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SYNTHESIS OF NEW DERIVATIVES OF PHENYLOXYPROPARGYL PIPERIDINES

Abstract. 4-(3-phenoxyprop-1-yn-1-yl)piperidine-4-ol has been obtained by condensation of 1-methyl-piperidine-4-one with phenoxypropargyl in the Favorsky reaction conditions in absolute benzene, in the presence of a fivefold excess of powdered technical KOH at the ratio of piperidone-4:phenoxypropargyl = 1:1.5. Upon acylation of tertiary phenoxypropynyl piperidol by cyclobutane-, cyclopentane-, cyclohexanecarbonyl chlorides in dioxane at the room temperature or upon heating, the corresponding hydrochlorides of esters have been formed. The structure of the synthesized compounds has been confirmed by the NMR and X-ray spectroscopy data.

Key words: phenoxypropargylpiperidine-4-ol, cyclobutane-, cyclopentane-, cyclohexanecarbonyl chlorides, esters.

The search of new compounds for antimicrobial and virucidal activities, including those capable of inducing a reversion of medicine susceptibility, is related to the priority direction for the development of new anti-infective medicinal preparations. The topicality of the research, despite of a large range of antibacterial remedies available, is connected, first and foremost, with a high adaptability of pathogenic organisms to medicinal preparations, including antibiotics [1-3].

The directed construction of new molecules from pharmacophore structural fragments, among which the saturated nitrogenous heterocycles play the leading role, being synthetic analogues of natural alkaloids, is deemed to be an efficient way of searching for effective biologically active compounds (BAS). Alkyloxy-, aryloxy- and heteroaryloxypropinylcarbinols, various by their structure [4-7], have proved to be convenient reactive “building blocks” in the organic synthesis, including those for BAS.

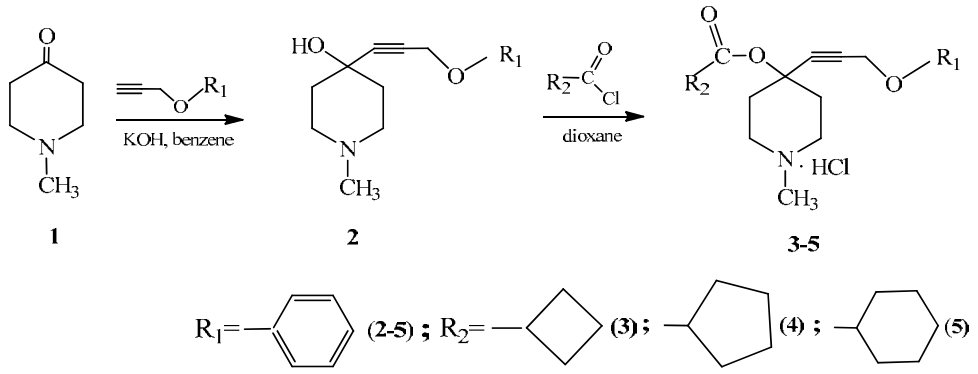
The current situation in organic chemistry reflects the lack of new leader structures, which may be optimized to therapeutically useful preparations. The scientific research, aimed at creating new materials for practical medicine and agriculture, is of top priority in the entire world.

The basis for the present studies has been a high biological activity of the previously synthesized esters of 1-(2-ethoxyethyl)-4-hydroxy-4-[3-(aryloxy)propyn-1-yl]piperidines [8] and piperidine-containing esters of cyclopropanecarboxylic acid [9-12].

A directed introduction of a cyclopropanecarbonyl fragment into the phenoxypropylpiperidine structure has lead to the compounds of an anti-infective activity. It has been shown, that hydrochloride of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-cyclopropanecarbonyloxypiperidine with the code AIP-36, displays an antimicrobial activity in relation to all seven archival strains of microorganisms, used in the experiment: *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 10031, *Candida albicans* ATCC 10231 in the concentration (MIC) of 1000 μg/ml, and in relation to *Escherichia coli* ATCC-BAA-196, *Klebsiella pneumoniae* ATCC 700603, *Staphylococcus aureus* ATCC 6538-P, *Staphylococcus aureus* ATCC-BAA-39 in the concentration (MIC) of 2000 μg/ml. Hydrochloride of 1-propyl-4-(3-phenoxyprop-1-yn-1-yl)-4-cyclopropanecarbonyloxypiperidine/ with the code AIP-37, suppresses the growth of 6 strains of microorganisms [9-14].

