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SYNTHESES OF SOME PHENOXATHIIN DERIVATIVES WITH ANTIMICROBIAL ACTIVITY

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ABSTRACT

Antimicrobial activity has been studied on eighteen substances of phenoxathiin class (six of them being not yet described in literature) evincing the fact that the oxidizing of the sulfur atom in position 10 leads to a severe decrease of the antibacterian activity.

RESUMO

Foi estudada a atividade antimicrobiana de dezoito compostos da classe da fenoxatiina, seis dos quais não foram descritos na literatura. Os resultados experimentais mostram que a oxidação do enxofre na posição 10 leva a uma grande diminuição da atividade antibacteriana.

Keywords:phenoxathiin,antimicrobial activity,sulfonium salts,O-methyl oximes.

INTRODUCTION

Following some research which revealed the antimicrobial activity of certain phenoxathiin derivatives [1-4],the present paper contains the results of the synthesis of new compounds from this class,for evincing the role played by the substituent upon the activity.

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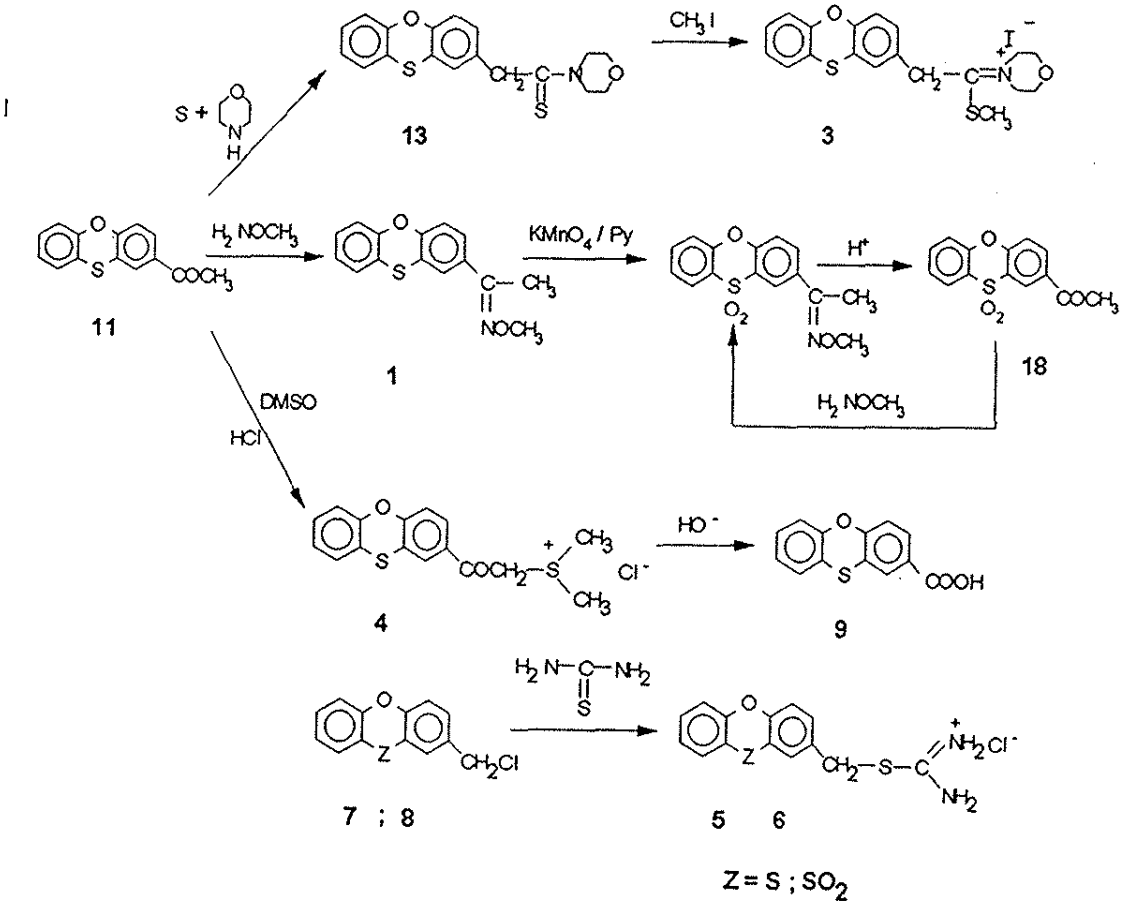
Six new compounds were synthesized starting from acetylphenoxathiin,together with other twelve already known products,which were obtained according to the literature,in order to complete the series of derivatives which were subject to the antimicrobial tests. (Scheme 1).

