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SYNTHESIS OF TRISUBSTITUTED PYRIDINE-2(1H)-ONES AND THEIR EVALUATION AS ANTIMICROBIAL ADDITIVES IN ENGINE OIL

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A three-component, single-stage condensation was used to produce trisubstituted pyridine-2(1H)-ones. The reaction proceeds with aryl cyanides, chloromethylallyl ether, and ethyl phenylpropiolate in the presence of catalytic amounts of pyridine. The reaction leads to the formation of target trisubstituted pyridine-2(1H)-ones in moderate yield. The optimal synthesis conditions were established as follows: the reaction was carried out in a benzene solution at an equimolar ratio of reagents, at a temperature of 45–55°C for 3–4 hours. Under these conditions, target products with yields of up to 69.5% were obtained. The synthesized compounds have been tested as antimicrobial agents against pathogenic and opportunistic microorganisms. Antimicrobial activity was determined by serial dilution. It was established that the new substances are more effective than the drugs widely used in practice (carbolic acid, pubanol, nitrofungin, furacilin, and chloramines). In addition, the effect of the obtained trisubstituted pyridine-2(1H)-ones on the antimicrobial properties of M-11 engine oil was studied. For this purpose, 0.5–1% solutions of the compounds in oil were prepared (in accordance with the state standard GOST 9-052-75). Aspergillus niger and Candida tropicalis fungi, as well as Pseudomonas aeruginosa bacteria, were used as test cultures. It was shown that 0.5–1% solutions of the tested compounds have more pronounced antimicrobial activity than the standard solution. It was found that at these concentrations, the new compounds do not adversely affect the performance of the oil product.

Keywords: condensation, IR spectroscopy, ^{1}H NMR spectroscopy, antimicrobial additives, trisubstituted pyridine-2(1H)-one.

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Introduction

Structural analogues of 2-pyridinone are found in many biologically active natural and synthetic compounds that have a number of therapeutic properties [1,2], including antibacterial and antifungal [3], and are also used as effective methods of treating HIV infections [4]. In most cases, the purpose of biological preparations containing pyridine is largely determined by the nature of the N-substituents in the pyridine cycle.

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Heterocyclic nitrogen-containing organic compounds occupy a special place among organic compounds, since they can be used as a building material in the production of various chemically pure substances [5], medicines [6] and agrochemical compounds [7], widely used in industry for elegant organic synthesis. Nowadays, the most effective drugs used to treat various diseases are antioxidant and antimicrobial additives to oils and fuels, as well as a large number of chemicals used in agriculture that simultaneously contain organic compounds containing nitrogen and sulfur [8–11]. One of the most important and promising methods for the synthesis of such compounds is the condensation of aryl cyanides with chloromethylallyl ethers and ethylphenylpropiolate in the presence of catalytic amounts of pyridine, which leads to the formation of trisubstituted pyridine-2(1H)-ones. The production of new valuable substances based on this reaction, carried out under favorable conditions, from easily obtained primary compounds occupies an important place in organic synthesis and petrochemistry and is extremely relevant [12]. In the laboratories of the world's leading countries, intensive research is being carried out in the field of synthesis of trisubstituted pyridine-2(1H)-ones [13]. Scientists carry out extensive scientific work in the field of synthesis and study of the properties of trisubstituted pyridine-2(1H)-ones, which have sufficient biological activity and other useful properties [14–16].

Results and discussion

We have developed a method for the three-component synthesis of trisubstituted pyridine-2(1H)-ones (**1–3**) by reacting aryl cyanides with chloromethylallyl ether and ethylphenylpropiolate in the presence of pyridine (Scheme 1).

The synthesis of trisubstituted pyridine-2(1H)-ones was carried out at a temperature of 45–55^{0}C for 3–4 hours in the equimolar ratio of the initial reagents.

The synthesized compounds (**1–3**) are yellow crystals with a specific odor. They are insoluble in water, but are well soluble in organic solvents (acetone, diethyl ether, benzene, chloroform, etc.).

The purity of the initial substances, the composition of the reaction mixture and the resulting products were controlled by gas-liquid chromatography (GLC). The structure of the synthesized compounds (**1–3**) was confirmed by the data of elemental analysis, IR, ^{1}H NMR spectroscopy.

