SYNTHESIS AND STUDY OF ANTIMICROBIAL PROPERTIES OF NEW AMIDES OF 1, 1-BIS-(CARBOXYMETHYLTHIO)-1-ARYLETHANES

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Abstract

The article describes a method for obtaining new bis-amides synthesized by the amidation reaction of 1,1-bis-(carboxymethyl)-1-arylethanes with some primary amines. Their physico-chemical characteristics are determined. The structure of the synthesized compounds is confirmed by the data of elemental analysis, IR and NMR (^{1}H and ^{13}C) spectra. It was found that with the ratio bis-acid:amine equal to 1:2 the yield of the corresponding amides is 56.0-96.0%. The fungicidal and bactericidal properties of the synthesized compounds were investigated. General analysis of antibacterial and antifungal activity showed that the synthesized compounds are active against Fusarium oxysporum and Klebsiella pneumoniae. Pyridine-2-amide of 1,1-bis-(carboxymethylthio)-1-phenylethane had the highest fungicidal and bactericidal activity among all studied amides introduced in 0.1% concentration into both dry and solid nutrient media.

Keywords: Bis-acid, amidation, primary amines, bis-amides, antimicrobial properties

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1. Introduction

The reaction products of aldehydes and ketones with mercaptoacetic acid, in particular compounds containing such functional groups as carboxyl and hydroxyl groups, are of considerable interest. These compounds can be valuable synthons for the synthesis of various esters,[1] amides,[2, 3, 4] heterocyclic compounds,[5, 6, 7] and a number of other derivatives.[8, 9, 10] Of particular interest among these derivatives are compounds containing amide groups.

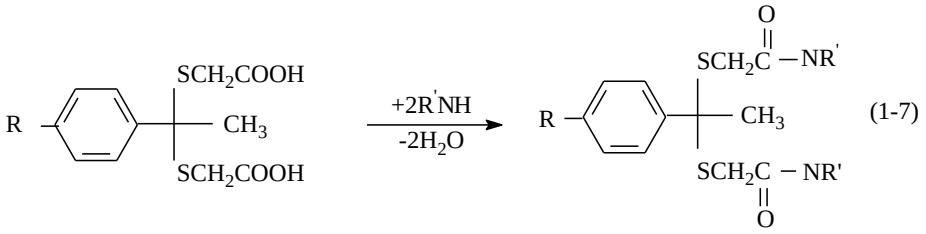
As the analysis of the data given in the literature shows, compounds containing amide groups in the molecule exhibit high biological activity and are used in medicine, chemical technology, and other fields.[11, 12, 13, 14, 15] In this regard, the development of efficient methods for the synthesis of compounds with an amide group is one of the important areas of modern organic synthesis. The amidation reactions of the simplest organic monoacids[16, 17, 18] and diacids[19, 20, 21] are described in the literature; however, there is no information on the amidation of bis acids containing heteroatoms in the molecule, in particular, sulfur atoms.

In this regard, we were the first to carry out direct amidation reactions of 1,1-bis-(carboxymethylthio)-1-arylethanes (bis-acids) with various primary amines. As starting amines, we used butylamine, benzylamine, 2-aminopyridine, p-aminobenzoic acid, which make it possible to synthesize bis-amides with various physiological properties.

2. Results And Discussion

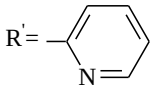
Synthesis

The amidation reaction was carried out by heating in a benzene solution in the presence of catalytic amounts of boric acid according to the scheme:



(1-7)

R=H R' = - C_4H_9 (1); - C_6H_4COOH (2); -$CH_2C_6H_5$ (3);

R' =  R=H (4); OH (5); OCH_3 (6) ; Br (7)

Scheme 1. Synthesis of bis-amides of 1,1-bis-(carboxymethylthio)-1-arylethanes (1-7)

The corresponding amine was added dropwise to the reaction medium with constant stirring. When mixing bis-acids and amines, an exothermic effect was observed, which may be due to the initial formation of salts. The synthesized bis-amides 1,1-bis-(carboxymethylthio)-1-arylethanes were crystal substances readily soluble in water and ether. The synthesized compounds 1-7 were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and purity of compounds were checked with elemental analysis.

