PECULIARITIES OF THE CHEMICAL PROPERTIES OF VICINALLY DISUBSTITUTED VERATROLE AND SYNTHESIS OF 1-METHYL-4,5-DIMETHOXYBENZIMIDAZOLE DERIVATIVES

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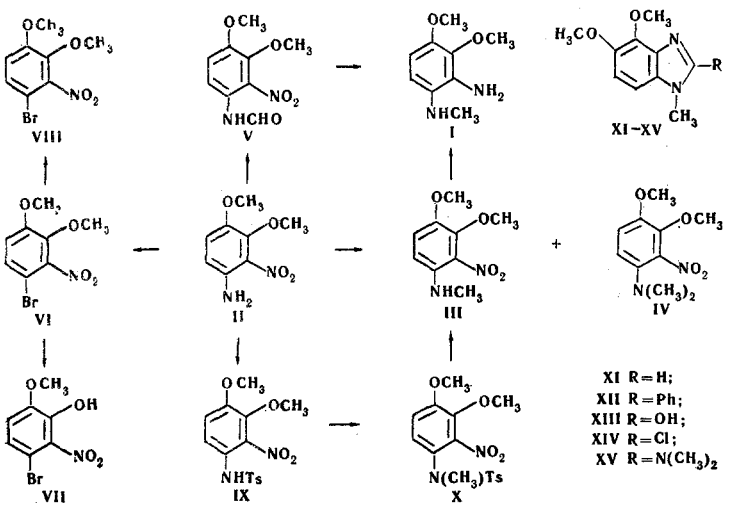
Various paths for the synthesis of 4-methylamino-3-aminoveratrole (I) from 4-amino-3-nitroveratrole (II) were investigated, and it was found that I can be obtained in a high overall yield of 65% through the tosyl derivative of II. 1-Methyl-4,5-dimethoxybenzimidazolone, 1-methyl-4,5-dimethoxybenzimidazole and its 2-phenyl-, 2-chloro-, and 2-dimethylamino derivatives were synthesized on the basis of I in order to investigate their biological activity. It was established that the chemical properties of vicinally disubstituted veratrole, particularly the increased basicity of II, are determined to a significant degree by steric strains caused by bulky substituents. It is shown that 85% formic acid can be successfully used in place of 98-100% formic acid for the N-formylation of aromatic amines with a mixture of formic acid and acetic anhydride.

Investigation of the biological activity of the previously synthesized dimethoxy derivatives of benzimidazole [1] has shown that several of them, particularly 1-methyl-6,7-dimethoxybenzimidazole and its 2-dimethylamino derivative, are capable of stimulating the resistance of an organism to infectious diseases [2]. In this connection we undertook the synthesis of the previously unknown number of 1-methyl-4,5-dimethoxybenzimidazole derivatives. The previously undescribed 4-methylamino-3-aminoveratrole (I) can serve as the key compound for this synthesis. I could be obtained by using 4-amino-3-nitroveratrole (II) as the starting compound [3-5].



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Several paths can be used to accomplish the transformation II → I. The simplest of these is the direct methylation of II. Thus unsubstituted o-nitroaniline is quite selectively methylated by methyl iodide [6,7], methanol [8], and, as shown by our experiments, by dimethyl sulfate to the N-methyl derivative. However, thin-layer chromatography (TLC) on aluminum oxide demonstrated that secondary (III) and tertiary (IV) amines are formed in approximately equal amounts during methylation of II with methyl iodide, dimethyl sulfate, and methyl tosylate. Their preparative separation is associated with large losses. Consequently, considering the laboriousness involved in obtaining II (from vanillin) [3-5], this method should be considered to be unsuitable for the synthesis of I.

A method based on reduction of the N-formyl derivative of II (V) seemed of equal attractiveness. It is well known that the formylamino group can be readily reduced with lithium aluminum hydride to the methylamino group [9]. The nitro group can be simultaneously reduced in the process to NH_2 [10]. Formylation of II occurs even on refluxing II with 85% formic acid, but the yield of V did not exceed 60%. One generally uses either 98-100% formic acid or a mixture of it with acetic anhydride [11] to raise the yield during N-formylation. It turned out that V can be obtained in high yield (approximately 90%) on treatment of II with a mixture of 85% formic acid with acetic anhydride taken in 10% excess with respect to the quantity required for reaction with the water contained in the formic acid and evolved during acylation. The formation of an acetyl derivative of II was detected by TLC only for large excesses of acetic anhydride. The use of a mixture of 85% formic acid with acetic anhydride is apparently expedient for the N-formylation of other amines.* Compound V was reduced with lithium aluminum hydride in ether to give a low yield of diamine I which was readily oxidized in air.