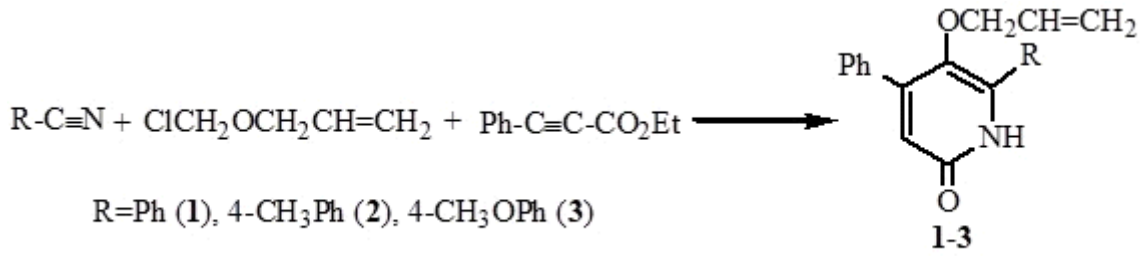
The antimicrobial activity of the obtained trisubstituted pyridine-2(1H)-ones against pathogenic and opportunistic microorganisms was studied at the Department of Microbiology and Immunology of the Azerbaijan Medical University. Gram-positive (*Staphylococcus aureus*), Gram-negative (*Pseudomonas aeruginosa, Escherichia coli*) bacteria, spore-forming bacteria (*Anthracoides*) and yeast-like bacteria were used as test cultures fungi of the genus *Candida*.

As a result of the research, it was found that the synthesized substances show higher antimicrobial activity compared to the drugs used in practice (ethanol, carbolic acid, nitrofungin, furacilin, chloramines). Compounds containing heterocyclic amines have a more pronounced antimicrobial effect than derivatives with aliphatic amines. Based on the results of the tests, these compounds can be recommended as promising antimicrobial agents.

At the same time, the effect of aminomethoxy derivatives of 2-benzylsulfonylethane on the antimicrobial properties of M-11 motor oil was studied. For this purpose, 0.5–1% solutions of substances in the oil were prepared (according to the state standard GOST 9-052-75). *Aspergillus niger*, *Candida tropicalis* fungi and *Pseudomonas aeruginosa* bacteria were used as test cultures. 8-hydroxyquinoline was used as a standard. It has been established that 0.5–1% solutions of the tested compounds have a higher antimicrobial activity than the standard solution. At the same time, these compounds in the specified concentration do not have a negative effect on the operational and physicochemical properties of the oil. The results are shown in Fig. 1. The studied compounds can be recommended as antimicrobial additives to oils.

Experimental

The IR spectra of the synthesized compounds were recorded on the UR-20 spectrometer by Spektrum BX (Germany) in the range of 4000–400 cm^{-1}. The ^{1}H NMR spectra were recorded on the Bruker WP-400 spectrometer (400 MHz, Germany).



Scheme 1

Tetramethylsilane (TMS) was used as an internal standard.

The purity of substances and the composition of the reaction mixture were monitored by gas-liquid chromatography on the LHM-8MD chromatograph with a catarometer detector. A 300×3 mm column filled with 5% polyethylene glycol on «Dinochrome P» impregnated with succinate was used. The temperature of the column is 150^{0}C, the consumption of the carrier gas (helium) is 40 cm^3/min.

Elemental analysis was performed on the EA1108 analyzer manufactured by Carlo Erba (Italy).

The antimicrobial properties of the synthesized substances as an additive to M-11 motor oil were studied in the form of 0.5−1% solutions. Antimicrobial activity was determined by two methods: the method of «wells» in a warm-moist chamber and the method of serial dilutions. The experiments were carried out at a temperature of 20−30^{0}C for 2−3 days. Meat-peptone agar (pH 7.2−7.4) for bacteria and Saburo medium for fungi were used as nutrient media. Dilutions of substances were prepared in ratios of 1:100, 1:200, 1:400 and 1:800. Sowing was carried out after 5, 15, 30, 45 and 60 minutes of exposure. For comparison, control drugs (ethanol) and standard drugs (Rivanol, furacilin, carbolic acid) were used in the same concentrations.

Compounds 1−3 (general methodology)

A solution of methanesulfonic acid (3.7 mg) was added to a zinc dust suspension (1.0 g, 15.3 mmol) in 4 mL of anhydrous THF. After 10 minutes, benzonitrile (0.8 mL, 7.6 mmol) was added to the reaction mixture, then chloromethylallyl ether (1.26 mL, 11.4 mmol) was added for 1 hour at a constant temperature and heated for another 1 h. The reaction mass was diluted with 12 mL of 45% NH_2Cl solution. The organic layer was extracted with ethyl acetate (3×30 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was chromatographed on silica gel (eluent: hexane-ethyl acetate, 9:1, then 7:3).

6-(4-Methoxyphenyl)-4-phenyl-5-(prop-2-en-1-yloxy)pyridin-2(1H)-one (1)

Yield 2.4 g (70.4%), mp 101−103^{0}C (EtOH). IR spectrum, ν, cm^{-1}: 3080, 3010, 2926, 1640, 1596, 1501, 1360, 1270, 1121, 992, 845, 757, 686. ^{1}H NMR spectrum (Fig. 2a), δ, ppm (*J*, Hz): 4.00 d.d (2H, CH_2O, ^3J 5.7, ^4J 1.5), 5.17 d.d.t (1H, H_2C=, J^{cis} 10.4, ^2J=^4J 1.6), 5.26 d.d (1H, H_2C=, J^{trans} 17.3, ^2J=4*J* 1.7), 5.89 d.d.t (1H, CH=, J^{cis} 10.4, ^2J=4*J* 1.6, J^{trans} 17.3), 6.45 s (1H, CH), 7.26−7.41 m (5H, Ph), 7.45−7.52 m (5H, Ph), 12.21 br.s (1H, NH).

