UDC 547.541.457

SYNTHESIS, CONVERSION AND ANTIMICROBIAL ACTIVITY OF DERIVATIVES OF 2-HYDROXY-1-HALOIDPHENOXYETHERS OF NONANOL-2

S.A.Mammadov, A.A.Mahmudova, G.G.Mammadova, V.S.Hasanov, N.P.Ladokhina,
L.F.Zeynalova

A.Guliyev Institute of Chemistry of Additives, NAS of Azerbaijan

nina62_62@mail.ru

Received 20.06.2019

Accepted 10.10.2019

Reactivity of hydroxyl group in 1-haloid-phenoxy-2-hydroxynonanes to nucleophilic substitution with acetoxymethylchloride was studied. It was found that regardless of the nature of haloids and their position in aryloxy radical the yields of acetoxymethyl ethers makes nearly 70% that proves high reactivity of hydroxyl group. Indeed, during the reaction with isocyanates phenoxynonanol-2 forms urethanes with yield 69–70%. Initial synthon was prepared by the reaction of 1-bromine-nonanol-2 with substituted phenols. Study of synthesized polyethers and urethanes as antimicrobial additives to lubricating oils gave positive results. It was determined that urethanes exhibit stronger antimicrobial effect than polyethers.

Keywords: *phenoxyethers, urethanes, polyethers, acetoxymethyl, antimicrobial additives.*

doi

Introduction

The most topical and promising studies in organic chemistry is the creation of new bio-active compounds with specified properties. Due to this the study of the properties of polyethers and urethanes containing phenoxygroups is highly relevant.

Previous studies showed that synthesized urethanes and thiourethanes containing polyethers [1, 2] and without them [3–5] have high antimicrobial properties. Therefore, the investigations on the synthesis and study of new derivatives of polyethers and urethanes containing phenoxyethers are of great interest.

Experimental part

IR-spectra of synthesized compounds were registered on spectrometer "Nicolet IS-10", NMR H^1 spectra – on spectrophotometer "Tesla-467" with operating frequency of 90 MHz. Purity of compounds were determined by gas-liquid chromatography analysis which was performed on chromatograph with flame ionization detector at temperature of column 200°C, evaporator temperature – 260°C, carrier-gas – helium, rate of carrier-gas – 25 ml/min, adsorbent – Colitfe-545, stationary phase – silicon oil.

1-(Haloidphenoxy)-2-nonanols (I–III).

General technique. 0.11 mol of 1-bromine-

nonanol-2 (obtained by the reaction of nonene-1 with N-brominesuccinimide) was added drop by drop into the mixture of 0.1 mol of *o*-Cl, or *o*-Br, or *m*-Br-phenol and 10 g of 40% aqueous solution NaOH at 80–85°C with strong mixing. After that the reaction mass it was kept at this temperature for 5 hours. Then the mixture was cooled, extracted with benzene, the solution was neutralized, benzene was distilled, but the residue was distilled under vacuum. Physical and chemical characteristics were given in the Table 1.

1-(Haloidphenoxy)ethoxymethyloxynonanes (IV–VI). General technique. 0.03 mol of freshly-distilled α -chlorinemethylethyl ether dissolved in 30 mol of non-aqueous benzene was added drop by drop into the mixture of 0.02 mol of compounds I, II and III, 50 ml non-aqueous benzene and 0.03 mol of freshly-distilled triethylamine during cooling. The mixture was mixed for an hour, then at 55–60°C – for 3–4 hours. After that the mixture solution was cooled and washed f with 5% solution of HCl and then with water. After drying and distilling the solvent the residue was distilled under vacuum. Compounds IV–VI were obtained with yield of 68%. Physical and chemical characteristics were given in the Table 1.

In NMR spectrum (Figure 1) of the compound IV (DMCO) two methyl groups oxyethyl and