The present work aims the directed synthesis of new phenoxypropargyl-piperidines with a potential antibacterial activity by varying the nature of an acyloxy group and introducing additional pharmacophors, the fragments of small cycles – cyclobutane-, cyclopentane-, cyclohexanecarbonyls, into the molecules.

Condensation of 1-methyl-4-oxopiperidine (1) with phenoxypropargyl in the Favorsky reaction conditions [13, 14] leads to a tertiary phenoxypropargyl alcohol (2).



Phenyloxypropynylpiperidol has been obtained with good yield (table 1) with the following optimum paraneters of the reaction: a ratio of piperidone:phenyloxypropine = 1:5, absolute benzene, a fivefold excess of technical caustic potassium.

Acylation of phenoxypropynyl piperidol (2) by cyclobutane-, cyclopentane-, cyclohexanecarbonyl chlorides, taken in excess, is carried out at the room temperature or upon heating in dioxane. The esters of cyclobutane-, cyclopentane-, cyclohexanecarboxylic acids (3-5) are crystalline powders of white, cream color, easily soluble in water, ethanol, and acetone.

The composition and structure of the synthesized compounds (2-5) have been confirmed by elemental analysis, IR spectroscopy, ^{13}C NMR-spectroscopy, individuality has been confirmed by TLC (table 1).

Table 1 – The yields and physical and chemical characteristics of the compounds 2-5

Compound	Yield, %	R_f	t m.p., °C	IR spectrum, cm^{-1}		Empirical formula
				OH	C=O of ester	
2	74.6	0.27	84-86	3414	–	$C_{15}H_{19}NO_2$
3	68.31	0.82	140-143	–	1735	$C_{20}H_{26}NO_3Cl$
4	72.1	0.91	163-165	–	1736	$C_{21}H_{28}NO_3Cl$
5	24.6	0.83	181-183	–	1737	$C_{22}H_{30}NO_3Cl$

In the IR spectrum of piperidol (2), absorption bands of stretch vibrations of a hydroxyl group are observed in the region of 3414 $см^{-1}$, and that of the aromatic ring – in the region of 617-774 $см^{-1}$. Intensive absorption bands in the region of 1735-1737 $см^{-1}$, caused by C = O vibrations of an ester group, testify to the formation of the target esters of 4-phenoxypropynyl piperidols-4 of cyclobutane-, cyclopentane-, cyclohexanecarboxylic acids (3-5).

Table 2 shows the values of chemical shifts of carbons, which fully confirm the carbon composition of esters of 4-phenoxypropynyl piperidols-4 of cyclobutane-, cyclopentane-, cyclohexanecarboxylic acids (3-5).

Table 2 – The values of chemical shifts of carbon atoms in ^{13}C NMR- spectra of esters of 4-phenoxypropynyl piperidine-4-ols of cyclobutane-, cyclopentane-, cyclohexanecarboxylic acids (3-5)

Compound	Chemical shift ($CDCl_3$), δ, ppm.										
	$C_{3,5}$	$C_{2,6}$	C_4	CH	CH_2	C=O	≡C-CH_2	C_4-C≡	O-CH_2	OPh	N-CH_3
3	33.83	48.69	72.35	42.35; cyclo-butane	18.22; 25.03 cyclo-butane	173.22	81.88	86.07	56.01	115.58; 121.86; 129.98; 157.67	37.96
4	36.37; 36.54	56.03; 56.16	78.38	50.83 cyclo-pentane	25.85; 29.83 cyclo-pentane	174.36	81.72	91.16	61.02	115.47; 121.72; 130.01; 157.89	48.85
5	33.15; 33.80	50.17; 50.84	80.04	42.76 cyclo-hexane	25.31; 25.77; 28.85 cyclo-hexane	174.36	70.84	81.74	56.03	115.48; 121.79; 129.92; 157.59	48.85

