

REACTIVITY OF PHENYLANTHRANILIC ACIDS DERIVATIVES. XXIII. SYNTHESIS AND ACID-BASE PROPERTIES OF 4,5-DIMETHOXY-N-(2'-CARBOXYPHENYL)ANTHRANILIC ACIDS

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Key words: synthesis; reactivity; N-phenylanthranilic acid

The alternative ways of synthesis of new 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids have been considered and new ways for their obtaining have been suggested. The structure of the compounds synthesized has been proven by the elemental analysis, IR- and NMR-spectroscopy. The purity has been controlled by the method of thin-layer chromatography. The reactivity of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids has been researched by studying the acid-base properties in the binary solvent of dioxane-water (60 vol% of dioxane). It has been found that the substances synthesized are dibasic subacids, which strength depends upon the nature and position of substituents. The quantitative assessment of the influence of substituents on two reactive centres of the acids synthesized has been carried out by the method of correlative analysis according to the Gamete equation. It has been proven that the reactive centres sensitivity is substantially different and dependent on the substituent distance. In addition, appearance of another reactive centre does not practically influence on sensitivity of the first one. It has been determined that the substances synthesized reveal the anti-inflammatory, analgesic, diuretic, bacteriostatic, and fungistatic effects. According to the classification by K.K. Sydorov the substances synthesized when introducing intragastrically belong to low-toxic compounds ($DL_{50} > 3000$ mg/kg).

РЕАКЦІЙНА ЗДАТНІСТЬ ПОХІДНИХ N-ФЕНІЛАНТРАНІЛОВИХ КИСЛОТ. XXIII. СИНТЕЗ ТА КИСЛОТНО-ОСНОВНІ ВЛАСТИВОСТІ 4,5-ДИМЕТОКСИ-N-(2'-КАРБОКСИФЕНІЛ)АНТРАНІЛОВИХ КИСЛОТ

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Ключові слова: синтез; реактивність; N-фенілантранилова кислота

Розглянуті альтернативні варіанти синтезу нових 4,5-диметокси-N-(2'-карбоксифеніл)антранилових кислот та запропоновані нові способи їх одержання. Будову синтезованих речовин доведено даними елементного аналізу, ІЧ- та ПМР-спектроскопії. Чистоту контролювали методом тонкошарової хроматографії. Досліджено реакційну здатність заміщених N-(2'-карбоксифеніл)антранилових кислот шляхом вивчення кислотно-основних властивостей у бінарному розчиннику діоксан-вода (60 об% діоксану). Встановлено, що синтезовані речовини є слабкими двоосновними кислотами, сила яких залежить від природи та положення замісників. Методом кореляційного аналізу проведено кількісну оцінку впливу замісників на два реакційних центри синтезованих кислот за рівнянням Гаммета. Доведено, що чутливість реакційних центрів суттєво відрізняється та залежить від віддаленості замісників. При цьому поява другого реакційного центру практично не впливає на чутливість першого. Було встановлено, що синтезовані речовини проявляють протизапальну, анальгетичну, діуретичну, бактеріостатичну та фунгістатичну активність. За класифікацією К.К.Сидорова синтезовані речовини при внутрішньо-шлунковому введенні належать до класу малотоксичних сполук ($DL_{50} > 3000$ мг/кг).

РЕАКЦИОННАЯ СПОСОБНОСТЬ ПРОИЗВОДНЫХ N-ФЕНИЛАНТРАНИЛОВЫХ КИСЛОТ. XXIII. СИНТЕЗ И КИСЛОТНО-ОСНОВНЫЕ СВОЙСТВА 4,5-ДИМЕТОКСИ-N-(2'-КАРБОКСИФЕНИЛ)АНТРАНИЛОВЫХ КИСЛОТ

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Ключевые слова: синтез; реактивность; N-фенілантранилова кислота