Table 1. Physical and chemical features of synthesized compounds

No comp.	Yield, %	T_{boil} /mm Hg or $T_{\text{melt.}}$, °C	n_D^{20}	d_4^{20}	MR_D		Chemical formula	Elemental analysis, %		
								C	H	N
					found	calculated		found	found	found
								calculated	calculated	calculated
I	72.3	176 – 177/3	1.4998	0.424	76.3	75.9	$C_{15}H_{23}O_2Cl$	$\frac{66.41}{66.54}$	$\frac{66.41}{66.54}$	–
II	71.8	174 – 175/2	1.5164	1.212	78.57	78.8	$C_{15}H_{23}O_2Br$	$\frac{57.45}{57.14}$	$\frac{7.08}{7.30}$	–
III	71.06	171 – 172/2	1.5180	1.2118	79.25	78.8	$C_{15}H_{23}O_2Br$	$\frac{56.91}{57.14}$	$\frac{7.1}{7.30}$	–
IV	68.8	177 – 178/5	1.4852	1.0266	96.08	96.448	$C_{18}H_{29}O_3Cl$	$\frac{65.65}{65.12}$	$\frac{8.81}{8.96}$	–
V	68.7	187 – 188/5	1.498	1.1482	95.0	95.448	$C_{18}H_{29}O_3Br$	$\frac{57.79}{57.91}$	$\frac{7.61}{7.85}$	–
VI	72.3	184 – 185/5	1.4992	1.1476	95.46	95.17	$C_{18}H_{29}O_3Br$	$\frac{57.80}{57.91}$	$\frac{7.60}{7.85}$	–
VII	84.0	66 – 67	–	–	–	–	$C_{22}H_{28}NO_3Cl$	$\frac{67.3}{67.77}$	$\frac{7.02}{7.18}$	$\frac{3.42}{3.59}$
VIII	83.9	67 – 68	–	–	–	–	$C_{22}H_{28}NO_3Br$	$\frac{60.54}{60.83}$	$\frac{6.21}{6.49}$	$\frac{3.08}{3.22}$
IX	79.9	65 – 66	–	–	–	–	$C_{22}H_{28}NO_3Br$	$\frac{60.65}{60.83}$	$\frac{4.35}{6.49}$	$\frac{3.01}{3.22}$
X	81.2	61 – 62	–	–	–	–	$C_{23}H_{30}NO_3Br$	$\frac{68.18}{68.40}$	$\frac{7.61}{7.33}$	$\frac{3.42}{3.35}$

Fig. 1. NMR spectrum of 1-oxyphenyl-2-*para*-methylphenylurethanenonane (IV).

heptyl appear together in the region of 0.45–2.0 ppm. Protons of OCH_2OCH_2 -, $\text{C}_6\text{H}_4\text{Cl-OCH}_2$ - and CH -groups appear together in the region of 3.0–4.1 ppm, but disubstituted aromatic protons are in the region of 7.0 ppm.

1-Ethoxymethyl-2-nonanoxyhaloidphenylurethanes (VII–X). General technique. 0.02 mol of one from the compounds I–III was dissolved in 20 ml of benzene, 0.001 ml of triethylamine was added and at 80–85°C 0.02 mol of phenylisocyanate in the solution of 20 ml of non-aqueous benzene was added drop by drop. At this temperature the mixture was mixed for 3–4 hours, 2/3 benzene was distilled, cooled and 25 ml of hexane was added. Obtained crystals were filtered and recrystallized from the mixture of benzene and hexane (1:1). Physical and chemical characteristics of the compounds VII–X are given in the Table 1.

In NMR-spectrum (Figure 2) of the compound VII (DMCO) protons of methyl and methylene groups of nonane appear in the region of 1.5–2.5 ppm, but protons of 2CH_2 and CH – in the range of 3.1–4.5 ppm. Proton of NH -group of urethane was observed in the region of 5.4 ppm. Protons of mono- and disubstituted aromatic nucleus are in the region of 7–7.6 ppm.

Results and Discussion

Ways of obtaining polyethers are quite diverse. Convenient and effective ways of obtaining 3,4,5-trimethoxybenzene sulfides and

ethers containing vinyl, allyl and propargyl groups basis on the of 3,4,5-trimethoxybenzene alcohol, sulphur and thiocarbamide in basic and basic-reduction systems (hydrazine hydrate, $\text{KOH}\cdot\text{DMPA}$, $\text{KOH}\cdot\text{DMCO}$) have been developed. Convenient transesterification by developed to synthesize drug preparations. The reaction is based on reetherification with alcohols of α,α -disubstituted ethers of carboxylic acids using N-heterocyclic carbenes as catalysts [6]. Obtaining of complex ethers [7] using organic compounds of actinide metals as catalysts of asymmetric tandem reaction of etherification with proton transfer between aldehydes and alcohols has been described. The developed method of etherification is suitable for obtaining a wide range of substrates in the synthesis of various ethers. It was determined that hydroxyl group in 1-phenoxy-2-hydroxynonane is activated with phenoxy group which allows performing not only the reaction of nucleophilic substitution of hydrogen of hydroxyl group, but also addition reaction with isocyanates and thiocyanates. Apart from hydroxyl group presence of active functional groups in the compounds leads obtaining of oxazidines and thiasolidines [8–12].