Experimental

Materials and measurements

Elemental analysis of the synthesized compounds was determined on a TruSpec Micro instrument, LECO. IR spectra were taken on a Nicolet iS-10 instrument with a frequency of 400-4000 Hz in the form of a suspension in vaseline oil. The NMR spectra were measured on a Bruker Avance 300 spectrometer with a frequency of 300 MHz in solutions in DMSO-d6 or deuterochloroform at 27°C. Residual solvent signals were used as an internal standard. Instrumental analyzes were performed at the Institute of Chemistry of Additives named after Academician Ali Guliyev of the Ministry of Science and Education of the Azerbaijan Republic and at the Institute of Petrochemical Processes named after Academician Yusif Mammadaliyev of Ministry of Science and Education of Azerbaijan Republic. Antimicrobial properties were investigated at the Institute of Microbiology of the Ministry of Science and Education of Azerbaijan Republic. Chemistry General procedure for the synthesis of bis-amides of 1.1-bis-(carboxymethylthio)-1-phenylethane In a three-necked flask equipped with a stirrer, a thermometer, and a reflux condenser, 0.035 mol of 1,1-bis-(carboxymethylthio)-1-arylethane and 0.07 mol of the corresponding amine were placed. The reaction was carried out in a solution of dry benzene in the presence of a catalytic amount of boric acid and heated for 2-11 hours. Upon completion of the reaction, benzene was distilled off using a water jet pump, the target product was isolated by recrystallization from the corresponding solvent. Butylamide 1,1-bis-(carboxymethylthio)-1-phenylethane **(1).** White crystals, yield 56.0%, Mp 118-120°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) ppm: δ = 0.96 (3H, m., CH_3), 1.33 (2H, d., CH_2), 1.55 (2H, m., CH_2), 8.01 (1H, m., NH-amide); 7.13-7.26 (4H, t., CH-Ar); ^{13}C-NMR (75 MHz, DMSO): 13.8, 19.8, 26.3, 36.4, 39.3, 43.5, 126.0, 147.8, 175.1. Anal. Calcd. for $C_{20}H_{32}S_2O_2N_2$: C, 60.61; H, 8.08; N, 7.07; S, 16.17. Found: C. 60.95; H, 8.29; N, 7.48; S, 16.79.

p-Carboxyphenylamide 1,1-bis-(carboxymethylthio)-1-phenylethane **(2).** White crystals, yield 96.0%, Mp 114-115°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) ppm: δ = 1.92 (3H, s., CH_3), 3.49 (2H, d., CH_2), 7.23 (1H, m., NH-amide), 7.27; 7.29; 7.40; 7.87; 8.04 (4H, m., CH-Ar); 11.0 (1H, s., COOH); ^{13}C-NMR (75 MHz, DMSO): 31.6, 35.6, 55.8, 118.1, 125.8, 128.6, 130.5, 139.2, 143.7, 168.2, 169.3; Anal. Calcd. for $C_{26}H_{24}S_2O_6N_2$: C, 59.55; H, 4.58; N, 5.35; S, 12.22. Found: C, 59.78; H, 4.73; N, 5.51; S, 12.56.

Benzylamide 1,1-bis-(carboxymethylthio)-1-phenylethane **(3).** White powder, yield 89.2%, Mp 135-137°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) ppm: δ = 1.37 (3H, t., CH_3), 4.22 (2H, m., CH_2), 7.25; 7.27; 7.31 (1H, s., CH-pyridine), 7.13; 7.18; 7.26 (4H, m., CH-Ar); ^{13}C-NMR (75 MHz, DMSO): 26.5, 36.8, 43.3, 46.7, 126.1, 128.6, 138.8, 141, 164, 171.8; Anal. Calcd. for $C_{26}H_{28}S_2O_2N_2$: C, 67.25; H, 6.04; N, 6.04; S, 13.80. Found: C, 67.54; H, 6.21; N, 6.32; S, 14.06.

Pyridine-2-amide of 1,1-bis-(carboxymethylthio)-1-phenylethane **(4).** White powder, yield 95.0%, Mp 92°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) ppm: δ = 1.92 (3H, s., CH_3), 2.02 (3H, s., CH_3), 3.33 (2H, d., CH_2), 7.45; 8.12; 8.25; 8.96 (4H, m., CH-Ar), 7.12; 7.26 (2H, t., CH-Ar), 10.01 (1H, m., NH); ^{13}C-NMR (75 MHz, DMSO): 24.6, 35.6, 55.8, 117.8, 123.8, 128.7, 129.0, 141.6; 143.6, 168.2; Anal. Calcd. for $C_{22}H_{22}S_2O_2N_4$: C, 60.28; H, 5.03; N, 12.79; S, 14.62. Found: C, 60.56; H, 5.28; N, 13.17; S, 15.07.

