pH did not exceed eight. It was then maintained at 45-50°C for 5-7 h, after which it was cooled and diluted with water, and the resulting crystals were separated, dried, and recrystallized from methanol (Vd, i, j), absolute ethanol (Vb, f, g, h, *l*), and ethanol–hexane (1:3) (Va, c, e, k).

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TETRAZOLES.

11.* ACIDITIES OF TETRAZOLYLACETIC ACIDS

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The acidities of two series of substituted 1- and 2-tetrazolylacetic acids, as well as some 1- and 2-substituted 5-tetrazolylacetic acids, in water and 50% ethanol were investigated. All of the investigated compounds are stronger acids than acetic acid and are comparable to haloacetic acids. The induction constants (σ_I) of the 1-, 2-, and 5-tetrazolyl groups (0.65, 0.62, and 0.41, respectively) were calculated from data on the acidities of tetrazolylacetic acids.

Tetrazolylacetic acids are used to obtain new semisynthetic antibiotics [2], growth regulators, and chemical agents for the protection of plants [3, 4], whereas very little information regarding the reactivities and acid-base properties of these compounds is available. In this connection we studied the acidities of a series of tetrazolylacetic acids and calculated the induction constants (σ_I) of the tetrazolyl group.

A σ_I value of 0.57 was previously found for the 1-tetrazolyl group from data on the basicities of m- and p-(1-tetrazolyl)dimethylanilines [5]. However, the calculation of the σ_I substituent induction constants by estimating the reactivities of aromatic compounds entails a number of assumptions [6, 7]. The method for the determination of the σ_I substituent induction constants in which aliphatic carboxylic acids of the XCH_2COOH type, for which the dependence $\sigma_I = -0.251\ pK_a + 1.186$ (1) with correlation coefficient 0.99 is observed for a large number of substituents, is more valid [8].

In conformity with this the σ_I induction constants of the tetrazolyl group can be calculated from the pK_a values of isomeric tetrazolylacetic acids. For this, we studied the acidities of 1-, 2-, and 5-tetrazolylacetic acids in water and calculated the σ_I constants by means of Eq. (1) (Table 1). It is apparent that the σ_I values for the 1-tetrazolyl group found by various methods agree satisfactorily. The dissociation constants of 1- and 2-tetrazolylacetic acids differ only slightly, whereas 5-tetrazolylacetic acid is weaker; this once again confirms the data in [9] regarding the weak aromatic character of the tetrazole ring.

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*See [1] for communication 10.

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TABLE 1. pK_a Values of Tetrazolylacetic Acids (TCH_2COOH) in Water and σ_I Values of the Tetrazolyl Group

T	pK_a	σ_I
1-Tetrazolyl	2,27	0,65; 0,57 [5]
2-Tetrazolyl	2,12	0,62
5(1H)-Tetrazolyl	3,10*	0,41

*The pK_a value for ionization of the N–H bond is 5.32.

TABLE 2. Dissociation Constants of Substituted Tetrazolylacetic Acids in Water and 50% Ethanol at 25°C

R	pK_a	R	pK_a
(5-R-1-Tetrazolyl)acetic acids			
NH_2	2,38*	p-ClC_6H_4	3,10
CH_3	2,16*	m-ClC_6H_4	3,13
C_6H_5	2,11*; 3,16	m-BrC_6H_4	3,14
p-$CH_3C_6H_4$	3,23	m-$NO_2C_6H_4$	3,05
m-$CH_3C_6H_4$	3,22		
(5-R-2-Tetrazolyl)acetic acids			
NH_2	2,60*[10]	p-ClC_6H_4	3,31
CH_3	2,23*	m-ClC_6H_4	3,25
C_6H_5	3,31	m-BrC_6H_4	3,22
p-$CH_3C_6H_4$	3,29	m-$NO_2C_6H_4$	3,28
m-$CH_3C_6H_4$	3,30		
(X-R-5-Tetrazolyl)acetic acids			
1-CH_3	2,83*	2-CH_3	3,44*
1-C_2H_5	2,85*	2-C_2H_5	3,45*

*In water.

In this connection it was of interest to trace the effect of substituents of various natures and their position in the ring on the acidities of isomeric tetrazolylacetic acids. Such data are known only for 5-amino-1-tetrazolylacetic acid, as well as 5-amino- and 5-trifluoromethyl-2-tetrazolylacetic acids [10]. For the examination we selected two series of substituted 1- and 2-tetrazolylacetic acids and some 1- and 2-substituted 5-tetrazolylacetic acids. The dissociation constants were determined by potentiometric titration in water or (when the compounds were not soluble enough) in 50% ethanol (Table 2). We first demonstrated that the pK_a values of tetrazolylacetic acids depend linearly on $1/\varepsilon$ on passing from water to 50% ethanol (Fig. 1).

