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THE REACTIVITY OF N-PHENYLANTHRANILIC ACIDS DERIVATIVES. XXIV.* KINETICS OF THE ALKALINE HYDROLYSIS OF METHYL ESTERS OF 4,5-DYMETHOXY-N-PHENYLANTHRANILIC ACIDS IN THE BINARRY DIOXAN-WATER SOLVENT

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Key words: N-phenylanthranilic acid; methyl esters; reactivity; alkaline hydrolysis reaction; correlation

The synthesis of methyl esters of 4,5-dymethoxy-N-phenylanthranilic acids has been carried out by Fisher etherification in the medium of absolute methanol in the presense of concentrated sulfuric acid. The structure of the compounds synthesized have been confirmed by elemental analysis, IR- and NMP-spectroscopy. The purity has been controlled by the method of thin-layer chromatography in the methanol – hexane mixture (1:3). The kinetics of the reaction of alkaline hydrolysis of methyl esters of 4,5-dymethoxy-N-phenylanthranilic acids has been studied in the binary dioxane-water solvent in the temperature range of 45-65°C. Its second order has been proven, the rate constants have been determined and their increase with the increase of electrophylic carbon atom of the reaction centre has been revealed. Based on the free energy linearity principle the kinetic parameters correlation with Hammet σ-constants has been carried out. It has been found that ρ is low due to the distance of substituents from the reaction centre and it decreases with the temperature increase. The $B_{AC}2$ mechanism has been determined. The computer prognosis of possible types of biological activity of 9 methyl esters of 4,5-dymethoxy-N-phenylanthranilic acids synthesized for the first time has been conducted with the help of PASS programme. It has been found experimentally that the substances synthesized reveal the anti-inflammatory, analgetic, diuretic, bacteriostatic and fungistatic activity. According to the classification by K.K. Sydorov the compounds synthesized when introduced intragastrically belong to low toxic compounds (DL_{50} = 1500-2000 mg/kg). The investigations testify perspectiveness of search of biologically active substances among the given chemical compounds.

Development and introduction of new drugs into medicine are science-intensive and high technological process providing social, economic and national safety of Ukraine in general. The group of aryl carbonic acids, in particular N-phenylanthranilic acids (N-PAA) and their derivatives [1-3, 7, 13-16], is a promising chemical scaffolds in drugs creation; on their basis effective medicines have been created (mefenamic and flufenamic acids, antral, diphtorant, etc.) [5]. Besides the significant biological activity N-PAA show also a high reactivity conditioned by the presence of carboxyl and secondary aminogroups, and it gives a possibility to obtain their diverse functional derivatives with new pharmacological properties. The circumstances mentioned above have stipulated the necessity of the synthesis of new methyl esters of 4,5-dymethoxy-N-phenylanthranilic acids and the study of their reactivity, biological activity; it allows to optimize the search of new biologically active compounds of this series and to forecast their biological effect.

The study of reactivity of 4,5-dymethoxy-N-PAA esters has been conducted on the model of alkaline hydrolysis reaction. The choice of the reaction is conditioned, on the one hand, by possibility of metabolism estimation of these compounds in the organism, and on the other hand, – by optimization of synthetic conditions for the appropriate amides and hydrazides. In scientific literature works concerning the reactivity of methyl esters of 4,5-dymethoxy-N-PAA are absent.

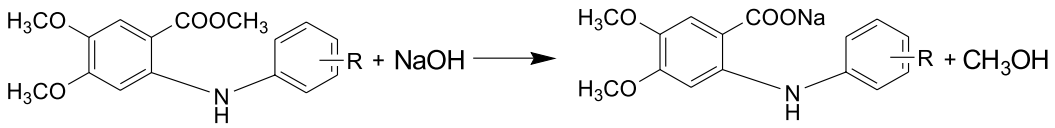
In the series of papers [3, 4, 6, 9-16] regarding the study of reactivity of biologically active derivatives of N-phenylanthranilic acids the kinetics of the reaction of alkaline hydrolysis of 2'- and 4'-substituted methyl esters of 4,5-dymethoxy-N-PAA in the binary dioxane-water solvent (60 vol% of dioxan) has been studied at the temperatures of 45 and 65°C. The reaction occurs by the following equation (Scheme 1).

The process can be described by the secondary order equation:

$$\frac{dx}{dt} = k(a-x)(b-x). \qquad (1)$$

where: *a, b* – are the initial concentrations of the ester and alkali (mole·l^{-1}), respectively; *x* – is the concentration of the reaction product (mole·1^{-1}) at the moment of time t(s); *k* – is the reaction rate constant ($1 \cdot mole^{-1} \cdot s^{-1}$).

