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Synthesis of S-(5-aryl-1,3,4-oxadiazol-2-yl) O-alkyl carbonothioate and alkyl 2-((5-aryl-1,3,4-oxadiazol-2-yl)thio) acetate, and their antimicrobial properties

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Abstract: The S-(5-aryl-1,3,4-oxadiazol-2-yl) O-alkyl carbonothioate (4-9) and the alkyl 2-((5-aryl-1,3,4-oxadiazol-2-yl)thio) acetate (10-15) were synthesized by interaction of 5-aryl-1,3,4-oxadiazole-2-thiones with alkyl esters of chloroformic acid and chloroacetic acid. The yields of target compounds (7-9) obtained with isobutyl chloroformate were 69-73%, compounds (4-6) with propyl chloroformate - 74-79% and compounds (10-15) with alkyl esters of chloroacetic acid - 86-92%, respectively. The structures of the synthesized compounds were confirmed by IR, UV, ^{1}H and ^{13}C NMR spectra. The antibacterial and antifungal activities of these compounds were investigated. The results of in *vitro* antimicrobial activity tests showed that S-(5-phenyl(2-chlorophenyl)-1,3,4-oxadiazol-2-yl) O-propyl carbonothioate (4-5) and S-(5-phenyl(2-chlorophenyl)-1,3,4-oxadiazol-2-yl) O-isobutyl carbonothioate (7-8) exhibited weak, but selective antibacterial activity against gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*). At the same time, no activity was shown by compounds with two chlorine atoms in the aromatic ring (13-15) and alkyl 2-((5-aryl-1,3,4-oxadiazol-2-yl) thio) acetate (10-15).

Keywords: 5-aryl-1,3,4-oxadiazole-2-thiones; alkyl esters of chloroformic acid and chloroacetic acid; antibacterial and antifungal activities.

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1. INTRODUCTION

A wide interest in the chemistry of derivatives of 5-substituted-1,3,4-oxadiazole-2-thiones is associated with a broad variety of biological and physiological activities exhibited by their derivatives. Recently, numerous works on synthesis and biological activities such as antibacterial, antifungal, antiviral, anticonvulsant, anti-inflammatory, antitumor of 5-substituted-1,3,4-oxadiazole-2-thione derivatives were reported (1-10). A distinctive structural feature of 5-aryl-1,3,4-oxadiazol-2-thiones is the presence of an ambident thioamide group NH-C=S in their molecule, therefore, depending on the nature of the attacking electrophilic agent, derivatives can be obtained at the exocyclic sulfur atom, and on the endocyclic nitrogen atom or simultaneously on both reaction centers (S- or N-). Continuing the research (11-13) on the synthesis of various derivatives of oxadiazole-2-thiones, in this work we have investigated the synthesis of derivatives of S-(5-aryl-1,3,4-oxadiazol-2-yl)O-alkyl carbonothioate and alkyl 2-((5-aryl-1,3,4-oxadiazol-2-yl)thio)acetate, as well as their antimicrobial activity.

2. EXPERIMENTAL SECTION

2.1. General Considerations

UV spectra of the synthesized compounds were recorded on the Perkin Elmer Lambda-16 spectrophotometer in ethanol, IR spectra on the FTIR system-2000 (Perkin Elmer) Fourier spectrometer in KBr tablets. ^{1}H and ^{13}C NMR spectra were recorded on a Unity 400 spectrometer at working frequencies 400 and 100 MHz, respectively, at 20-25°C in $CDCl_3$, with HMDS internal standard. The reaction flow and the individuality of the obtained compounds were controlled by TLC on ALUGRAM® SIL G/UV254 plates in the CHCl3-EtOH system, 24:1, visualization in UV light. Melting points were determined using a Boethius hot-stage microscope.

2.2. General Procedure for the Synthesis of S-(5-aryl-1,3,4-oxadiazol-2-yl) O-alkyl carbonothioate 4-9 and alkyl 2-((5-aryl-1,3,4-oxadiazol-2-yl)thio)acetate (10-15).

5-Aryl-1,3,4-oxadiazole-2-thions (**1-3**) were synthesized according to the method (14).

