SOI: 1.1/TAS DOI: 10.15863/TAS

International Scientific Journal

Theoretical & Applied Science

p-ISSN: 2308-4944 (print) **e-ISSN:** 2409-0085 (online)

Year: 2016 **Issue:** 11 **Volume:** 43

Published: 30.11.2016 **http://T-Science.org**

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PROPERTIES AND SYNTHESIS OF ALKOXY- AND AMINOMETHYLENE DERIVATIVE GUANIDINE SULFAMATES AND THEIR HETEROCYCLIZATION

Abstract: *The alkoxylation and aminomethylation reactions of guanidine sulfamates were studied. It is found that ternary guanidine sulfamates reaction with alcohols and amines in the presence of formaldehyde is terminated with a high yield. Compounds obtained as dipolars are easily heterocyclisize with polarophiles forming functionally substituted pyrimidines. Synthesized compounds are studied as biocides by Hansch's method. It was found that regardless of the heterocyclic fragment content have high bactericidal properties.*

Key words: *Alkoxymethyl, aminomethyl, guanidine sulfamate, polarophil, heterocyclization, bactericide*

Language: *English*

Citation: Mammadov SA, Mammadova SI, Ladokhina NP, Kazimzade SK, Huseinov IS (2016) PROPERTIES AND SYNTHESIS OF ALKOXY- AND AMINOMETHYLENE DERIVATIVE GUANIDINE SULFAMATES AND THEIR HETEROCYCLIZATION. ISJ Theoretical & Applied Science, 11 (43): 77-84.

Soi: http://s-o-i.org/1.1/TAS-11-43-15 ***Doi***: http://dx.doi.org/10.15863/TAS.2016.11.43.15

UDC 547.541.521.621

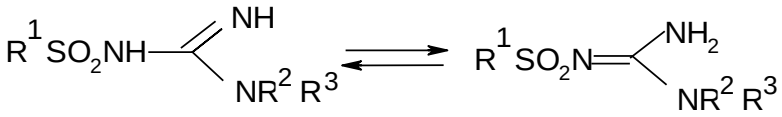
Introduction

Guanidines are basic synthons for synthesis of widely used pyrimidines which are structural basis of alkaloids, vitamins, ferments and coenzymes, nucleic acids. Hetarylsulfamides are widely used in preparation of many medical preparations and biocides. Production of functionally-substituted derivatives of pyrimidinesulfamides is required to intensify their biocide and medical effect. In direct introduction of functional groups into pyrimidine fragment results in definite difficulties. That's why synthesis of new dipolar synthons has high theoretical and practical value.

Considering high application value of guanidine sulamides, the synthesis of them was widely studied. The main obtaining method is reaction of arylsulfochlorides with guanidine and with their N-substituted derivatives [1-4].

Many works are also conducted [5, 6] on synthesis of guanidinesulfamides by non-standard method in which reaction of N-sulfonyltrifluorosulfonimide with urea or with dicyclohexylcarbodiimide.

According to literature data [6, 7], reaction of arylsulfochlorides with guanidine leads to monosubstituted derivatives which are in tautomeric state:



Synthesis of N-functionally substituted derivatives of sulfanylguanidines and use of them as synthons for synthesis of substituted pyridinesulfamides are very promising. One of such directions – three-component reaction of guanidinesulfamides with amines and alcohols with paraform.

The data on synthesis of sulfamides using three-component reaction of sulfamides with compounds which have active hydrofen in the presence of paraform or keton also exists [8-10].

Experimental part

PMR-spectra of some synthesized sulfamides were recorded on spectrophotometer «Tesla-467» with operating frequency of 90 MHz, IR-spectra – on «NicoletIS-10».

N-3-Alkoxy- and aminomethyleneguanidinesulfamides (Ia-g). General technique. 0.1 mol of guanidinesulfamide, 0.1 mol of paraform and butyl (or amyl) alcohol or amino compound were dissolved in 50 ml of benzene or toluene. The mixture was boiled till complete extraction of water in Dean-Stark trap. Then 20-30 ml of hexane was added. Obtained crystals were filtered and crystallized from ethanol.

