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MODERN ADVANCES IN THE SYNTHESIS OF NEW DERIVATIVES OF ACETYLENE DITHIOCARBAMATE AND THEIR BIOLOGICAL ACTIVITY

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Abstract

The article shows the results of the preparation of 1-bromopropargyl esters of substituted benzoates based on bromo-substituted benzoates and propargyl alcohol by interaction with NaSH, the synthesis of 1-thiol-propargyl esters of substituted benzoates with high yields. It was shown that the reaction between 1-thiol propargene benzoate and 1-isocyanate proceeds according to the A_N nucleophilic addition mechanism with the quantitative formation of dithiocarbamate compounds. The structures of the synthesized compounds were established and their bio-stimulating activity was shown.

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1. Introduction

In recent years, efforts are being made to find more effective drugs among sulfur compounds, since the presence of sulfur atom in organic compounds molecules increasesthe physiological, pharmacological, biological activity, while reducing toxicity, and also shows anti-fungal, anti-tuberculosis, antimicrobial, anti-ulcer properties [1 -4].

It is known that diacetylenic derivatives have different types of biological activity. Thus, diacetylenic and thiol-acetylenic esters containing aromatic and heterocyclic substituents possess pesticidal, herbicidal, fungicidal, insecticidal, growth-promoting, anticholinergic, antitumor, and many other activities [5–9].

In the literature [10-16], the synthesis of various acetylene sulfides, sulfoxides with a terminal triple bond is described. However, we did not find information on the syntheses of 1-thiol propargyl substituted benzoate and their derivatives of the

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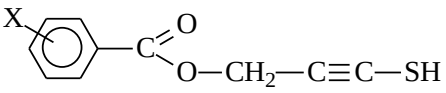
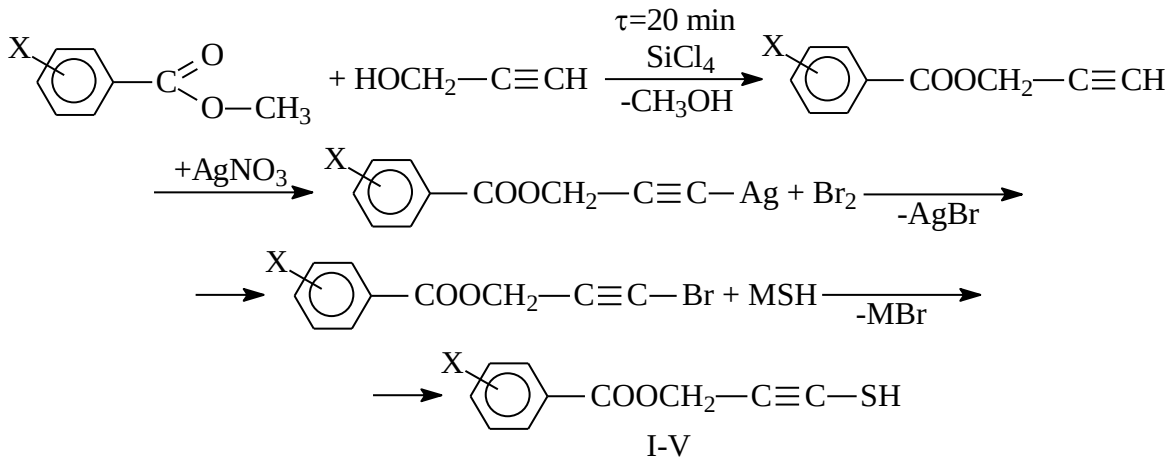
type  . These little-known compounds essentially represent a new kind of compounds, the properties of which have not been studied.

2. Research Method

The object of the study was the 1-thiol propargyl substituted benzoate and their derivatives. Their physical and chemical properties, PMR and IR spectroscopy, biostimulating activity were studied. IR spectra recorded on a VR-20 spectrometer in KBr tablets.

3. Results and Analysis

Inconnection with this, we obtained 1-thiol-propargyl esters of substituted benzoates [17-18]. For the synthesis of thiols of this kind by the interaction with alkali metal hydrosulfide, we used the 1-bromopropargyl esters of the substituted benzoates obtained by us according to the scheme:



where: X = 2-bromo; 3-bromo; 4-bromo; 2,4-dibrom;
M = Na; K; NH_4^+;

The reaction was carried out in anhydrous ethyl alcohol at a temperature of 75-78 °C in a dry nitrogen atmosphere with a yield of 81-88,8 %.