Equimolar amounts of 5-aryl-1,3,4-oxadiazole-2-thion, corresponding alkyl esters of chloroformic acid (alkyl chloroformates) or chloroacetic acid and K_2CO_3 were boiled in dry acetone for 5 hours. The reaction was controlled by TLC. Then the solvent was removed from the mixture. The residue was sequentially washed with water, NaOH solution (2-3%) and then again with water until a neutral reaction. After air drying, target products (**4-15**) were obtained.

2.2.1. S-(5-phenyl-1,3,4-oxadiazol-2-yl) O-propyl carbonothioate (4)

White powder, yield 74%, mp 89-90°C (from ethanol); R_f = 0,66; UV (ethanol), λ_{max} (nm): 286. IR (KBr, cm^{-1}) ν: 1788 ($COOC_3H_7$), 1220 (C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.05 (3H, t, J = 7.4 Hz, CH_3), 1.86 (2H, sextet, J = 7.3 Hz, CH_2-CH_3), 4.44 (2H, t, J = 6.6 Hz, O-CH_2), 7.50 (2H, t, J = 7.2 Hz, ArH-3′, 5′), 7.59 (1H, t, J = 7.4 Hz, ArH-4′), 7.98 (2H, dd, J = 7.2, 1.4 Hz, ArH-2′, 6′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.38 (C-11), 21.95 (C-10), 71.15 (C-9), 121.64 (C-1′), 127.21 (C-2′, 6′), 129.31 (C-3′, 5′), 133.25 (C-4′), 148.19 (C-2), 158.55 (C-5), 174.10 (C-7).

2.2.2. S-(5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl) O-propyl carbonothioate (5)

White powder, yield 69%, mp 84-85°C (from ethanol); R_f = 0,61; UV (ethanol), λ_{max} (nm): 283; IR (KBr, cm^{-1}) ν: 1769($COOC_3H_7$), 1197(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.05 (3H, t, J = 7.4 Hz, CH_3), 1.85 (2H, sextet, J = 7.2 Hz, CH_2-CH_3), 4.44 (2H, t, J = 6.6 Hz, O-CH_2), 7.41 (1H, t, J = 7.1 Hz, ArH-4′), 7.51 (1H, t, J = 7.1 Hz, ArH-3′), 7.55 (1H, dd, J = 8.0, 1.2 Hz, ArH-2′), 7.90 (1H, dd, J = 7.9, 1.3 Hz, ArH-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.36 (C-11), 21.94 (C-10), 71.17 (C-9), 120.91 (C-1′), 127.29 (C-3′), 131.10 (C-2′), 131.66 (C-5′), 133.66 (C-4′), 133.83 (C-6′), 148.01 (C-2), 156.82 (C-5), 173.62 (C-7).

2.2.3. S-(5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl) O-propyl carbonothioate (6)

White powder, yield 73%, mp 132-133°C (from ethanol); R_f = 0,63; UV (ethanol), λ_{max} (nm): 284; IR (KBr, cm^{-1}) ν: 1778 ($COOC_3H_7$), 1195 (C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.05 (3H, t, J = 7.4 Hz, CH_3), 1.85 (2H, sextet, J = 7.4 Hz, CH_2-CH_3), 4.44 (2H, t, J = 6.6 Hz, O-CH_2), 7.40 (1H, dd, J = 8.5, 2.0 Hz, ArH-3′), 7.57 (1H, d, J = 2.0 Hz, ArH-5′), 7.86 (1H, d, J = 8.5 Hz, ArH-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.35 (C-11), 21.94 (C-10), 71.25 (C-9), 119.41 (C-1′), 127.87 (C-3′), 131.73 (C-5′, 2′), 134.66 (C-6′), 139.62 (C-4′), 147.92 (C-2), 156.05 (C-5), 173.28 (C-7).