An attempt was subsequently made to obtain III by the action of methylamine on 4-bromo-3-nitroveratrole (VI) synthesized by the Sandmeyer reaction from II [13]. However, it turned out that the methoxy group in the ortho position with respect to the nitro group is primarily replaced rather than the bromine atom. In the process, nitrophenol VII (the structure was demonstrated by conversion to VI on methylation with dimethyl sulfate) with insignificant contamination by 4-bromo-3-nitro-2-methylaminoanisole (VIII) is primarily formed in the aqueous alcohol solution. The unusual behavior of VI is undoubtedly due to weakening of the bond of the methoxy group with the aromatic ring because of steric hindrance created by the adjacent substitutents, since the bromine atom is smoothly replaced in the isomeric 4-nitro-3-bromoveratrole under the same conditions [3].

We succeeded in obtaining III only by using methylation of the tosyl derivative of II (X) (variant II IX → X → III → I). In the process, it was observed that a whole series of side reactions occur along with the major reactions during tosylation of II and detosylation of X under the conditions used for o-nitroaniline [14] and 2-nitro-p-anisidine [15] (heating with toluene sulfonyl chloride in pyridine and hydrolysis by heating in concentrated sulfuric acid). We therefore attempted to accomplish these reactions under milder conditions. In fact, by monitoring the course of the reaction by TLC, we found that II is almost quantitatively tosylated in pyridine in room temperature in 15 min, while saponification of X (also at room temperature) gives 95% of III in 1.5 h. It is interesting to note that tosylation of o-nitroaniline under these conditions does not go to one-half of its extent in 24 h, while more than 12 h is necessary for the complete saponification of the tosylate of o-nitroaniline (as monitored by TLC).

These results attest to the appreciably greater nucleophilicity of the amino group of 4-amino-3-nitroveratrole (II) as compared with o-nitroaniline. It might be assumed that the basicity of II is also appreciably higher than the basicity of o-nitroaniline. In fact, a pK_a value of 1.4 ± 0.1 was found for II in aqueous medium by spectrophotometry; this exceeds the pK_a value of o-nitroaniline [16] by a factor of 1.7 (Fig. 1). Simple calculation by the Hammett equation indicates that such a high pK_a value for II cannot be due only to the donor effect of the methoxy group in the para position with respect to the amino group. Thus, the calculated pK_a for the isomeric 5-amino-4-nitroveratrole is about −0.1.† The basicity of the amino group in II is apparently elevated due to deflection of the nitro and 2-methoxy groups from the plane of the molecule. Thus, the chemical properties of the vicinally disubstituted veratroles are determined to a significant extent by steric strains due to the large bulk of the substituents.

*In our laboratory this modification of the method was successfully used for the N-formylation of 5-aminolepidine for a somewhat large excess of acetic anhydride (the amount of acetic anhydride was also selected during a determination of the reaction products by TLC on Al_2O_3 [12]).

† The pK_a of 4-methoxy-2-nitroaniline is 0.77 [17]; the pK_a^0 and ρ values of the reaction series for ionization of 4- and 5-substituted 2-nitroanilines were used in the calculations [17, 18].

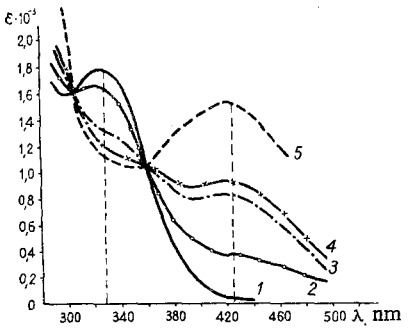

Fig. 1. UV spectra of 3-nitro-4-aminoveratrole (II) in aqueous solutions of various acidity: 1) H_0 0.09; −3.3; 2) pH 1.03; 3) pH 1.43; 4) pH 1.65; 5) pH 2.87; 4.25.