SCHEME 1



EXPERIMENTAL

Melting points were determined in open capillary for compounds **1-5**,with Boetius apparatus for compound **6**,and are uncorrected.

IR spectra were recorded in KBr pellet with an UR-20 apparatus.

H-NMR spectra were recorded on a BRUCKER apparatus in DMSO-d_6.

Thin-layer chromatography (TLC) was realised on silica gel Merck plates, unidimessional technic,the development was done by using different solvent systems (Table 1).Visualisation was done with iodine for phenoxathiin-10,10-dioxides or with conc. sulfuric acid for phenoxathiins (coloured spots of phenoxathin cation radical).

Aminooxymethyl-(2-phenoxathiinyl)-ethanone (**1**):

To 1.5 g (6.1 mmole) 2-acetylphenoxathiin and 1 g (11 mmole) O-methyl-hydroxylamine hydrochloride,a mixture of 4 ml (49 mmole;d=0.978) pyridine and 4 ml methanol was added.

The reaction mixture was warmed for 45 minutes on steam-bath.After cooling,an oil was formed,which crystallized by adding 20 ml water.The precipitate was filtered off, washed with 2 ml methanol and air dried.1.55 g (92.8% yield) of **1** were obtained ; m.p.=79-80° (methanol).

Aminooxymethyl-(2-phenoxathiinyl-10,10-dioxide)-ethanone (**2**):

A. To 1.7 g (6.2 mmole) 2-acetylphenoxathiin-10,10-dioxide and 1 g (11 mmole) O-methylhydroxylamine hydrochloride,a mixture of 7 ml (86 mmole;d=0.978) pyridine and 5 ml methanol,was added.The reaction mixture was warmed for 4 h on steam-bath and then 20 ml water were added.The white precipitate which formed was filtered off, washed with 2 ml methanol and air dried.1.7 g (90.8% yield) of **2** were obtained; m.p.=153-154° (isopropanol).

B. To 0.6 g (2.2 mmole) of **1** dissolved in 2 ml (24 mmole;d=0.978) pyridine, 0.87 g (5 mmole) potassium permanganate in 3 ml water were added.The reaction mixture was warmed for 1.5 h on steam-bath,and then 20 ml water were added.

Mangan dioxide was filtered off and extracted with 20 ml methylene chloride.The filtrate was also extracted with 5 ml methylene chloride.The organic phases were reunited and concentrated.0.35 g (52.2% yield) crude of **2** with m.p.=147-149° were obtained.

After recrystallization from isopropanol,the product has m.p.=153-154° .

S-methyl-(2-phenoxathiinyl)-acetomorpholidium iodide (**3**):

0.7 g (2 mmole) thiomorpholide of 2-phenoxathiinacetic acid were treated at room temperature with 7 ml (112 mmole;d=2.28) iodometane.A clear solution,which was left overnight,was obtained.The yellow precipitate formed,was filtered off and washed with 1 ml methylene chloride.0.8 g (80.8% yield) of **3** were obtained;m.p.=156-157° .

^{1}H-NMR: 4.53 (s,-CH_2-),2.77 (s,-CH_3),4.09-4.18 (two triplets of two -CH_2-groups bonded to morpholine's nitrogen),3.77-3.92 (two triplets of the two -CH_2-groups bonded to morpholine's oxygen) and 7.04-7.29 (multiplet aromatic) ppm.

1-[(2-Phenoxathiinylcarbonyl) methyl] dimethylsulfonium chloride (**4**):

To 1.21 g (5 mmole) 2 acetylphenoxathiin and 20 ml dimethyl sulfoxide,gaseous hidrochloric acid is bubbled inside this mixture at temperature under 10 °C.

After saturation with hydrochloric acid,the reaction mixture was left overnight at room temperature,the acid in excess was removed at low pressure.The reaction mixture was treated with 45 ml diethyl ether.The layer of dimethyl sulfoxide was separated,the precipitation of **4** was intensified by adding 25 ml methanol.