Рассмотрены альтернативные варианты синтеза новых 4,5-диметокси-N-(2'-карбоксифеніл)антраниловых кислот и предложены новые способы их получения. Строение синтезированных веществ доказано данными элементного анализа, ИК- и ПМР-спектроскопии. Чистоту контролировали методом тонкошаровой хроматографии. Исследована реакционная способность замещенных N-(2'-карбоксифеніл)антраниловой кислоты путем изучения кислотно-основных свойств в бинарном растворителе диоксан-вода (60 об% диоксана). Установлено, что синтезированные вещества являются слабыми двухосновными кислотами, сила которых зависит от природы и положения заместителей. Методом корреляционного анализа проведено количественную оценку влияния заместителей на два реакционных центра синтезированных кислот согласно уравнению Гаммета. Доказано, что чувствительность реакционных центров существенно отличается и зависит от удаленности заместителей. При этом появление второго реакционного центра практически не влияет на чувствительность первого. Было установлено, что синтезированные вещества проявляют противовоспалительную, анальгетическую, диуретическую, бактериостатическую и фунгиостатическую активность. По классификации К.К.Сидорова синтезированные вещества при внутривнутреннем введении следует относить к классу малотоксичных соединений ($DL_{50} > 3000$ мг/кг).

* Post XXII see [15]

Analysis of the research data [1-11] indicates the widespread use of derivatives of N-phenylanthranilic acids in medicine, pharmacy, industry and various fields of science. N-phenylanthranilic acids derivatives have a wide synthetic and pharmacological potential [1-3, 8-11]. The circumstances above caused the necessity to carry out the synthesis of new 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids, study of their reactivity and biological activity. It will allow to optimize the search for new biologically active compounds of this series and forecast their biological effect.

Substituted 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids have been obtained by the Ullmann reaction by the interaction of 4,5-dimethoxy-chlorobenzoic acids (1) with o-halogenbenzoic acid (method 1) and by arylation of 4,5-dimethoxyanthranilic acid by o-halogenbenzoic acid (method 2) in the medium of N-amylalcohol (method 1A, 2A), DMF (method 1B, 2B), without a solvent (method 1C, 2C) in the presence of copper or copper (II) oxide [1-3]. The same as a counter synthesis of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids (5) condensation of N-acetyl-4,5-dimethoxyanthranilic acids (3) with substituted o-halogenbenzene acid follow by hydrolysis of N-acyd derivatives has been used (Method 3). In order to increase solubility of copper ions in the aprotic low-polar phase to accelerate the arylation reaction various solvent (Tween-80, sodium salt of oleic acids, stearic acid) added to the reaction mixture in the amount of 3-5 weight percent have been used. The use of sodium oleate as a phase trans-

fer catalyst allows to accelerate 1,4 times the arylation reaction (Scheme 1).

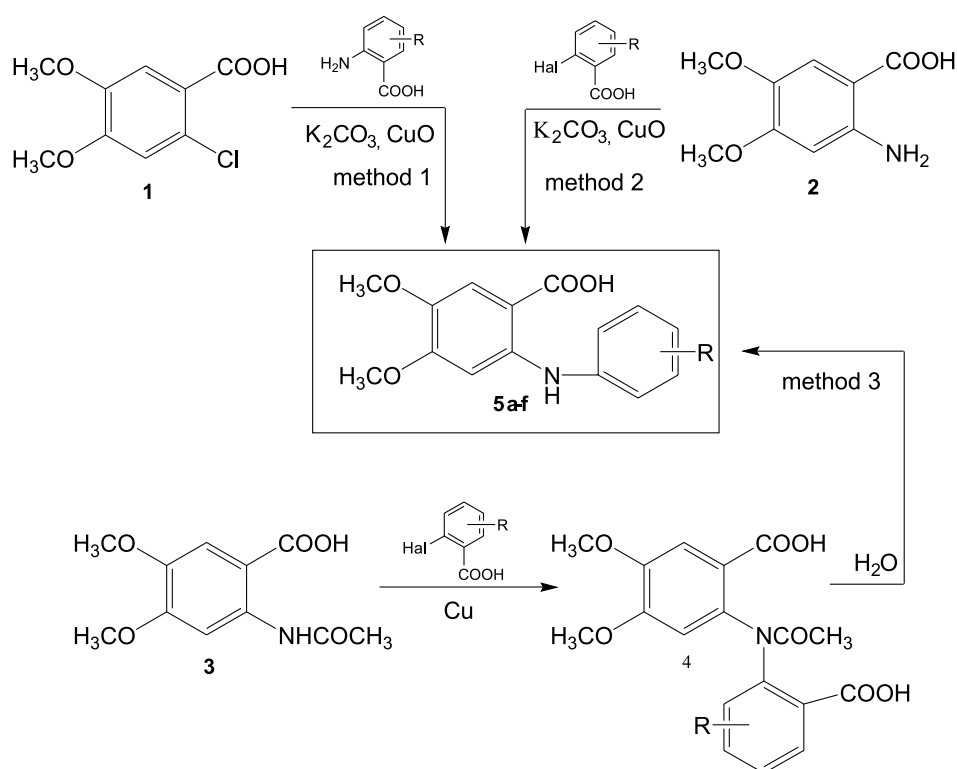
The structure and identity of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids have been confirmed by elemental analysis, IR-, NMR-spectroscopy, chromatographic analysis and qualitative reactions (Table 1, 2, 3).