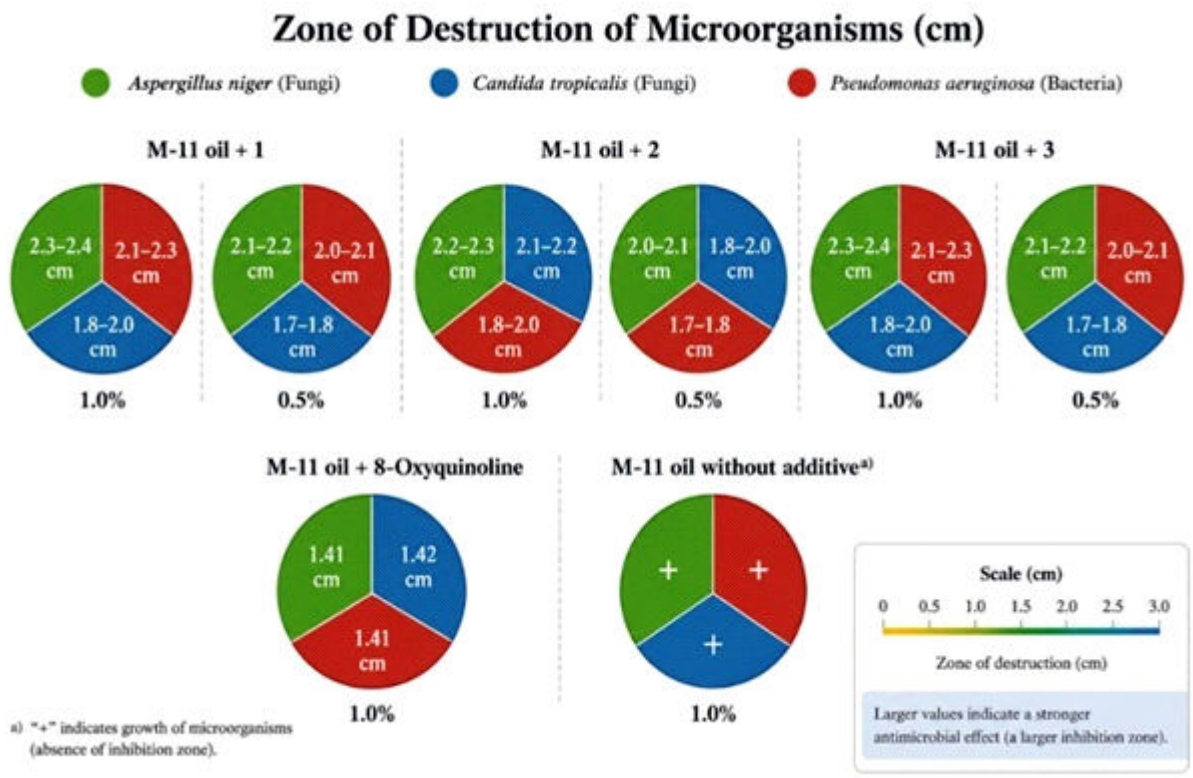


Fig. 1. Results of tests for antimicrobial additive of synthesized compounds (**1−3**). [a)](+) indicates development of microorganisms

^{13}C NMR spectrum (Fig. 2b), δ, ppm (*J*, Hz): 72.3 (=C−CH_2O), 117.6 (H_2C=), 134.6 (HC=), 14.3, 118.5, 127.2, 128.2, 128.4, 128.7, 128.8,130.3, 132.9, 138.1, 147.2, 154.0, 163.7, 166.7. Found, %: C 79.33; H 5.61; N 4.55. $C_{20}H_{17}NO_2$. Calculated, %: C 79.19; H 5.65; N 4.62.