* Report XXIII see [14]



Scheme 1

where R = H (1), 2'-CH_3 (2), 4'-CH_3 (3), 3',4'-$(CH_3)_2$ (4), 4'-OCH_3 (5), 4'-OC_2H_5 (6), 4'-OC_3H_7 (7), 4'-Cl (8), 4'-Br (9).

Division of the variables and integration of the equation (1) enables us to find the reaction rate constant:

$$\frac{dx}{dt} = k(a-x)(b-x). \qquad (2)$$

The value *k* obtained was adjusted to volume expansion of the solvent while changing the temperature during the experiment from 25°C till *t*°C multiplying by the factor $T = d_{25}/d_t$, where d_{25} and d_t – are density of the binary dioxane-water solvent at temperatures 25°C and t°C.

The reaction rate constants were calculated by changes of the concentration of sodium hydroxide in time according to equation (2). The ratios of the nucleophile and substrate concentrations varied, but the value of the rate constant remained the same in the range of the experimental error, i.e. the reaction is described by the equation of the second order.

Constants of alkaline hydrolysis of esters (1-9) depend on the electronic nature and the position of substituents in the non-anthranilic fragment of the molecule (Table). Addition of donor substituents to the ester molecule decreases the rate of the reaction. Acceptor substituents lead to the opposite effect by stabilizing of 4,5-dymethoxy-N-PAA anion due to delocalization of its charge. It must be mentioned that lengthening of the carbonic chain (OCH_3, OC_2H_5, OC_3H_7) in esters (5-7) causes decrease in the reaction rate at all experimental temperatures. It indicates the growth of electron density on the reaction centre in transition from the original state to active complex and allows to concede that alkaline hydrolysis of methyl esters of 4,5-dymethoxy-N-PAA derivatives occurs based on the $B_{AC}2$ mechanism known in the literature [7] (Scheme 2).

It is interesting to note that the rate of the reaction of alkaline hydrolysis of esters of (1-9) depends symbatically on the strength of the appropriate N-PAA in the experimental temperature interval. Dependence $lgk_{(T)} - f(pK_a)$ belongs to the linear type; it allows to calculate parameters for correlative equations of these dependences:

T = 318 K

$$lg\ k_{318} = (5.89\pm0.04) - (1.46\pm0.06)\ pK_a \qquad (3)$$

n = 9 r = 0.995 $S = 6.52\cdot10^{-2}$

T = 338 K

$$lg\ k_{338} = (5.01\pm0.03) - (1.29\pm0.04)\ pK_a \qquad (4)$$

n = 9 r = 0.996 $S = 4.86\cdot10^{-2}$.

These equations can be applied for prediction of the rate of the reaction at the certain values of pK_a of the appropriate acid because it is experimentally much easier to obtain pK_a or prognose it.

The quantitative assessment of the influence of the substituents electronic nature on reactivity of methylic esters of 4,5-dymethoxy-N-PAA was conducted according to the Hammet equation:

T = 318 K

$$lg\ k_{318} = (-4.974\pm0.005) + (1.059\pm0.023)\ \sigma \qquad (5)$$

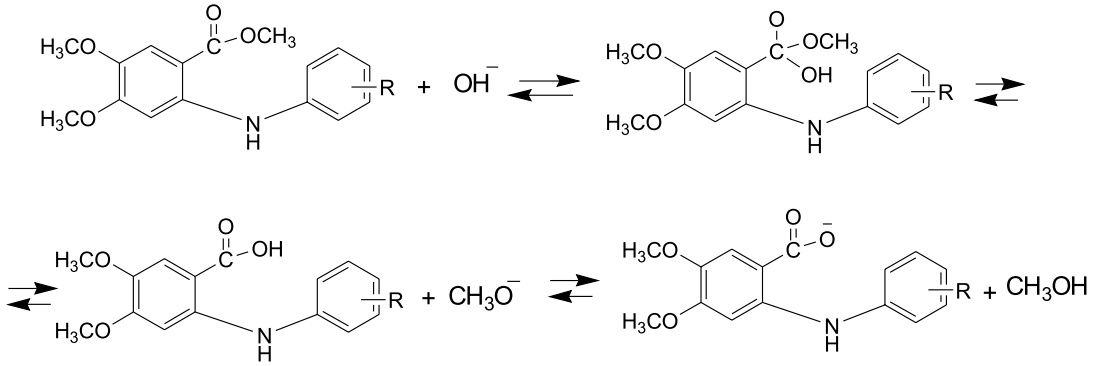
n = 9 r = 0.998 $S = 3.7\cdot10^{-2}$

T = 338 K

$$lg\ k_{338} = (-4.560\pm0.006) + (0.931\pm0.024)\ \sigma \qquad (6)$$

n = 9 r = 0.998 $S = 3.9\cdot10^{-2}$.