IR-spectra of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids (5a-f) are characterized by a number of intense bands, which correspond to the main structural fragments of molecules of the substances synthesized, ν , cm^{-1} : 3362-3258 (ν_{NH}), 1709-1659 ($\nu_{\text{C=O}}$), 1591-1570 (δ_{NH}), 1235-1206 (ν_{CN}). The strong bands of nitrogroup $\nu \frac{\text{as}}{\text{s}} \text{NO}_2$ 1523 cm^{-1} and $\nu \frac{\text{s}}{\text{NO}_2}$ 1351-1350 cm^{-1} are also characteristic for the spectra of compounds (5a-f).

In the NMR-spectra of acids (5a-f) signals of aromatic protons in the range of 6.50-7.90 ppm have been identified. The proton signals of the secondary amino group appear as a broad singlet in the region of 8.05-11.18 ppm. The proton signals of the methoxy group are one or two singlets at 3.60-3.80 ppm (Table 3).

As a continuation of a number of papers [4, 12-19] related to the study of reactivity of biologically active substituted N-phenylanthranilic acids, dissociation of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids (5a-f) has been examined according to the equation.

Ionization constants of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids have been determined by potentiometric titration in the binary solvent of dioxane-water (60 vol% of dioxane) at 25°C (Scheme 2) [18, 19]. The given method allows to obtain concen-



Scheme 1

Table 1

Characteristics of 4,5-dymethoxy-N-(2'-carboxyphenyl)anthranilic acids synthesized

| Com- pound | R | Yield ¹ , % | | | | | | M.p., °C | Found, % | | Formula | Calculated, % | | | |
|---------------|-----------------------|------------------------|----|----|----------|----|----|----------|----------|---------|---------|---------------|--|-------|-------|
| | | Method 1 | | | Method 2 | | | | Method 3 | N | | C | N | C | |
| | | A | B | C | A | B | C | | | | | | | | A |
| 5a | H | 62 | 69 | 88 | 63 | 74 | 88 | 35 | 50 | >300 | 4.45 | 60.61 | C ₁₆ H ₁₅ NO ₆ | 4.41 | 60.57 |
| 5b | 4'-Br | 67 | 70 | 92 | 65 | 74 | 90 | 45 | 56 | >300 | 3.59 | 48.53 | C ₁₆ H ₁₄ BrNO ₆ | 3.54 | 48.51 |
| 5c | 5'-Cl | 68 | 71 | 90 | 65 | 72 | 89 | 47 | 55 | 260-264 | 3.91 | 54.58 | C ₁₆ H ₁₄ ClNO ₆ | 3.98 | 54.64 |
| 5d | 6'-NO ₂ | 65 | 74 | 92 | 62 | 70 | 90 | 44 | 57 | >300 | 7.82 | 52.99 | C ₁₆ H ₁₄ N ₂ O ₈ | 7.73 | 53.04 |
| 5e | 4',6'-Br | 65 | 75 | 90 | 63 | 72 | 88 | 40 | 55 | >300 | 3.05 | 40.41 | C ₁₆ H ₁₃ BrNO ₆ | 2.95 | 40.45 |
| 5f | 4',6'-NO ₂ | 69 | 79 | 94 | 65 | 75 | 93 | 43 | 55 | 254-257 | 10.38 | 47.22 | C ₁₆ H ₁₃ N ₃ O ₁₆ | 10.32 | 47.18 |

