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FLUOROBENZOATES OF 1-PROPYL-4-KETOXIMEPIPERIDINE AS POTENCIAL LOCAL ANESTHETICS

Abstract. p-Fluoro-, m-fluoro-, o-fluorobenzoates of 1-propyl-4-ketoximepiperidine, displaying a local anesthetic activity in varying degrees, have been synthesized. An introduction of fluorine leads to the formation of local anesthetics of different efficiency. Depending on the position of a fluorine atom in the phenyl ring, the greatest activity has been displayed by p-isomers, then o-isomers, whereas m-fluorobenzoates have proved to be less active.

Key words: p-fluoro-, m-fluoro-, o-fluorobenzoylcarbonylchloride, N-propylpiperidine-4-ketoxime, esters, 1-propyl-4-(p-fluoro-, m-fluoro-, o-fluorobenzoyloxyimino)piperidine, local anesthetic activity.

Elimination and prevention of a pain syndrome is a pressing problem of medicine. One of the most important directions for its solution is the development and creation of medicinal preparations of a local anesthetic activity. In surgery, when general anesthesia is not the only possible anesthetic method, it is expedient to apply the methods of infiltration and conduction anesthesia as the simplest and most secure ones. In recent times, the proportion of local anesthesia has especially increased, which is connected with the new notions of the role of local anesthesia, as well as the emergence of new effective “green” local anesthetics [1, 2].

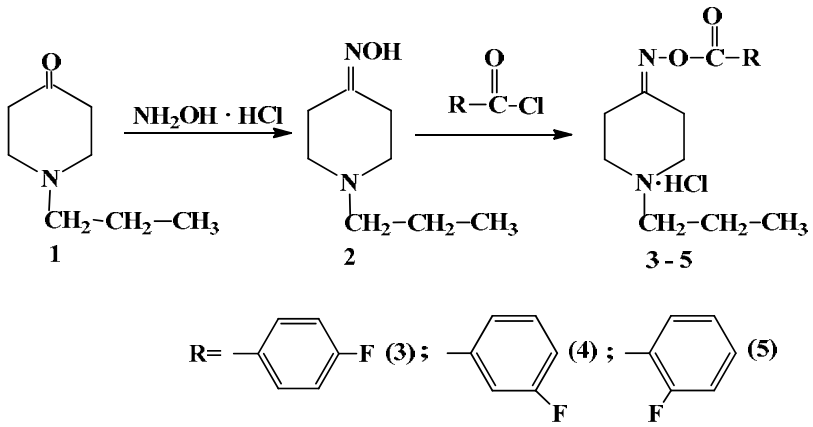
The modern period of the development of organic chemistry demonstrates not only a potential of organic synthesis, but also its importance for the development of both chemistry in general and many related fields of science and practice, in particular, the provision of the mankind with medicines. Due to a high physiological activity of azacyclanes, in particular, piperidine derivatives, these studies acquire the status of one of the topical tasks of modern chemistry, biology and medicine [3, 4].

The most characteristic derivatives of 4-oxopiperidines are azomethins, including oximes. Oximes of carbonyl compounds and their derivatives are well known as one of the main classes of organic substances, which are promising in searching for new biologically active preparations of broad spectrum [5-7].

In this connection, the task of this work has been defined as the synthesis of oxime and its acyl derivatives, in particular, fluorine-containing derivatives on the basis of N-propyl-4-oxopiperidine (1).

Upon the interaction of hydrochloric hydroxylamine with 1-propyl-piperidine-4-one (1) in the presence of alkali in isopropanol, an oxime has been obtained (2).

With the purpose to determine the effect of the introduction of a fluorine atom on a pharmacological activity of the compounds, the corresponding esters (3-5) have been synthesized by acylation of the obtained oxime (2) with 4-fluorobenzoyl chloride, 3-fluorobenzoyl chloride and 2-fluorobenzoyl chlorides. The reaction has been carried out in absolute dioxane upon heating, with the ratio of ketoxime : acylating agent as 1:1.5.



The obtained appropriate hydrochlorides of aminoesters (3-5) represent white crystalline substances.

The yields, melting points, R_f and IR spectra data (absorption bands of ester carbonyl as the most characteristic features for esters and C=N) are presented in table 1.

Table 1 – The yields and physical and chemical characteristics of hydrochlorides of 1-propylpiperidin-4-ketoxime fluorobenzoates.