It is established that in a dilute solution of sodium hydrosulfide, the reaction mixture proceeds weakly and the yield of the target products is insignificant. When using a saturated solution, the reaction proceeds selectively, easily, smoothly and the yield of the target product is much higher, the products of which have a weak characteristic odor of 1-thiols. Derivatives of 1-thiol-propargyl esters of substituted benzoates are crystalline substances, well soluble in many organic solvents and insoluble in water. Physico-chemical parameters of 1-thiol derivatives (I-V) are given in table1.

Purification of 1-thiol-propargyl esters of substituted benzoates was carried out using preparative thin-layer chromatography on Al_2O_3 in the benzene-hexane system (24: 1). To prove the structure of 1-thiol-propargyl esters, substituted benzoates, the method of IR and PMR spectroscopy was applied (Table 2).

In the IR spectrum there are the following absorption bands –C≡C– (2222-2240cm^{-1}); - SH (2542-2563 cm^{-1}).

In the PMR spectra of 1-thiol-propargyl ethers, signals are in the region of 7,5-6,1 ppm. belong to the protons of the benzene ring, signals from protons - O - CH_2 - and –SH groups are at 4,72-4,61 and 2,13-2,0 ppm respectively.

In addition, the chemical properties of 1-thiol-propargyl substituted benzoic acid esters have been studied.

It has been established that the –SH group easily reacts with sodium hydroxide solution to form sodium 1-thiolate (I-V).

Of interest was the interaction of 1-isothiocyanate propargyl esters of substituted benzoates with 1-thiol propargyl ethers, with the aim of obtaining new little-known compounds of the type

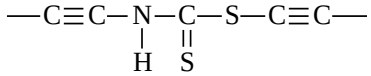


Table 1. Physical and chemical parameters of 1-thiol-propargyl esters of substituted benzoates (I-V)

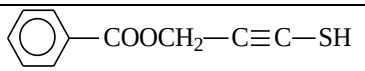
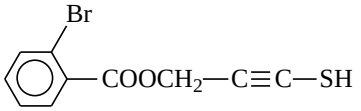
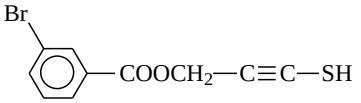
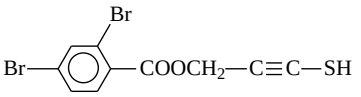
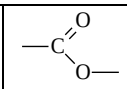
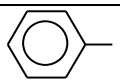
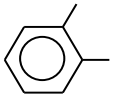
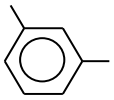
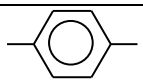
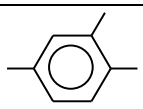
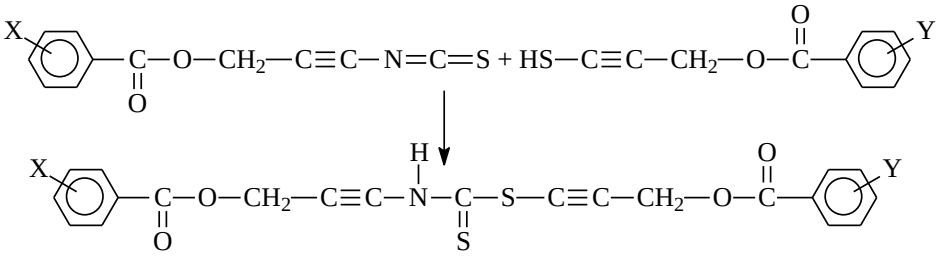
№	Structural formula	Out-put, %	T_{mt}, °C	R_f	Gross formula	Elemental analysis, %		Мм
						Calcu-lated	Found	
I		81,2	54-55	0,73	$C_{10}H_8SO_2$	16,69	16,58	191,06
II		83,7	60-61	0,69	$C_{10}H_7SBrO_2$	11,78	11,79	271,96
III		85,1	65-66	0,71	$C_{10}H_7SBrO_2$	11,78	11,66	271,96
IV		88,8	80-81	0,74	$C_{10}H_7SBrO_2$	11,78	11,73	271,96
V		85,6	97-98	0,70	$C_{10}H_6SBr_2O_2$	9,16	9,09	349,86