4,6-Diphenyl-5-(prop-2-en-1-yloxy)pyridin-2(1H)-one (2)

Yield 3.1 g (66.3%), mp 196−198^{0}C (EtOH). IR spectrum, ν, cm^{-1}: 3080, 3009, 2925, 1640, 1596, 1501, 1361, 1270, 1121, 993, 845, 757, 685. ^{1}H NMR spectrum (Fig. 3a), δ, ppm (*J*, Hz): 3.84 s (3H, CH_3), 6.42 s (1H), 4.02 d.d (2H, CH_2O, ^3J 5.7, ^4J 1.5), 5.18 d.d.t (1H, H_2C=, J^{cis} 10.4, ^2J=^4J 1.6), 5.26 d.d.d (1H, H_2C=, J^{trans} 17.3, ^2J=^4J 1.7), 5.89 d.d.t (1H, CH=, J^{cis} 10.4, ^2J=^4J 1.6, J^{trans} 17.3), 6.95 d (2H, *J* 8.8), 7.31−7.40 m (5H, Ph), 7.47 d (2H, *J* 8.8), 12.25 br.s (1H, NH). ^{13}C NMR spectrum (Fig. 3b), δ, ppm (*J*, Hz): 72.3 (=C−CH_2O), 116.4 (H_2C=), 133.6 (−HC=), 61.2, 113.7, 114.2, 118.1, 125.3, 127.2, 128.4, 128.7, 129.7, 138.4, 146.9, 153.9, 161.1, 163.5, 167.0. Found, %: C 78.51; H 6.24; N 4.62. $C_{20}H_{19}NO_2$. Calculated, %: C 78.66; H 6.27; N 4.59.

6-(4-Methylphenyl)-4-phenyl-5-(prop-2-en-1-yloxy)pyridin-2(1H)-one (3)

Yield 6.7 g (68.1%), mp 211−213^{0}C (EtOH). IR spectrum, ν, cm^{-1}: 3081, 3010, 2926, 1642, 1596, 1501, 1359, 1270, 1121, 992, 845, 757, 686. ^{1}H NMR spectrum (Fig. 4a), δ, ppm (*J*, Hz): 2.39 s (3H, CH_3), 4.02 d.d (2H, CH_2O, ^3J 5.7, ^4J 1.5), 5.16 d.d.t (1H, H_2C=, J^{cis} 10.4, 2*J*=4*J* 1.6), 5.26 d.d (1H, H_2C=, J^{trans} 17.3, 2*J*=4*J* 1.7), 5.88 d.d.t (1H, CH=, J^{cis} 10.4, ^2J=^4J 1.6, J^{trans} 17.3), 6.47 s (1H, CH), 7.25 d (2H, *J* 7.1), 7.28−7.42 m (7H, Ph), 11.03 br.s (1H, NH). ^{13}C NMR spectrum (Fig. 4b), δ, ppm (*J*, Hz): 72.32 (=C−CH_2O), 117.67 (H_2C=), 134.63 (−HC=), 61.2, 113.8, 118.3, 127.2, 128.1, 128.4, 128.6, 129.4, 130.1, 138.3, 140.4, 147.4, 153.8, 163.7, 167.0. Found, %: C 74.41; H 5.74; N 4.31. $C_{20}H_{19}NO_3$. Calculated, %: C 74.75; H 5.96; N 4.36.

Conflict of interest

The authors declare that they have no conflict of interest.