We found that all of the investigated compounds are stronger acids than acetic acid and are comparable to haloacetic acids. Regardless of the nature of the substituent and its position in the ring, the pK_a values of the tetrazolylacetic acids change within the limits of one order of magnitude. The weak effect of substituents on the acidities of 1- and 2-tetrazolylacetic acids is explained by the remoteness of the substituent from the reaction center, whereas in the case of substituted phenyl groups it is explained by the bridging effect of the phenyl ring [11]. At the same time, a decrease in the acidity is observed on passing from substituted 1- and 2-tetrazolylacetic acids to isomeric 5-tetrazolylacetic acids. These results are in good agreement with the data obtained for unsubstituted 1-, 2-, and 5-tetrazolylacetic acids (Table 1).

EXPERIMENTAL

The tetrazolylacetic acids were obtained by known methods. The characteristics of all of the compounds were in agreement with the literature data [10, 12, 13]. The previously undescribed substituted 5-phenyl-1- and 5-phenyl-2-tetrazolylacetic acids were synthesized by alkaline hydrolysis of the corresponding ethyl esters obtained by the methods in [10, 12] and were purified by repeated recrystallization from 50% ethanol. The structures and individual-

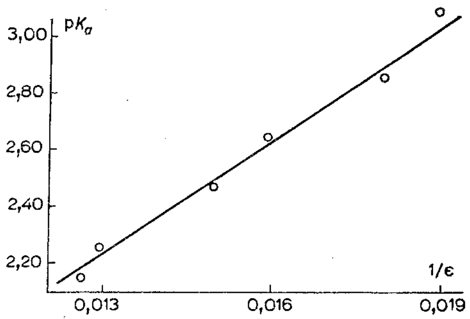

Fig. 1. Dependence of the pK_a of 5-phenyl-1-tetrazolylacetic acid on 1/ε in ethanol—water mixtures.

TABLE 3. (5-Aryltetrazolyl)acetic Acids

R	mp, °C	$\nu_{C=O}$, cm^{-1}	δ_{CH_2}, ppm	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
(5-R-Phenyl-1-tetrazolyl)acetic acids											
p-CH_3	174—175	1750	5,42	55,3	4,7	26,0	$C_{10}H_{10}N_4O_2$	55,0	4,6	25,7	68
m-CH_3	201—202	1750	5,55	55,3	4,4	26,0	$C_{10}H_{10}N_4O_2$	55,0	4,6	25,7	64
p-Br	207—209	1760	5,52	38,2	2,3	19,9	$C_9H_7BrN_4O_2$	38,2	2,5	19,8	72
p-Cl	206—207	1750	5,57	45,2	2,7	23,7	$C_9H_7ClN_4O_2$	45,3	2,9	23,5	74
m-Cl	183—184	1755	5,58	45,4	2,8	23,8	$C_9H_7ClN_4O_2$	45,3	2,9	23,5	62
m-NO_2	216—217	1760	5,55	43,5	3,0	28,4	$C_9H_7N_5O_4$	43,4	2,8	28,1	85
p-NO_2	217—218	1760	5,60	43,4	3,1	28,2	$C_9H_7N_5O_4$	43,4	2,8	28,1	84
(5-R-Phenyl-2-tetrazolyl)acetic acids											
p-CH_3O	167—168	1735	5,70	51,3	3,9	24,0	$C_{10}H_{10}N_4O_3$	51,3	4,3	23,9	58
p-CH_3	182—183	1730	5,70	55,3	4,7	25,6	$C_{10}H_{10}N_4O_2$	55,0	4,6	25,7	60
m-CH_3	176—177	1725	5,75	55,3	4,6	25,6	$C_{10}H_{10}N_4O_2$	55,0	4,6	25,7	64
p-Br	206—207	1730	5,72	38,3	2,5	19,6	$C_9H_7BrN_4O_2$	38,2	2,5	19,8	58
m-Cl	173—174	1725	5,70	45,4	3,0	23,7	$C_9H_7ClN_4O_2$	45,3	2,9	23,5	68
m-NO_2	175—176	1730	5,85	43,3	2,8	28,1	$C_9H_7N_5O_4$	43,4	2,8	28,1	54
p-NO_2	180—181	1735	5,85	43,4	2,7	28,2	$C_9H_7N_5O_4$	43,4	2,8	28,1	72

ity of the compounds obtained were confirmed by IR and NMR spectroscopy and the results of TLC and elementary analysis. Thin-layer chromatography was carried out on Silufol UV-254 plates at 20°C in an acetone—hexane system (1:2). The IR spectra were recorded with a Perkin-Elmer 457 spectrometer. The NMR spectra were recorded with a Perkin-Elmer R-12 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The data obtained are presented in Table 3.

The potentiometric measurements in water and 50% ethanol were made with a pH-121 pH meter with a thermostatted cell (at 25 ± 0.1°C). An ESL 63-07 glass electrode was used as the indicator electrode, and an ÉVL-1MZ silver chloride electrode was used as the reference electrode. The titrant was a 0.1 N solution of NaOH. The concentration of the investigated acid at the half-neutralization point was $\sim 10^{-2}$ mole/liter. The pK_a values of the tetrazolylacetic acids were calculated by the method in [14]. The average value of three to five measurements was taken as the pK_a value, and the reproducibility of the results was ±0.02 pH units.

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