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Research Article

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Antimicrobial Activity of Some Halogenated Isoalkyl Phenols

Dmitrii A. Pisanenko[1*], Yurii E. Klimko[1], Irina V. Kostij[1], Larisa N. Shunko[1], Yurii L. Voljanskii[2]

[1]Chemical Technologies of Organic Substances, Igor Sikorsky Kyiv Polytechnic Institute, Kiev, Ukraine.
[2]Mechnikov Institute of Microbiology and Immunology, Academy of Medical Sciences of Ukraine, Charkov, Ukraine
*e-mail: dpisanenko@ukr.net

Abstract Halogenated isopropyl-, sec-butyl-, sec-pentyl-, sec-hexyl, sec-heptylphenols were synthesized and screened for possible antibacterial and antifungal activities against *Staphylococcus aureus, Streptococcus viridans, Escherichia coli, Shigella flexneri, Salmonella typhi, Salmonella typhimurium, B. proteus vulgaris, Pseudomonas aeruginosa, Bacterium antracoides, Bacterium subtilis, Klebsiella rhinoscleuromatis* and *Candida albicans* using the microdilution method. Antimicrobial tests results indicated that all compounds have reasonable activity. They displayed the highest antimicrobial activity against *Streptococcus aureus, Streptococcus viridans* and *Candida albicans*. The isoalkyl phenols containing chlorine atoms were the most active than the fluorine containing phenol in the series against majority tested bacteria and fungi strains.

Keywords Chlorine- and fluorine containing isoalkyl phenols, synthesis, antibacterial activity, antifungal activity

1. Introduction

The emergence of resistance in microorganisms to existing bactericides requires the use of new disinfectants, among which attract attention alkylhalogenphenols as low-toxic bactericides and biological antioxidants [1-8]. Biological effects of phenols associated with their ability to affect microbial cell wall to form complexes with polysaccharides and proteins coagylating [9]. The introduction into the structure of phenols halogen atoms s may affect the ability of cell wall permeability and, correspondingly, on the biological properties of phenols [10]. Previously, we synthesized some halogenated isopentyl phenols and evaluated them to their antimicrobial activities [11]. The results showed that isopentyl radicals attached to the phenol structure cause a significant change in the antimicrobial effect. In this connection it is of interest to further study the effect of the structure of isoalkyl phenols on their antimicrobial properties . To do this in the present work has been synthesized several halogenated isoalkyl phenols **2-8** by the most reasonable published methods. Phenols **2-8** were prepared to investigate the effects of the structural modifications on the anticipated antimicrobial activity. It was studied for their antimicrobial activity against Gram positive, Gram-negative, spore, bacteria capsular and yeasts.

2. Experimental

General

^{1}H-NMR spectra were recorded on a JEOL spectrometer (90MHz) in DNSO-d_6 or $CDCl_3$ with TMS as internal reference, chemical shifts were measured in the δ scale. IR spectra of compounds were recorded as potassium

bromide pellets on a Specord 75-IR instrument. GLC- gel-60 was performed on a Biokhrom device (5% Apieson L on Inerton N-AW-HMDSW, carrier gas He). TLC and column chromatography were performed on silica gel-60.

Procedure for Synthesis of Halogenated Isoalkyl Phenols

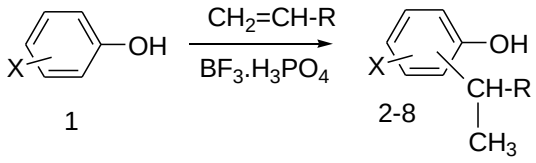
Phenols **2-8** were obtained by the alkylation of 2- and 4-chlorophenol and 4-fluorophenol with corresponding alkenes in the presence of catalyst $BF_3 \cdot H_3PO_4$ [12] using 0.1 mol alkenes in 10 ml CCl_4 and the appropriate amounts of halogenated phenols. The reaction products were washed with sodium carbonate solution, water and dried $MgSO_4$. After drying, the solvent and the starting materials were distilled off and the residue was distilled under vacuum, carrying GLC analysis before and after distillation, yield calculated on the starting alkenes. Following rectification, TLC and column chromatography on silica gel-60 individual phenols **2-8** were isolated under control of the purity by GLC [13]. Individuality of phenols **2-8** was examined by GLC, the structures were determined by spectral analyses and spectroscopic properties were in accord with data reported previously [12].