2.2.4. S-(5-phenyl-1,3,4-oxadiazol-2-yl) O-isobutyl carbonothioate (7)

White powder, yield 67%, mp 98-99°C (from ethanol); R_f = 0,63; UV (ethanol), λ_{max} (nm): 286; IR (KBr, cm^{-1}) ν: 1765 ($COOCH_2(CH_3)_2$), 1222 (C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.04 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.15 (1H, septet, J = 6.7 Hz, $CH(CH_3)_2$), 4.26 (2H, d, J = 6.6 Hz, O-CH_2), 7.51 (2H, t, J = 7.8 Hz, ArH-3′,5′), 7.59 (1H, t, J = 7.5 Hz, ArH-4′), 7.99 (2H, dd, J = 7.7 and 1.4 Hz, ArH-2′, 6′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.03 (C-11), 19.04 (C-12), 27.85 (C-10), 75.46 (C-9), 121.67 (C-1′) 127.20 (C-2′, 6′), 129.30 (C-3′, 5′), 133.23 (C-4′), 148.21 (C-2), 158.59 (C-5), 174.11 (C-7).

2.2.5. S-(5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl) O-isobutyl carbonothioate (8)

White powder, yield 64%, mp 88-89°C (from ethanol); R_f = 0,65; UV (ethanol), λ_{max} (nm): 282; IR (KBr, cm^{-1}) ν: 1787($COOCH_2(CH_3)_2$), 1226(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.03 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.14 (1H, septet, J = 6.7 Hz, $CH(CH_3)_2$), 4.26 (2H, d, J = 6.5 Hz, O-CH_2), 7.41 (1H, t, J = 7.8 Hz, ArH-3′), 7.51 (1H, dd, J = 8.1 and 1.4 Hz, ArH-4′), 7.55 (1H, dd, J = 8.0, 1.3 Hz, ArH-2′), 7.90 (1H, dd, J = 7.8, 1.4 Hz, ArH-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.99 (C-11,12), 27.84 (C-10), 75.44 (C-9), 120.90 (C-1′), 127.29 (C-3′), 131.06 (C-2′), 131.68 (C-5′), 133.64 (C-4′), 133.83 (C-6′), 148.02 (C-2), 156.81 (C-5), 173.61 (C-7).

2.2.6. S-(5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl) O-isobutyl carbonothioate (9)

White powder, yield 68%, mp 130-131°C (from ethanol); R_f = 0,66; UV (ethanol), λ_{max} (nm): 285; IR (KBr, cm^{-1}) ν: 1772($COOCH_2(CH_3)_2$), 1211(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.03 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.14 (1H, septet, J = 6.7 Hz, $CH(CH_3)_2$), 4.26 (2H, d, J = 6.5 Hz, O-CH_2), 7.40 (1H, dd, J

= 8.5, 2.0 Hz, ArH-3′), 7.57 (1H, d, J = 1.9 Hz, ArH-5′), 7.86 (1H, d, J = 8.5 Hz, ArH-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.99 (C-11,12), 27.84 (C-10), 75.51 (C-9), 119.40 (C-1′), 127.86 (C-3′), 131.70 (C-5′, 2′), 134.66 (C-6′), 139.59 (C-4′), 147.92 (C-2), 156.05 (C-5), 173.28 (C-7).

2.2.7. Propyl 2-((5-phenyl-1,3,4-oxadiazol-2-yl)thio)acetate (10)

White powder, yield 89%, mp 67-68°C (from ethanol); R_f = 0,68; UV (ethanol), λ_{max} (nm): 280; IR (KBr, cm^{-1}) v: 1725($CH_2COOC_3H_7$), 1176(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.92 (3H, t, J = 7.4 Hz, CH_3), 1.65 (2H, sextet, J = 7.2 Hz, CH_2-CH_3), 4.10 (2H, s, S-CH_2), 4.14 (2H, t, J = 6.7 Hz, O-CH_2), 7.45-7.53 (3H, m, ArH-3′,5′,4′), 7.97 (2H, dd, J = 7.6, 1.1 Hz, ArH-2′,6′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.37 (C-12), 21.94 (C-11), 34.49 (C-7), 68.04 (C-10), 123.55 (C-1′), 126.80 (C-2′, 6′), 129.16 (C-3′, 5′), 131.88 (C-4′), 163.02 (C-2), 166.18 (C-5), 167.63 (C-8).