Pyridine-2-amide of 1,1-bis-(carboxymethylthio)-1-p-hydroxyphenylethane **(5).** White powder, yield 95.1%, Mp 116-118°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) ppm: δ = 1.92 (3H, m., CH_3), 2.02 (3H, m., CH_3), 3.33 (2H, d., CH_2), 7.31; 7.86; 7.99; 8.36 (1H, m., CH- pyridine); 6.65; 6.96 (4H, s., CH-Ar), 10.61 (1H, d., NH-amide); 9.83 (д., 1H, OH); ^{13}C-NMR (75 MHz, DMSO): 35.6, 115.8, 119.8, 138.7, 146.7, 149.9, 168.2; Anal. Calcd. for $C_{22}H_{22}S_2O_3N_4$: C, 58.15; H, 4.85; N, 12.34; S, 14.10. Found: C, 58.44; H, 5.08; N, 12.59; S, 14.51.

Pyridine-2-amide of 1,1-bis-(carboxymethylthio)-1-p-methoxyphenylethane **(6).** White powder, yield 94.7%, Mp 131-133°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) ppm: δ = 1.63 (3H, m., CH_3), 3.72 (3H, m., CH_3), 3.03 (2H, d., CH_2), 10.58 (1H, d., NH-amide), 7.26; 7.40; 7.92; 8.53 (8H, m., CH-pyridine), 6.69; 7.02 (4H, s., CH-Ar); ^{13}C-NMR (75 MHz, DMSO): 24.6, 35.7, 55.8, 115.8, 124.7, 127.1, 138.8, 141, 157.8; Anal. Calcd. for $C_{23}H_{24}S_2O_3N_4$: C, 58.98; H, 5.13; N, 11.97; S, 13.68. Found: C, 59.16; H, 5.32; N, 12.30; S, 14.29.

Pyridine-2-amide of 1,1-bis-(carboxymethylthio)-1-p-bromophenylethane **(7).** White powder, yield 89.0%, Mp 110-112°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) ppm: δ = 1.36 (3H, m., CH_3), 3.33 (2H, d., CH_2), 7.39; 7.86; 7.99; 8.36 (8H, s., CH-pyridine), 8.00; 10.61 (1H, d., NH-amide), 7.02–7.35 (4H, m., CH-Ar); ^{13}C-NMR (75 MHz, DMSO): 25.6, 36.0, 109.9, 113.3, 115.8, 119.8, 121.5, 138.3, 146.7, 149.8, 158.5, 161, 168.2; Anal. Calcd. for $C_{22}H_{21}S_2O_2N_4Br$: C, 51.07; H, 4.07; N, 10.84; S, 12.38. Found: C, 51.38; H, 4.29; N, 11.15; S, 12.69.

Biological assays

The following method[22] was used to find out whether the presented chemical compounds have antimicrobial activity. Various fungi as tested kultura (Aspergillus niger, Aspergillus ochraceus, Penicillium purpurogenum, Candida albicans, Fusarium oxysporum) and bacteria (Klebsiella pneumoniae, Pseudomonas aeroginosa, Staphylococcus aureus) as well as the association of pure cultureas separated from oil products were used. Since the presented substances are dissolved in water, a 0.1% solution is prepared from it or added to liquid or solid nutrient media. Then the studied test cultures are planted there. The assessment of antimicrobial activity was carried out based on the amount of biomass formed by microorganisms in the liquid medium(mg/ml) and the diameter of the colony in the solid medium (mm). We determine the effect of the taken substance on microbes after 3-5 days. For this, the covered glass container is kept for 3 days, after the specified exposure period (3 days), 1 test piece is removed and placed on the surface of meat-peptone agar. Then, with the help of tweezers, we move it a little further so that a larger growth surface is obtained. It should be noted that unlike bacteria, Saburo nutrient medium is used in the cultivation of funguses. We keep the Petri dishes in which microbes are planted in a thermostat at a temperature of 30°C for 1-2 days. For fungi, including Candida albicans, the cultivation temperature regime is different, equal to 28°C. Any changes that occur at this time are recorded. If there is significant growth of cultures in the cups, then the test substance does not have any antimicrobial effect. However, if the growth process is not noted in any test object after a certain exposure period, then the substance we are studying has a bactericidal effect. Biological evaluation Antimicrobial activity Antimicrobial

properties were determined by measuring the zone of inhibition against test organisms. All synthesized compounds were tested for their antibacterial activity against two Gram-negative (Klebsiella pneumoniae and Staphylococcus aureus) and one Gram-positive (Pseudomonas aeruginosa) bacterial strains. They were also evaluated for antifungal action potential against five fungal strains (Penicillium purpurogenum, Fusarium oxysporum, Aspergillus niger, Aspergillus ochraceus, Candida albicans). The results of the antimicrobial properties of the synthesized compounds are shown in Figure 1 and Figure 2.