Table 2. IR and PMR spectra R-$COOCH_2$-C≡C-SH (I-V)

i/o	R-	IR - spectra, γ, cm^{-1}				ПМР-, δ, m.d.		
		–SH	–C≡C–			–SH	–O–CH_2–	Ar–
I		2542	2226	710-690	1726	2,13	4,61	6,1-7,3
II		2544	2222	770-735	1728	2,11	4,65	6,2-7,4
III		2548	2225	810-750	1730	2,07	4,66	6,6-7,1
IV		2550	2233	900-860	1725	2,08	4,69	6,6-7,1
V		2563	2240	860-800	1726	2,0	4,72	6,75-7,50

The reaction of the interaction of 1-thiol-propargyl esters of substituted benzoic acids with 1-isothiocyanate propargyl esters was carried out in dimethylformamide at 84-92 °C for 5,5-6,0 hours as follows:

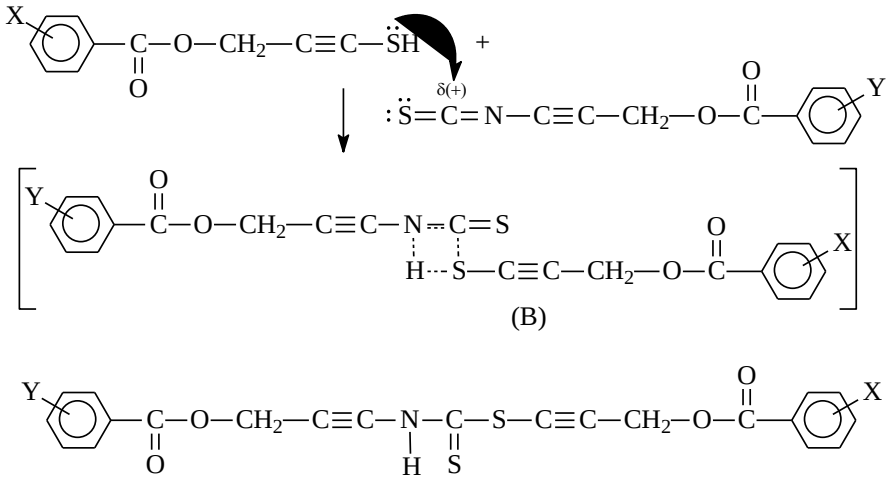


where: У=X = 2-bromo; 3-bromo; 4-bromo; 2,4-dibrom.

High density, selectivity and easy mobility of the electron cloud of the group - C ≡ C - N = C = S cause its high reactivity. The outputs of the products amounted to 93 %. As expected, they were obtained in good yields by the reaction of A_N.

The physico-chemical characteristics of the bis-acetylenicdithiocarbamate derivatives are apparently due to the high density and easy mobility of the electron cloud of the conjugated (- C ≡ C - N = C = S) group, which leads to an increase in the positive charge on the carbon of the isothiocyanate group, facilitating this atom's attack by a nucleophilic agent, and also on whether it happens by increasing the positive charge on the carbon atom or by stabilizing the transition state.

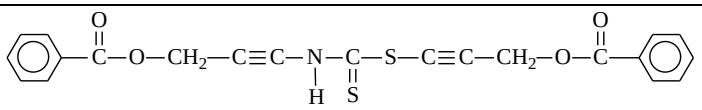
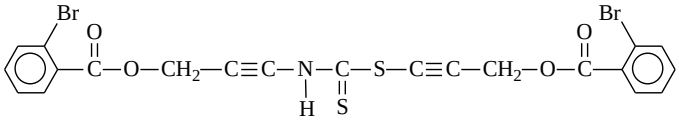
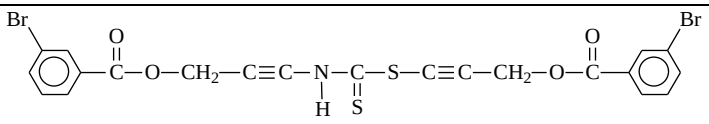
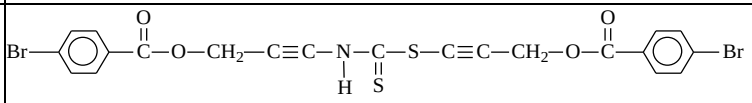
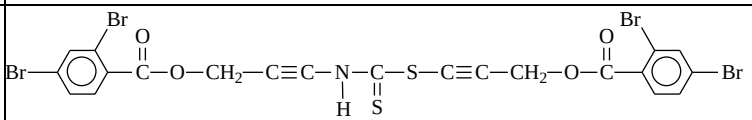
However, in our cases - the SH group of a thiol having a free pair, attacks the electrophilic center in the 1-isothiocyanate molecule of propargyl ethers with the formation of an intermediate product (B), which is then regrouped into the final reaction product. Based on our assumptions and literature data, the probable mechanism of the interaction of 1-thiol-propargyl ethers with 1-thioisocyanate of propargyl ethers can be represented by the scheme:



where: У=X = 2-bromo; 3-bromo; 4-bromo; 2,4-dibrom.

Physico-chemical parameters of derivatives dithiocarbamate are given in table 3.

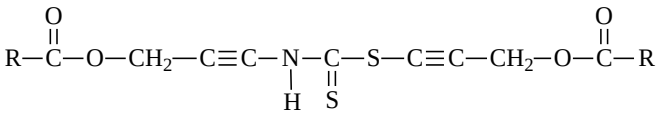
Table 3. Physico-chemical parameters of derivatives dithiocarbamate (VI-X)

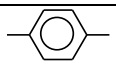
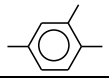
i/o	Structural formula	Out-put %	T_{mt}, °C	R_f	Мм
VI		79,7	174	0,69	397,12
VII		84,5	177-178	0,71	554,92
VII I		88,4	183-184	0,72	554,92
IX		92,2	192-193	0,74	554,92
X		90,6	203-204	0,69	712,72

The structure is determined by IR spectroscopy data and elemental analysis data.

Some characteristics and spectral data of bis (propynyl benzoates) derivatives of substituted dithiocarbamates (VI-X) are given in Table 4.

Table 4. Characteristics and spectral data of bis (propynyl benzoates) derivatives of substituted dithiocarbamates (VI-X)



i/o	R-	IR - spectra, γ, cm^{-1}					Gross formula	Elemental analysis, %			
		—N—C— (H, S)	—C≡C—	—C(=O)—O—		—O—CH_2—		Calcu-lated		Found	
								N	S	N	S
VI		1124	2218	1736	3060	1111	$C_{21}H_{15}S_2NO_4$	3,42	15,67	3,40	15,54
VII		1126	2220	1730	770-735	1112	$C_{21}H_{13}S_2Br_2NO_4$	2,46	11,31	2,36	11,26
VIII		1128	2222	1724	810-750	1110	$C_{21}H_{13}S_2Br_2NO_4$	2,46	11,31	2,31	11,27
IX		1129	2224	1728	860-800	1110	$C_{21}H_{13}S_2Br_2NO_4$	2,46	11,31	2,38	11,29
X		1123	2223	1725	900-860	1112	$C_{21}H_{11}S_2Br_4NO_4$	1,93	8,84	1,91	8,93

With an increase in the nucleophilicity of the HS groups (in the presence of Et_3N or Ru), the rate of addition and the yields of the final products increase, as the basicity decreases and the steric factors of the radicals increase, and the yield rates of the final products slightly decrease.

The structure of newly synthesized bis - [(propynyl benzoate) -substituted dithiocarbamate (VI-X) derivatives was established by IR spectroscopy and confirmed by elemental analysis data, as well as configurations and conformations of molecular models (Table 4 and Figure 1)