2.2.8. Propyl 2-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetate (11)

White powder, yield 90%, mp 44-45°C (from ethanol), R_f = 0,66; UV (ethanol): λ_{max} (nm): 278; IR (KBr, cm^{-1}) v: 1726 ($CH_2COOC_3H_7$), 1179(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.92 (3H, t, J = 7.4 Hz, CH_3), 1.67 (2H, sextet, J = 6.8 Hz, CH_2-CH_3), 4.11 (2H, s, S-CH_2), 4.14 (2H, t, J = 6.7 Hz, O-CH_2), 7.38 (1H, t, J = 7.7 Hz, ArH-4′), 7.44 (1H, t, J = 7.9 Hz, ArH-3′), 7.52 (1H, dd, J = 8.0, 1.3 Hz, ArH-2′), 7.91 (1H, dd, J = 7.7, 1.8 Hz, ArH-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.37 (C-12), 21.94 (C-11), 34.46 (C-7), 68.08 (C-10), 122.83 (C-1′), 127.20 (C-3′), 131.07 (C-2′), 131.36 (C-5′), 132.58 (C-4′), 133.15 (C-6′), 163.74 (C-2), 164.47 (C-5), 167.55 (C-8).

2.2.9. Propyl 2-((5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetate (12)

White powder, yield 87%, mp 62-64°C (from ethanol), R_f = 0,63; UV (ethanol): λ_{max} (nm): 280; IR (KBr, cm^{-1}) v: 1742($CH_2COOC_3H_7$), 1177(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.92 (3H, t, J = 7.4 Hz, CH_3), 1.67 (2H, sextet, J = 6.8 Hz, CH_2-CH_3), 4.11 (2H, s, S-CH_2), 4.13 (2H, t, J = 6.7 Hz, O-CH_2), 7.36 (1H, dd, J = 8.5, 2.0 Hz, ArH-3′), 7.53 (1H, d, J = 2.0 Hz, ArH-5′), 7.87 (1H, d, J = 8.5 Hz, ArH-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.37 (C-12), 21.93 (C-11), 34.45 (C-7), 68.10 (C-10), 121.35 (C-1′), 127.74 (C-3′), 131.30 (C-2′), 131.70 (C-5′), 133.88 (C-6′), 138.27 (C-4′), 163.74 (C-2), 163.96 (C-5), 167.46 (C-8).

2.2.10. Isopropyl 2-((5-phenyl-1,3,4-oxadiazol-2-yl)thio)acetate (13)

White powder, yield 92%, mp 76-77°C (from ethanol); R_f = 0,65; UV (ethanol), λ_{max} (nm): 276; IR (KBr, cm^{-1}) v: 1772($CH_2COO(CH_3)_2$), 1172(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.25 (3H, s, CH_3), 1.27 (3H, s, CH_3), 4.07 (2H, s, S-CH_2), 5.08 (1H, septet, J = 6.3 Hz, O-CH), 7.45-7.54 (3H, m, ArH-3′,5′,4′), 7.97-8.00 (2H, m, ArH-2′,6′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.78 (C-11,12), 34.81 (C-7), 70.45 (C-10), 123.58 (C-6′), 126.80 (C-2′, 6′), 129.17 (C-3′, 5′), 131.87 (C-4′), 163.07 (C-2), 166.16 (C-5), 167.04 (C-8).

2.2.11. Isopropyl 2-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetate (14)

White powder, yield 88%, mp 66-67°C (from ethanol), R_f = 0,63; UV (ethanol): λ_{max} (nm): 279; IR (KBr, cm^{-1}) v: 1736 ($CH_2COO(CH_3)_2$), 1179(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.25 (3H, s, CH_3), 1.26 (3H, s, CH_3), 4.07 (2H, s, S-CH_2), 5.07 (1H, septet, J = 6.3 Hz, O-CH), 7.37 (1H, t, J = 7.7 Hz, ArH-4′), 7.44 (1H, t, J = 8.0 Hz, ArH-3′), 7.52 (1H, dd, J = 8.1, 1.2 Hz, ArH-2′), 7.91 (1H, dd, J = 7.7, 1.7 Hz, ArH-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.78 (C-11,12), 34.78 (C-7), 70.49 (C-10), 122.85 (C-1′), 127.19 (C-3′), 131.06 (C-2′), 131.36 (C-5′), 132.56 (C-4′), 133.13 (C-6′), 163.77 (C-2), 164.43 (C-5), 166.96 (C-8).