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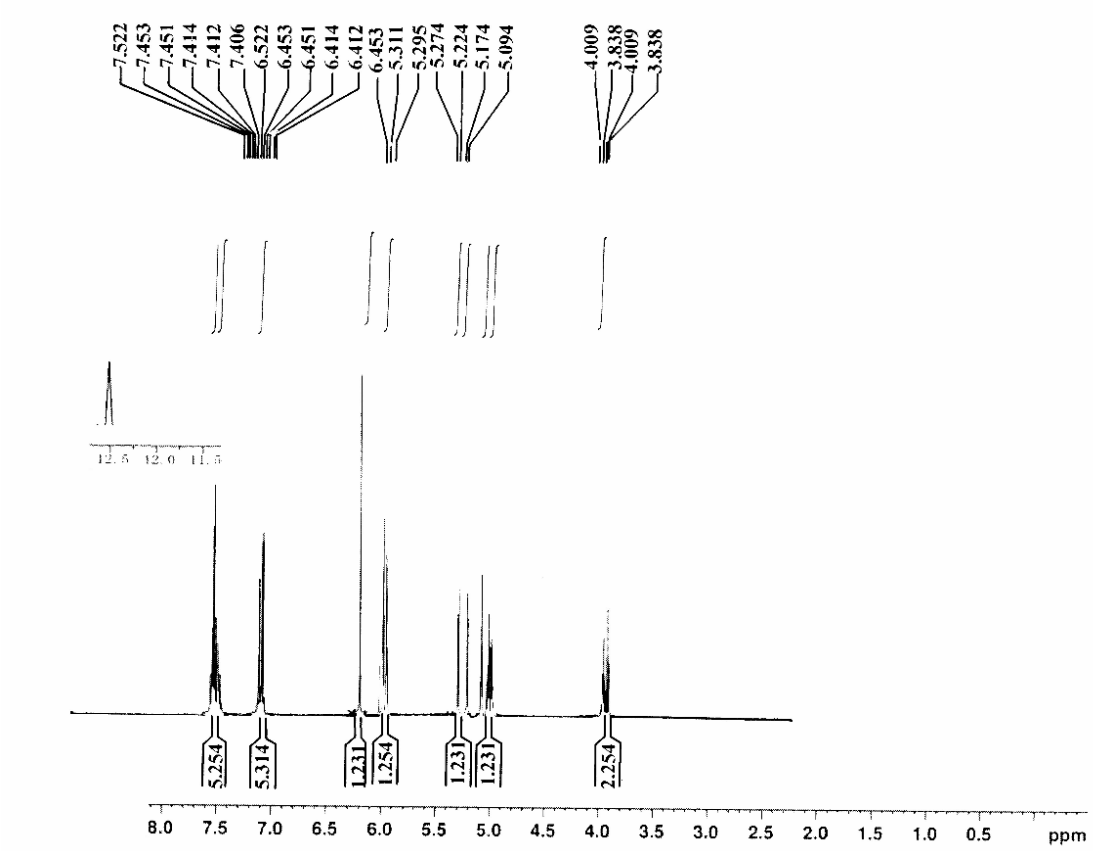
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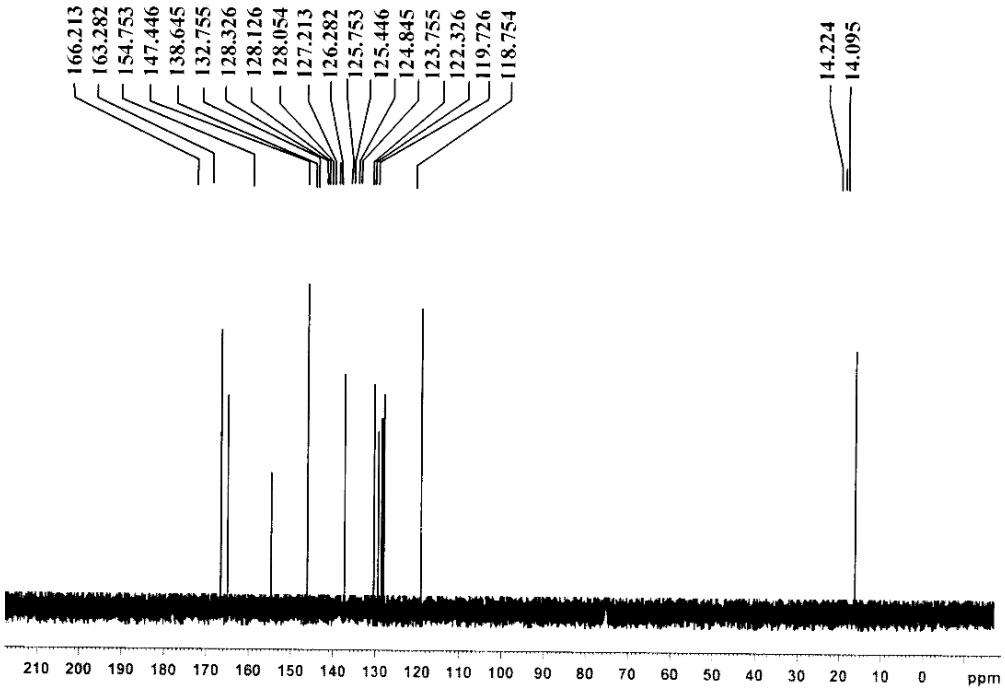
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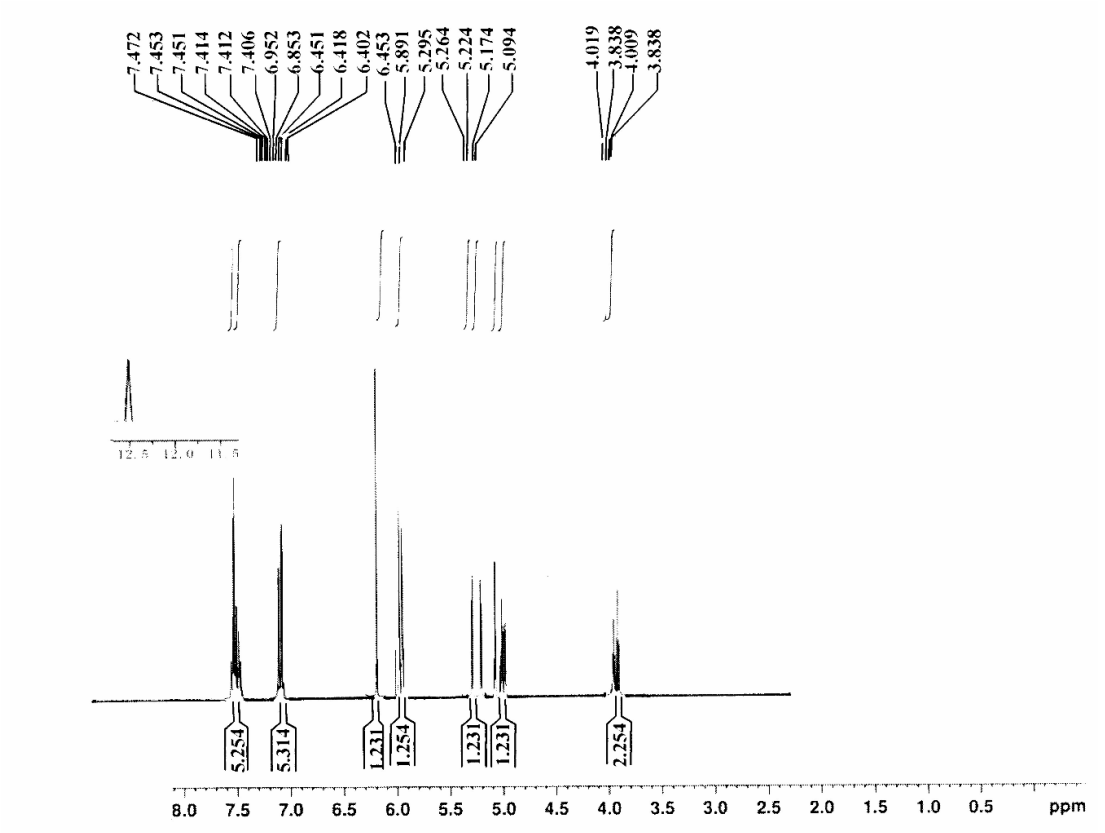