Antimicrobial Activity

The minimal inhibitory concentration (MIC) was determined by microdilution method [14]. *In vitro* antimicrobial activity of the compounds 5-8 was evaluated against standard strains; *Staphylococcus aureus* 209-P, *Streptococcus viridans* 171, *Escherichia coli* 675, *Shigella Flexneri* 2a-516, *Salmonella typhi* 495, *Salmonella typhimurium* 5710, *B. proteus vulgaris* 296, *Pseudomonas aeruginosa* 128, *Bacterium antracoides* 297, *Bacterium subtilis* ATCC, *Klebsiella rhinoscleuromatis* 348 and *Candida albicans* 688. All the synthesized phenols were weighed, dissolved in DMSO and diluted with water to prepare the stock solutions. A bacterial suspension, obtained from a 24h culture was added to each probe with a final DMSO concentration. Each experiment was carried out in duplicate.

3. Results and Discussion

In the present study has been synthesized the halogenated isoalkyl phenols by the procedures were based on the simply methods with using accessible reagents [12]. The yield of the products in this reaction was 73 -80%: The reaction proceeds with high positional selectivity ($H_S = 0$), for 2-chlorophenol in position 4, and for 4-chloro- and 4-fluorophenols in position 2.



1 X=2-Cl 2 X=2-Cl R=CH_3 3 X=2-Cl R=C_2H_5 4 X=2-Cl R=C_3H_7 5 X=2-Cl R=C_4H_9 6 X=2-Cl R= C_5H_{11} 7 X=4-Cl R=C_2H_5 8 X=4-F R=CH_3

Figure 1: Synthesis of Phenols

By distillation of products and using TLC and column chromatography were isolated individual phenols **2-8**, purity of the synthesized compounds was examined by GLC and the structures were determined by spectral analyses. The series of phenols **2-8** were evaluated for antimicrobial activity toward the Gram positive and Gram negative bacteria and fungus. Their antibacterial activities were assessed by measuring minimum inhibitory concentration (MIC) with standard broth dilution assay (Table 1.)

Table 1: Antimicrobial Activity of 2-Chlorophenol and Halogenated Isoalkyl Phenols (MIC) 1-8 in μg/mL

Phenol No	*S. aureus*	*S. viridans*	*E.coli*	*Sh. flexneri*	*Sal.typhi*	*Sal. typhimurium*	*B.proteus vulgaris*	*Ps. aeruginosa*	*Bac. antracoides*	*Bac. subtilis*	*Kl.rhinos-leuromatis*	*Candida albicans*
1	31.25	15.62	62.5	62.5	125.0	62.5	62.5	62.5	62.25	125.0	125.0	15.6
2	15.62	15.62	31.25	31.25	62.5	250.0	62.5	62.5	15.6	125.0	62.5	7.8
3	15.6	31.25	62.5	62.5	31.25	125.0	62.5	125.0	15.6	125.0	62.5	7.8
4	31.25	7.8	62.5	62.5	61.5	125.0	125.0	125.0	7.8	125.0	125.0	31.25
5	31.25	31.25	62.5	62.5	62.5	125.0	125.0	62.5	62.5	62.5	62.5	31.25
6	3.9	3.9	15.6	7.8	15.6	15.6	62.5	62.5	62.5	125.0	62.5	7.8
7	7.8	7.8	125.0	62.5	62.5	125.0	125.0	125.0	250.0	250.0	125.0	15.6
8	125.0	125.0	250.0	125.0	125.0	125.0	125.0	250.0	62.5	125.0	125.0	250.0

As can be seen from Table 1, all halogenated isoalkyl substituted phenols **2-7** have sufficiently antimicrobial activity against tested bacteria and fungi. According to the antimicrobial activity results, all compounds were found to have the highest antimicrobial activity against *Streptococcus aureus*, *Streptococcus viridans* and *Candida albicans*. The isoalkyl phenols containing chlorine atoms were the most active than the fluorine containing phenol **8** in the series against majority tested bacteria and fungi strains. Our study revealed that all the compounds had stronger antibacterial activity against Gram positive bacteria when compared to Gram negative bacteria. The findings suggest that the halogen substituted isoalkyl phenols act on the cell membranes and surface activity of these compounds may be chiefly responsible for the antibacterial properties of the compounds. However, all the tested compounds exhibited the antifungal activity against *Candida albicans.* The reason for the stronger antifungal activity according to antibacterial effect might be postulated as different action in the mechanism of the compounds such as inhibition effect on respiratory systems of fungus cells, rather than cell wall destruction [15].