2.2.12. Isopropyl 2-((5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetate (15)

White powder, yield 86%, mp 96-98°C (from ethanol), R_f = 0,62; UV (ethanol): λ_{max} (nm): 276; IR (KBr, cm^{-1}) v: 1737 ($CH_2COO(CH_3)_2$), 1177(C-O-C, oxadiazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.26 (3H, s, CH_3), 1.28 (3H, s, CH_3), 4.08 (2H, s, S-CH_2), 5.08 (1H, septet, J = 6.3 Hz, O-CH), 7.38 (1H, dd, J = 8.5, 2.0 Hz, ArH-3′), 7.56 (1H, d, J = 2.0 Hz ArH-5′), 7.89 (1H, d, J = 8.5 Hz, ArH-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.79 (C-11,12), 34.78 (C-7), 70.56 (C-10), 121.39 (C-1′), 127.74 (C-3′), 131.32 (C-2′), 131.71 (C-5′), 133.90 (C-6′), 138.28 (C-4′), 163.74 (C-2), 164.02 (C-5), 166.89 (C-8).

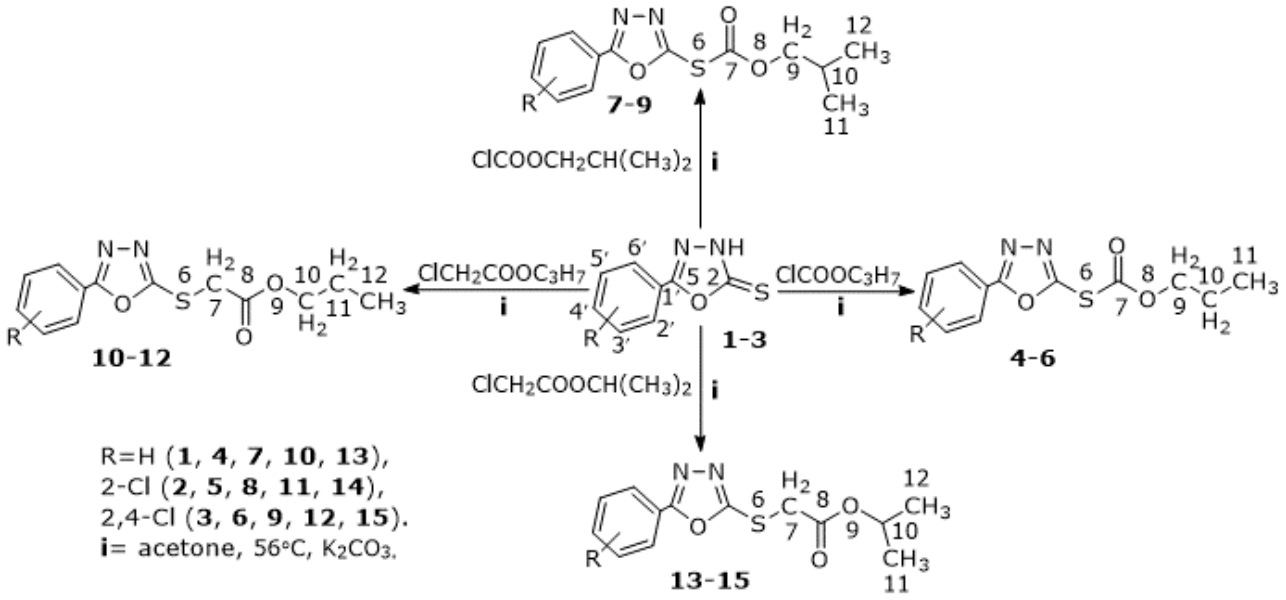
2.3. Determination of Antibacterial and Antifungal Activity

Test microorganisms: *Staphylococcus aureus* (ATCC - 25923), *Bacillus subtilis* (RKMUz - 5), *Pseudomonas aeruginosa* (ATCC 27879), *Escherichia coli* (RKMUz - 221) and *Candida albicans* (RKMUz - 247). The RKMUz bacteria and fungi strains were obtained from the microorganism cultures collection of the Institute of Microbiology, Republic of Uzbekistan. The antibacterial and antifungal activity of synthesized compounds were evaluated by modified agar disk diffusion method (15). The average value of inhibition zones was calculated for the three replicates in independent assays.