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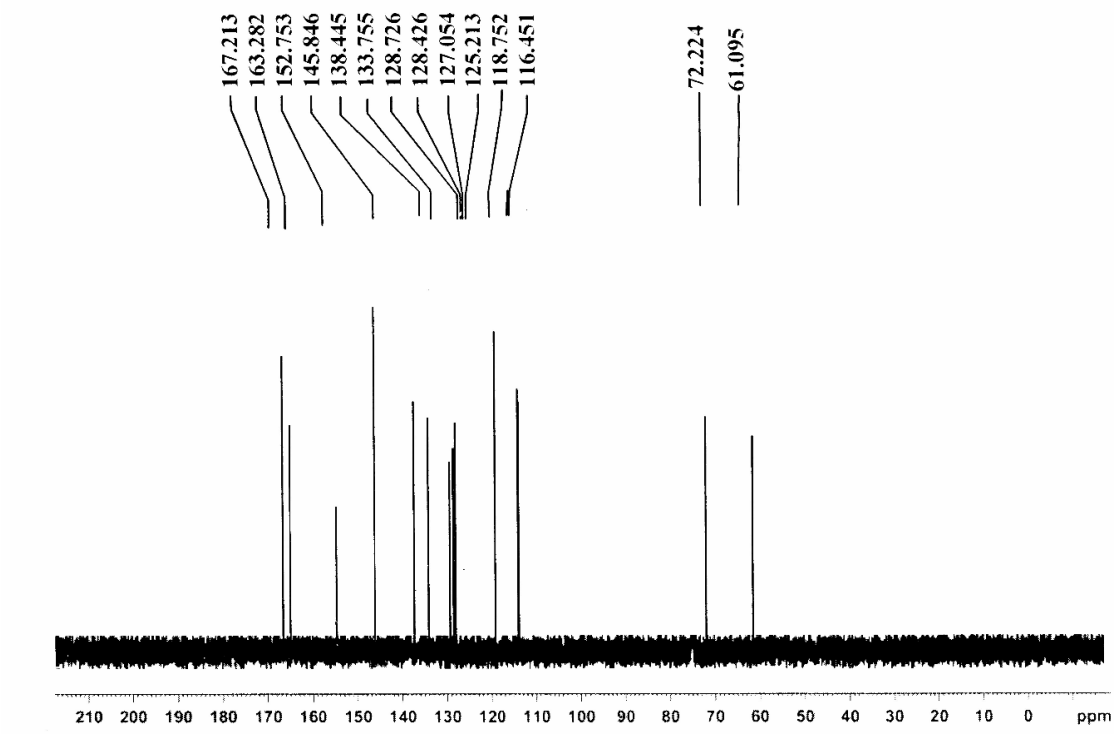


b

Fig. 2. a – ^{1}H NMR (400 MHz, $CDCl_3$) and b – ^{13}C NMR (100 MHz, $CDCl_3$) of compound 1