Compound	Yield, %	R_f	Melting point, °C	IR-spectrum, cm^{-1}		Molecular formula
				C=N	C=O ester	
3	61.0	0.72	170-172	1639.3	1751.2	$C_{15}H_{20}N_2O_2FCl$
4	46.8	0.7	159-161	1659.8	1740.2	$C_{15}H_{20}N_2O_2FCl$
5	44.5	0.69	169-171	1654.4	1752.4	$C_{15}H_{20}N_2O_2FCl$

It has turned out that oximes of N-substituted 4-ketopiperidines are most easily acylated with *p*-fluorobenzoyl chloride; fluorine in the *o*-position of the benzene ring deactivates the process to the greatest extent. Accordingly, *p*-fluorobenzoates have been obtained with the best yields, *m*-fluorobenzoates have fallen in between, *o*-fluorobenzoates have been formed with the least yields. The optimum ratio of alcohol/oxime:fluorobenzoate is 1:1.5. The best yields of fluorobenzoates have been obtained when using dioxane as a solvent.

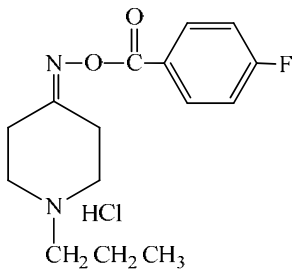
^{13}C NMR spectra have proved to be most informative for the determination of the structure of hydrochlorides of ketoxime fluorobenzoates of 1-propylpiperidine-4-one (table 2).

The occurrence of a signal of carbonyl carbon in the weak field (153-172 ppm) testifies to the formation of ester. The C_4 atom of the piperidine cycle of ketoxime fluorobenzoates also resonates in this field. The different position of a fluorine atom is confirmed by a shift of a signal of the corresponding aromatic carbon to the weak field (160 ppm). The carbon atoms of the piperidine cycle and substituents at the nitrogen atom appear in the expected field.

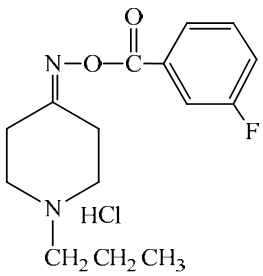
Table 2 – The values of chemical shifts of the carbon atoms in the ^{13}C NMR spectra of hydrochlorides of 1-propylpiperidine-4-ketoxime fluorobenzoates (δ, ppm.)

Compound	$C_{2.6}$	$C_{3.5}$	C_4	C=O	C_6H_4F	C-F	N-R
3	50.51; 49.60	27.92; 23.91	162.92	162.42	16.56-132.82	*n*-F 167.15	CH_2 CH_2 CH_3 57.07;17.39;11.51
4	50.47; 49.63	27.91; 23.95	163.28	161.32	116.36-131.04	*м*-F 162.28	CH_2 CH_2 CH_3 57.05;17.39;11.52
5	50.55; 49.48	27.84; 24.11	162.70	153.30	117.65-132.45	*o*-F 161.23	CH_2 CH_2 CH_3 57.07;17.48;11.50

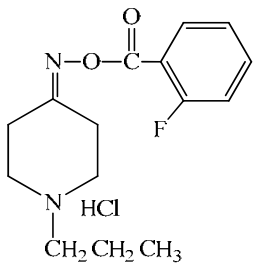
Study of a biological activity. An experimental study of a specific activity of hydrochlorides of 1-propylpiperidine-4-ketoxime fluorobenzoates under the laboratory codes LAS-202 – LAS-204 (LAS – Local Anesthetic Substance) has been carried out upon infiltration and conduction anesthesia at the Department of Pharmacology of S.D. Asfendiyarov Kazakh National Medical University, using the methods of primary screening, recommended by the RK Pharmacological Committee and Guidelines for experimental (pre-clinical) study of new pharmacological substances [8].



LAS-202



LAS-203



LAS-204

It has been established that all studied compounds display a certain effect (table 3). The greatest most activity is marked in case of LAS-202 (hydrochloride of 1-propyl-(4-fluorobenzoyloxy)-4-ketoximepiperidine), which in 0.25% solution by its strength (anesthesia index) is equal to trimecaine, and statistically sig-

nificantly exceeds the indices of lidocaine and novocaine by a factor of 1.4 and 1.3, respectively.

The duration of total anesthesia under the effect of LAS-202 has made up 19.6 min, like that of trimecaine, exceeding the values of lidocaine and novocaine by a factor of 1.38 and 19.6, respectively. The "transfer" of fluorine to the *m*- and *o*- positions results in the reduction of an anesthetic effect of the fluorobenzoates of piperidineketoximes.

The duration of total anesthesia is approximately the same for all studied compounds. The compounds LAS-202, LAS-203, LAS-204 are statistically significantly more active than trimecaine by a factor of 1.4, have the same effect as that of lidocaine, and are more efficient as compared with novocaine by a factor of 1.9. The total effective duration of LAS-202 is within the range of 162 min, which is 2.9 times higher than that of trimecaine, lodocaine and novocaine. The compound LAS-203 falls in between by its activity.