4. Conclusions

In summary we have synthesized some halogenated isoalkyl phenols by means of simply methods with using accessible reagents. The purity of the synthesized compounds was examined by GLC and the structures were determined by spectral analyses. Antimicrobial tests results indicated that all compounds have reasonable activity. The 4-*sec*-heptyl-2-chloro- and 2-*sec*-pentyl-4-chlorophenols were found to have high activity against *Staphylococcus aureus, Streptococcus viridans* and *Candida albicans*. Our study also covered the relationship between antimicrobial activity and structure of halogenated isoalkyl phenols.

References

[1]. Beckett A.H., Patki S.J., Robinson A.E. (1959) The Interaction of Phenolic compounds with Bacteria. Part III. Evaluation of the Antibacterial Activity of Hexylresorcinol against *Esherichia coli. J.Pharmacy and Pharmacology*. https://doi.org/10.1111/j.2042-7158.1959.tb1275.

[2]. Block S.S. (2001) Disinfection, Sterilization and Preservation. Lippincott Williams and Wilkins, 1481.

[3]. Oh K.B., Lee J.H., Yoon K.M. et al. (2009) Synthesis and antimicrobial activities of halogenated bis(hydroxyphenyl)methanes. *Biorg.Med.Chem.Lett*., 19(3), 945-948.

[4]. Tagari T., Tanaka T., Kouno J. (2004) Antimicrobial activity of different plant polyphenols against bacteria causing food-borne disease. *Biol. Pharm.Bull.,* 27:1965-1969. https://doi.org/10.1248/bpb.1965.

[5]. Rua J., Fernendes-Alvares, Castro C. et al. (2011) Antibacterial Activity against Foodborne Staphylococcusaureus and Antioxident Capacity of Various Pure Phenolic Compounds. *Foodborne Pathogens.Disease*, v.8(1).// doi.org/10.1089/fpd.2010.0659.

[6]. Anitha J., Jayraaj I.A. (2013) *In vitro* antibacterial activity and evaluation of flavonoid and phenol in earth worm powder world. *J. Pharmacy and Pharm.Sci.*, v.2(6), 4917-4928.

[7]. Makwana S., Choudhary R., Haddock J., Kohli P. (2015) *In vitro* antibacterial activity of plant based phenolic compounds for food safety and preservation. *LWT- Food Science and Technology*, v.62(2), 935-939. https://doi.org/10.1016/j.lwt.2015.02.013.

[8]. Walsh D.J., Livinghouse T., Goeres D.M. et al. (2019). Antimicrobial Activity of Naturally Accuring Phenols and Derivations against Biofilm and Planktonic Bacteria. *Med.Pharm.Chem.*, 01.10.2019. https://doi.org/10.3389/fchem.2019.00653.

[9]. Nikolaev Yu. A, Borzenkov I. A., Kalinin M. V. et al. (2010) Antimicrobial features of phenolic lipids, *Appl. Biochem. Microbiol. (in Russ.)*, 46(2), 172-179.

[10]. Kongkathip N., Hasitapan K., Pradidphol N. (2006) Synthesis of novel 2-(20-cyclopentyl) – and 2-(20-cyclohexyl)substituted 1-naphtol derivatives with anticyclooxygenase, *Curr.Med.Chem.*, 13(30), 3663-3674.

[11]. Pisanenko Dmitrii A., Klimko Yurii E., Voljanskii Yurii L. (2017) Synthesis and antimicrobial activity of some halogenated isopentyl phenols. *Chem. Res. Journal*, 2(2), 23-27.

[12]. Topchiev A.V., Zavgorodnii S.V., Kruchkova V.G. (1962) Reaktsija alkilirovanija organicheskich soedinenii olephinami, *AN SSSR*, 189 *(in Russ.)*

[13]. Zakupra V.A., Dobrov V.S. (1970) Inform.pismo VNIIneftechim., №9, *Naukova dumka, Kiev (in Russ.)*

[14]. Pisanenko D.A., Grigorenko A.A., Palii G.K. (2000) Synthesis and Antimicrobial Activity of 2-(4-halophenyl)-2-(oxyaryl)propanes. *Khim.Farm.Zh.*, 34(12), 40-42.

[15]. Pisanenko D.A., Voljanskii Yu.L. (2016) Synthesis and Antimicrobial Activity of Some Substituted Cyclopentyl Phenols, *Intern. J. Chem. Biomol. Sci.*, 2(1), 1-3.