The precipitate was filtered off and 1 g (59.1% yield) of **4** with m.p.=159-160°,was obtained.

^{1}H-NMR : 2.96 (s,-CH_3),5.44 (s,-CH_2-),7.11-7.93 (multiplet aromatic) ppm.

S-(2-phenoxathiinomethyl)-isothiouronium chloride (**5**):

To 0.2g (2 mmole) thiourea dissolved in 6 ml anhydrous acetone,0.6 g (2 mmole) 2-chloromethylphenoxathiin [8] were added and heated on steam-bath for 10 minutes.

The precipitate formed on cooling,was filtered off and washed with 1 ml acetone.

0.6 g (76.4% yield) with m.p.=230-231.5° (dec.; anhyrdous ethanol) were obtained.

S-(2-phenoxathiinomethyl-10,10-dioxide) isothiouronium chloride (**6**):

The synthesis of **6** was done in the same way,the isothiouronium salt of 2-chloromethyl phenoxathiin-10,10-dioxide was obtained with m.p.=254-256° and 71.4% yield.

2-Phenoxathiincarboxylic acid (**9**):

0.3 g (0.88 mmole) of **4** and 7 ml sodium hydroxide 8% were heated under reflux for 2 h.The solution obtained was treated with activated carbon and filtered off.
The filtrate was extracted with 10 ml ethyl acetate.The aqueous phase,in which the sodium salt of **9** partially precipitated,was acidified with conc. hydrochloric acid up to pH=3.

2-Phenoxathiincarboxyl acid which precipitated,was filtered off.0.5 g (71.4% yield) of **9** with m.p.=247° were obtained ,according to literature data.

2-Acetylphenoxathiin-10,10-dioxide (**18**):

0.1 g (0.33 mmole) of **2** was heated on steam-bath,at 60-70°,with 5 ml hydrochloric acid 3 N for 2.5 h.

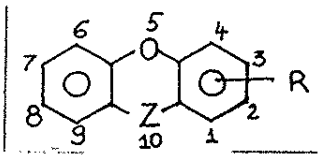
The reaction mixture was extracted with methylene chloride and the organic phase was concentrated.

0.085 g (yield 93.8%) of 2-acetylphenoxathiin-10,10-dioxide with m.p.=167-168° were obtained (according to literature data [7],m.p.=166-167°).

RESULTS AND DISCUSSION

In this paper an antimicrobial screening was done for a series of eighteen compounds from the phenoxathiin class.In this respect,the **4** and **5** phenoxathiin derivatives showed a strong antibacterial activity,while the **6-12** ; **14** derivatives had a low activity and the **1-3**;**13**;**15-18** compounds showed a rather unsignificant biological activity (Table 1).

TABLE 1



The compounds **1-18** microbiologically tested.

Nr.	R	the position of R	Z	Rf	% S		Ref.
					% S calc.	% S found	
1	$-\overset{\overset{NOCH_3}{\|}}{C}-CH_3$	2	S	0.87	11.81	11.73	--
2	$-\overset{\overset{NOCH_3}{\|}}{C}-CH_3$	2	SO_2	0.65	10.57	10.35	--
3	$-CH_2-\overset{\overset{S-CH_3}{\|}}{C}=\overset{+}{N}$⟨⟩$OI^-$	2	S	0.96	13.21	13.00	--
4	$-\overset{\overset{O}{\|}}{C}-CH_2\overset{+}{S}\overset{CH_3}{\underset{CH_3}{<}}Cl^-$	2	S	0.51	18.92	18.92	--
5	$-CH_2-S-\overset{\overset{NH_2}{\|}}{C}=\overset{+}{N}H_2Cl^-$	2	S	0.75	19.74	19.66	--
6	$-CH_2-S-\overset{\overset{NH_2}{\|}}{C}=\overset{+}{N}H_2Cl^-$	2	SO_2	0.64	17.92	17.96	--
7	$-CH_2Cl$	2	S	--	--	--	[8]
8	$-CH_2Cl$	2	SO_2	--	--	--	[8]
9	$-COOH$	2	S	--	--	--	[8]
10	$-COOH$	2	SO_2	--	--	--	[8]
11	$-COCH_3$	2	S	--	--	--	[10]
12	$-COCH_3$	3	S	--	--	--	[11]
13	$-CH_2-\overset{\overset{S}{\|}}{C}-N$⟨⟩$O$	2	S	--	--	--	[7]
14	$-CH_2COOH$	2	S	--	--	--	[7]
15	$-CH_2COOH$	2	SO_2	--	--	--	[7]
16	$-\overset{\overset{NOH}{\|}}{C}-CH_3$	2	S	--	--	--	[13]
17	$-\overset{\overset{NOH}{\|}}{C}-CH_3$	3	S	--	--	--	[12]
18	$-COCH_3$	2	SO_2	--	--	--	[7]