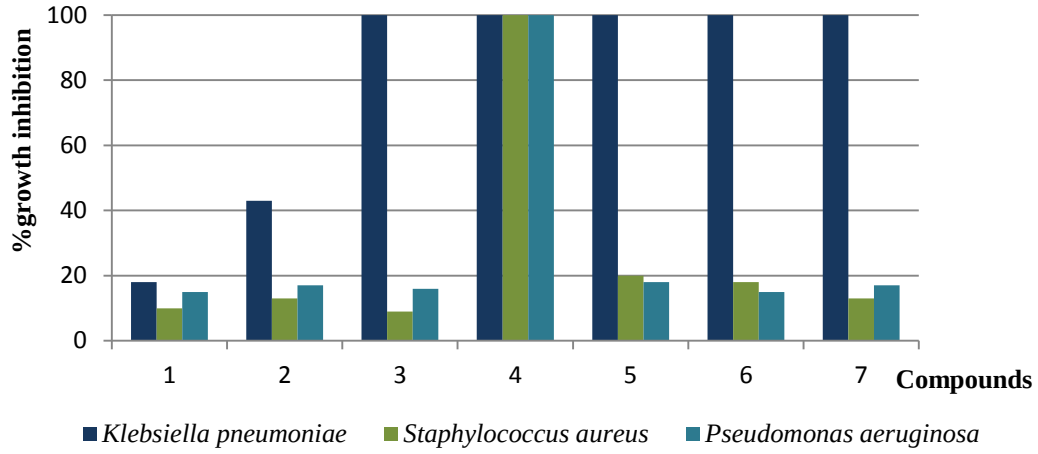


Fig 1**.** Antibacterial activities of some novel bis-amides of 1,1-bis-(carboxymethylthio)-1-arylethanes

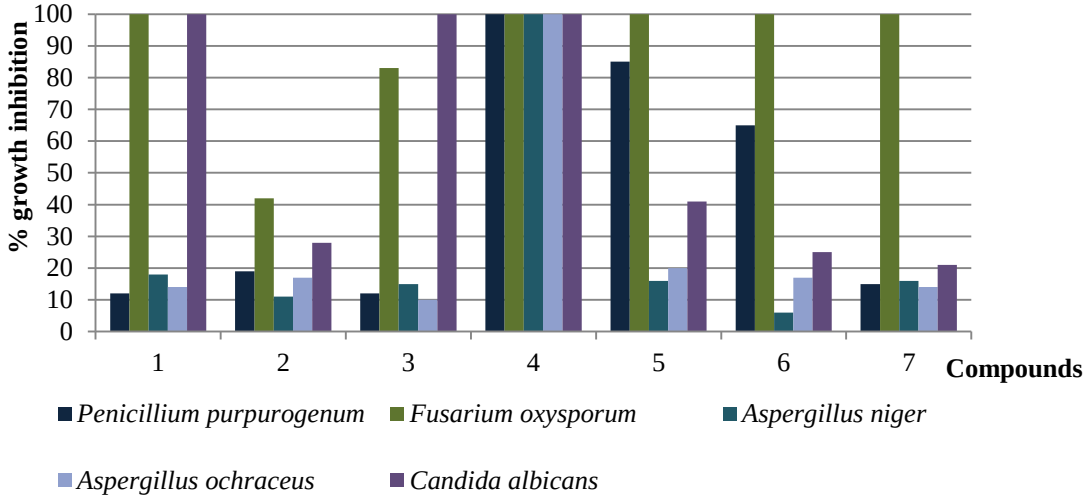


Fig. 2**.** Antifungal activities of some novel bis-amides of 1,1-bis-(carboxymethylthio)-1-arylethanes

As can be seen from Fig. 1 and Fig. 2, pyridine-2-amide of 1,1-bis-(carboxymethylthio)-1-phenylethane (4) had the highest fungicidal and bactericidal activity among all the studied amides introduced in 0.1% concentration into both dry and solid nutrient media.

3. Conclusion

Thus, as a result of our studies, we have synthesized new previously undescribed bis-amides, which, unlike their closest analogs, contain two amidogroups in the molecule, as well as sulfur atoms, which enhance their antimicrobial properties.

4. References

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