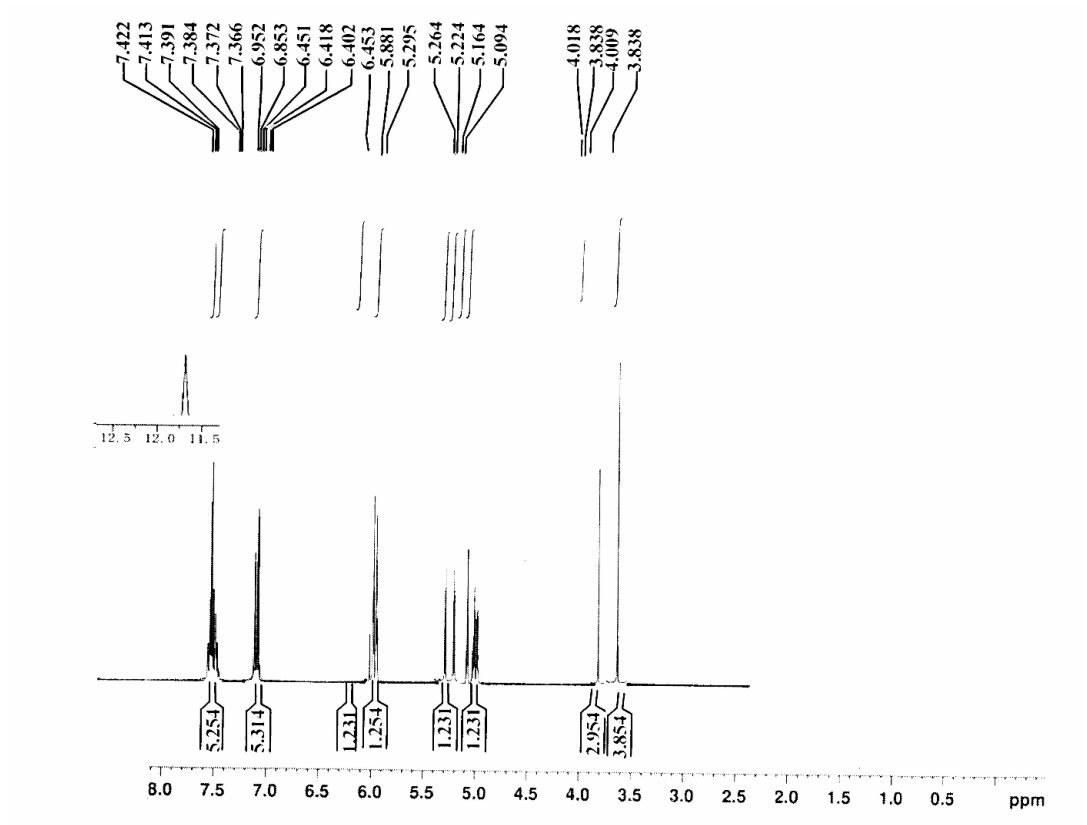


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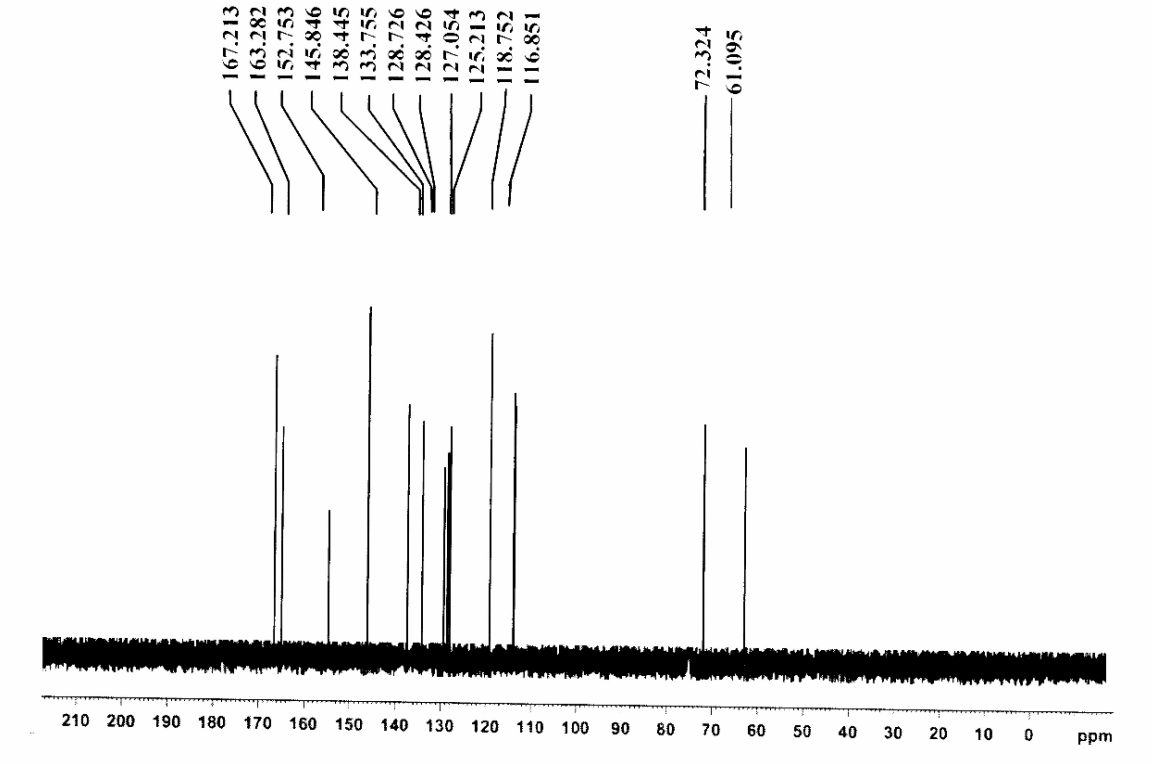


