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Synthesis and antimicrobial activity of some halogenated isopentyl phenols

Dmitrii A. Pisanenko[1]*, Yurii E. Klimko[1], Yurii L. Voljanskii[2]

[1]Chemical Technologies of Organic Substances, Igor Sikorsky Kiev Polytechnic Institute, Kiev, Ukraine
[2]Mechnikov Institute of Microbiology and Immunology, Academy of Medical Sciences of Ukraine, Charkov, Ukraine

Abstract Some halogenated isopentyl phenols 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 isopentyl phenols containing chlorine atoms were the most active than the fluorine containing phenols in the series against majority tested bacteria and fungi strains.

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

1. Introduction

It is known that interest in phenolic compounds is related to their high biological activity of and using as microbicides [1]. The phenols both synthetic [2,3] and plant origin [4-8] are of interest for both low-toxicity bactericides and biological antioxidants [9]. Among them are the alkyl phenols which are used as individual compounds [10] and in the composition of natural mixtures of phenols [11] and in industrial compositions of phenols [12-13]. Biological effects of phenols associated with their ability to affect microbial cell wall to form complexes with polysaccharides and proteins coagylating [14]. They cause changes in the cell walls of microorganism permeability inactivation of respiratory enzymes. The antimicrobial effect of shielded and hindered phenols is due to the effect on the cell membrane blocking lipid peroxidation [15-16]. The introduction into the structure of phenols halogen atoms may affect the ability of cell wall permeability and, correspondingly, on the biological properties of phenols [17]. Previously, we synthesized some cycloalkyl phenols and evaluated them to their antimicrobial activities [18]. The results showed that cyclic radicals attached to the phenol structure cause a significant change in the antimicrobial effect. The research for the study of these properties in a number of phenols with cyclopentyl substituent's demonstrated the possibility of using some of them as insecticides [19] and disinfectants [20].

In this connection it is of interest to further study the effect of the structure of alkyl phenols on their antimicrobial properties. To do this in the present work has been synthesized halogenated isopentyl phenols by the most reasonable methods. They 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 TESLA BS-487 spectrometer (80MHz) in CCl_4 with TMS as internal reference, chemical shifts were measured in the δ scale. IR spectra of compounds were recorded on a UR-20 IR instrument. GLC-analysis was performed on a Tsvet-4 device (10% Apieson N on Chromosorb W, carrier gas He).

Procedure for Synthesis of Halogenated Isopentyl Phenols

For experiments used freshly distilled commercial isoprene. The reaction of the halogenated anisoles with isoprene is carried out according to the reported procedure [21] using 0.05 mol cooled diene in 10 ml CCl_4 and the appropriate amounts of arenes in the presence catalyst –anhydrous H_3PO_4. 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 diene.

Mixture of 2-isopentenylchloroanisoles was obtained with in yield of 73% and mixture of 2-isopentenylfluoroanisoles in a yield 80%. A mixture of 4,2g of 2-isopentylcnloroanisoles was refluxed in 5% $KMnO_4$ and 2.21g of obtained 3-chloro-4-methoxybenzoic acid was filtered and washed with cool ethanol. Yield 59.4%, mp 215^{o}C [22]. Mixture of 3.9g 2-isopentenylfluoroanisoles gave 2.55g 3-fluoro-4-methoxybenzoic acid. Yield 74.8%, mp 206^{o}C[23].Following rectification of mixtures individual 4-(3-methyl-2-butenyl)-2-fluoro- and chloroanisoles **1-2** were isolated under the control of the purity by gas-liquid chromatography.

4-(3-methyl-2-butenyl)-2-fluoroanisole **1:** Yield 72%, b.p.87^{o}C at 3 mm, d_4^{20} 1.0324, n_D^{20}1.5065. Found %: C 74.01, H 7.65.$C_{12}H_{15}FO$. Calcd.%: C 74.23, H 7.73. IR(cm^{-1}): 833(δ, -CH=C=). ^{1}H-NMR (CCl_4): 1.7(6H,s, 2CH_3), 3.23(2H,d, CH_2), 3,71(3H,s, OCH_3), 5.11-5.60(1H,t, -CH=C=).

4-(3-methyl-2-butenyl)-2-chloroanisole **2**: Yield 66%, b.p.124^{o}C at 2 mm, d_4^{20} 1.0780, n_D^{20}1.5390. Found %: C 68.52, H 7.22, Cl 16.76. $C_{12}H_{15}ClO$. Calcd.%: C 68.41, H 7.14, Cl 16.86. IR(cm^{-1}): 840(δ, -CH=C=). ^{1}H-NMR (CCl_4): 1.6(6H, s, 2CH_3), 3.16(2H,d, CH_2), 3.6(3H,s, OCH_3), 5.08-5.53(1H,t, -CH=C=).

They were converted into 4-isopentyl-2-fluoro- and chloroanisoles **3-4** by hydrogenation over Ni-Raney. Demethylation of these compounds in AcOH in the presence pyridinium chloride yielded the chromatographically pure 4-isopentyl-2-fluoro- and chlorophenols **5-6.** 2-Isopentyl-4-fluoro- and chlorophenols **7-8** were synthesized by the same procedure using 4-fluoro- and chloroanisoles and isoprene:

4-(3-methylbutyl)-2-fluorophenol **5**: Yield 90%, b.p.84-85^{o}C at 2 mm, d_4^{20} 1.0446, n_D^{20} 1.4970. Found %: C 72.01, H 8.07. $C_{11}H_{15}FO$. Calcd. %: C 72.53, H 8.24.

4-(3-methylbutyl)-2-chlorophenol **6**: Yield 61%, b.p.117^{o}C at 5 mm, d_4^{20} 1.0612, n_D^{20} 1.5220. Found %: Cl 17.51. $C_{11}H_{15}ClO$. Calcd. %: Cl 17.88.