To synthesize phenoxyethers 1-brominepropanol-2 was first synthesized using the reaction of nonene-1 with brominesuccinimide in aqueous medium by known technique, then by the interaction of the obtained compound with haloidphenols in the presence of NaOH the following reaction was carried out:

Hal = *o*-Cl (I); *o*-Br (II); *m*-Br (III).

Fig. 2. NMR spectrum of phenylurethane-2-*o*-chlorinephenylnonane (VII).

Yields of phenoxyethers make 70–72%.

Hydroxyl group in the compounds I–III under the impact of phenoxy group has a high reactivity as a result of which at interaction in basic medium these compounds with ethoxymethylchloride polyethers form:

R = *o*-Cl (IV), *o*-Br (V), *m*-Br (VI)

As is known, an increase in the tension of reaction center in molecule due to joint repulsion of ethoxy and phenoxy fragments through methylene group in ethoxymethylchloride must cause the increase of practical yield and reaction rate. However, regardless of reaction conditions the yield of ethoxy-methoxy ether does not exceed 68.7%

High yields (79–81%) of urethanes (VII–X), obtained by the reaction of isocyanates with 1-phenoxy-2-nonanol prove high reactivity of hydroxyl group:

R² = H, R¹ = *o*-Cl (VII), *o*-Br (VIII), *m*-Br (IX). R² = *o*-CH₃, R¹ = *o*-Cl (X)

As is known, addition reactions includes polar and ionic transition state. Addition of isocyanates or isothiocyanates to hydroxyl group has both transition states, therefore, this addition reaction runs synchronously. Addition reaction of isocyanates to hydroxyl is carried out in the presence of catalytic amount of triethylamine which allows the reaction to run on ion

mechanism. Under such condition the reaction mechanism is similar to the mechanism of addition reaction of halogen hydrides to unsaturated compounds the only difference being that in case of isocyanate fragment carbanion is formed under the impact of triethylamine, and then addition of hydroxyl anion is generated:

Considering that polyether compounds which include phenoxyethers have an extremely various physiological activity, investigations of synthesized compounds as antimicrobial compounds were carried out.

Experimental data of compounds in oil M-8 are presented in the Table 2. As Table shows phenoxyethers containing hydroxyl group (compounds II–III), has a moderate antibacterial effectiveness. It is interesting that when bromine atom

is in meta-position the compounds are more effective than at its present in *ortho*-position. To obtain ethers using ethoxymethylchloride effectiveness of antibacterial action of compounds (I–VI) sharply increases, but fungicide properties weaken. Among synthesized compounds urethanederivatives are highly-effective bactericides. Interestingly, the compounds containing urethane fragment exhibit both antibacterial and fungicide activity.

Table 2. Antimicrobial property of some compounds in oil M-8

No compound	Concentration, %	Inhibition zone diameter, cm			
		Bacteria		Fungi	
		<i>Pseudomonas aeruginosa</i>	<i>Mycobacterium lacticola</i>	<i>Aspergillus niger</i>	<i>Candida tropicalis</i>
II	0.1	14	12	1.0	15
	0.25	18	16	12	18
	0.5	23	20	16	22
	1.0	27	25	18	25
III	0.1	16	13	10	18
	0.25	20	18	16	22
	0.5	24	22	18	24
	1.0	30	27	22	16
IV	0.1	19	18	12	14
	0.25	21.5	22	14	18
	0.5	28	26	18	22
	1.0	27	28	20	14
VIII	0.1	34	24	18	20
	0.25	29	28	26	28
	0.5	35	34	28	30
	1.0	39	38	32	34
IX	0.1	24	26	10	12
	0.25	28	30	14	14
	0.5	32	34	16	18
	1.0	36	36	20	21
X	0.1	20	26	10	16
	0.25	28	30	16	18
	0.5	36	34	18	24
	1.0	38	38	24	26
Oil	M-8	+	+	+	+
Sulfaksid	0.1	10	9	10	10
	0.25	12	10	11	12
	0.5	14	13	12	13
	1.0	19	16	16	14
Grotan	0.25	16	12	–	–
	0.5	20	16	–	–

Thus, antimicrobial and fungicide properties of synthesized compounds depend on the content and nature of functional groups and position of haloid atoms in aromatic nucleus.

