

RESEARCH ON 6- AND 7-SUBSTITUTED 2-  
AND 4-THIOQUINOLOLONES. TRANSMISSION OF THE  
ELECTRONIC EFFECTS OF SUBSTITUENTS IN THE  
BENZENE RING OF THIOQUINOLOLONES TO THE REACTION  
CENTER

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The electronic effect of substituents on the acid-base properties of 6- and 7-substituted 2-thionolepidines and 4-thionoquininaldines were investigated. It is shown that the  $pK_a(-H^+)$  values for 6- and 7-substituted 2- and 4-thioquinolones and the  $pK_a(+H^+)$  values for 7-substituted 2-thionolepidines and 6-substituted 4-methylmercaptoquininaldines correlate with the  $\sigma_M$  substituent constants of Jaffe and Taft. The effect of a substituent is transmitted primarily via an inductive mechanism, regardless of its position.

Mesomerism of the thione  $\leftrightarrow$  zwitterion type is characteristic for 2- and 4-thioquinolones [1, 2]. In view of the intimate relationship between the prototropic properties and acid-base characteristics, the ionization constants [3] were determined for I-XI (Table 1). Two series of values -  $pK_a(+H^+)$  during titration with acid (addition of a proton) and  $pK_a(-H^+)$  during titration with alkali (loss of a proton) - were obtained in the determination of the  $pK_a$  values of the thioquinolones. The  $pK_a(+H^+)$  value for the thione structure should pertain to the basic group, and the  $pK_a(-H^+)$  value should pertain to the acid group. On the other hand, for a zwitterion structure the  $pK(+H^+)$  value characterizes the acid group, and the  $pK(-H^+)$  value characterizes the basic group. The ionization constants of the investigated thioquinolones were assigned by means of the UV and IR spectra [1, 2]. The ionization constants obtained were compared with

TABLE 1.  $pK_a$  Values of 6- and 7-Substituted 2-Thionolepidines and 4-Thionoquininaldines\*

Series 1-3			Series 4			Series 5		
R	substituent position	$pK_a$		R	substituent position	$pK_a$		
		+H <sup>+</sup>	-H <sup>+</sup>			+H <sup>+</sup>	-H <sup>+</sup>	
OCH <sub>3</sub>	6	—	12,32	H	6	—	10,46	
Cl	6	—	11,48	OCH <sub>3</sub>	6	—	10,08	
NO <sub>2</sub>	6	—	10,43	Cl	6	—	9,26	
H	6,7	2,80	12,42	NO <sub>2</sub>	6	—	8,26	
OCH <sub>3</sub>	7	2,98	12,20	H	6	5,30	—	
Cl	7	3,40	11,50	OCH <sub>3</sub>	6	5,06	—	
HNCOCH <sub>3</sub>	7	3,16	12,00	Cl	6	4,50	—	
				NO <sub>2</sub>	6	3,73	—	

\* In 70% ethanol at 20°C.

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TABLE 2. Results of a Correlation Analysis of Series 1-5

Series	Ionization constant	Parameters*	$pK_a$			
			Jaffe $\sigma$		Taft $\sigma$	
			meta	para	meta	para
1	$pK_a(-H^-)$	$r$	0,994	0,949	0,993	0,974
		$\rho$	-2,914	-1,996	-3,019	-2,117
		$lg K_a$ (calc.)	12,53	12,04	12,57	12,16
		$lg K_a$ (exptl.)	12,42	12,42	12,42	12,42
2	$pK_a(-H^-)$	$S_0$	0,122	0,357	0,129	0,258
		$r$	0,995	0,670		0,797
		$\rho$	-2,564	-1,345		-1,826
		$lg K_a$ (calc.)	12,48	12,02		12,10
3	$pK_a(+H^+)$	$lg K_a$ (exptl.)	12,42	12,42		12,42
		$S_0$	0,046	0,369		0,299
		$r$	0,998	0,640		0,762
		$lg K_a$ (calc.)	2,80	3,09		3,04
4	$pK_a(-H^-)$	$lg K_a$ (exptl.)	2,80	2,80		2,80
		$S_0$	0,014	0,241		0,203
		$r$	0,999	0,911	0,999	0,954
		$\rho$	-3,094	-2,000	-3,169	-2,467
5	$pK_a(-H^-)$	$lg K_a$ (calc.)	10,44	9,88	10,46	10,05
		$lg K_a$ (exptl.)	10,46	10,46	10,46	10,46
		$S_0$	0,026	0,490	0,031	0,356
		$r$	0,999	0,930	0,998	0,960
	$lg K_a$ (calc.)	$\rho$	-2,173	-1,434	-2,224	-1,530
		$lg K_a$ (exptl.)	5,28	4,90	5,30	4,99
		$S_0$	5,26	5,26	5,26	5,26
		$r$	0,031	0,306	0,048	0,233