2-(3-methylbutyl)-4-fluorophenol 7: Yield 83%, b.p. 91-92^{o}C at 3 mm, d_4^{20} 1.0451, n_D^{20} 1.4980. Found %: C 72.11, H 8.12. $C_{11}H_{15}FO$. Calcd. %: C 72.53, H 8.24.

2-(3-methylbutyl)-4-chlorophenol **8**: Yield 72%, b.p. 121^{o}C at 5 mm, d_4^{20} 1.0623, n_D^{20} 1.5211. Found %: Cl 17.68. $C_{11}H_{15}ClO$. Calcd. %: Cl 17.88.

Individuality of phenols **5-6** was examined by GLC, the structures were determined by spectral analyses and spectroscopic properties were in accord with data reported previously. The new synthesized phenols **7-8** were examined by the same procedure.

Antimicrobial Activity

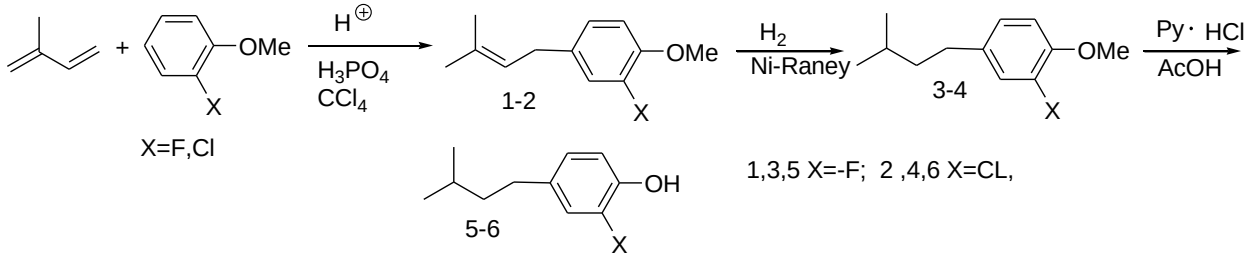
The minimal inhibitory concentration (MIC) was determined by microdilution method [24]. *In vitro* antimicrobial activity of the compounds **5-8** was evaluated against standard strains; *Staphylococcus aureus 209-P, Streptococcus viridans 171, Escherichia coli 675, Shigella Flexneri 2a-516, Salmonella 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

It is known that some isoprenyl phenols and their esters are biologically active compounds [25]. For the synthesis of these phenols is used the reaction of phenols with isoprene both via silicon organic intermediates [26] and in the presence of promoters –complexes Pt(2+) and Pd(2+) [27]. It is developed the simple method for the alkynelation of anisoles by reacting in the presence of phosphoric acid [28].

In the present work has been synthesized the halogenated isopentyl phenols by the last method. In the first step 2-fluoro- and chlororoanisoles were stirred with isoprene in CCl_4 in the presence H_3PO_4 in reactants and catalyst ratio of 10:1:0.6 at 30^oC and the reaction time 2.5 hours. The yield of the products in the reaction with 2-chloroanisole was 73% and with 2-fluoroanisole 80%. By distillation of products were isolated pure 4-isopentenyl-2-fluoro- and chloroanisoles **1-2** yield respectively 72 and 66%, the structure of which is confirmed by spectral data. There is the absorbance in IR - spectrum at 833 and 840 cm^{-1} typical of a three-substituted double bond, the NMR spectrum contains a doublet of two protons CH_2-group at 3.16-3.23 ppm and triplet olefin protons at 5.5-5.8 ppm. Position of the substituents in the benzene ring was shown by oxidation reaction products- 4-(3-methyl-2-butenyl)-2-fluoro - and chloroanisoles **1-2** into the corresponding 3- fluoro or 3-chloro-4-methoxybenzoic acids. By hydrogenation over Ni-Raney of the reaction products were obtained individual 4-isopentyl-2-fluoro- and 2-chloroanisoles **3-4**, by demethylation of the lasts in acetic acid in the presence pyridinium chloride were isolated 4-isopentyl-2-fluoro- and 2-chlorophenols **5-6** [21]. These transformations are shown in Scheme 1.



*Scheme 1: Synthesis of the Halogenated Isopentyl Phenols **5-6***

2-Isopentyl-4-fluoro- and chlorophenols **7-8** were synthesized by the same scheme using 4-fluoro- and chloronisoles and isoprene.

The procedures were based on the simply methods with using accessible reagents. The purity of the synthesized compounds was examined by GLC and the structures were determined by spectral analyses. The series of phenols **5-8** 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 Halogenated Isopentyl Phenols (MIC) **5-8** 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*
5	31,25	31,25	125	62,5	62,5	62,5	62,5	62,5	31,25	62.5	31,25	125
6	7,8	7,8	31,25	31,25	31,25	62,5	62,5	62,5	3,9	62.5	62.5	15,6
7	62,5	62,5	250	62,5	62,5	62,5	62,5	125	31,25	62.5	62.5	250
8	3,9	1,98	62,5	31,25	31,25	62,5	62,5	62,5	125	125	62.5	7,8

As can be seen from Table 1, all halogenated isopentyl substituted phenols **5-8** 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 isopentyl phenols containing chlorine atoms were the most active than the fluorine containing phenols in the series against majority tested bacteria and fungi strains.

According to the bactericidal properties of the compounds we were found that in order to achieve the death of the test bacteria under the influence of substances necessary to increase minimum inhibitory concentrations (MIC) only 1.5-2 times. 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 isopentyl 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 destrucrion.

4. Conclusions

In summary we have synthesized some halogenated isopentyl 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-isopentyl-2-chloro- and 2-isopentyl-4-chlorophenols **6,8** 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 isopentyl phenols.

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