Note. ¹Crystallized from aqueous ethanol**Table 2**

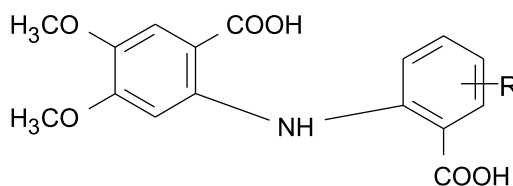
Acid-base, spectral and chromatographic characteristics of 4,5-dymethoxy-N-(2'-carboxyphenyl)anthranilic acids

| Com- pound | R | pKa(1) | pKa(2) | NMR-spectra, chemical shifts (pph) | | | | IR-spectra, absorption maxima, cm ⁻¹ | | | | | | R _f ¹ |
|---------------|-----------------------|-----------|-----------|------------------------------------|---------------|--------------------------|-----------------|---|------------------|-------------------|-----------------|----------------------------------|-------------------|-----------------------------|
| | | | | COOH (1H, s.) | NH (1H, w.s.) | OCH ₃ | ArH | V _{NH} | V _{C=O} | V _{C-Ph} | δ _{NH} | v $\frac{ds}{s}$ NO ₂ | V _{C-NH} | |
| 5a | H | 6.37±0.02 | 6.95±0.03 | 12.95 | 10.65 | 3.71 (6H,s) | 6.80-7.99(6H,m) | 3350 | 1659 | 1597 | 1575 | - | 1235 | 0.45 |
| 5b | 4'-Br | 5.74±0.02 | 6.72±0.02 | 13.01 | 10.70 | 3.65 (6H,s) | 6.88-7.90(5H,m) | 3356 | 1668 | 1613 | 1582 | - | 1213 | 0.40 |
| 5c | 5'-Cl | 6.14±0.01 | 6.74±0.03 | 12.93 | 10.72 | 3.75 (6H,s) | 6.69-7.80(5H,m) | 3362 | 1669 | 1613 | 1583 | - | 1234 | 0.43 |
| 5d | 6'-NO ₂ | 5.14±0.03 | 6.55±0.01 | 13.10 | 10.92 | 3.82 (6H,s) | 7.05-8.75(5H,m) | 3258 | 1675 | 1616 1589 | 1570 | 1523 1351 | 1206 | 0.46 |
| 5e | 4',6'-Br | 3.75±0.01 | 5.76±0.02 | 12.98 | 8.05 | 3.72(3H,s) 3.60(3H,s) | 6.50-7.33(4H,m) | 3348 | 1665 | 1602 | 1576 | - | 1230 | 0.35 |
| 5f | 4',6'-NO ₂ | 3.2±0.03 | 5.83±0.01 | 12.90 | 10.80 | 3.80 (6H,s) | 6.72-7.55(4H,m) | 3332 | 1709 1672 | 1614 | 1591 | 1523 1350 | 1211 | 0.38 |

Note. ¹R_f values are given in the solvent system of ethanol-hexane (1:2.5)

Table 3

The proton chemical shift value of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids



| Compound | R | The chemical shifts (pph) | | | |
|----------|-----------------------|---------------------------|--------------|----------------------------------|-----------------|
| | | COOH (1H, s) | NH (1H, w.s) | (OCH ₃) ₂ | ArH |
| 5a | H | 12.95 | 10.65 | 3.71 (6H,s) | 6.80-7.85(6H,m) |
| 5b | 4'-Br | 12.93 | 10.72 | 3.75 (6H,c) | 6.69-7.80(5H,m) |
| 5c | 5'-Cl | 12.90 | 10.80 | 3.80 (6H,s) | 6.72-7.55(4H,m) |
| 5d | 6'-NO ₂ | 13.01 | 10.70 | 3.65 (6H,s) | 6.88-7.90(5H,m) |
| 5e | 4',6'-Br | 12.98 | 8.05 | 3.72(3H,s) 3.60(3H,s) | 6.50-7.30(5H,m) |
| 5f | 4',6'-NO ₂ | 13.20 | 11.18 | 3.80 (6H,s) | 7.10-8.70(5H,m) |

tration of pKa only. However, O.M.Svechnikova has proven that these data do not differ practically from thermodynamic pKa [20]. The results obtained are presented in Table 2.

It has been found while pre-studying the titration curves of compounds (1 a-f) obtained by the electrometric method that N-phenylantranilic acids under research are dibasic subacids, ΔpK_a ($pK_a(II) - pK_a(I)$) less than 4. It allowed to use the Noies's method [21] to calculate pKa.