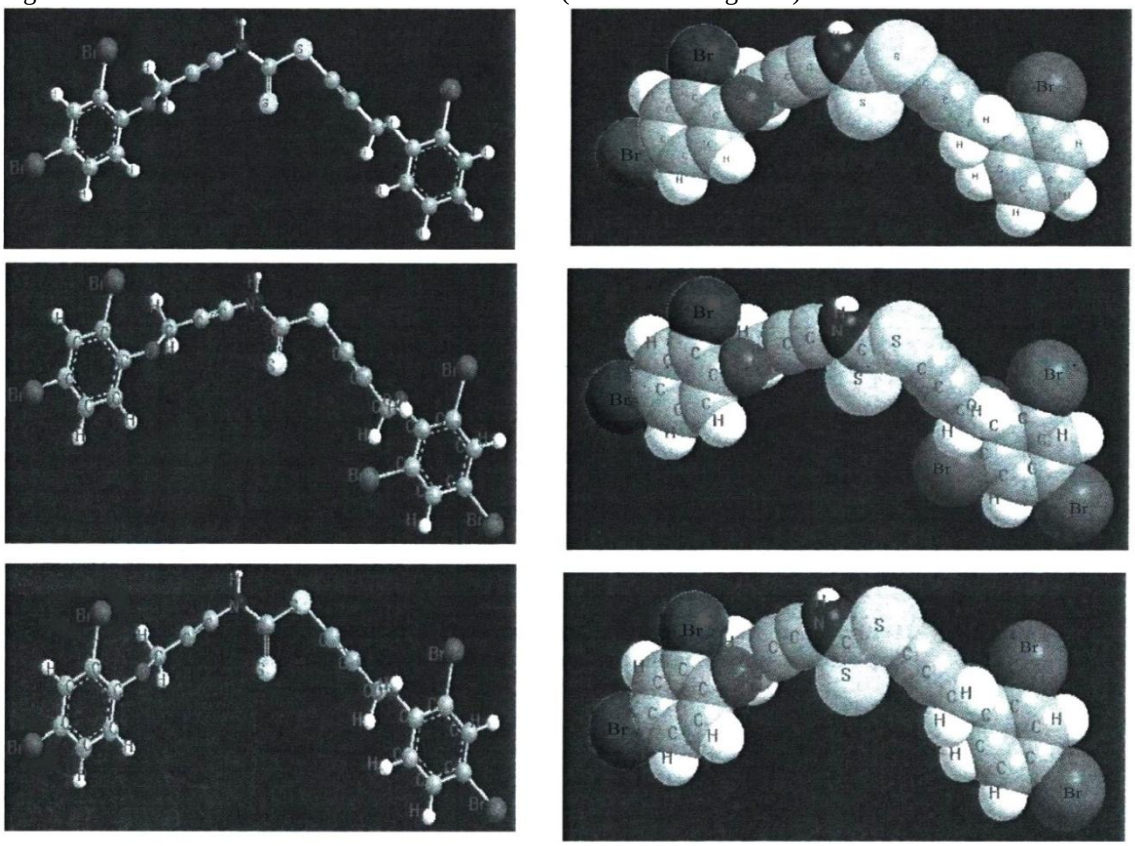


Figure 1. Molecular models of dithiocarbamate derivatives.

In the IR spectra of derivatives of bis - [(propinyl) bromo-benzoates] -dithiocarbamate, the absorption bands of stretching vibrations of –NHCS groups (1123-1129 cm^{-1}); groups (1724-1730 cm^{-1}); -groups (1008 cm^{-1}); for —C≡C- bonds (2218-2224 cm^{-1}) are characteristic.

Experimental part

Synthesis of p-bromobenzoate propargyl ester

2,15 g (0,01 mol) of p-bromobenzoic acid and 10 ml of absolute propynol are placed in a flask. Then 1,6 g of $SiCl_4$ are added, the reaction mixture is heated to boiling for 20 minutes. P-bromobenzoic acid propargyl ester is obtained with a yield of 90,7 %; MP = 86-87 °C.

Found, %: C 50,19; H 2,88; N 2,01; Br 33,21.

Calculated for $C_{10}H_7BrO_2$, %: C 50,23; H 2,92; Br 33,3.

1-thiol-propargyl ester of benzoate (I).

In a four-necked flask with a capacity of 250 ml equipped with an auto mixer, a thermometer, a gas-intake tube and a reflux condenser with a calcium chloride tube, 2,39 g (0,01 mol) of 1-bromo propargyl benzoate are mixed with 60 ml of absol. ethyl alcohol and 0,56 g (0,01 mol) of freshly prepared NaSH with vigorous stirring in a nitrogen atmosphere at 30 ° C. To obtain high yields, the reaction mixture is maintained at 70 °C for three hours. The mixture is cooled, acidified with 5 % HCl and extracted with ethyl ether and dried. Yield (I) – 1,29 g (81,2 %); MP = 54-55 °C.

