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REACTIVITY OF N-PHENYLANTHRANILIC ACIDS DERIVATIVES. XXII*. SYNTHESIS AND ACID-BASE PROPERTIES OF 4,5-DYMETHOXY-N-PHENYLANTHRANILIC ACIDS

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The alternative ways of synthesis of new 4,5-dymethoxy-N-phenylanthranilic acids have been considered and new methods for their obtaining have been offered. The reactivity of 4,5-dymethoxy-N-phenylanthranilic acids has been investigated by studying the acid-base properties in the binary solvent of dioxane-water (60 vol% of dioxane). The influence of nature and the position of substituents in the non-anthranilic fragment of N-phenylanthranilic acids on their pKa has been analyzed. The subordination of the reaction series studied to Gamete equation has been found, and insignificant sensitivity of the reaction center to the influence of substituents in the non-anthranilic fragment of the molecule has been shown. The single correlation equation pKa – f(σ) for 4,5-dymethoxy-N-phenylanthranilic acids has been calculated; it allows to predict the acid-base properties of the compounds of this homologous series. It has been determined that the substances synthesized have the anti-inflammatory, analgesic, diuretic, bacteriostatic and fungistatic activity. According to the classification by K.K.Sydorov the compounds synthesized belong to low toxic compounds (DL_{50} > 3000 mg/kg).

Substituted N-phenylanthranilic acids and their derivatives are known as products with the high anti-inflammatory, reparative, gastroprotective activity and are widely used in medicine both as individual drugs or in combination with other drugs [8, 9]. Among them the most famous are mefenamic acid, meclofenamic acid, flufenamic acid, antral, difluorant, etc.

Derivatives of N-phenylanthranilic acids have an extensive synthetic and pharmacological potential as demonstrated in the patent and scientific literature [2-6, 9-11, 15, 18-21]. The circumstances mentioned above led to necessity of carrying out synthesis of 4,5-dymethoxy-N-phenylanthranilic acids previously undescribed in the literature and to study their reactivity. This fact will enable us to optimize the search of new biologically active substances of this series and to predict their biological effects. It should be noted that the pKa value (or the negative logarithm of the ionization constant) is one of the important characteristics of organic compounds reflecting their acid-base properties. Besides, the pKa value data are necessary for understanding such phenomena as the biological activity and transport of substances at the molecular level.

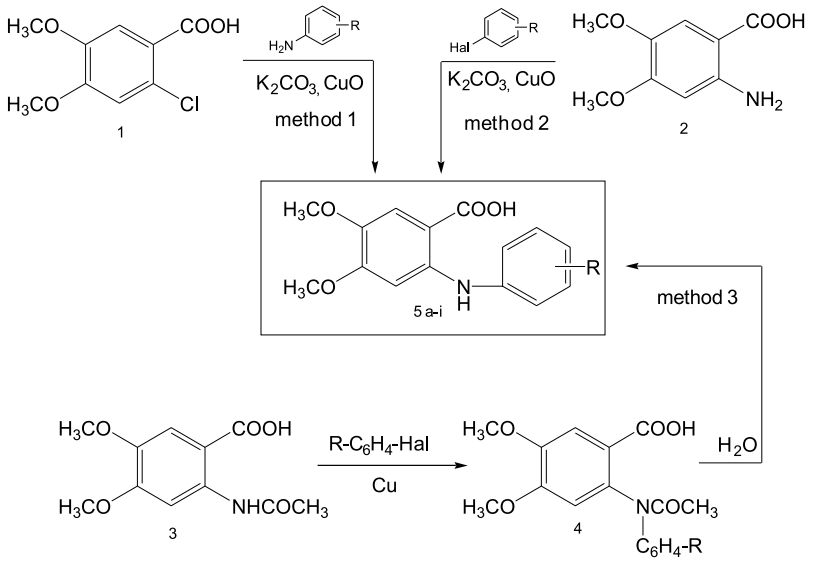
Substituted 4,5-dymethoxy-N-phenylanthranilic acids have been obtained by Ullmann reaction by interaction of 4,5-dymethoxy-2-chlorobenzoic acids (1) with arylamines (method 1) and by arylation of 4,5-dymethoxyanthranilic acid by halogenbenzenes derivatives (method 2) in the media of n-amylalcohol (method 1A, 2A), in the media of dimethylfomamide (method 1B, 2B), without a solvent (method 1C, 2C) in the presence of copper or copper (II) oxide [2, 4, 5, 11]. In addition, as a counter synthesis of 4,5-dymethoxy-N-phenylanthranilic acids (5) condensation of N-acetyl-4,5-dymethoxyanthranilic acids (3) with substituted halogenbenzenes with subsequent hydrolysis of N-acyl derivatives has been used (method 3). In order to increase the solubility of copper ions in the aprotic low-polar phase for accelerating the arylation reaction various solvents (Tween-80, sodium salt of oleic acids, stearic acid) have been used; they have been added to the reaction mixture in the amount of 3-5% w/w. The use of sodium oleate as a phase transfer catalyst allows to make 1.4 times faster the arylation reaction (Scheme 1).

