pyrimidin-4(3*H*)-one (Va) was obtained from compound **IIIa**. Yield 43%, mp 262–264°C (96% ethanol–DMF) {260–261°C (benzene–cyclohexane) [5]}.

2-(Methylsulfanyl)-6-(2,6-dichlorobenzyl)-5-isopropylpyrimidin-4(3*H*)-one (Vc) was obtained from compound **IIIc**. Yield 50%, mp 247–248°C (toluene). Found, %: C 52.00; H 4.81; N 8.50. $[M]^+$ 343. $C_{15}H_{16}Cl$-

$_2N_2OS$. Calculated, %: C 52.48; H 4.70; N 8.16. *M* 343.3.

2-(Methylsulfanyl)-6-(2,6-dichlorobenzyl)-pyrimidin-4(3*H*)-one (Vd) was obtained analogously from compound **IIId**. Yield 65%, mp 238–241°C (96% ethanol–DMF) {237–238°C (benzene) [5]}.

5-Methyl-2-(methylsulfanyl)-6-(2-fluoro-6-chlorobenzyl)pyrimidin-4(3*H*)-one (VIa) was obtained from compound **IVa**. Yield 62%, mp 241°C (96% ethanol–DMF). ^{1}H NMR spectrum, δ, ppm: 2.12 s (3H, CH_3), 2.13 s (3H, CH_3), 3.99 s (2H, CH_2), 6.91 m (1H, CH), 7.09 m (2H, CH), 11.68 s (1H, NH). Found, %: C 52.04; H 4.22; N 8.99. $[M]^+$ 298. $C_{13}H_{12}ClFN_2OS$. Calculated, %: C 52.26; H 4.05; N 9.38. *M* 298.8.

2-(Methylsulfanyl)-6-(2-fluoro-6-chlorobenzyl)-5-ethylpyrimidin-4(3*H*)-one (VIb) was obtained from compound **IVb**. Yield 75%, mp 209–211°C (96% ethanol–DMF). ^{1}H NMR spectrum, δ, ppm: 1.01 t (3H, CH_3, *J* 8.33 Hz), 1.09 s (2H, CH_2), 2.00 s (3H, CH_3), 3.98 s (2H, CH_2), 7.14 m (1H, CH), 7.28 m (2H, CH), 12.49 s (1H, NH). Found, %: C 54.04; H 4.56; N 9.07. $[M]^+$ 312. $C_{14}H_{14}ClFN_2OS$. Calculated, %: C 53.76; H 4.51; N 8.96. *M* 312.8.

2-(Methylsulfanyl)-6-(2-fluoro-6-chlorobenzyl)-5-isopropylpyrimidin-4(3*H*)-one (Vc) was obtained from compound **IVc**. Yield 55%, mp 227–228°C (toluene). Found, %: C 55.52; H 5.02; N 9.00. $[M]^+$ 326. $C_{15}H_{16}ClFN_2OS$. Calculated, %: C 55.12; H 4.94; N 8.57. *M* 326.8.

2-(Methylsulfanyl)-6-(2-fluoro-6-chlorobenzyl)pyrimidin-4(3*H*)-one (VId) was obtained from compound **IVd**. Yield 60%, mp 217–219.5°C (96% ethanol–DMF). ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 3.90 s (2H, CH_2), 5.70 s (1H, CH), 7.20 m (1H, CH), 7.30 m (2H, CH). Found, %: C 51.04; H 3.54; N 9.90. $[M]^+$ 284. $C_{12}H_{10}ClFN_2OS$. Calculated, %: C 50.62; H 3.54; N 9.84. *M* 284.7.

6-(2-Fluoro-6-chlorobenzyl)pyrimidin-2,4(1*H*,3*H*)-dione (VIId). A mixture of 10 ml of AcOH, 0.9 ml (38.7 mmol) of 30% H_2O_2, and 0.411 g (1.43 mmol) of compound **IVd** was heated for 7 h at 75°C. Then the volume of the reaction mixture was filled with water to 100 ml, and 6 h later the precipitate formed was filtered off, recrystallized, and dried to the constant weight. Yield 0.162 g (35%), mp 268–269°C (acetone–toluene). ^{1}H NMR spectrum, δ, ppm: 1.69 s (3H, CH_3), 3.68 s (2H, CH_2), 7.24 m (3H, CH), 10.73 br.s (1H, NH), 10.97 br.s (1H, NH). Found, %: C 52.01; H 3.20; N 11.00. $[M]^+$ 254. $C_{11}H_8ClFN_2O_2$. Calculated, %: C 51.88; H 3.17; N 11.00. *M* 254.6.

Compounds **VIIa, VIIb** were similarly obtained.

5-Methyl-6-(2-fluoro-6-chlorobenzyl)pyrimidin-2,4(1*H*,3*H*)-dione (VIIa) was obtained from compound **VIa**. Yield 18%, mp >300°C (acetone–toluene). ^{1}H NMR spectrum, δ, ppm: 3.75 s (2H, CH_2), 4.50 s (1H, CH), 7.27 m (2H, CH), 7.37 s (1H, CH), 10.99 br.s (1H, NH), 11.13 br.s (1H, NH). Found, %: C 54.04; H 4.10; N 10.08. $[M]^+$ 268. $C_{12}H_{10}ClFN_2O_2$. Calculated, %: C 53.65; H 3.75; N 10.43. *M* 268.7.

6-(2-Fluoro-6-chlorobenzyl)-5-ethylpyrimidin-2,4(1*H*,3*H*)-dione (VIIb) was obtained from compound **Vb**. Yield 48%, mp 271–272°C (acetone–toluene). ^{1}H NMR spectrum, δ, ppm: 0.47 t (3H, CH_3, *J* 8 Hz), 2.05 m (2H, CH_2), 3.88 s (1H, CH), 7.20 m (1H, CH), 7.40 m (2H, CH), 10.72 br.s (1H, NH), 10.99 br.s (1H, NH). Found, %: C 55.04; H 4.22; N 10.01. $[M]^+$ 282. $C_{13}H_{12}ClFN_2O_2$. Calculated, %: C 55.23; H 4.28; N 9.91. *M* 282.7.

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