\* Calculated by the method of least squares [6];  $n=4$  in all series.

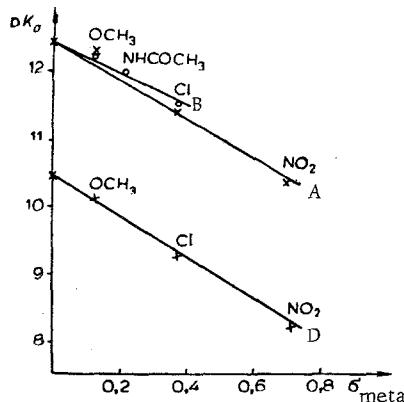


Fig. 1

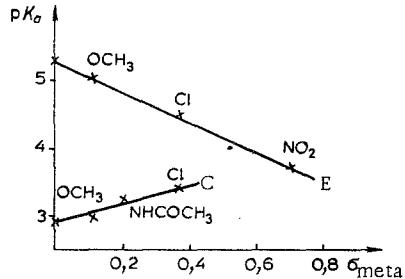


Fig. 2

Fig. 1. Correlation of the acidity constants of thioquinolones with the  $\sigma_M$  constants: A) series 1; B) series 2; D) series 4.

Fig. 2. Correlation of the basicity constants of thioquinolones (C, series 3) and of S-methylthioquinolines (E, series 5) with the  $\sigma_M$  constants.

the various substituent constants [4]. The results of the correlation analysis are presented in Table 2. Investigations established a linear dependence of the acidity constants of the thioquinolones in series 1, 2, and 4 (Fig. 1, lines A, B, and D, respectively) and of the basicity constants for series 3 and 5 (Fig. 2, lines C and E) with the Jaffe and Taft  $\sigma_M$  substituent constants. The correlation of the ionization constants with the Jaffe  $\sigma_M$  and induction constants ( $\sigma_O$ ) indicates the primary inductive character of the transmission of the electronic effect of a substituent. It is seen from the data in Table 2 that the  $\rho$  values for thioquinolones of series 1 and 4 are higher than those in series 2; this indicates the great effect of substituents in the 6 position on the reaction center. The reaction constant of series 3 of thioquinolones differs from the  $\rho$  values of the other series with respect to sign; this probably attests to the occurrence of titration through a transition state other than that in the other series. The ionization constants [ $pK_a(+H^+)$ ] in series 3 and 4 were determined during titration with acid, but they characterize the basicities of the various functional

TABLE 3. Characteristics of 7-Substituted 2- and 4-Thioloquinolones and Their S-Methyl Derivatives