The 3-nitro-4-methylaminoveratrole (III) obtained by the tosylate method was reduced with hydrogen in the presence of Raney nickel. To avoid oxidation of I its alcohol solution was filtered from the catalyst in a carbon dioxide atmosphere, and the base was immediately converted to the dihydrochloride, which is completely stable in the crystalline state. The dihydrochloride of I was used to obtain 1-methyl-4,5-dimethoxybenzimidazole (XI) (by refluxing with formic acid), its 2-phenyl derivative (XII) (via the method in [19]), and 1-methyl-4,5-dimethoxybenzimidazolone (XIII) (by fusing with urea). The latter was converted to the 2-chloroderivative (XIV) by the action of phosphorus oxychloride; the action of dimethylamine in benzene on XIV yielded 1-methyl-2-dimethylamino-4,5-dimethoxybenzimidazole (XV).

EXPERIMENTAL

3-Nitro-4-aminoveratrole (II) [3]. o-Nitroveratriamide [3] [101 g (0.45 mole)], triturated with a small amount of water, was added to 325 g (8.1 mole) of NaOH in 1800 ml of water. The mixture was cooled to 0°, and 1 kg of crushed ice and 28 ml (0.53 mole) of bromide were added with vigorous stirring below the liquid surface, thereby maintaining a temperature no higher than 0°. The mixture was stirred for 20 min at 0°, heated to 50°, the orange-red solution was filtered, and the filtrate was heated to 90-95° In the process II separated in the form of a red oil. This was cooled to 5° and the resulting red crystals of II were filtered to give 73 g (82%) of II with mp 67-69°; after one crystallization from 50% alcohol (1:20) the product had mp 71-73° (74° [3]). R_f 0.21 (chloroform), 0.6 (ether).*

3-Nitro-4-formylaminoveratrole (V). Acetic anhydride [13.5 ml (0.13 mole)] was added with stirring to 12.5 ml (0.25 mole) of 85% formic acid and after 10 min 0.5 g (0.0025 mole) of II was added at room temperature, and the mixture was stirred for 40 min. The mixture was then evaporated in vacuo to dryness, 2 ml of water was added, and the mixture was neutralized with sodium carbonate to pH 4-5. The precipitate was filtered and washed with water to give 0.5 g (88%) of V with mp 107-109°. To purify V it was dissolved in boiling water (1:100), the solution was treated with charcoal, and the filtrate was evaporated to 20 ml. After cooling, V precipitated in the form of slightly yellowish crystals with mp 111-113° which were readily soluble in alcohol, acetone, chloroform, and benzene and insoluble in petroleum ether. R_f 0.7 (chloroform−acetone, 3:1). Found %: N 12.0. $C_9H_{10}N_2O_5$. Calculated %: N 12.3.

4-Bromo-3-nitroveratrole (VI). Compound II [7 g (0.035 mole)] was dissolved with heating in a mixture of 6 ml of concentrated H_2SO_4 with 40 ml of water. The solution was cooled and a solution of 2.8 g (0.04 mole) of $NaNO_2$ in 5 ml of water was added gradually with vigorous stirring at 0-5°. The reaction was complete in 2 h (the sulfate of II dissolved completely). The solution of diazonium salt was filtered with charcoal and slowly added to a boiling solution of 1.5 g (0.01 mole) of cuprous bromide in 40 ml of 22% HBr. The mixture was refluxed for 30 min, and the side reaction nitrophenol formed was removed by distillation with steam; the hot residue was extracted with ether, washed once with 4% NaOH and water, dried with magnesium sulfate, and the ether was removed to give 7 g (76%) of VI with mp 43-45° (46-47° [13]), R_f 0.3 (benzene−hexane, 1:3).

3-Nitro-4-acetamidoveratrole. A mixture of 0.2 g of II and 3 ml of acetic anhydride was refluxed for 1 h and then poured into 5 ml of cold water. The mixture was partially neutralized by addition of sodium carbonate, and 0.2 g of colorless crystals were filtered. They were purified by crystallization from water (1:10, dissolved slowly) and had mp 102-104°. The compound was soluble in acetone, ether, chloroform, and insoluble in CCl_4. R_f 0.83 (acetone−chloroform, 3:1). Found %: N 11.8. $C_{10}H_{12}N_2O_5$. Calculated %: N 11.7.