In the ^{13}C NMR spectra (table 2) of cyclobutane-, cyclopentane-, cyclohexane- carbonyloxy derivatives (3-5), singlet signals of carbon atoms of the ester carbonyl region are observed in the region of 173.22-174.36 ppm, a singlet signal of C_4 resonates in the region of 72.35 -80.04 ppm, a carbon atom of a methylene group of the propylene fragment is observed in the region of 56.01-61.02 ppm. The weak-field region (115-157 ppm.) of the spectra is "populated" by the signals

of aromatic carbons. The signals in the region of 18.22-29.83 ppm. and 42.35-50.83 ppm. are assigned to carbons of the cyclobutane, cyclopentane, cyclohexane rings. Besides, there is a doublet set of $C_{3.5}$ and $C_{2.6}$ signals, respectively, in the region of 33.80-36.54 ppm. and 48.69-56.16 ppm. of the piperidine cycle, associated with a slow inversion of the latter due to the bulky substituents at C_4.

EXPERIMENTAL CHEMICAL PART

The course of the reaction and individuality of the compounds were controlled by TLC on aluminum oxide of the III degree of activity, with the development of spots by iodine vapors. The IR spectra were recorded on a Nicolet 5700 spectrometer in a thin layer between the KBr plates. ^1H and ^{13}C NMR spectra were recorded on a JNM-ECA400 spectrometer of the company JEOL (400 and 100,8 MHz, respectively) in $CDCl_3$, HMDS was used as an internal standard.

1-methyl-4-(3-phenoxypropyn-1-yl)-4-hydroxypiperidine (2). 14.85 g (0.2652 mol.) of powdered potassium hydroxide in 40 ml. of absolute benzene was introduced into a flat bottom flask, after 10 min. 34.03 ml. (0.2652 mol.) of 3-phenoxypropine-1 in 40 ml. of absolute benzene was slowly added dropwise upon stirring. Herewith, a slight heating and change of color of the solution were observed. After 30 min. a solution of 10 g (0.0884 mol.) of 1-methyl-piperidine-4-one in 30 ml. of absolute benzene was added dropwise. The reaction mixture was stirred for 5-6 hours at the room temperature. The reaction course was controlled by TLC. 150 ml. of distilled water was added to the reaction mixture, the layers were separated. The aqueous layer was extracted with benzene. The combined organic layers were washed with a 10% solution of hydrochloric acid, and the aqueous-acidic layer was extracted with benzene for the complete removal of the neutral products. Then it was alkalinized with a saturated solution of sodium hydroxide NaOH, extracted with benzene, and dried over magnesium sulfate. The drying agent was filtered, the solvent was vaporized, and the residue was re-crystallized from hexane. 17.51 g (74.6% of the theoretic value) of alcohol (2) was obtained in the form of white crystals, m.p. 84-86 °C, R_f 0.27 (eluent - benzene:dioxane-4:1).

Hydrochloride of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-cyclobutanecarbonyloxypiperidine (3). A solution of 1.05 ml. (0.0092 mol.) of cyclobutanecarbonyl chloride in absolute dioxane was slowly added upon stirring to a solution of 1.5 g (0.0061 mol.) of 1-methyl-4- (3-phenoxypropyn-1-yl)-4-hydroxypiperidine (2) in absolute dioxane. Herewith, a heating of the reaction mixture was observed. The mixture was kept at the room temperature for 24 hours. The reaction course was controlled by TLC. The solvent was removed. The residue was washed with diethyl ether, re-crystallized from isopropanol. 1.52 g (68.31% of the theoretical value) of hydrochloride of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-cyclobutanecarbonyloxypiperidine (3) was obtained in the form of crystals, m.p. 140-143 ^0C, R_f 0.82 (Al_2O_3, eluent - benzene:dioxane - 3:2).