Physical-chemical properties of compounds are shown in table 1.

Table 1

Physical-chemical properties of N-alkoxy- and aminomethyl derivatives of guanadinesulfamides (Ia-g).

Cipher of compounds	Yield, %	$T_{melt.}$, ^0C	Chemical formula	Found / calculated, %	
				N	S
1	2	3	4	5	6
I a	74.8	310 - 312	$C_{13}H_{21}N_3O_3S$	14.51 / 14.09	10.97 / 10.70
I b	71.3	238 - 240	$C_{14}H_{23}N_3O_3S$	13.68 / 13.46	10.46 / 10.23
I c	72.1	227 - 229	$C_{13}H_{21}N_3O_3S$	14.42 / 14.09	10.39 / 10.70
I d	78.9	168 - 170	$C_{13}H_{21}N_4O_2S$	19.23 / 18.90	10.93 / 10.77
I e	79.5	150 - 153	$C_{13}H_{20}N_4O_2S$	19.36 / 18.97	11.14 / 10.81
I f	70.4	65 - 67	$C_{17}H_{30}N_4O_2S$	16.22 / 15.89	9.39 / 9.06
I g	58.7	209 - 212	$C_{18}H_{21}N_5O_3S$	18.51 / 18.14	8.49 / 8.27

Functionally substituted pyrimidines(IIa, b).General technique.20 mol of compounds (Ia) or (Id) and 22 mol of acetylaceton were dissolved in 20 ml of ethanol. 10 drops of 0.1N solution NaOH were added into ethyl alcohol. The mixture was boiled 1,5 – 2 hours, cooled, precipitated crystals were filtered off and crystallized from ethanol.

3,4-Diphenyl-5-butylamino-(4-methylphenylsulfonyl) pyrimidine (IIc). Synthesis method is similar to obtaining method of pyrimidines (IIa, b) with the difference that 3-butylaminomethyleneguanidinesulfamide (Ia) and benzoin were taken.

3-Amyloxy- orbutylamino-4-methyl-(4-methylsulfonyl) pyrimide-5-ons (IId, e).

Synthesis method is similar to obtaining method of (IIa, b). However, for reaction compounds (Ia) and (Ib), and ethyl alcohol of acetacetic acid were taken, morpholinium was used as a base.

Physical-chemical properties of compounds are shown in table2.

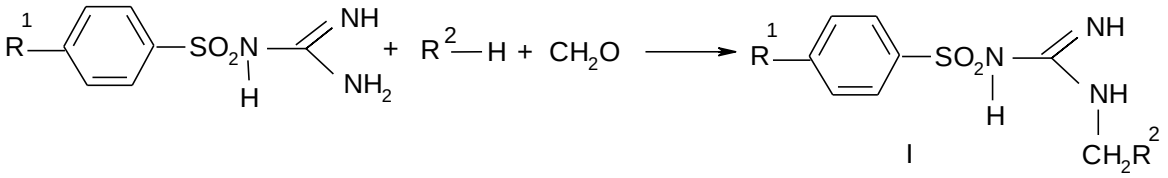
Table 2

Physical-chemical properties of derivatives of pyrimidines (IIa-e).

Cipher of compounds.	Yield, %	$T_{melt.}$, ^0C	Chemical formula	Found calculated, %	
				N	S
1	2	3	4	5	6
II a	71.2	250 - 252	$C_{19}H_{25}N_3O_4S$	11.09 10.77	8.48 8.19
II b	74.3	198 - 200	$C_{18}H_{23}N_4O_3S$	15.61 14.98	8.92 8.54
II c	69.6	195 - 197	$C_{27}H_{27}N_4O_2S$	12.23 11.92	7.29 6.80
II d	68.9	320 - 322	$C_{17}H_{22}N_3O_4S$	12.21 11.57	9.12 8.79
II e	70.2	208 - 210	$C_{17}H_{24}N_4O_3S$	12.46 12.03	9.32 9.14