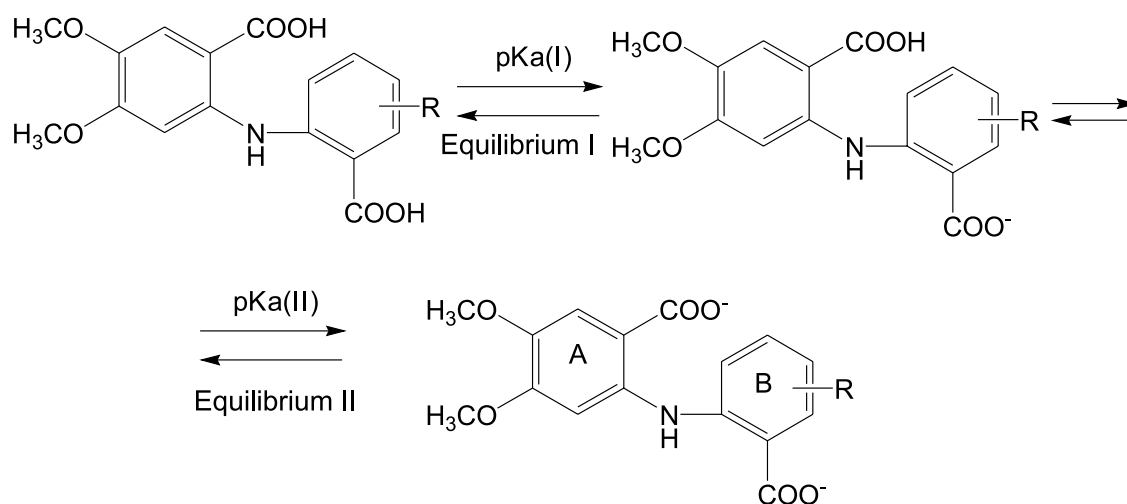
Analysis of the structure of compounds of the isostructural series has demonstrated that dissociation of 2'-carboxyphenylic radical is stronger comparing with the ionogenic carboxyl group of the anthranilic fragment of the molecule (A) due to the presence of strong acceptor substitutes (NO₂, Cl, Br) in the ring (B), and two donor methoxy groups in the ring (A).

The data presented in Table 2 testify that the nature and position of substitutes have influence upon the acid-base balance of both 4,5-dimethoxy-N-(2'-

carboxyphenyl)anthranilic acids. Introduction of electron-acceptor substitutes strengthens dissociation of acids due to the greater anion stabilization. Electron donor substitutes cause an opposite effect. However, the reactive centres sensitivity to the influence of substitutes differs greatly. For balance (I) $-pK_a(6) = 1.23$, and for balance (II) $-pK_a(1) - pK_a(6) = 0.40$, i.e. the carboxyl group sensitivity in the ring (B) of 4,5-dimethoxy-N-(2'-carboxyphenyl) anthranilic acids molecules to the influence of substitutes is much greater than sensitivity of the same ionogenic group in the anthranilic fragment (A).

The quantitative assessment of the influence of substitutes in the nonanthranilic fragment of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids (5a-f) molecule has been carried out in the range of the principle of linear free energy (LFE) by the Gamete equation (Fig.).

The pKa indices of all compounds studied were used for correlation because schemes of $pK_a(I) - f(\sigma)$,



Scheme 2

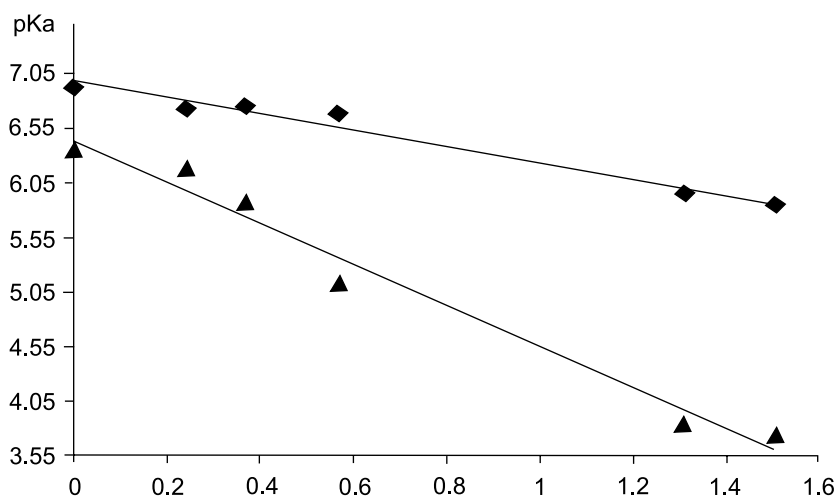


Fig. Dependence of $pK_a(I) - f(\sigma)$, $pK_a(II) - f(\sigma)$ for 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids in the binary solvent of dioxane-water (60% vol. dioxane) at 25°C.