*Here and elsewhere the R_f values presented were obtained by thin-layer chromatography in a thin layer of Al_2O_3 of activity II.

Reaction of VI with an Aqueous Alcoholic Solution of Methylamine. A mixture of 4 g (15.3 mmole) of VI, 8 ml of 25% aqueous methylamine (57.6 mmole), and 8 ml of alcohol was heated in a sealed tube for 2.5 h at 125-130°. After cooling, 2.2 g of brownish-orange crystals was filtered from the dark red solution. Neither the mother liquor nor the precipitate contained 3-nitro-4-methylaminoveratrole (III); only a small, contaminating amount of some nitroaniline, apparently 3-nitro-4-bromo-2-methylaminoanisole (R_f ~ 0.8 in chloroform), was observed. After evaporation of the mother liquor and dilution with water 0.9 g of a greasy dark precipitate was obtained. Both precipitates were dissolved in 60 ml of 6% NaOH, the solutions were washed with two 10 ml portions of chloroform, treated with charcoal, and acidified with concentrated HCl to pH 1 to give 1.6 g (50%) of 4-bromo-3-nitro-2-hydroxyanisole (VII) with mp 105-107°. Recrystallization from 15-20 ml of 50% alcohol with activated charcoal yielded 1.3 g of VII with mp 108-109° in the form of yellow plates which are readily soluble in alcohol, somewhat less soluble in chloroform and acetone, slightly soluble in cold water, and insoluble in hexane. On chromatography with the usual organic solvents the sample remained at the point of application, but had an R_f value of about 0.35 in chloroform during chromatography on a gypsum-fixed layer of Al_2O_3 prepared from a suspension of gypsum with Al_2O_3 in 50% acetic acid dried at 70°.* Found %: N 5.7; Br 32.4. $C_7H_6BrNO_4$. Calculated %: N 5.6; Br 32.3. Methylation of VII in alkaline solution with dimethyl sulfate yielded starting VI, which was identified from the melting point and R_f value.

3-Nitro-4-tosylaminoveratrole (IX). A solution of 50 g (0.26 mole) of p-toluenesulfonyl chloride in 100 ml of pyridine was added to a solution of 25 g (0.125 mole) of II in 125 ml of anhydrous pyridine. The reaction mass heated spontaneously to 40°. It was allowed to stand for 15 min, after which 150 ml of pyridine was removed by distillation, and the residue was poured into 500 ml of water. A yellow oil separated which crystallized on trituration. The precipitate was filtered and washed with water to give 44 g (98%) of IX with mp 133-134°. Crystallization from 70% alcohol (1 : 15) and CCl_4 (1 : 50) gave IX with mp 134-135°. Compound IX was soluble in acetone, ether, benzene, and chloroform, insoluble in petroleum ether and water, but dissolved on heating in 10% NaOH (1 : 10) to give a red solution. R_f 0.3 (alcohol). Found %: N 8.2; S 9.3. $C_{15}H_{16}N_2O_6S$. Calculated %: N 8.0; S 9.1.

3-Nitro-4-tosylmethylaminoveratrole (X). A reddish-brown suspension of 47 g (0.13 mole) of IX in 33 ml of 4 N NaOH was heated to 70-80°, and 20 ml (0.21 mole) of dimethyl sulfate was added dropwise to it. In the process a colorless precipitate of X formed, and the solution turned yellow. The precipitate was filtered, washed with water, and dried at 100° to give 42 g (85%) of X with mp 154-155°. Two crystallizations from alcohol (1 : 30, dissolved slowly) and CCl_4 (1 : 70) gave X with mp 157-159°. Compound X was soluble in acetone, ether, chloroform, and benzene, and insoluble in water, alkalis, and petroleum ether. R_f 0.96 (alcohol), 0.83 (ether), 0.26 (chloroform). Found %: N 7.6; S 9.0. $C_{16}H_{18}N_2O_6S$. Calculated %: N 7.6; S 8.8.