Eluent: a) petroleum ether:methylene chloride:diethyl ether:ethyl acetate-7.5:2:1:1.
b) n-butanol:acetic acid:water-4:1:1.
c) methylene chloride:ethyl acetate-9:1.

The microbiological tests of these compounds were realised on both standard strains,Gram-positive and Gram-negative germs clinically isolated from varied infections sources.

In bacteriological tests,N,N-dimethylformamide,was used as solvent,which did not have its own antimicrobial activity.

For the diffusion tests,a Mueller-Hinton medium pH=7.2 was used,supplemented with ram blood in case of Streptococci [5].For preparation of inocula,the glucose-broth was used.

The antibacterial activity was determined by the inhibition zone method [6] on Mueller-Hinton plates,with the concentration of the tested substances of 200 μg/disk or respectively 100 μg/disk. The impregnated disks of 5 mm diameter were initially sterilised by autoclavation.

The disks impregnated with substances were applied on plates sown with bacteria.After an overnight incubation at 37 °C,the inhibition zones were read (in mm including the diameter of the disk),the measurement being made in two or three different directions.For comparison,on each plate were applied two classical antibiotics,ampicillin (10 μg/microtablet) and kanamicin (30 μg/microtablet).The experimental results were expressed by the inhibition zone diameter (mm) produced by each substance against the clinical isolates of bacteria.Also,the inhibition zone diameter for standard strains,tested under the same conditions as the clinical isolates,were measured.

So,from the microbiological data (Tables 2 and 3),compared to 2-chloromethyl-phenoxathiin,the corresponding 10,10-dioxide (compound **8**) shows a lower antimicrobial activity on a much smaller number of bacteria strains.The corresponding isothiouronium salts were obtained starting from these two compounds.The isothiouronium salt of 2-chloromethylphenoxathiin had a large antibacterial spectra both on Gram-positive and Gram-negative strains,while its corresponding 10,10-dioxide had an antibacterial activity only on Morganella morganii strains.

Also,2-acetyl- respectively 3-acetylphenoxathiin showed a significant antibacterial activity on Morganella morganii strains,while their oximes and aminooxy derivatives did not have any activity at all (Table 3).

Starting also from 2-acetylphenoxathiin,the corresponding thiomorpholide was obtained through the Willgerodt reaction [7],which treated with iodomethane in excess,lead to the compound **3**.None of these two compounds have any antimicrobial activity,but the acid hydrolysis of thiomorpholide leads to 2-phenoxathiinacetic acid,which has as low an antimicrobial activity as his corresponding 10,10-dioxide.

A strong antibacterial activity is also shown by the sulfonium salt **4**,which through alcaline hydrolysis leads to 2-phenoxathiincarboxylic acid with a much lower biological activity.

TABLE 2

Antimicrobial activity of the compounds **4-6** and **11-12**.

Compound	**4**	**5**	**6**	**11**	**12**	**A**	**K**
Strain							
Staph.aureus 13204	15[a]	12[a]	-	-	-		
Staph.Oxford 10279	14[a]	12[a]	-	-	-		
Ps.aeruginosa 13202	-	-	-	-	-		
E.coli 13203	-	15[a]	-	-	-		
Staph.aureus (othical secretion)	12[b]	15[a]	-	-	-	20	24
Staph.aureus (nasal secretion)	14[b]					15	22
Staph.aureus (urethral secretion)	10[a]					20	29
Strpt.haemolyticus (purulent secretion)	10[b]						
Staph.aureus (purulent secretion)	12[a]	12[a]	-	-	-	-	-
Shigella S.	-	12[a]	6[a]	-	-	-	19
E.coli	-	12[a]	-	-	-	-	22
Shigella Flexneri	-					-	26
Ps.aeruginosa (uroculture)	-	14[a]	-	-	-	-	-
Pr.vulgaris	8[b]	-	-	-	-	-	-
Salmonella enteritidis	-	10[a]	-	-	-	19	26
Staph.aureus (hemoculture)	-	12[a]	-	-	-	24	-
Bacillus subtilis	-	10[a]	-	-	-		
Morganella morganii	-	20[a]	14[a]	10[a]	10[a]	-	24
Citrobacter	-	6[a]	-	-	-	-	-