Our studies are based on high potential of obtained compounds and prospect of using as synthons in the synthesis of hard-to-reach various multi-functional compounds with wide range of usefulness which makes them suitable substrates for thin organic synthesis. Synthesized compounds were studied as additives to lubricating oils. Experimental data were given in the Table 3. As Table 3 shows when compounds I–III contain hydroxyl group their anticorrosive properties are satisfactory. However, tribological effectiveness is low. Polyethers (compounds IV–VI) are effective additives.

Their anticorrosive action is moderate, while tribological properties are high. In concentration of 10 mmol their wear scar diameter is close to industrial additives (DF-11), but load wear index is high than those. This proves that polyethers can be used as extreme pressure additives. Unlike ethers urethane additives (compounds II–IX) are more effective additives to lubricating oils. In concentration of 10 mmol in 100 g of oil the value of wear scar diameter is similar under the action of industrial additives.

Extreme pressure properties of urethanes are very high and therefore, they can be recommended as anticorrosive, antiwear and extreme pressure additives. Their high effectiveness is related to synergism of phenoxy- and urethane fragments in one molecule.

Table 3. Tribological and anticorrosive properties of some compounds

No compound	Content of compound in 100 g oil		Corrosion, g/m ²	Antiwear and extreme pressure properties at 392 H, 1 h	
	mmol	g		wear scar diameter, d_{MM}	load wear index, I_3
II	5	1.6	26.8	0.58	46
	10	3.2	17.1	0.05	49
IV	5	1.65	28.3	0.56	58
	10	3.3	16.4	0.52	52
V	5	1.87	21.2	0.55	60
	10	3.74	14.3	0.50	52
VII	5	1.95	11.4	0.52	65
	10	3.90	9.5	0.49	67
VIII	5	2.2	10.8	0.50	68
	10	4.3	6.1	0.43	70
IX	5	2.17	9.2	0.43	68
	10	4.34	4.8	0.40	70
Масло М-8			180–200	–	–
Масло АК-15			–	0.68	20.1
ДФ-11		1	27.7	0.63	61
		2	3.9	0.40	–

References

- Balazadə P.Ş., Mahmudova Ə.Ə., Həsənov V.S. 1-(o-Bromfenoksi)-3-noniltio-2-propanolun bəzi törəmələrinin sintezi və xassələrinin tədqiqi // Azerb. Chem. Journ. 2009. № 1. S. 182–185.
- Həsənov V.S., Mahmudova Ə.Ə., Babayeva G.V., Rəhimov İ.S. 1-Fenoksi-3-propiltio-2-propanolun bəzi törəmələrinin sintezi və xassələrinin tədqiqi // Azerb. Chem. Journ. 2014. № 1. S. 104–108
- Həsənov V.S., Mahmudova Ə.Ə., Babayeva G.V., Zeynalova L.F. N,N-dimetilditiokarbamin turşusunun β-hidroksipropil efirinin sintezi və bəzi cəv-
- rilmələri // Azerb. Chem. Journ. 2013. № 3. S. 121–124.
- Həsənov V.S., Mahmudova Ə.Ə., Babayeva G.V., Baxşıyeva Ü.Ş. 1-(m-bromfenoksi)-2-dekanolun sintezi, cəvrlmələri və cəvrlmə məhsullarının mikrob əleyhinə xassələrinin tədqiqi // Azerb. Chem. Journ. 2013. № 4. S. 101–105.
- Həsənov V.S., Mahmudova Ə.Ə., Babayeva G.V., Baxşıyeva Ü.Ş., Əkbərli H.N. 1-(m-Toliloksi)-2-oktanolun sintezi cəvrlmələri və cəvrlmə məhsullarının mikrob əleyhinə xassələrinin tədqiqi // Azerb. Chem. Journ. 2014. №3. S.110–116.