The structure and identity of 4,5-dymethoxy-N-phenylanthranilic acids have been confirmed by elemental analysis, IR- and NMR-spectroscopy, chromatographic analysis and the qualitative reaction.

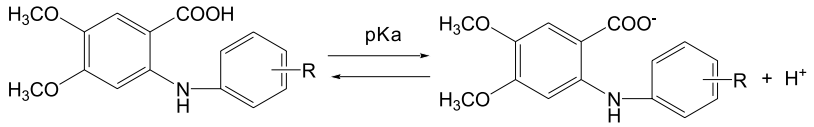
In the NMR-spectra of acids the signals of aromatic protons in the range of 6.50-7.90 ppm have been identified. The secondary amino group proton signals appear as a broad singlet in the region of 8.05-11.72 ppm. The proton signals of the methoxy group are as one or two singlets at 3.50-3.80 ppm.

Ionization constants of 4,5-dymethoxy-N-phenylanthranilic acids have been determined by potentiometric titration in the binary solvent of dioxane-water (60 vol% of dioxane) at 25ºC (Scheme 2) [16, 17]. The experimental method is described bellow.

* Report XXI see [6]



Scheme 1



Scheme 2

It follows from Table 1 that the properties and position of substituents affect the value of ionization constants of 4,5-dymethoxy-N-phenylanthranilic acids (5 a-i) in both anthranilic and non-anthranilic fragments of the molecule. In both cases introduction of acceptor substituents (5 h, i) leads to stronger acids, while the donor ones (5 b-g) have the opposite effect.

The quantitative assessment of the influence of substituents in the non-anthranilic fragment of the molecule of 4,5-dimethoxy-N-phenylanthranilic acids (5 a-i) have been carried out at the range of the principle of linear free energy (LFE) in Gamete equation (Fig.). At first the correlation for N-phenylanthranilic acids, which have substituents in meta- and para-position in the non-anthranilic fragment of the molecule, has been investigated. The resulting correlation equation (1) is statistically significant:

$$pKa = (7.44\pm0.03) - (0.72\pm0.01) \cdot \sigma \qquad (1)$$

where: $n = 8$, $s = 1.99 \cdot 10^{-2}$, $r = 0.998$

Introduction of compound (5 a) containing the methyl group in 2'-position in the non-anthranilic fragment to the correlation of pKa acids has improved the statistical characteristics of the equation with pKa – f(σ) relationship:

$$pKa = (7.44\pm0.03) - (0.72\pm0.01) \cdot \sigma \qquad (2)$$

where: $n = 9$, $s = 1.94 \cdot 10^{-2}$, $r = 0.999$

Table

Properties of substituted 4,5-dymethoxy-N-phenylanthranilic acids

Compound	R	Yield, %								pKa	R_f*	
		Method 1			Method 2			Method 3			1	2
		A	B	C	A	B	C	A	B			
5a	H	64	75	89	65	75	90	42	59	4.44±0.03	0.03	0.72
5b	2′-CH_3	67	77	90	63	80	92	44	55	7.56±0.02	0.32	0.70
5c	4′-CH_3	68	79	92	60	80	93	39	54	7.58±0.03	0.33	0.69
5d	3′,4′-$(CH_3)_2$	69	78	92	-	-	92	44	62	7.61±0.04	0.30	0.65
5e	4′-OCH_3	65	75	90	-	-	90	-	-	7.63±0.02	0.29	0.59
5f	4′-OC_2H_5	68	75	93	-	-	-	-	-	7.65±0.02	0.28	0.55
5g	4′-OC_3H_7	65	72	92	-	-	-	-	-	7.67±0.01	0.25	0.52
5h	4′-Cl	69	77	94	-	-	-	-	-	7.27±0.02	0.23	0.44
5i	4′-Br	69	80	94	-	-	-	-	-	7.38±0.03	0.21	0.42