3. RESULTS AND DISCUSSION

The reactions of 5-aryl-1,3,4-oxadiazole-2-thions (aryl = phenyl; 2-chlorophenyl; 2,4-dichlorophenyl) with such electrophilic reagents as alkyl esters of chloroformic acid (alkyl chloroformates) and chloroacetic acid were

carried out in order to study the influence of the nature (length and branching) of the alkyl radical on the yield and direction of the interaction products. The propyl, iso-propyl and iso-butyl groups were selected as alkyl radicals.
The interaction of thions (**1**-**3**) with alkyl chloroformates and alkyl esters of chloroacetic acid was carried out in dry acetone (in the presence of K_2CO_3) at the boiling point of the solvent, the ratio of reagents was equimolar (1:1:1, alkyl ether, K_2CO_3, Scheme 1):



Scheme 1: Synthesis of S-(5-aryl-1,3,4-oxadiazol-2-yl) O-alkyl carbonothioate (**4-9**) and alkyl 2-((5-aryl-1,3,4-oxadiazol-2-yl)thio)acetate (**10-15**).

The course of interaction was controlled by TLC, all synthesized compounds were solids. The obtained data showes higher yield of the corresponding target products in reactions of three oxadiazolthions (**1-3**) with propyl chloroformate (**4-6**) – 74-79% were higher than with iso-butyl chloroformate (**7-9**) – 69-73%. The yields of products of propyl (**10-12**) – 87-90% and iso-propyl esters (**13-15**) - 86-92% of chloroacetic acid with the (**1-3**) thions were very close. However, the yields of products of propyl ester of chloroacetic acid (**10**-**12**) were significantly higher than products obtained with propyl chloroformate (**4**-**6**). A significant difference (17-19%) can be observed when comparing the yields of derivatives (**7**-**9**) and (**13**-**15**) obtained by reaction with alkyl esters having branched alkyl radicals (iso-propyl and iso-butyl).

The structure of the obtained derivatives was esatblished and characterized by the data of ^{1}H and ^{13}C NMR, IR, and UV spectra. In the IR spectra of compounds (**4**-**15**) there are characteristic absorption bands of the C(O)OR (R=alkyl) group at 1725-1788 cm^{-1}. The absorption maximum (272-286 nm) of all synthesized compounds (**4**-**15**) in the UV spectra corresponded to the literature data for S-derivatives (16-18), which shows that the interaction proceeds exclusively in the S-center to obtain S-(5-aryl-1,3,4-oxadiazol-2-yl) O-alkyl carbonothioate (**4**-**9**) and alkyl 2-((5-aryl-1,3,4-oxadiazol-2-yl)thio)acetate (**10**-**15**). The possible N-products were not detected neither by TLC method, nor by spectral data (^{1}H NMR, UV-spectroscopy).

In the ^{1}H NMR spectra of compounds (**4**-**6**), the proton signals of the propyl fragment were observed in the corresponding regions: 1.05 ppm (3H, t, CH_3), 1.85-1.86 (2H, sextet, $C\underline{H}_2CH_3$), 4.44 (2H, t, -OCH_2) and protons of the isobutyl fragment of substances (**7**-**9**) in the range of 1.03-1.04, 1.05-1.06 ppm (6H, s, $(C\underline{H}_3)_2$), 2.14-2.15 (1H, septet, CH), 4.26 (2H, d, -OCH_2). All protons chemical shifts of compounds (**10**-**15**) fully correspond to their structure: substances (**10**-**12**), 0.92 ppm (3H, t, CH_3), 1.65-1.67 (2H, sextet, $C\underline{H}_2CH_3$), 4.10-4.11 (2H, s, S-CH_2), 4.13-4.14 (2H, t, -OCH_2) and substances (**13**-**15**), 1.25-1.26, 1.26-1.28 ppm (6H, d, -$CH(C\underline{H}_3)_2$), 4.07-4.08 (2H, s, S-CH_2), 5.07-5.08 (1H, septet,- $C\underline{H}(CH_3)_2$). At the same time, the signals of protons of aromatic groups in all compounds (**4**-**15**) were observed in the range of 7.32-8.05 ppm, which are familiar for these groups.

