

# ACID-BASE PROPERTIES OF SUBSTITUTED 6-NITRO-N-(R-PHENYL)ANTHRANILIC ACIDS

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## ABSTRACT

The ionization constants of nine substituted 6-nitro-N-(R-phenyl)anthranilic acids have been determined in a mixed solvent dioxane-water at a temperature of 25°C. The influence of the nature and positions of substituents in the non-anthranilic fragment of molecule on acid-base properties has been analyzed. The correlation equation of the relationship between  $pK_a$  and Hammett's  $\sigma$ -constants has been calculated and low sensitivity of the reaction center to the influence of the substituents in the non-anthranilic fragment of molecule has been shown.

**Keywords:** Substituted 6-nitro-N-(R-phenyl)anthranilic acids; ionization constants; correlation equation

## INTRODUCTION

N-Phenylanthranilic acid and its derivatives attracted for a long period of time the attention of researchers in finding new pharmacophores in its isomeric series. It is caused by the fact that its derivatives possess different pharmacological activities: anti-inflammatory, analgesic, diuretic, antifungal, etc. with low toxicity (1-5). These compounds are widely used in modern medicine (mefenamic acid, meclofenamic acid, niflumonic acid, flufenamic acid and its aluminum salt, antral, diphtorant, etc.). In addition, they are initial substances for obtaining acridine and phenothiazine derivatives. Therefore, the study of reactivity of substituted 6-nitro-N-(R-phenyl)anthranilic acids causes indisputable scientific and practical interest. In the literature there are no data on the reactivity of these compounds.

## MATERIALS AND METHODS

Substituted 6-nitro-N-(R-phenyl)anthranilic acids have been obtained by the Ullmann reaction by heating 6-nitro-2-chlorobenzoic acid and corresponding arylamines without solvent in the presence of potassium carbonate and copper or copper (II) oxide (6). Physico-chemical parameters of the compounds are shown in Table 1.

Ionization constants ( $pK_a$ ) of 6-nitro-N-(R-phenyl)anthranilic acids were identified in a mixed solvent dioxane-water (60 vol % of dioxane) at a temperature of 25°C by potentiometric titration (7).

Titration for each compound was carried out three times. Assessment of the accuracy of the obtained results was carried out by MS Excel (relative confidence interval – 0.95) (8).

For the preparation of the mixed solvent freshly boiled bidistillate liberated from CO<sub>2</sub> and purified dioxane were used. Dioxane was purified by distillation over metallic sodium. Preliminarily, it was heat-

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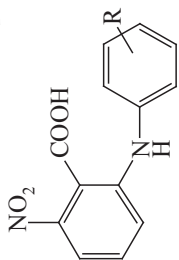
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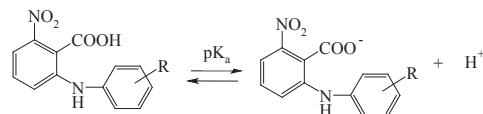
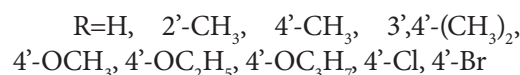
Table 1. Properties of substituted 6-nitro-N-(R-phenyl)anthranilic acids

Com- pound	R	Yield, %	M.p., °C	pK <sub>a</sub>	Found, %			Calculated, %		
					C	N	H	C	N	H
1	H	80	196-198	5,30±0,02	60,43	10,86	3,94	60,47	10,85	3,90
2	2-CH <sub>3</sub>	86	198-200	5,40±0,04	61,73	10,29	4,42	61,76	10,29	4,44
3	4-CH <sub>3</sub>	87	218-221	5,42±0,03	61,72	10,27	4,45	61,76	10,29	4,44
4	3,4-(CH <sub>3</sub> ) <sub>2</sub>	85	222-224	5,43±0,01	62,91	9,78	4,90	62,93	9,79	4,93
5	4-OCH <sub>3</sub>	86	180-182	5,51±0,01	58,30	9,71	4,19	58,33	9,72	4,20
6	4-OC <sub>2</sub> H <sub>5</sub>	88	194-196	5,52±0,02	59,64	9,25	4,66	59,60	9,27	4,67
7	4-OC <sub>3</sub> H <sub>7</sub>	79	180-183	5,53±0,04	60,77	8,81	4,96	60,75	8,86	5,10
8	4-Cl	82	173-175	5,13±0,02	53,30	9,61	3,15	53,35	9,57	3,10
9	4-Br	83	195-198	5,14±0,02	46,29	8,34	2,73	46,31	8,31	2,70



ed with a solution of HCl for 6 hours under reflux and after cooling it was saturated with solid KOH (9). The quality of dioxane was controlled by gas-liquid chromatography. The choice of solvent was conditioned by the fact that in a mixture of this composition the same relative shift between pK<sub>a</sub> compounds is retained as in water (10). These compounds are practically insoluble in water and that is why it is impossible to determine their acidity. The potentiometric titration method which was used allows to get only semi-concentration ionization constants, but earlier (11) it was proved that for substituted 6-nitro-N-(R-phenyl)anthranilic acids their value within the error of the experiment coincides with the thermodynamic constants pK<sub>a</sub>.