6. Chen Xingkuan, Jasgueline Zi Mei, Xu Jianfeng, Mou Chengli. Dynamic kinetic identification of ethers of carboxylic acids catalyzed with carbenes. *J. Amer. Chem. Soc.* 2016. V. 138. No 23. P. 7212–7215.
7. Liu Heng, Eisen Moris S. Selective, catalyzed with actinides etherification between aldehydes and alcohols with proton transfer for obtaining of asymmetric complex ethers. *Organometallics*. 2017. V. 36. No 8. P. 1461–1464.
8. Wu Xia, Geng Xiao, Jhao Peng, Zhang Zungjing. J_2 -promoted formal [3+2] cycloaddition of α -metyulenyl isocyanides with metyl ketons: a route to 2,5-disubstituted oxazoles. *Chem. Commun.* 2017. V. 53. No 4. P. 3439–3441.
9. Young Jae Choi, Yoo Chang Kim, Sook Jin Park, Jun Min Jung, Young Hoon Jung. Total synthesis of (–)-codonopsinine via regioselective and diastereoselective amination using chlorosulfonyl isocyanate. *Tetrahedron*. 2017. V. 73. No 30. P. 4458–4463.
10. Wi Xiao, Masen Jess, Norh L. Formation of isocyanurates in synthesis process of oxazolidinones from epoxides and isocyanates catalyzed with chromium complex (Chrom Salphen). *J. Chem. Eur J.* 2018. V. 23. No 52. P. 12937–12943.
11. Tamula Nagarajo, J. Nagesh, P.R., Krishna S. Balasubramanian S. Catalyzed Oxidative N,S-Bond Formation: Metal-Free Regiospecific Synthesis of N-Fesed and 3,3-Disubstituted 5-amino-1, 2, 4-thiadiazoles. *J. Org. Chem.* 2012. V. 82. No 10. P. 5310–5316.
12. Guo Wei, Zhen Mingminq, Tan Wen, Zheng Leyin. Three-component tandem annealing promoted with visible light in the synthesis of 2-iminothiazolin-4-ones. *J. Org. Chem.* 2018. No 3. P. 1402–1413.

2-HİDROKSİ-1-HALİDFENOKSİ EFİRLƏRİN SİNTEZİ, ÇEVİLMƏLƏRİ VƏ ONLARIN ANTİMİKROB AKTİVLİYİ

S.Ə.Məmmədov, Ə.Ə.Mahmudova, G.H.Məmmədova, V.S.Həsənov, N.P.Ladoxina, L.F.Zeynalova

1-Haloidfenoksinonanol-2 ilə asetoksimetilxlorid arasındakı nukleofil əvəzetmə reaksiyası əsasında hidroksil qrupunun reaksiya aktivliyi öyrənilmişdir. Müəyyən edilmişdir ki, halogen atomunun təbiətindən və onların aromatik həlqədə yerləşmə vəziyyətindən asılı olmayaraq asetooksimilmetil efirlərinin çıxımı 70%-ə qədər olur. Bu isə hidroksil qrupunun yüksək reaksiya qabiliyyətini göstərir. Doğurdan da fenoksinonanol-2 izosianatla çox asan 69–70% uretanlar əmələ gətirirlər. İlk maddə 1 brom-nanoanol-2 ilə haloïdfenollarla reaksiyadan alınır. Sintez olunmuş poliefirlər və uretanlar sürtkü yağlarına antimikrob aşqarı kimi sınaqdan çıxarılmışdır və müsbət nəticələr alınmışdır. Uretanlar daha yüksək antimikrob xassəyə malikdirlər.

Açar sözlər: fenoksiefirlər, uretanlar, poliefirlər, asetoksimetil, antimikrob aşqarlar.

СИНТЕЗ, ПРЕВРАЩЕНИЕ И АНТИМИКРОБНАЯ АКТИВНОСТЬ ПРОИЗВОДНЫХ 2-ГИДРОКСИ-1-ГАЛОИДФЕНОКСИЭФИРОВ НОНАНОЛА-2

С.А.Мамедов, А.А.Махмудова, Г.Г.Мамедова, В.С.Гасанов, Н.П.Ладохина, Л.Ф.Зейналова

Исследована реакционная способность гидроксильной группы в 1-галоид-фенокси-2-гидроксинонанах при нуклеофильном замещении с ацетоксиметилхлоридом. Найдено, что независимо от природы галоида и их расположения в арилокси радикале выходы ацетоксиметилэфиров составляют около 70%, что доказывает высокую реакционную способность гидроксильной группы. Действительно, феноксинонано-2 при реакции с изотиоцианатами образует уретаны с выходом 69–70%. Исходный синтон получен реакцией 1-бром нонанола-2 с замещенными фенолами. Исследование синтезированных полиэфиров и уретанов в качестве антимикробных присадок к смазочным маслам дало положительные результаты. Установлено, что уретаны проявляют более сильное антимикробное действие, чем полиэфиры.

Ключевые слова: феноксиэфиры, уретаны, полиэфиры, ацетоксиметил, антимикробные присадки.