There were in the ^{13}C NMR spectra signals of all carbon atoms of the obtained compounds (**4-15**). The signals of C-7 carbons bound to the S atom in compounds (**10-15**) obtained with chloroacetic acid esters were in a strong field at

34.45-34.81 ppm, while the signals of similar C-7 carbon atoms in the form of C=O in compounds (**4-9**) obtained from the corresponding alkyl formates were shifted to a weaker field and have values of 173.28-174.11 ppm. The opposite situation was observed when comparing the values of C-10 carbon atoms in the form of CH in both series of synthesized compounds. Thus, the C-10 signals in the compounds obtained with alkyl chloroformates (**7-9**) were in a stronger field (2.14-2.15 ppm) than the signals (5.07-5.08 ppm) for the analogous carbon atom of compounds (**13-15**) obtained with alkyl ethers of chloroacetic acid.

Antibacterial activity. All synthesized compounds (**4**-**15**) and initial oxadiazolthions (**1**-**3**) were tested for antibacterial and antifungal activity by a modified disc diffusion method on agar (14). The test results (Table 1) showed that unsubstituted oxadiazoles (**1**-**3**) exhibited significant antibacterial activity, mainly against gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*. The activity of oxadiazolthione (**1**) without substituents in the phenyl ring was minimal (diameters of the bacterial growth inhibition zone 7-9 mm at the concentration of 0.2 mg/disc), while in compound (**3**) with Cl atoms in positions 2 and 4 the inhibition diameters were largest (13-17 mm). Oxadiazolthione (**2**) with one Cl at position 2 showed an intermediate result (10-12 mm). It should be noted that the introduction of propyl and isobutyloxycarbonyl fragments into 5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-thione led to a loss of activity of the observed in unsubstituted oxadiazolthione (**3**). At the same time, these compounds exhibit minimal (6-8 mm) fungicidal activity against *C. albicans.* Compounds (**10**-**15**) obtained by propyl and isopropyl esters of α-chloroacetic acid with three oxadiazolthiones (**1**-**3**) exhibited no antimicrobial activity (Table 1).

Table 1: Antimicrobial activity evaluated by diameter of inhibition zone (mm) for compounds (1-15) using agar disk diffusion test

Compound	Gram-positive bacteria		Gram-negative bacteria		Fungus
	S. aureus	***B. subtilis***	***P. aeruginosa***	***E. coli***	***C. albicans***
1	7.08±0.12	9.04±0.10	na	na	na
2	10.08±0.12	12.04±0.10	6.12±0.13	6.12±0.13	na
3	13.08±0.12	17.04±0.10	8.12±0.13	na	na
4	7.08±0.12	7.04±0.10	na	na	8.04±0.10
5	7.08±0.12	6.04±0.10	na	na	6.04±0.10
6	na*	na	na	na	na
7	7.08±0.12	6.04±0.10	na	na	6.04±0.10
8	7.08±0.12	6.04±0.10	na	na	6.04±0.10
9	na	na	na	na	na
10	na	na	na	na	na
11	na	na	na	na	na
12	na	na	na	na	na
13	na	na	na	na	na
14	na	na	na	na	na
15	na	na	na	na	na
Ampicillin (10μg/disc)	25.08±0.12	26.04±0.10	25.12±0.13	nt	nt
Ceftriaxone (30 μg/disc)	na*	nt	nt	26.12±0.13	nt
Fluconazole (25 μg /disc)	nt	nt	nt	nt	27.04±0.10

na*- not active; nt* – not tested.

4. CONCLUSION

Thus, the reactions of 5-aryl-1,3,4-oxadiazole-2-thiones with propyl(isobutyl)chloroformates and propyl(isopropyl)esters of chloroacetic acid have been studied. Only the corresponding S-derivatives were obtained. It has been established that the yields of target products are much higher when using alkyl esters of chloroacetic acid. The lowest yields were observed in reactions with isobutyl chloroformate having a branched alkyl radical of 69-73% (compounds **7-9**), the highest yields of 86-92% were observed with alkyl esters of chloroacetic acid containing propyl and isopropyl radicals (compounds **10-15**), and propyl chloroformate with normal propyl radical has intermediate values of 74-79% (compounds **4-6**). A relationship has been established between the structure of the synthesized compounds and their antimicrobial activity, which makes further research in this direction interesting.

5. CONFLICT OF INTEREST

The authors declare no conflict of interest.

6. ACKNOWLEDGMENTS

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