The reactivity of this isostructural series was investigated on the model of acid-base balance in inverse conditions:



Measurement of pK<sub>a</sub> was carried out by the method described in this article (7). The method is based on measuring pH during the potentiometric titration of the acid solution. As titrant, 0.05M aqueous KOH solution liberated from CO<sub>2</sub> was used. The concentration of the KOH solution was 0.005 mol/l at the point of semi-neutralization. Potentiometric titration was carried out on an EV-74 ionomer using glass (ESP 43-074) and silver-silver chloride (EVL-1) electrodes at 25°C. The obtained data are presented in the Table 1.

## RESULTS

All investigated compounds exhibit weak acidic properties (Table 1). The results are shown in Table 1 and confirm the fact that the power of acids depends on the

nature and position of substituents in the non-anthranilic fragment of the molecule: introduction of the donor substituents ( $\text{CH}_3$ ,  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{OC}_3\text{H}_7$ ) naturally reduces the power of acids and the acceptor substituents (Cl, Br) have the opposite effect due to the stabilizing effect on the anion.

Quantitative relationships were established within the borders of the principle of linearity of free energies (LFE) by correlation analysis of ionization constants of the investigated compounds with Hammett's  $\sigma$ -constants. A graph of the correlation is shown in Fig. 1.

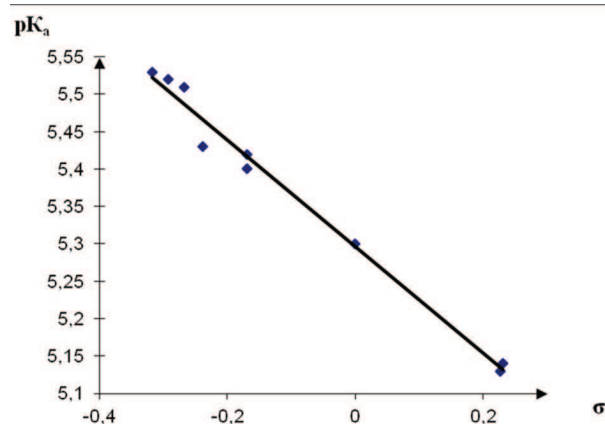


Fig. 1. Dependence of the  $pK_a$ - $f(\sigma)$  for substituted 6-nitro-N-(R-phenyl)anthranilic acids in binary solvent dioxane-water (60 vol % of dioxan) at 25°C.

At first, the correlation for the meta- and para-substituted 6-nitro-N-(R-phenyl)anthranilic acids (compounds 1, 3-9) have been investigated.

The resulting correlation equation  $pK_a = pK_a^0 + \rho\sigma$  with statistically significant parameters were obtained (equation 1):

$$pK_a = (5,30 \pm 0,01) - (0,72 \pm 0,03)\sigma \quad (1)$$

$n=8 \quad s=4,69 \cdot 10^{-2} \quad r=0,994$

Introduction to the correlation  $pK_a$  ortho-substituted 6-nitro-N-(R-phenyl)anthranilic acids (compound 2) has not alter significantly the static parameters (equation 2):

$$pK_a = (5,30 \pm 0,01) - (0,72 \pm 0,03)\sigma \quad (2)$$

$n=9 \quad s=5,06 \cdot 10^{-2} \quad r=0,993$

The obtained equation 2 allows modeling of this isostructural series of compounds with the given level of acidity.

## DISCUSSION

The absolute value of the reaction constant  $\rho$  of equation 2 is small i.e. the reaction center sensitivity to the substituents effects is low. Likely reasons for this are remoteness the reaction center from substituents or insulating effect of action imino-group to the transmission of electronic influences of substituents due to non-coplanarity of molecule N-phenylanthranilic acid (12). It should be noted that the  $\rho$  values for substituted 6-nitro-N-(R-phenyl)anthranilic acids within the error of the experiment coincides with  $\rho$  of other homologous series N-phenylanthranilic acid with different substituents in the anthranilic fragment of the molecule (10-13).

The proximity of parameter values equations 1, 2 attracts interest that indicates no or little impact on the ortho-effect  $\text{CH}_3$ -substituent probably due to the remoteness of the substituent from the reaction center or non-complanarity of the non-anthranilic phenyl radical (11,12).

The results obtained are used to create optimal conditions for purposeful synthesis of biologically active compounds and QSAR-analysis in this isostructural series.

## CONCLUSIONS

1. The activity of compounds of the isostructural series of 6-nitro-N-(R-phenyl)anthranilic acid in inverse conditions on a model of their acid dissociation was investigated.
2. The  $pK_a$  of nine compounds in this series were calculated, influence nature and position of substituents in the non-anthranilic fragment of the molecule on this parameter were analyzed.
3. The correlation equation of the relationship  $pK_a$ - $f(\sigma)$  with statistically significant parameters within the borders of the principle of linearity of free energies was obtained.
4. Low sensitivity of the reaction center of the carboxyl group to the effects of substituents in the non-anthranilic fragment of the molecule was proven.
5. The results obtained are used to create optimal conditions for purposeful synthesis of biologically active compounds of series of derivatives of 6-nitro-N-(R-phenyl)anthranilic

acid and QSAR-analysis in this isostructural series.

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