* Note. The values of Rf are given in the following systems: 1) acetone – hexane – chloroform (2:3:1);
2) ethanol – methanol – hexane (8.5:3:1)

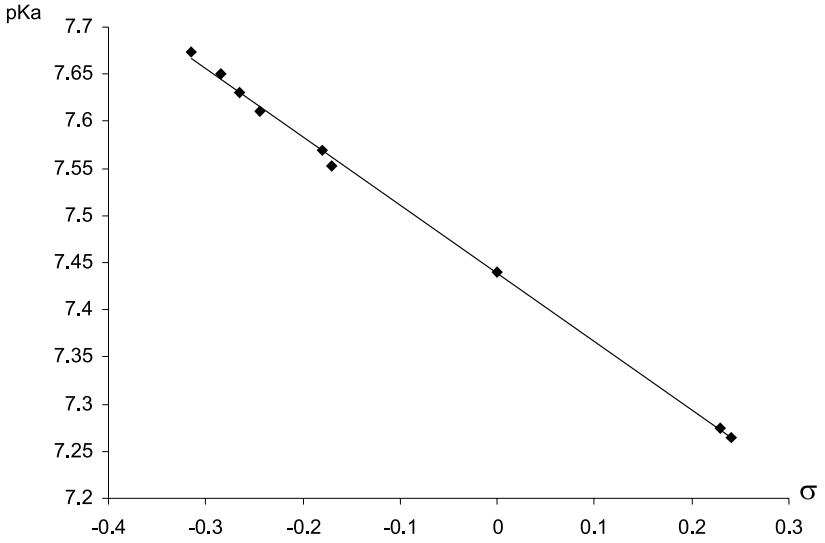


Fig. Dependence of pKa – f(σ) for substituted 4,5-dimethoxy-N-phenyl-anthranilic acids in the binary solvent of dioxane-water (60 vol% of dioxane) at 25ºC.

It indicates the absence or insignificant ortho-effect on the methyl substituent. The unified equation (2) obtained for relationship of acidic properties of substituted 4,5-dymethoxy-N-phenylanthranilic acids (5 a-i) with Gamete σ-constants allows to simulate this isostructural series of compounds with the given level of acidity. Analysis of the parameters of the correlation equation (2) indicates the low sensitivity of the reaction center (-COOH) to the influence of substituents in the non-anthranilic fragment of the molecule of 4,5-dimethoxy-N-phenylanthranilic acids (the reaction parameter ρ = 0.72). This is possible due to both the distance of substituents from the reaction center and with an insulating effect of NH-group at the expense of complanarity of N-phenylanthranilic acids molecules [16]. It should be noted that the reaction parameter ρ of the isostructural series studied within the experimental error coincides with ρ of other homologous series of substituted N-phenylanthranilic acids with electron-accepting substituents in the anthranilic fragment of the molecule [5, 6, 12-14, 16, 17]. It has been also determined that the substances synthesized have the anti-inflammatory, analgesic, diuretic, bacteriostatic, fungistatic activity. According to the classification by K.K.Sydorov the compounds synthesized belong to low toxic compounds (DL_{50} > 3000 mg/kg).

Experimental Methods

Reagents. Dioxane used («oscillating») was not purified additionally.

For preparation of mixed solvents a freshly boiled bidistillate free from CO_2 was used [1].

The derivatives of phenylanthranilic acid were synthesized by a modified Ullmann reaction [2, 4]. The compounds obtained were recrystallized from ethanol three times and dried at 105ºC up to the constant weight. The purity of the compounds was checked by thin-layer chromatography.

The methods of measurements were similar to those described in [1]. 0.05 M of aqueous solution of KOH purified from CO_2 served as a titrating agent. The concentration of the solutions titrated was 0.005 mol/l. Potentiometric titration was conducted on an EV-74 ionometer using a glass electrode ESP-43-074 and silver chloride electrodes EVL-1 M at 25ºC. The pKa value of acetic acid in the binary solvent of dioxane-water solution (60 vol% of dioxane) was determined as a standard (pKa exp. = 7.50; 5.52; 7.49).

The pKa measurements were conducted for each compound independently. The accuracy of the results obtained was estimated using the methods of mathematical statistics (at CI 0.95) [7].