a = tested substance conc. 10 mg/ml (200 μg/disk).
b = tested substance conc. 5 mg/ml (100 μg/disk).
A = ampicillin (10 μg/microtablet).
K = kanamicin (30 μg/microtablet).
- = normal growth of bacteria.

TABLE 3

Antimicrobial activity of the compounds **7-10** and **14**.

Compound	**7**	**8**	**9**	**10**	**14**
Strain					
Staph. 12793	7	6.5	-	-	7
Staph. 11020	9	7	-	-	7.4
Staph. 11345	7	-	6	7	6.2
Staph. 313	6	-	-	-	7
Staph.aureus 19	6	8	6	-	-
Staph. citr. 52	8	6	6	6	-
Staph. 12449	9	6	-	6	6.6

In literature is well known the fact that the phenoxathiin nucleus oxidizing in position 10 [1],generates a strong diminution of the biological activity,data which are confirmed also in the present paper.In this respect,the turning through oxidizing of compounds **5**,**7**,**9**,**11** and **14** into their analogues 10,10-dioxides leads to a strong decrease of the antibacterial activity.

The 2-phenoxathiincarboxylic acid,prepared in literature also through the King reaction,starting from 2-acetylphenoxathiin [8] was obtained by means of a new way, respectively through the alcaline hydrolysis of sulfonium salt obtained as a result of the reaction between dimethyl sulfoxide,hydrochloric acid and 2-acetylphenoxathiin.

The hydrolysis of this salt with methanolic sodium hydroxide,in the conditions described in literature for the acetophenone sulfonium salt [9],did not lead to satisfactory results.

The protection of 2-acetylphenoxathiin carbonyl group as aminooxy derivative,in the oxidizing reaction with potassium permanganate,allowed the obtaining of 10,10-dioxide without the oxidation of the side chain.

The removing of the protective group in acid conditions leads to 2-acetyl-phenoxathiin-10,10 dioxide.

IR spectra for the compounds **1-6** are presented in Table 4.

TABLE 4

Characteristic vibrations of the compounds **1-6**.

Compound	γ_{4CH} (cm^{-1})	γ_{2CH} (cm^{-1})	$\nu_{C=O}$ (cm^{-1})	$\nu_{C=N}$ (cm^{-1})	ν_{C-O-C} (cm^{-1})	SO_2 (cm^{-1})	Other vibrations (cm^{-1})
1	745	832	-	1592	1230	-	-
2	760	840	-	1596	1232	562 1158 1232	-
3	750	820	-	1580	1275	-	1340-$\nu_{s\text{-}CH_3}$ 1115-$\nu_{C\text{-}O\text{-}C}$ morpholine ring
4	755	825	1675	-	1230	-	1350-$\nu_{s\text{-}CH_3}$
5	750	825	-	1648	1245	-	3040-$\nu^{sim}_{NH_2}$ 3190-$\nu^{as}_{NH_2}$
6	770	840	-	1640	1252	570 1170 1290	3080-$\nu^{sim}_{NH_2}$ 3235-$\nu^{as}_{NH_2}$

CONCLUSIONS

Six new compounds of the phenoxathiin class were obtained and characterised. They were tested for their antimicrobial activity together with other twelve compounds from this class.

The compounds **4** and **5** have a significant antibacterial activity.

The oxidizing of the sulfur atom on position 10 of the phenoxathiin nucleus leads to a strong decrease or loss of the antimicrobial activity.

The protection of carbonyl group in 2-acetylphenoxathiin was done by turning it into aminooxy derivate which allowed the sulfur atom in position 10 to be oxidized without affecting the side chains.

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