3-Nitro-4-methylaminoveratrole (III). Compound X [40 g (0.11 mole)] was added in small portions to 112 ml (2 mole) of H_2SO_4 (sp. gr. 1.84), and the dark-brown solution obtained was allowed to stand at room temperature for 1.5 h. It was then poured into 2 liters of water, the mixture was made alkaline with ammonia to pH 8-9, and the dark-red crystals that precipitated were filtered and washed with water to give 22.6 g (97%) of III with mp 55-56°. This was purified by dissolving in 400 ml of ether and passing the solution through a column (20 cm long and 6 cm in diameter) filled with Al_2O_3. After removal of the ether, 20.4 g (88%) of III with mp 59-61° was obtained. Two crystallizations from 50% alcohol (1 : 20) gave III with mp 59-61°. Compound III is readily soluble in acetone, ether, chloroform, and benzene, and slightly soluble in water. R_f 0.5 (chloroform), 0.9 (ether), 0.6 (chloroform–ether, 3 : 1; in the same system the 4-dimethylamino derivative formed simultaneously with III by direct methylation of II has R_f 0.7). Found %: N 13.0; C 50.9; H 5.9. $C_9H_{12}N_2O_4$. Calculated %: N 13.2; C 50.9; H 5.7.

3-Amino-4-methylaminoveratrole Dihydrochloride (I). A solution of 20 g (0.1 mole) of III in 150 ml of alcohol was reduced with hydrogen in the presence of 10 g of an alcoholic paste of W-4 Raney nickel at 50-60° at atmospheric pressure. The calculated amount of hydrogen was absorbed in 1.5 h. The colorless solution was filtered under CO_2 from the nickel into 50 ml of 40% HCl in alcohol. The slightly colored solution was evaporated in vacuo to 50 ml, cooled, and the resulting almost colorless crystals of I were filtered and washed with three 10-ml portions of acetone to give 17 g (70%) of I with mp 153-156° (decomp.). The filtrate was evaporated in vacuo to dryness to give an additional 4.65 g of I which was used for condensation

*The isomeric 4-nitro-3-bromo-2-hydroxyanisole has R_f 0.66 under these conditions.

with urea. Additional purification of I is complicated because of its ready oxidizability, particularly in solution. I is readily soluble in water and moderately soluble in alcohol. Found %: N 11.3; Cl 27.4. $C_9H_{14}N_2O_2 \cdot 2HCl$. Calculated %: N 11.0; Cl 27.8.

1-Methyl-4,5-dimethoxybenzimidazolone (XIII). A mixture of 5 g (0.02 mole) of I and 5 g (0.08 mole) of urea was fused at 140-150° for 3 h. The melt was dissolved in 70 ml of boiling water and treated with charcoal. Cooling of the solution yielded long, slightly yellow needles of XIII [2.4 g (59%) with mp 171-174°]. Two crystallizations from water (1 : 20) and one from CCl_4 (1 : 100) yielded a product with mp 174-175°. Compound XIII is insoluble in petroleum ether, soluble in acetone, chloroform, and benzene, and is crystallized from alcohol. Found %: N 13.3. $C_{10}H_{12}N_2O_3$. Calculated %: N 13.5.

1-Methyl-4,5-dimethoxybenzimidazole Hydrochloride (XI). Compound I [4 g (0.016 mole)] was refluxed with 27 ml (0.7 mole) of 94% formic acid for 3 h. The mixture was then evaporated to dryness in vacuo and the crystalline residue was washed with three 5 ml portions of acetone to give 3.1 g (87%) of colorless crystals of XI with mp 182-184° (decomp.). Compound XI was purified by dissolving with heating in chloroform (1 : 10), treatment of the solution with charcoal, and precipitation with petroleum ether to give a product with mp 183-184.5°. Compound XI is soluble in water and alcohol and insoluble in acetone and benzene. Found %: N 12.0; Cl 15.1. $C_{10}H_{12}N_2O_2 \cdot HCl$. Calculated %: N 12.2; Cl 15.5.

Neutralization of an aqueous solution of XI and subsequent extraction with ether or chloroform yielded base XI in the form of colorless, uncrystallized oil, readily soluble in the usual organic solvents. The R_f value of base XI did not differ from the R_f value of the isomeric 1-methyl-6,7-dimethoxybenzimidazole: 0.2 (chloroform); 0.3 (chloroform—acetone, 10 : 1), 0.8 (acetone); dark spots in UV light.