b

Fig. 3. a – ^{1}H NMR (400 MHz, $CDCl_3$) and b – ^{13}C NMR (100 MHz, $CDCl_3$) of compound 2



a



b

Fig. 4. a – ^{1}H NMR (400 MHz, $CDCl_3$) and b – ^{13}C NMR (100 MHz, $CDCl_3$) of compound 3

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СИНТЕЗ ТРИЗАМІЩЕНИХ ПІРИДИН-2(1Н)-ОНІВ І ЇХ ОЦІНЮВАННЯ ЯК АНТИМІКРОБНИХ ПРИСАДОК ДО МОТОРНИХ МАСЕЛ

Г.М. Талибов, С.В. Ібрагімова

В результаті трикомпонентної одностадійної конденсації були одержані тризаміщені піридин-2(1Н)-они. Реакція протікає між арилціанідами, хлорметилаліловим ефіром та етилфенілпропіолатом у присутності каталітичних кількостей піридину. Реакція приводить до утворення цільових тризаміщених піридин-2(1Н)-онів з помірним виходом. Були встановлені наступні оптимальні умови синтезу: реакцію проводили в розчині бензолу при еквімолярному співвідношенні реагентів, при температурі 45–55^{0}С протягом 3–4 годин. У цих умовах були одержані цільові продукти з виходом до 69,5%. Синтезовані сполуки були протестовані як антимікробні засоби проти патогенних та умовно-патогенних мікроорганізмів. Антимікробну активність визначали шляхом послідовного розведення. Встановлено, що нові речовини більш ефективні, ніж широко застосовуються на практиці препарати (карболова кислота, пубанол, нітрофунгін, фурацилін і хлораміни). Крім того, було вивчено вплив отриманих тризаміщених піридин-2(1Н)-онів на антимікробні властивості моторного масла м-11. Для цього готували 0,5–1%-ні розчини речовин в маслі (відповідно до ГОСТ 9-052-75). Як тест-культур використовували Aspergillus niger і Candida tropicalis, а також синьогнійну паличку. Було показано, що 0,5–1% розчини досліджуваних сполук мають більш виражену антимікробну активність порівняно зі стандартним розчином. Було встановлено, що в цих концентраціях нові сполуки не мають негативного впливу на експлуатаційні характеристики нафтопродукту.

Ключові слова: конденсація, ІЧ-спектроскопія, ^{1}Н ЯМР-спектроскопія, антимікробні добавки, тризаміщений піридин-2(1Н)-он.

SYNTHESIS OF TRISUBSTITUTED PYRIDINE-2(1H)-ONES AND THEIR EVALUATION AS ANTIMICROBIAL ADDITIVES IN ENGINE OIL

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A three-component, single-stage condensation was used to produce trisubstituted pyridine-2(1H)-ones. The reaction proceeds with aryl cyanides, chloromethylallyl ether, and ethyl phenylpropiolate in the presence of catalytic amounts of pyridine. The reaction leads to the formation of target trisubstituted pyridine-2(1H)-ones in moderate yield. The optimal synthesis conditions were established as follows: the reaction was carried out in a benzene solution at an equimolar ratio of reagents, at a temperature of 45–55^{0}C for 3–4 hours. Under these conditions, target products with yields of up to 69.5% were obtained. The synthesized compounds have been tested as antimicrobial agents against pathogenic and opportunistic microorganisms. Antimicrobial activity was determined by serial dilution. It was established that the new substances are more effective than the drugs widely used in practice (carbolic acid, pubanol, nitrofungin, furacilin, and chloramines). In addition, the effect of the obtained trisubstituted pyridine-2(1H)-ones on the antimicrobial properties of M-11 engine oil was studied. For this purpose, 0.5–1% solutions of the compounds in oil were prepared (in accordance with the state standard GOST 9-052-75). Aspergillus niger and Candida tropicalis fungi, as well as Pseudomonas aeruginosa bacteria, were used as test cultures. It was shown that 0.5–1% solutions of the tested compounds have more pronounced antimicrobial activity than the standard solution. It was found that at these concentrations, the new compounds do not adversely affect the performance of the oil product.

Keywords: condensation; IR spectroscopy; ^{1}H NMR spectroscopy; antimicrobial additives; trisubstituted pyridine-2(1H)-one.

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