Table 3 – Activity and effective duration of action of LAS-199 – LAS-204

Compounds	Infiltration anesthesia			Conduction anesthesia	
	0.25%			1.0 %	
	Anesthesia index, M±m	Total anesthesia duration, min	Effective duration, min	Total anesthesia duration, min	Effective duration, min
LAS-202	32.7±0.8	19.6±2.38	53,33±1,66	69.16±2.37	161.3±13.6
LAS-203	30.2±1.32	13.8±0.91	40.8±3.01	65.0±3.1	145.8±11.7
LAS-204	28.8±2.98	15.0±3.42	46.7±8.26	67.5±3.19	84.1±4.2
Trimecaine	33.6±0.33	20.0±1.7	38.3±1.05	47.3±8.4	56.9±12.8
Lidocaine	23.1±0.9	14.2±0.8	30.8±0.8	65.0±18.4	90.8±18.4
Novocaine	25.0±1.0	10.0±1.2	29.1±1,5	35.2±7.1	42.3±13.6

Thus, fluorobenzoic esters of piperidineketoximes cause profound and prolonged anesthesia, the introduction of fluorine leads to the formation of local anesthetics of different efficiency. Depending on the position of a fluorine atom in the phenyl ring, the greatest activity has been displayed by *p*-isomers, then *o*-isomers, whereas *m*-fluorobenzoates have proved to be less active.

EXPERIMENTAL CHEMICAL PART

The course of the reaction and individuality of the compounds are controlled by TLC on aluminum oxide of the III degree of activity, with the development of spots by iodine vapors. The IR spectra are recorded on a Nicolet 5700 spectrometer in KBr tablets and between KBr plates. ^{13}C NMR spectra of the studied compounds in $CDCl_3$ are recorded on a JNM-ECA400 spectrometer, manufactured by JEOL firm, with an operating frequency 100 MHz at the carbon nuclei. An internal standard is HMDS. The data of elemental analysis of all synthesized compounds are presented in the corresponding tables in the experiment discussion.

Hydrochloride of 1-propyl-4-(p-fluorobenzoyloxyimino)piperidine. 1.5 g (0.01 mol) of oxime of 1-propylpiperidine-4-one is dissolved in a small quantity of absolute dioxane, then 2.27 l (0.02 mol) of hot solution of *p*-fluorobenzoylchloride in absolute dioxane is slowly added dropwise, while stirring, to the solution. Herewith, a white precipitation is immediately observed. The reaction mixture is held for 24 hours at the room temperature. The course of the reaction is controlled by TLC. The reaction mixture is washed by diethyl ether and the precipitation is filtered, recrystallized from isopropyl alcohol. 1.93 g (61 % of the theoretic value) of hydrochloride of *1-propyl-4-(p-fluorobenzoyloxyimino)piperidine* is obtained, mp of 170-172^{0}C, R_f of 0.85 (Al_2O_3, eluent - benzene : dioxane - 4:1).

Found, %: C 56.99; H 6.32. $C_{15}H_{20}ClFN_2O_2$.

Calculated, %: C 57.23; H 6.40.

Hydrochloride of 1-propyl-4-(m-fluorobenzoyloxyimino)piperidine. 1.5 g (0. mol) of oxime of 1-propylpiperidine-4-one is dissolved in a small quantity of absolute dioxane, then 2.27 l (0.02 mol) of *m*-fluorobenzoylchloride in absolute dioxane is slowly added dropwise, while stirring, to the solution. As the solution is cooled the white precipitation is observed. The reaction mixture is held for 24 hours at the room temperature. The course of the reaction is controlled by TLC. The reaction mixture is washed by diethyl ether and the precipitation is filtered, recrystallized from isopropyl alcohol. 1.47 g (46.8 % of the theoretical value) of hydrochloride of 1-*propyl-4-(m-fluorobenzoyloxyimino)piperidine* is obtained, mp 159-161^{0}C, R_f of 0.7 (Al_2O_3, eluent - benzene : dioxane - 4:1).

Found, %: C 57.59; H 6.29. $C_{15}H_{20}ClFN_2O_2$.

Calculated, %: C 57.23; H 6.40.

Hydrochloride of 1-propyl-4-(o-fluorobenzoyloxyimino)piperidine. 1.5 g (0.01 mol) of oxime of 1-propylpiperidine-4-one (2.2) is dissolved in a small quantity of absolute dioxane, then 2.27 l (0.02 mol) of hot solution of *o*-fluorobenzoylchloride in absolute dioxane is slowly added dropwise, while stirring, to the solution. The reaction mixture is held for 24 hours at the room temperature. Several drops of diethyl ether are added to the solution, and a white precipitation is formed. The course of the reaction is controlled by TLC. The reaction mixture is washed by diethyl ether and the precipitation is filtered, recrystallized from isopropyl alcohol. 1.4 g (44.5 % of the theoretic value) of hydrochloride of *1-propyl-4-(o-fluorobenzoyloxyimino)piperidine* is formed, mp of 169-171^{0}C, R_f of 0.7 (Al_2O_3, eluent - benzene : dioxane - 4:1).