The data obtained indicate that the values of the reaction parameter ρ are added in the experimental temperature interval; it also specifies $B_{AC}2$ mechanism of the reaction. The low values of ρ can be explained by the distance of substituents from the reaction centre of the substrate. The ρ values practically coincide (in terms of the experimental error) with ρ of β-dialkilaminoethylic esters of 4-nitro, 4-nitro-5-chloro-, 4-sulphamoile-N-phenilanthranilic acids derivatives [9-11]. This allows to suppose the common mechanism of transfer of electronic influences on the reaction centre. The value ρ decreases with the temperature increase, i.e. that sensitivity of the reaction centre to the influence of substituents decreases.



Scheme 2

Table

Rate constants (k) of alkaline hydrolysis reaction of methyl esters derivatives of 4,5-dymethoxy-N-phenylanthranilic acids at various temperatures

Compound	R	$k \cdot 10^5$, $l \cdot mol^{-1} \cdot s^{-1}$ at T, K	
		318	338
1	H	1.05±0.06	2.75±0.04
2	2′-CH_3	0.69±0.05	1.81±0.03
3	4′-CH_3	0.76±0.04	1.90±0.03
4	3′,4′-$(CH_3)_2$	0.59±0.04	1.64±0.03
5	4′-OCH_3	0.55±0.05	1.53±0.02
6	4′-OC_2H_5	0.52±0.02	1.46±0.02
7	4′-OC_3H_7	0.48±0.02	1.49±0.03
8	4′-Cl	1.82±0.02	4.52±0.04
9	4′-Br	1.87±0.02	4.55±0.04

Based on the PASS programme the computer prognosis of possible types of biological activity of 9 methyl esters of 4,5-dymethoxy-N-phenylanthranilic acids synthesized for the first time has been conducted. It has been found experimentally that the substances synthesized reveal the anti-inflammatory, analgetic, diuretic, bacteriostatic and fungistatic activity. According to the classification by K.K. Sydorov the compounds synthesized when introduced intragastrically belong to low toxic compounds (DL_{50}=1500-2000 mg/kg).

Experimental Part

The synthesis of methyl esters of 4,5-dymethoxy-N-phenylanthranilic acids (1-9) was carried out by Fisher esterification in the medium of absolute methanol in the presence of concentrated sulfuric acid [7]. The compounds (1-9) obtained were recrystallized thrice from methanol and dried at 105°C up to the constant weight. The structure of the compounds synthesized has been confirmed by elemental analysis, IR- and NMP-spectroscopy. The purity was controlled by the method of thin-layer chromatography in the methanol-hexane mixture (1:3).

Kinetic measurements were conducted according to the method described [6]. The sodium hydroxide concentration in the solution was determined by potentiometric titration on an EV-74 ionometer using the standard aqueous solution of HCl. The kinetics of the reaction was studied at 45 and 65°C. Experiments were repeated thrice and consisted of 6-8 measurements each (the depth of transformations being at least 80%). The accuracy of the parameters obtained was assessed by means of the methods of mathematical statistics for small sets (with 0.95% confidence interval) [4].

CONCLUSIONS

1. The kinetics of the reaction of alkaline hydrolysis of methyl esters of 4,5-dymethoxy-N-phenylanthranilic acids has been studied in the binary dioxane-water solvent in the temperature range of 45-85°C.

2. The quantitative analysis of the effect of the nature and position of substituents in the non-anthranilic fragment of the molecule by Hammet equation has shown little sensitivity of the reaction centre, which decreases with the temperature increase.

3. The symbasis of the reaction rate from the strength of the corresponding acid has been proven.

4. The results of the research give possibility to predict reactivity of esters from this isostructured series; it provides optimization of the synthesis of the corresponding amides, hydrazides and their derivatives, and modeling of the biological activity of these pharmaceutical groupings.