1-thiolpropargyl ester of p-bromobenzoate (IV).

In a four-necked flask with a capacity of 250 ml equipped with an automatic mixer, thermometer, gas-flow tube and reflux condenser with a calcium chloride tube, 3,18 g (0,01 mol) of 1-bromopropargyl ester of p-bromobenzoate are mixed with 60 ml of absol. ethanol and 0,56 g (0,01 mol) of freshly prepared NaSH with vigorous stirring in a nitrogen atmosphere at 30-35 °C. To obtain high yields, the reaction mixture is kept at 70 °C for three hours. The mixture is cooled, acidified with 5 % HCl and extracted with ethyl ether and dried. Yield (IV) – 2,12 g (88,8 %). Mp = 80-81 °C.

Similarly, 1-thiol-propargyl esters were obtained: 2-Br-C_6H_4-; 3- —BrC_6H_4 - and 2,4-diBr-C_6H_3.

[1- (2,4-dibromobenzoate-propyne) -1 ′ - (2 ′, 4′-dibromobenzoate-propyne)] - dithiocarbamate

In a four-necked flask with a capacity of 0,25 l equipped with an automatic mixer, thermometer, dropping funnel and reflux condenser with a calcium chloride tube, 3,5 g (0,01 mol) of 1-thiol propargyl ether-2,4-dibromobenzoate in 35 ml DMF are placed. The reaction mixture is heated on a glycerin bath to 35-45 °C. With continuous stirring in small portions, 3,75 g (0,01 mol) of 1-isothiocyanate propargyl ester of 2,4-dibromobenzoate in 40 ml of DMF are added. The reaction mixture is maintained at 85-88 °C for 5 hours. Upon completion of the reaction, the mixture is cooled, 120 ml of water are added and the mixture is extracted with ethyl ether (2-3 times). The ether extract is washed several times with water and dried over anhydrous $CaCl_2$. The obtained target product after TLC on Al_2O_3 has a melting point of 203-204 ^oC. Yield (X) - (90,6 %);

Found, %: C 34,59; H 1,41; N 1,91; S 8,83; Br 44,08.

Calculated for $C_{21}H_{11}S_2Br_4NO_4$, %: C 34,77; H 1,51; N 1,93; S 8,84; Br 44,09.

[1- (3-Bromobenzoate-propyne) -1 ′ - (3′-Bromobenzoate-propyne)] - dithiocarbamate

In a four-necked flask with a capacity of 0,25 l equipped with an auto-stirrer, thermometer, dropping funnel and reflux condenser with a calcium chloride tube, 3,66 g (0,01 mol) of 1-thiol-propargil 3-bromobenzoate are placed in 35 ml of DMF. The reaction mixture is heated on a glycerin bath to 35-45 ° C. With continuous stirring, 2,96 g (0,01 mol) of 1-isothiocyanate propargyl ester of 3-bromobenzoate 35 ml of DMF are added in small portions. The reaction mixture is maintained at 86-87 °C for 5 hours. Upon completion of the reaction, the mixture is cooled, 120 ml of water are added and the miture is extracted with ethyl ether (2-3 times). The ether extract is washed several times with water and dried over anhydrous $CaCl_2$. The obtained target product after TLC on Al_2O_3 has T m = 183-184 °C; Output (VIII) - (88,4% of theoretical.).

Found,%: C 44,31; H 2,82; N 2,31; S 11,27; Br 28,07.

Calculated for $C_{21}H_{13}S_2NBr_2O_4$,%: C 44,45; H 2,99; N 2,46; S 11,31; Br 28,18.

According to the above method, the remaining dithiocarbamate derivatives were obtained.

To identify the growth-promoting activity of compounds 1-[(3-bromobenzoate-propynyl)-1′-(3′-bromobenzoate-propynyl)-dithiocarbamate] with the conditional name (AGM-97) and 1-[(2,4-dibromobenzoate-propinyl)-1′-(2′,4′-dibromobenzoate-propynyl) -dithiocarbamate] (AGM-99) tests were carried out in the laboratory of the Institute of Chemistry of Plant Substances of the Academy of Sciences of

the Republic of Uzbekistan in laboratory conditions, the seeds of vegetable crops and cotton served as biotests.