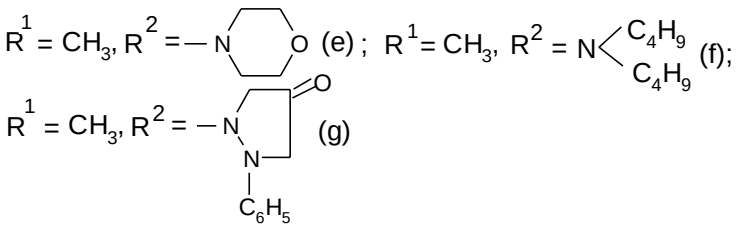
Results and discussion

We studied the reaction of guanadinesulfamides with amines and alcohols in the presence of paraform:



$R^1 = CH_3$, $R^2 = C_4H_9O$ (a); $R^1 = CH_3$, $R^2 = C_5H_{11}O$ (b);

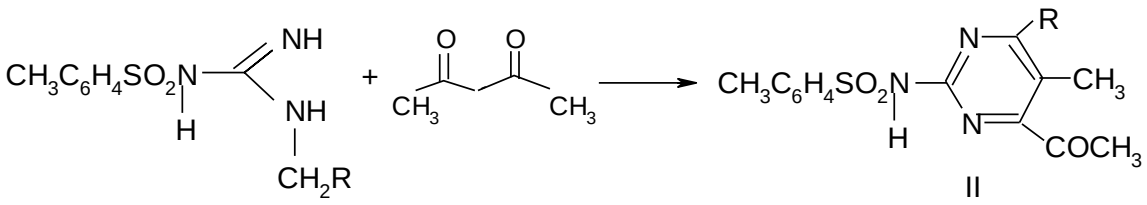
$R^1 = H$, $R^2 = C_5H_{11}O$ (c); $R^1 = CH_3$, $R^2 = NHC_4H_9$ (d);



In PMR-spectra (fig.1) of 3-N-butylaminomethylene-4-methylohenylsulfanylguanadine (compound Id) methyl protons of n-toluene appear in 1.0 ppm. Methyl and methylene protons of NC_4H_9 appear in 2.3 and 3.8 ppm. Proton of NHC_4H_9-group is in 50ppm, proton of amino group $NHCH_2$ appears in 5.8 ppm under the effect of methylene group, but proton of imino group is in 6.8 ppm. Proton of amino group appears in weaker zone in 7.5 ppm under the effect of sulfamide, imine, and methylene groups. Protons of methylene group appear after aromatic fragment in 8.3 ppm. Amonimm ethylation of guanidine sulfamides must occur through active imino group. However, inPMR-spectra we observed four NH-groups which means that methylation reaction goes through NH_2-group.

As is known, more promising way of synthesizing hetarylsulfamides is 1,3-dipolar connection to dipolarophilic compounds. This reaction is a general synthesis method of heterocyclic compounds. Some types of molecules (azides, nitriles, amides, guanadines and others), which have resonant (or activated) structure andeven one element which is characterized by the presence of opposite charges in 1,3-position, are inclined to 1,3-dipolar synchronous additions.

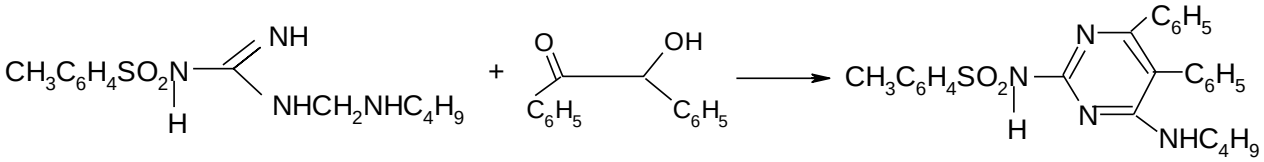
In synthesized compounds I – VII, except sulfamide group, alkoxy- and amino methyl groups are in position 3. Presence of electrophilic sulfamide and electron donor amino group leads to increase of molecule intensity, which strongly influences on activation value (especially methylene group) and on ring closure in synchronous reactions. That's why synthesized compounds enter into heterocyclization reaction with polarophiles. During heterocyclization of compound Ia and Id with acetylacetone in the presence of alkali or morpholine substituted pyrimidines are formed:



II

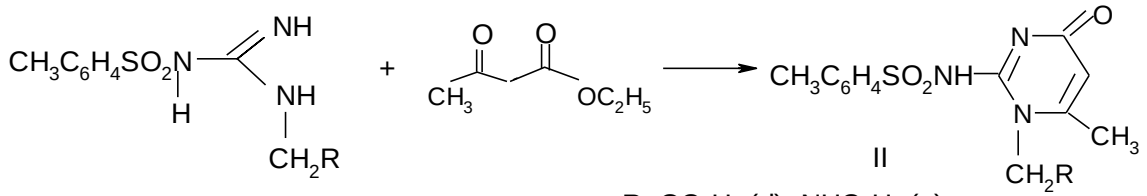
R=OC_5H_{11} (a); NHC_4H_9 (b)

Heterocyclization of compound Id with benzoin results in 3,4-diphenyl-5-butylamino-4-methylsulfonylamidopyrimidine:



II c

Compound Ic and Id with acetaceticethyl ether form pyrimidinons:



II

R=OC_2H_5 (d), NHC_4H_9 (e)

PMR-spectra (fig.2) of 2-N-butylaminomethyl-4-methyl-(4-methylphenylsulfonamido)pyri-midone-5 (IIe) showed that protons of methylene group of n-tolyl, butyl fragment and pyrimidine appear in 0.9 – 1.3 ppm, but protons of methylene group of butyl radical appear in 2.1 – 3.2 ppm. Proton of amino group of butyl radical is in 5.05 ppm, but proton of amino group of sulfamide appears in 6.1 ppm. Protons of methylene group N-CH_2-N appear in a weaker zone after aromatic fragment in 8.1 ppm, which confirms intensity of methylene group.

Our previous studies [11, 12] revealed high antimicrobial properties of sulfamide derivatives. That's why synthesized compounds were tested as bactericides. Estimation of fungicide and bactericide properties of substances by GOST does not provide clear quantitative ranking of biocides on their activity due to the fact that in most cases antimicrobial effect can be fogged with low transportation rate of molecules to blocking receptors. Considering this circumstance, we used Hansh method for more complete characteristics of biocide properties of synthesized compounds of guanadinesulfamides and their heterocyclic derivatives [13].

This method is based upon the assumption on correlation between factors defining biochemical

activity and physical-chemical parameters of substances.

Tests of synthesized compounds by Hansh method (estimation results of hydrophobic parameters, effective concentrations of preparations and other data) are given in table 1. Dependence laws of biological action speed on effective concentration with mixture of bacteria are shown in fig.3, but with mixture of fungi are given in fig.4.

Effect of synthesized compounds against fungi is distinguished by the fact that pyrimidine derivatives of guanidinesulfamides are more effective than functionally-substituted guanidines without heterocyclic fragment. Compounds (IIa), (IIb) and (IIe) are stronger fungicides than other compounds. It should be noted that pyrimidinesulfamides containing aminogroup are more effective than alkoxyderivatives. Among alkoxy- and aminomethyleneguanidinesulfamides compound (Ie) is more effective than compound (Ia), (Ib) and (Ic), and tangent of angle is lower: correspondingly tg_{28}=0.47, tg_{38}=0.65, tg_{53}=1.33, tg_{44}=0.966. This means that biological effect rate of compound (Ie) is higher than in compound (Ib).