^{1}H NMP-spectra were registered on a Varian M 200 spectrophotometer with the operation frequency of 200 MHz from solutions of DMSO-d_6 with TMS as an internal standard.

CONCLUSION

1. The preparative methods for the synthesis of 4,5-dimethoxy-N-phenylanthranilic acids in the solid phase and in the aqueous medium with the use of a phase transfer catalyst – sodium oleate have been developed.

2. The reactivity of 4,5-dimethoxy-N-phenyl-anthranilic acids (9 compounds) has been invetigated by studying the acid-base equilibria of these compounds in a binary solvent of dioxane-water.

3. According to the principle of linear free energy (LFE) by Gamete equation the correlation equation of pKa – f(σ) relationship has been obtained with convincing statistical parameters.

4. The low sensitivity of the carboxyl group reaction center to the effects of substituents in the non-anthranilic fragment of the molecule has been proven.

5. The correlation equation of pKa – f(σ) for 4,5-dymethoxy-N-phenylanthranilic acids obtained allows to predict the acid-base properties of other compounds of the given isostructural series.

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РЕАКЦИОННАЯ СПОСОБНОСТЬ ПРОИЗВОДНЫХ N-ФЕНИЛАНТРАНИЛОВЫХ КИСЛОТ. XXII. СИНТЕЗ И КИСЛОТНО-ОСНОВНЫЕ СВОЙСТВА 4,5-ДИМЕТОКСИ-N-ФЕНИЛАНТРАНИЛОВЫХ КИСЛОТ

С.Г.Исаев, Е.Н.Свечникова, А.А.Девяткина, Т.В.Жукова, Т.М.Святская

Рассмотрены альтернативные варианты синтеза новых 4,5-диметокси-N-фенилантраниловых кислот и предложены новые способы их получения. Исследовано реакционную способность замещенных 4,5-диметокси-N-фенилантраниловых кислот путем изучения кислотно-основных свойств в бинарном растворителе диоксан-вода (60 об. % диоксана). Проанализировано влияние природы и положение заместителей в неантраниловом фрагменте N-фенилантраниловых кислот и их pKa. Доказано подчиненность исследуемых реакционных серий уравнению Гаммета и показана небольшая чувствительность реакционного центра к влиянию заместителей в неантраниловом фрагменте молекулы. Рассчитано единое корреляционное уравнение pKa – f (σ) для 4,5-диметокси-N-фенилантраниловых кислот, которое позволяет прогнозировать кислотно-основные свойства соединений этого ряда. Было установлено, что синтезированные вещества обладают противовоспалительным, обезболивающим, мочегонным, бактериостатическим, фунгистатическим действием. Согласно классификации К.К.Сидорова синтезированные соединения относятся к малотоксичным веществам (DL_{50} > 3000 мг/кг).

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РЕАКЦІЙНА ЗДАТНІСТЬ ПОХІДНИХ N-ФЕНІЛАНТРАНІЛОВИХ КИСЛОТ. XXII. СИНТЕЗ ТА КИСЛОТНО-ОСНОВНІ ВЛАСТИВОСТІ 4,5-ДИМЕТОКСИ-N-ФЕНІЛАНТРАНІЛОВИХ КИСЛОТ

С.Г.Ісаєв, О.М.Свєчникова, А.О.Девяткіна, Т.В.Жукова, Т.М.Святська

Розглянуті альтернативні варіанти синтезу нових 4,5-диметокси-N-фенілантранілових кислот та запропоновані нові способи їх одержання. Досліджено реакційну здатність заміщених 4,5-диметокси-N-фенілантранілових кислот шляхом вивчення кислотно-основних властивостей у бінарному розчиннику діоксан-вода (60 об.% діоксану). Проаналізовано вплив природи та положення замісників у неантраніловому фрагменті N-фенілантранілових кислот та їх pKa. Доведено підпорядкованість досліджуваних реакційних серій рівнянню Гаммета та показана невелика чутливість реакційного центру до впливу замісників у неантраніловому фрагменті молекули. Розраховано єдине кореляційне рівняння pKa – f(σ) для 4,5-диметокси-N-фенілантранілових кислот, що дозволяє прогнозувати кислотно-основні властивості сполук цього ряду. Було встановлено, що синтезовані речовини мають протизапальну, знеболюючу, сечогінну, бактеріостатичну, фунгістатичну дію. Відповідно до класифікації К.К.Сидорова синтезовані сполуки відносяться до класу малотоксичних речовин (DL_{50} > 3000 мг/кг).