In the experiments, cucumbers of the variety "Uzbekistan-740", tomatoes of the variety "Temp" and medium-fiber cotton of the variety "S-6524" were used. The preparations were dissolved in DMF and used by the method of presowingseed locking for 17-19 hours. There were used concentrations: 0,01; 0,001; 0,0001 and 0,00001%. The repetition of experiments 4x. Accounting was carried out by measuring the length of the stem and root in 10 day old seedlings of cotton.

It was noted that all drugs tend to stimulate the growth of the root systems of young seedlings, both vegetables and cotton.

Primary screening was carried out according to the method of Yu.V. Rakitin. This method allows you to quickly determine the degree of physiological activity of new chemical compounds, which is detected by stimulating or inhibiting the germination of plant seeds, as well as by changing the length of the roots and the length of the stem part.

The preparations were tested by the method of locking seeds in solutions of different concentrations, followed by germination in Petri dishes. Control seeds were soaked in distilled water.

Each series of experiments is accompanied by control. In the control variants, only pure solvent is added to the nutrient medium.

The result of the experiments is recorded in 3, 5, 7 and 10 days after inoculation (Table 5-7).

Comparative tests also show that the tested drug is AGM-97, i.e. derivative 1-[(3-bromobenzoate-propynyl) -1′-(3′-bromobenzoate-propynyl) -dithiocarbamate] showed a higher growth-promoting activity at a lower concentration, from 7,5 to 75,000 times less than currently used branches of agriculture in Uzbekistan drug "Roslin".

Table 5. The effect of the drug AGM-97 on seed germination and growth of seedlings of cotton varieties "C-6524"

Experiences A drug	Concentration, %	Germination, %	Cotton	
			Root growth,%	Stem growth,%
Control - water	w/p	80,0	100,0	100,0
1-(3-bromobenzoate-propynyl)-1′-(3′-bromo-benzoate-propynyl)-dithiocarbamate]	0,1	87,3	113,0	107,7
	0,01	84,6	112,3	109,2
	0,001	86,4	124,6	115,6
	0,0001	83,3	115,5	109,0
	0,00001	80,0	121,7	114,3
«Roslyn» (famous)	0,75-1,0	80,0	104,1	102,4

The drug AGM-97 showed biological activity in cotton culture, at a concentration of 0,00001 % (diluted 75,000 times.) stimulated root growth 121,7 %, and stem growth 114,3 % above the control and the well-known drug Roslin (concentration 0,75-1,0 %).

Table 6. The effect of the drug AGM-97 on the germination of seeds and the growth of seedlings of cucumber varieties "Uzbekistan-740"

Experiences A drug	Concentration, %	Germination, %	Cucumber	
			Root growth,%	Stem growth,%
Control - water	w/p	100,0	100,0	100,0
1-(3-bromobenzoate-propynyl)-1′-(3′-bromo-benzoate-propynyl)-dithiocarbamate]	0,1	100,0	106,2	108,2
	0,01	100,0	107,0	111,8
	0,001	100,0	115,7	109,6
	0,0001	100,0	120,6	112,3
	0,00001	100,0	128,4	116,2
«Roslyn» (famous)	0,75-1,0	100,0	103,4	101,7

The preparation AGM-97 on the cucumber culture also showed biological activity at a concentration of 0,00001 % (ie, at a dilution of 75,000 times). Contributed to root growth of 128,4 %, slightly lower - stem growth by 116,2 % above the control and the well-known drug Roslin (concentration 0,75-1,0 %).

The preparation AGM-97 on tomatoes, similarly to previous cultures, showed a very high biological activity of 118,3 % at a concentration of 0,00001 % (even in dilution 75,000 times).

Thus, the low toxic (LD_{50} = 2947 mg / kg) preparation AGM-97 showed high stimulating properties on the seeds of tomato, cucumbers and cotton at 0,00001 % concentration.