From these facts important consequences follow for theory and practical developments of effective antimicrobial preparations: by direct variation of structure of potential inhibitors of biodeterioration, as well as by regulating with hydrophobic behavior and penetration into intracellular space of microorganisms we may achieve maximum value of effective concentration of preparation.

Results showed that all synthesized compounds have high ability to control vital functions of aerobic bacteria and mold fungi. They are more effective than industrial biocide «Sulfaxide». Rate of biological effect of compounds depends not on composition of heterocyclic fragment, but on nature of functional groups. As shown on figure 3 compound containing alkoxymethyl group is more effective than substances with aminomethyl group. Pyrimidinederivatives with butylamino group are more effective biocides than pyrimidine with alkoxy group. With increase of effective concentration in pyrimidinone containing alkoxy group (compound IId), rate of biological action sharply decreases. This means that this substance is more effective than other pyrimidines.

With decrease of biological action rate against bacteria and with increase of transport properties to intracellular space at low concentrations compounds can be arranged in the following order:

I c > I a > I b >I d> I g > II a

Table 3

Antimicrobial properties of alkoxy - and aminomethylenederivatives of guanidinesulfamides and pyrimidine by Hansh technique

Biocides and compounds	Distribution coefficient of octanol-water, lg Ps	Hydrophobic parameter, δ	Steric factor, A	Concentration of biocides in nutritive medium, C, mol/l	Effective concentration of biocide, A·C, mol/l	Bacteria mixture		Fungi mixture	
						Absorption rate of oxygen, W_{O2} mol/l·hr	Rate of biological action, $K_p \cdot hr^{-1}$	Absorption rate of oxygen, W_{O2} mol/l·hr	Rate of biological action, $K_p \cdot hr^{-1}$
1	2	3	4	5	6	7	8	9	10
Without biocide	---	---	---	---	---	1.360	---	0.970	---
Sulfaxide	3.98 -//-	1.18 -//-	0.2012 -//-	18.6 27.9	3.74 5.61	0.763 0.398	0.744 0.645	0.446 0.093	0.146 0.125
I a	3.27 -//- -//-	2.49 -//- -//-	0.212 -//- -//-	5.57 9.28 18.56	1.18 1.97 3.93	0.326 0.245 0.05	0.42 0.38 0.23	0.82 0.72 0.41	0.135 0.119 0.068
I b	3.14 -//- -//-	2.26 -//- -//-	0.229 -//- -//-	5.82 9.72 19.4	1.33 2.23 4.38	0.276 0.245 0.043	0.40 0.38 0.34	0.78 0.66 0.436	0.129 0.109 0.072
I c	3.41 -//- -//-	1.69 -//- -//-	0.226 -//- -//-	5.67 9.47 18.9	1.28 2.14 4.27	0.041 0.039 0.034	0.31 0.29 0.19	0.818 0.72 0.486	0.135 0.12 0.081

Continuation of table.3

1	2	3	4	5	6	7	8	9	10
I d	2.75 -//- -//-	1.879 -//- -//-	0.2011 -//- -//-	5.92 8.91 17.8	1.191 1.79 3.58	0.65 0.54 0.39	0.67 0.595 0.46	0.192 0.171 0.122	0.082 0.074 0.052
I g	3.11 -//- -//-	1.96 -//- -//-	0.171 -//- -//-	7.76 11.63 23.27	1.33 1.99 3.98	0.48 0.42 0.134	0.71 0.68 0.55	0.235 0.216 0.167	0.10 0.092 0.071
II a	2.98 -//- -//-	1.790 -//- -//-	0.1965 -//- -//-	7.83 11.75 23.50	1.54 2.31 4.62	0.69 0.52 0.46	0.74 0.71 0.66	0.199 0.188 0.150	0.085 0.08 0.064
II d	3.21 -//- -//-	1.91 -//- -//-	0.1895 -//- -//-	7.29 10.93 21.88	1.38 2.07 4.14	0.38 0.19 0.069	0.52 0.41 0.18	0.146 0.138 0.154	0.062 0.050 0.051
II c	3.18 -//- -//-	1.86 -//- -//-	0.1911 -//- -//-	7.51 11.27 22.54	1.435 2.154 4.30	0.691 0.47 0.44	0.76 0.74 0.60	0.168 0.161 0.145	0.072 0.069 0.059