Found, %: C 57.09; H 6.35. $C_{15}H_{20}ClFN_2O_2$.

Calculated, %: C 57.23; H 6.40.

EXPERIMENTAL BIOLOGICAL PART

The studies have been carried out on guinea-pigs by the Bulbring and Wade method and on rats by the “tail flick” method. The infiltration method is based on the principle of summation of the threshold mechanical stimuli, applied with a

certain rhythm, and allows one to estimate the intensity of an anesthetic effect. Each concentration has been tested on 6 animals. The average values of the results of the studies during 30 min have been taken as an anesthesia index. Compounds and reference preparations (novocaine, lidocaine, trimecaine) have been compared by the time of anesthesia onset, the duration of total anesthesia, and the total duration of an anesthetic effect of the preparation.

1. *An infiltration anesthetic activity* has been studied by the Bulbring and Wade method on guinea-pig males with the weight of 200-250 g. 0.2 ml of isotonic solutions of the compound under study and reference preparations have been introduced intracutaneously in four points (at the angles of a square 3 cm on a side) in the dorsal area of each animal, having preliminarily removed the hair covering. A local anesthetic activity has been estimated 6-8 times for each of the selected concentrations. Sensitivity at the place of introduction has been determined by touching with an obtuse injection needle, in series of 6 touches with the intervals of 3-4 after each 5 min, during 30 min. The profundity of anesthesia, expressed in 'anesthesia indices" (the average of 6 experiments, the maximum index – 36), the duration of total anesthesia and the total duration of an anesthetic effect have been determined. The activities of the compounds have been compared with that of the reference preparations − trimecaine, lidocaine and novocaine in the corresponding concentrations. The compound and reference preparations have been tested in 0.25% solutions.

2. *Conduction anesthesia model. The modified "tail flick" method on rats.* The "tail flick" method has been developed at the of Pharmacology of I.P. Pavlov St. Petersburg State Medical University. This method allows one to determine the rate of anesthesia onset, its profundity, the duration of total anesthesia, and the total duration of an anesthetic effect of the preparation. The activities of the compounds and reference preparations have been studied in 1% solutions. The study has been carried out on white outbred rat males with the weight of 200-250 g.

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Резюме

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ЖЕРГІЛІКТІ АНЕСТЕЗИЯЛЫҚ БЕЛСЕНДІ
1-ПРОПИЛ-4-КЕТОКСИМПИПЕРИДИН ФТОРБЕНЗОАТТАР

Түрлі деңгейдегі жергілікті анестезиялық белсенділік көрсететін 1-пропил-4-кетоксимпиперидиннің п-фтор, м-фтор, о-фтор-бензоаттары синтезделді. Фторды енгізу жергілікті анестетиктерге әртүрлі тиімділік дәрежесімен әкеледі. Фенил сақинасында фтор атомының орнына байланысты ең көп белсенділікті пара-изомерлер көрсетті, содан кейін орто- және аз белсенді метафторобензоаттар болды.

Түйін сөздер: п-фтор, м-фтор, о-фтор-бензоилкарбонилхлорид, N-пропилпиперидин-4-он, күрделі эфирлер, 1-пропил-4-(п-фтор-, м-фтор-, о-фторбензоилоксиимино)пиперидиндер, жергілікті анестезиялық белсенділік.

Резюме

Г. С. Ахметова, У. Б. Исаева, В. К. Ю, К. Д. Пралиев, Э. М. Сатбаева, Д. М. Кадырова, М. К. Амиркулова, Г. С. Смагулова, Т. М. Сейлханов

ФТОРБЕНЗОАТЫ 1-ПРОПИЛ-4-КЕТОКСИМПИПЕРИДИНА
С МЕСТНОАНЕСТЕЗИРУЮЩЕЙ АКТИВНОСТЬЮ

Синтезированы п-фтор, м-фтор, о-фтор-бензоаты 1-пропил-4-кетоксимпиперидина, проявившие в разной степени местноанестезирующую активность. Введение фтора приводит к местным анестетикам с различной степенью эффективности. В зависимости от положения атома фтора в фенильном кольце наибольшую активность показали *пара*- изомеры, затем *орто*- и менее активными были *мета*- фторбензоаты.

Ключевые слова: п-фтор, м-фтор, о-фтор-бензоилкарбонилхлорид, N-пропилпиперидин-4-он, сложные эфиры, 1-пропил-4-(п-фтор-, м-фтор-, о-фторбензоилоксиимино)пиперидины, местноанестезирующая активность.