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РЕАКЦІЙНА ЗДАТНІСТЬ ПОХІДНИХ N-ФЕНІЛАНТРАНІЛОВИХ КИСЛОТ.
XXIV. КІНЕТИКА РЕАКЦІЇ ЛУЖНОГО ГІДРОЛІЗУ МЕТИЛОВИХ ЕСТЕРІВ ЗАМІЩЕНИХ 4,5-ДИМЕТОКСИ-N-ФЕНІЛАНТРАНІЛОВИХ КИСЛОТ У БІНАРНОМУ РОЗЧИННИКУ ДІОКСАН-ВОДА

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Ключові слова: *N-фенілантранілова кислота; метилові естери; реакційна здатність; реакція лужного гідролізу; кореляція*

Метилові естери 4,5-диметокси-N-фенілантранілових кислот синтезовані естерифікацією відповідних кислот за Фішером у середовищі абсолютного метанолу в присутності концентрованої сульфатної кислоти. Будову синтезованих сполук підтверджено даними елементного аналізу, ІЧ-, ПМР-спектроскопією. Чистоту контролювали методом тонкошарової хроматографії у системі метанол-гексан (1:3). Досліджено кінетику реакції лужного гідролізу метилових естерів заміщених 4,5-диметокси-N-фенілантранілових кислот у бінарному розчиннику діоксан-вода при температурах 45, 65°С. Доведений її другий порядок, визначені константи швидкості і виявлено їх зростання зі збільшенням електрофільності атома вуглецю реакційного центру. На основі принципу ЛВЕ здійснена їх кореляція кінетичних параметрів з σ-константами Гаммета, встановлено, що ρ невеликі через віддаленість замісників від реакційного центру і зменшуються зі зростанням температури. Встановлено її $B_{AC}2$ механізм. За програмою PASS проведено комп'ютерний прогноз можливих видів біологічної активності дев'яти вперше синтезованих метилових естерів 4,5-диметокси-N-фенілантранілових кислот. Експериментально встановлено, що синтезовані речовини проявляють протизапальну, аналгетичну, діуретичну, бактеріостатичну і фунгістатичну активність. За класифікацією К.К. Сидорова синтезовані сполуки при внутрішньошлунковому введенні відносяться до класу малотоксичних сполук (DL_{50} = 1500-2000 мг/кг). Дослідження свідчать про перспективність пошуку біологічно активних речовин у даному ряду хімічних сполук.

РЕАКЦИОННАЯ СПОСОБНОСТЬ ПРОИЗВОДНЫХ N-ФЕНИЛАНТРАНИЛОВЫХ КИСЛОТ.
XXIV. КИНЕТИКА РЕАКЦИИ ЩЕЛОЧНОГО ГИДРОЛИЗА МЕТИЛОВЫХ ЭФИРОВ ЗАМЕЩЕННЫХ 4,5-ДИМЕТОКСИ-N-ФЕНИЛАНТРАНИЛОВЫХ КИСЛОТ

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Ключевые слова: *N-фенилантраниловая кислота; метиловые эфиры; реакционная способность; реакция щелочного гидролиза; корреляция*

Метиловые эфиры 4,5-диметокси-N-фенилантраниловых кислот синтезированы эстерификацией соответствующих кислот по Фишеру в среде абсолютного метанола в присутствии концентрированной сульфатной кислоты. Строение синтезированных соединений подтверждено данными элементного анализа, ИК-, ПМР-спектроскопией. Чистоту контролировали методом тонкослойной хроматографии в системе метанол-гексан (1:3). Исследована кинетика реакции щелочного гидролиза метиловых эфиров замещенных 4,5-диметокси-N-фенилантраниловых кислот в бинарном растворителе диоксан-вода при температурах 45, 65°С. Доказан ее второй порядок, определены константы скорости и выявлено их увеличение с возрастанием электрофильности атома углерода реакционного центра. На основе принципа ЛСЭ осуществлена корелляция кинетических параметров с σ-константами Гаммета; установлено, что ρ небольшие из-за удаленности заместителей от реакционного центра и уменьшаются с ростом температуры. Установлен ее $B_{AC}2$ механизм. По программе PASS проведен компьютерный прогноз возможных видов биологической активности девяти впервые синтезированных метиловых эфиров 4,5-диметокси-N-фенилантраниловой кислоты. Экспериментально установлено, что синтезированные вещества проявляют противовоспалительную, анальгетическую, диуретическую, бактериостатическую и фунгистатическую активность. По классификации К.К.Сидорова синтезированные соединения при внутрижелудочном введении относятся к классу малотоксичных соединений (DL_{50} = 1500-2000 мг/кг). Исследования свидетельствуют о перспективности поиска биологически активных веществ в данном ряду химических соединений.