Compound	R	mp, °C	Empirical formula	Found, %			Calc., %			UV spectra			IR spectra ν - XI	Yield, %		
				N	S	N	λ <sub>m,α,ν</sub> , nm			λ <sub>ε</sub>						
							S	ν	ε	ν	ε	ν				
I - IV																
V - VI																
VII - IX																
X - XI																
1	OCH <sub>3</sub>	244-245	C <sub>11</sub> H <sub>11</sub> NOS	6.9	15.5	6.8	265; 380	4.30; 4.32	1400 m 1520 w, 1610-1630 m, 2700-3140 m	83						
II	Cl	264-265	C <sub>10</sub> H <sub>8</sub> CINS <sup>a</sup>	6.6	16.2	6.7	270; 380	4.30; 4.20	1400 m, 1540 w, 1600-1630 s, 2800-3140 m	83						
III	NH <sub>2</sub>	225 (dec.)	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> S	14.5	16.9	14.7	16.8	380	3.17	1570-1660 m, 2700-2900 w	70					
IV	NHCOCH <sub>3</sub>	285 (dec.)	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> OS	12.1	13.7	12.0	13.8	285; 385-390	4.48; 3.90	1410 w, 1500-1700 m	72					
V	OCH <sub>3</sub>	215-216	C <sub>11</sub> H <sub>11</sub> NOS	6.7	15.6	6.8	265; 375	3.93; 4.27	1415 m, 1570-1630 s 2600-3100 s	87						
VI	Cl	225-227	C <sub>10</sub> H <sub>8</sub> CINS <sup>b</sup>	6.6	15.2	6.7	15.3	265; 390	4.06; 4.24	1415 m, 1585 s, 1640 m, 2500-3100 s	86					
VII	OCH <sub>3</sub>	85-86	C <sub>12</sub> H <sub>12</sub> NOS	6.3	14.6	6.4	14.6	245; 335	4.30; 4.15	-	87					
VIII	Cl	41-42	C <sub>11</sub> H <sub>10</sub> CINSC <sup>c</sup>	6.2	14.3	6.3	14.4	245; 335	4.32; 3.95	-	90					
IX	NHCOCH <sub>3</sub>	210-211	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> OS	11.3	13.1	11.4	13.0	245; 345	4.25; 3.76	-	72					
X	OCH <sub>3</sub>	97-97.5	C <sub>12</sub> H <sub>11</sub> NOS	6.2	14.5	6.4	14.6	235; 305	4.60; 4.13	-	96					
XI	Cl	139-140	C <sub>11</sub> H <sub>10</sub> CINS <sup>d</sup>	6.4	14.2	6.3	14.4	230; 310	4.55; 4.03	-	95					

Note: <sup>a</sup>Found: Cl 16.9%. Calculated: Cl 16.8%. <sup>b</sup>Found: Cl 15.9%. Calculated: Cl 15.9%. <sup>c</sup>Found: Cl 16.9%. Calculated: Cl 15.9%.



groups: in series 3 the  $pK(+H^+)$  values characterize the basic properties of the sulfur atom, while they characterize the basic properties of the nitrogen atom in series 5. Judging from the absolute value of reaction constant  $\rho$ , it can be assumed that the degrees of polarity of the transition states in series 1 and 4 are close and higher than in series 2 and 5. Although the substituents are in different positions in the thioquinolones in series 1 and 2, the  $\sigma_M$  constants give the best correlation coefficient for both series. The benzene ring of the thioquinolone molecules, regardless of the position of the substituent, can be regarded as an overall substituent with respect to the reaction center. An induction mechanism, regardless of the position of the substituent, apparently plays the decisive role in the transmission of the effect of a substituent to the reaction center.

## EXPERIMENTAL

The purity and authenticity of the products were monitored by thin-layer chromatography (TLC) on  $Al_2O_3$ . The solvent was  $CHCl_3$ , and the chromatograms were developed in UV light. The  $pK$  values were determined by potentiometric titration with an LPU-01 potentiometer.

The 7-substituted 2- and 4-thioquinolones were obtained by the method in [2]. The characteristics of the 7-substituted thioquinolones and their S-methyl derivatives are presented in Table 3. The other substances were described in [1, 5].

7-Amino-2-hydroxylepidine (XII). A solution of 8.4 ml (0.1 mole) of diketene in 20 ml of dry benzene was added in the course of 15 min to 10.8 g (0.1 mole) of m-phenylenediamine in 50 ml of dry benzene, after which the reaction mixture was refluxed for 1 h. The benzene was then removed by distillation to dryness, and the residue was dissolved in absolute ethanol. The ethanol solution was filtered, and the filtrate was diluted with water and cooled to precipitate a light-gray substance [93% (80% by the method in [5])] with mp 270-272°. No melting-point depression was observed for a mixture of this product with a genuine sample of XII [5].

7-Acetamido-2-chlorolepidine (XIII). A mixture of 0.96 g (5 mmole) of 7-amino-2-chlorolepidine and 6 ml (6 mmole) of acetic anhydride was refluxed until the solid had dissolved completely, after which the solution was poured into water. The yellow precipitate was washed repeatedly with water until it was neutral to give a product (73%) with mp 178-180° (dec., from alcohol). Found: Cl 15.0; N 11.7%.  $C_{12}H_{11}N_2OCl$ . Calculated: Cl 15.1; N 11.9%.

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