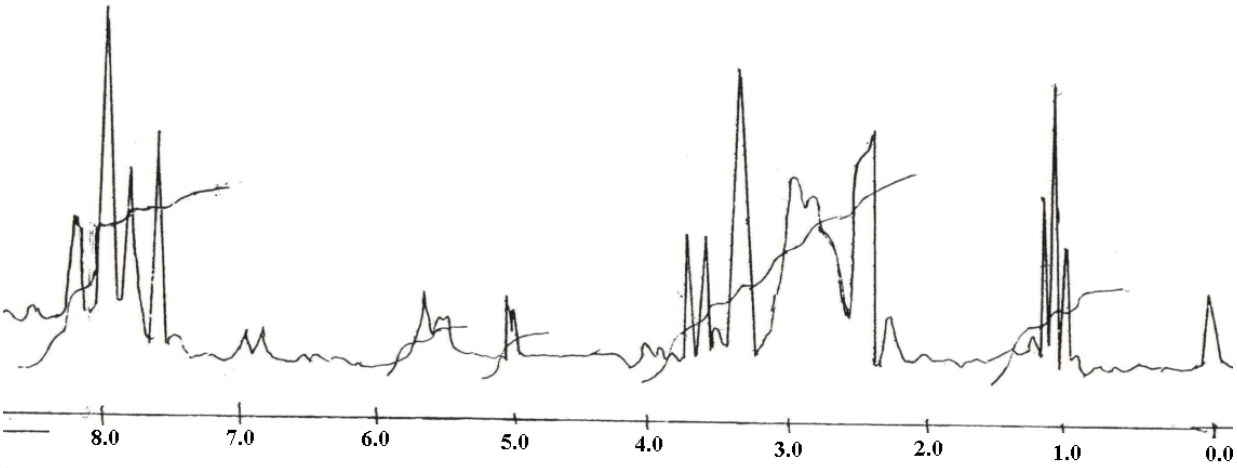


Fig.1 - PMR-spectra of 3-N-butylaminomethylene-4-methylphenylsulfanylguanidine (compound Id).