1-Methyl-2-phenyl-4,5-dimethoxybenzimidazole (XII). A solution of 4 g (0.016 mole) of I in 20 ml of water and 1.6 ml (0.016 mole) of benzaldehyde in 6 ml of alcohol were added to a solution of 6.4 g (0.035 mole) of cupric acetate in 95 ml of water, and the mixture was stirred for 30 min at room temperature and 30 min on a boiling water bath. The precipitated copper complex was filtered, washed with water, dissolved in 100 ml of hot 7% HCl, and H_2S was passed through the solution at 70-80° until precipitation of copper was complete. The copper sulfide was filtered, and the filtrate was evaporated to dryness to give 3.6 g (75%) of the hydrochloride of XII, which is soluble in water and chloroform and insoluble in acetone and benzene; it was crystallized from alcohol (1 : 4). Neutralization of the aqueous solution of the hydrochloride of XII with ammonia yielded base XII with mp 106-109°. Two crystallizations from 30% alcohol (1 : 30) gave XII with mp 109-110.5°, which is soluble in acetone, ether, chloroform, and benzene, and insoluble in water and petroleum ether. R_f 0.9 (acetone, blue luminescence in UV light); 0.7 (ether); 0.14 (chloroform). Found %: N 10.6. $C_{16}H_{16}N_2O_2$. Calculated %: N 10.4.

1-Methyl-2-chloro-4,5-dimethoxybenzimidazole (XIV). A mixture of 4 g (0.019 mole) of XIII and 25 ml (0.28 mole) of $POCl_3$ was heated in a sealed tube at 132-134° for 3 h. The excess $POCl_3$ was removed in vacuo, and the crystalline residue was dissolved in 24 ml of water with cooling by ice and neutralized with ammonia to pH 8-9. The resulting oil crystallized readily during trituration to give 4 g (92%) of XIV with mp 54-56°. Compound XIV was purified by dissolving in CCl_4 (1 : 10), treatment of the solution with charcoal, addition of n-heptane (1 : 30) to the filtrate, and removal of CCl_4 in vacuo. Compound XIV was isolated in the form of colorless needles with mp 61-63°. Compound XIV was slightly soluble in water and petroleum ether and readily soluble in the other organic solvents. R_f 0.9 (acetone, dark spot in UV light), 0.8 (ether), 0.25 (chloroform). Traces of the starting XIII in XIV could be readily detected on a chromatogram from the presence of a less mobile spot (blue luminescence). Found %: N 12.5. $C_{10}H_{11}ClN_2O_2$. Calculated %: N 12.4.

1-Methyl-2-dimethylamino-4,5-dimethoxybenzimidazole Hydrochloride (XV). Compound XIV [2 g (8.8 mmole)] was heated in a sealed tube with 12 ml of a 4 N benzene solution of dimethylamine at 154-156° for 12 h. After cooling, the benzene solution of base XV was separated from the dimethylamine hydrochloride and evaporated in vacuo. The oily residue did not crystallize; it was insoluble in water and petroleum ether but readily soluble in alcohol, acetone, and chloroform; R_f 0.4 (ether, dark spot in UV light), 0.9 (acetone). Base XV was purified by dissolving in acetone and filtering the solution through a layer of aluminum oxide (2 cm in diameter and 4 cm long). The slightly colored solution was evaporated to dryness, 15 ml of benzene was added and the solution was saturated with dry HCl to give 1.7 g (70%) of XV in the form of colorless crystals with mp 98-100°; two crystallizations from acetone (1 : 20) gave a product with mp 99-101°. Found %: N 15.3; Cl 12.9. $C_{12}H_{17}N_3O_2 \cdot HCl$. Calculated %: N 15.5; Cl 13.1.

The electronic absorption spectra were obtained with an SF-4 spectrophotometer. The pK_a of 3-nitro-4-aminoveratrole (II) was determined from the absorption spectra of solutions of II in H_2SO_4 solutions with H_0 of −3.6 and 0.09 and in citrate buffer solutions with pH 1.03, 1.43, 1.65, 2.87, and 4.25. The pK_a was calculated for two wavelengths (325 and 422 nm) from the formula

$$pK_a = pH \pm \lg \frac{\varepsilon_1 - \varepsilon}{\varepsilon - \varepsilon_2}.$$

The results are presented below:

λ, nm	325			422		
pH	1,03	1,43	1,65	1,03	1,43	1,65
pK_a	1,53	1,33	1,38	1,54	1,39	1,48

$pK_{a\,av} = 1{,}4 \pm 0{,}1.$

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