Table 7. The influence of the drug AGM-97 on the germination of seeds and the growth of seedlings of tomato varieties "Temp"

Experiences A drug	Concentration, %	Germination, %	Tomato	
			Root growth,%	Stem growth,%
Control - water	w/p	50,0	100,0	100,0
1-(3-bromobenzoate-propynyl)-1′-(3′-bromo-benzoate-propynyl)-dithiocarbamate]	0,1	50,0	105,0	117,3
	0,01	58,0	116,3	122,2
	0,001	57,3	139,7	126,4
	0,0001	49,8	114,6	108,5
	0,00001	52,3	118,3	105,6
«Roslyn» (famous)	0,75-1,0	52,1	101,9	100,7

The results of determining the growth-promoting activity of compound 1 - [(2,4-dibromobenzoate-propynyl)-1′-(2′,4′-dibromobenzoate-propynyl) -dithiocarbamate] are presented in Table 8,9,10.

Table 8. The effect of the drug AGM-99 on the germination of seeds and the growth of seedlings of cotton varieties "C-6524"

Experiences A drug	Concentration,%	Seed germination, after 5 days, %	The growth of seedlings on the 10th day, in %	
			Cotton	
			root	stem
Control - water	w/p	100,0	100,0	100,0
1 -[(2,4-dibromobenzoate-propynyl) -1′ -(2′, 4′-dibromobenzoate-propynyl) -dithiocarbamate] (AGM-99)	0,1	100,0	102,8	105,4
	0,01	100,0	108,8	116,3
	0,001	100,0	104,4	114,2
	0,0001	100,0	105,7	112,6
	0,00001	100,0	109,5	115,4
«Roslyn» (famous)	0,75-1,0	102,6	101,7	102,3

Table 9.The effect of the drug AGM-99 on seed germination and growth of seedlings tomato varieties "Temp"

Experiences A drug	Concentration, %	Seed germination, after 5 days, %	The growth of seedlings on the 10th day, in %	
			Tomato	
			root	stem
Control - water	w/p	50,0	100,0	100,0
1 -[(2,4-dibromobenzoate-propynyl) -1′ -(2′, 4′-dibromobenzoate-propynyl) -dithiocarbamate] (AGM-99)	0,1	52,0	109,5	106,5
	0,01	50,5	114,4	110,1
	0,001	45,0	109,4	126,0
	0,0001	62,5	104,3	115,2
	0,00001	55,0	109,5	105,9
«Roslyn» (famous)	0,75-1,0	51,4	101,6	100,7

Table 10. The effect of the drug AGM-99 on seed germination and growth of seedlings Cucumber varieties "Uzbekistan-740"

Experiences A drug	Concentration,%	Seed germination, after 5 days, %	The growth of seedlings on the 10th day, in %	
			Cucumber	
			root	stem
Control - water	w/p	100,0	100,0	100,0
1 -[(2,4-dibromobenzoate-propynyl) -1′ -(2′, 4′-dibromobenzoate-propynyl) -dithiocarbamate] (AGM-99)	0,1	100,0	107,3	106,2
	0,01	100,0	109,1	108,4
	0,001	100,0	108,8	118,3
	0,0001	100,0	104,3	114,2
	0,00001	100,0	102,4	114,8
«Roslyn» (famous)	0,75-1,0	100,0	102,6	99,8

AGM-99 in cotton culture showed biological activity at a concentration of 0,00001 % (75,000 times diluted), stimulated root growth 109,5 %, and stem growth 115,4 % above the control and the well-known drug Roslin (concentration 0,75-1,0 %).

The preparation AGM-99 on tomatoes, similarly to previous cultures, showed a very high biological activity, where a root growth of 114,4 % and a stem growth of 126 % at a concentration of 0,001 % (even in dilution 750 times) were observed.

The preparation AGM-99 on the cucumber culture also showed biological activity at a concentration of 0,001 % (i.e., a dilution of 750 times). The root growth was increased by 108,8 %, and the stem growth was 118,3 % higher than the control and the well-known drug Roslin (concentration 0,75-1,0 %).

4. Conclusion

In conclusion, both tested compounds 1 - [(3-bromobenzoate-propynyl) -1 ′ - (3′-bromo-benzoate-propynyl) -dithiocarbamate] (preparation AGM-97) and 1 - [(2,4-dibromobenzoate-propynyl) -1 ′ - (2 ′, 4′-dibromobenzoate-propynyl) -dithiocarbamate] (AGM-99 preparation), synthesized using waste-free technology, even at dilution 75,000 times, are 1,1-1,3 times higher than the currently used known drug Roslin.

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