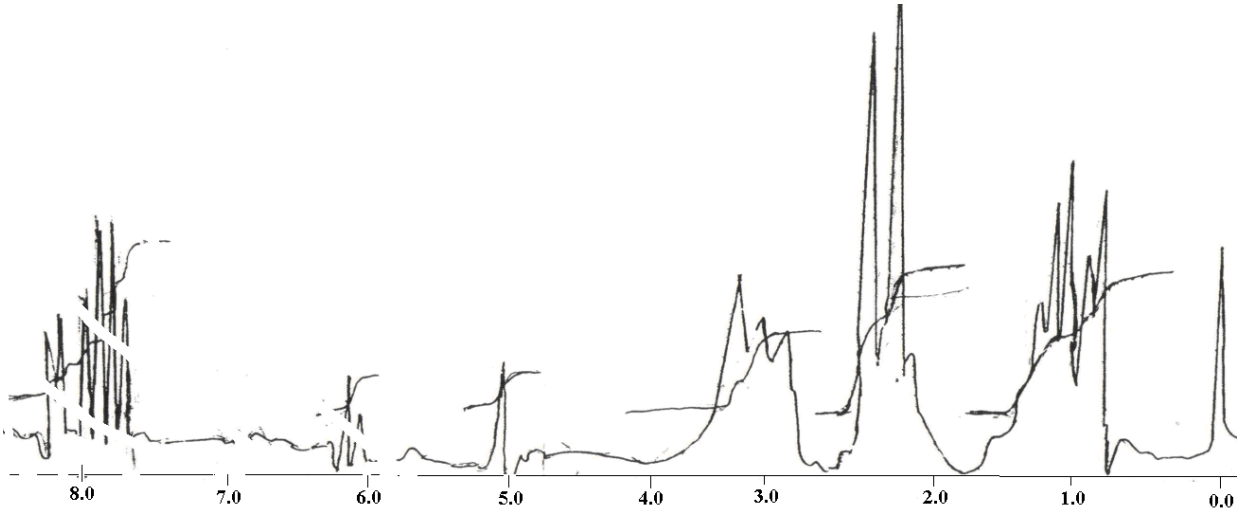


Fig.2 - PMR-spectra 2-N-butylaminomethyl-4-methyl-(4-methylphenylsulfonamide) pyrimidone-5 (compound IIe).

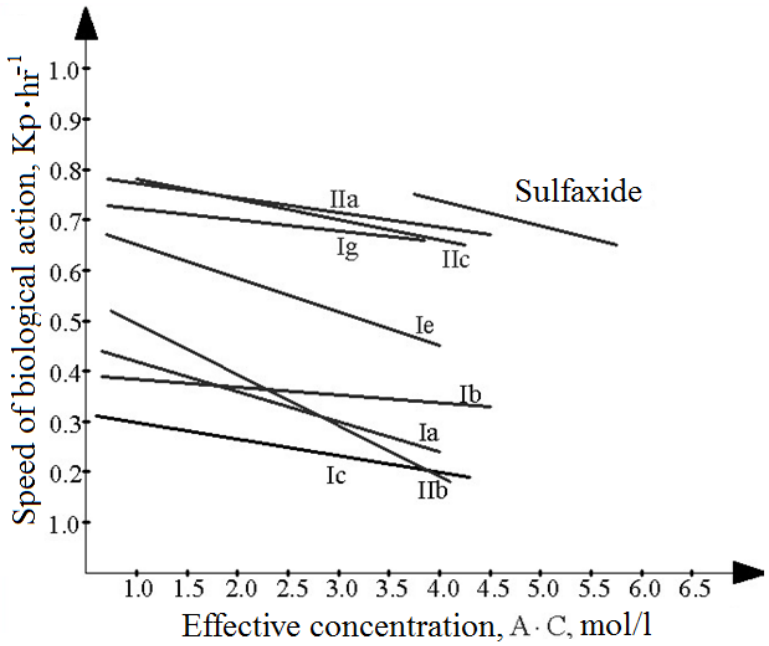


Fig.3 - Dependence of biological action speed on effective concentration with mixture of bacteria.

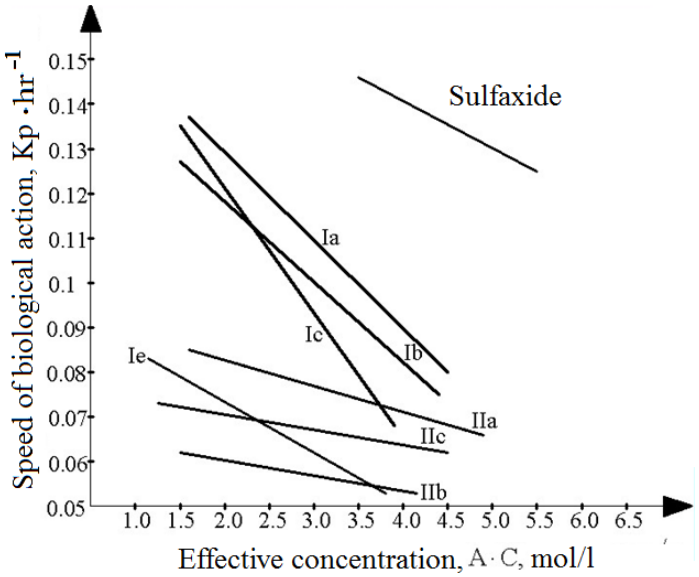


Fig.4 - Dependence of biological action speed on effective concentration with mixture of fungi.

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