Hydrochloride of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-cyclopentanecarbonyloxypiperidine (4). A solution of 1.11 ml. (0.00915 mol.) of cyclopentanecarbonyl chloride in absolute dioxane was slowly added upon stirring to a solution of 1.5 g (0.0061 mol.) of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-hydroxypiperidine (2) in absolute dioxane. Herewith, a heating of the reaction mixture was observed. The mixture was kept at the room temperature for 24 hours. The reaction course was controlled by TLC. The solvent was removed, and the residue was washed with diethyl ether, re-crystallized from isopropanol. 1.66 g (72.1% of the theoretic value) of hydrochloride of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-cyclopentanecarbonyloxypiperidine (4) was obtained in the form of crystals, m.p. 163-165 ^{0}C, R_f 0.91 (Al_2O_3, eluent - benzene:dioxane - 4:1).

Hydrochloride of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-cyclohexanecarbonyloxypiperidine (5). 1.5 g (0.007 mol.) of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-hydroxypiperidine (2) was dissolved in a small amount of absolute dioxane, then a solution of 1.26 ml. (0.014 mol.) of cyclohexanecarbonyl chloride in absolute dioxane was added. Herewith, a heating of the reaction mixture and change of color of the solution from light yellow to light brown were observed. The mixture was held overnight at the room temperature. The solvent was removed, and the residue was re-crystallized from isopropanol. 1.5 g (24.6% of the theoretical value) of hydrochloride of 1-methyl-4-(3-phenoxypropyn-1-yl)-4-cyclohexanecarbonyloxypiperidine (5) was obtained, mp. 181-183 ^{0}C, R_f 0.83 (Al_2O_3, eluent - diethyl ether).

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Резюме

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ФЕНИЛОКСИПРОПАРГИЛПИПЕРИДИНДЕР ҚАТАРЫНЫҢ ЖАҢА ТУЫНДЫЛАРЫН СИНТЕЗДЕУ

Фаворский реакциясы жағдайында 1-метил-пиперидин-4-он- ды абсолютты бензолда бес есе артық мөлшерде алынған техникалық КОН ұнтөғы қатысында, пиперидон-4:феноксипрорпаргил = 1:1,5 қатынасында феноксипропаргилмен конденсациялау арқылы сәйкесінше 4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-ол алынды. Үшіншілік феноксипропинилді пиперидолды циклобутан-, циклопентан-, циклогексанкарбонилхлоридтермен диоксанда ацилирлеу кезінде бөлме температурасында немесе қыздырғанда сәйкесінше күрделі эфирлердің гидрохлоридтері түзіледі. Синтезделген қосылыстардың құрылымы ЯМР және ИҚ спектроскопия арқылы дәлелденді.

Түйін сөздер: феноксипропаргилпиперидин-4-ол, циклобутан-, циклопентан-, циклогексанарбонилхлоридтер, күрделі эфирлер.

Резюме

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СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ РЯДА ФЕНИЛОКСИПРОПАРГИЛПИПЕРИДИНОВ

Конденсацией 1-метил-пиперидин-4-она с феноксипропаргилом в условиях реакции Фаворского в абсолютном бензоле в присутствии пятикратного избытка порошкообразного технического КОН при соотношении пиперидон-4:феноксипрорпаргил = 1:1,5 получен соответствующий 4-(3-феноксипроп-1-ин-1-ил)пиперидин-4-ол. При ацилировании третичного феноксипропинилового пиперидола циклобутан-, циклопентан-, циклогексанкарбонилхлоридами в диоксане при комнатной температуре или нагревании образуются соответствующие гидрохлориды сложных эфиров. Строение синтезированных соединений подтверждены данными спектроскопии ЯМР и ИКС.

Ключевые слова: феноксипропаргилпиперидин-4-ол, циклобутан-, циклопентан-, циклогексанарбонилхлориды, сложные эфиры.