$pK_a(II) - f(\sigma)$ dependence testify their closeness to linearity.

The equations I and II obtained have statistically significant parameters:

$$\begin{array}{l} \text{Balance I} \\ pK_a(I) = (6.43 \pm 0.06) - (1.78 \pm 0.06)\sigma \quad (1) \\ n=6 \quad \quad \quad s=0.182 \quad \quad \quad r=0.997 \end{array}$$

$$\begin{array}{l} \text{Balance II} \\ pK_a(II) = (6.98 - 0.05) - (0.78 - 0.05)\sigma \quad (2) \\ n=6 \quad \quad \quad s=0.154 \quad \quad \quad r=0.991 \end{array}$$

Comparison of the reaction constants $\rho_I=1.78$ and $\rho_{II}=0.78$ shows that sensitivity of the reactive centre I (carboxyl group in the ring B) is 2.3 times higher than sensitivity of the reactive centre II (carboxyl group in the ring A). Probably, it is connected with the different distance between carboxyl groups and substitutes in the ring B. It should be noted that appearance of another reactive centre does not practically influence upon sensitivity (within the limits of experimental error ρ_{II} corresponds to ρ from the other isostructural series of N-phenylanthranilic acids) [12, 13, 18-20]. For balance I sensitivity of the reactive centre is sufficiently high because of closeness of substitutes.

It has been found that the substances synthesized have the anti-inflammatory, analgesic, diuretic, bacteriostatic and fungistatic activity. According to the classification by K.K. Sydorov the substances synthesized when introducing intragastrically belong to low-toxic compounds ($DL_{50} > 3000$ mg/kg).

Experimental Part

Melting points ($^{\circ}C$) were measured with the Koeffler's point apparatus and were not corrected. IR-spectra were recorded by the FT-IR Bruker Tensor 27 spectrometer in KBr. 1H NMR-spectra were recorded by the Varion Mercury 200 (200 Mhz) spectrometer in

$DMSO-d_6$ using TMS as an internal standard (chemical shifts are reported in ppm).

The derivatives of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acid were synthesized by a modified Ullmann reaction [1, 3]. The compounds obtained were recrystallized three times from ethanol and dried to $105^{\circ}C$ up to the constant weight. The purity of the compounds was checked by thin-layer chromatography.

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

For preparing mixed solutions a fresh boiled bi-distillate liberated from CO_2 was used [21].

The methods of measurements were similar to those described in [21]. 0.05 M aqueous solution of KOH purified from CO_2 served as a titration agent. The concentration of titration solutions was 0.005 mol/l. Potentiometric titration was conducted at $25^{\circ}C$ on an EV-74 ionometer using a glass electrode ESP-43-074 and a silver chloride electrode EVL-1 M. The pK_a of acetic acid in the binary solvent of dioxane-water solution (60 vol% of dioxane) was determined as a standard (pK_a exp. = 7.50; 5.52; 7.49).

The pK_a measurements were conducted for each compound independently. The accuracy of the results obtained was estimated by the methods of mathematical statistics (with the reliability level of 0.95) [22].

Conclusions

1. The preparative methods for synthesis of 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids in the solid phase and in the aqueous medium with the use of a phase transfer catalyst – sodium oleate have been developed.

2. Reactivity of 4,5-dimethoxy-N-(2'-carboxyphenyl) anthranilic acids (6 compounds) has been investigated by studying the acid-base balance of these compounds in the binary solvent of dioxane-water.

3. It has been found that 4,5-dimethoxy-N-(2'-carboxyphenyl) anthranilic acids are dibasic subacids,

which strength depends upon the nature and position of substituents.

4. The quantitative assessment of the influence of substituents on two reactive centres of the acids synthesized has been carried out by the method of correlation analysis according to the Gamete equation.

5. It has been proven that sensitivity of the reactive centres substantially differs and depends on the

distance of the substituents. Herewith, appearance of another reactive centre does not practically influence on sensitivity of the first centre.

6. The correlation equations $pK_{a(i,ii)} - f(\sigma)$ obtained for 4,5-dimethoxy-N-(2'-carboxyphenyl)anthranilic acids allow to predict acid-base properties of the other compounds of this isostructural series and to use them for QSAR-analysis.

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