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THE ACIDITIES AND THE TAUTOMERIC STRUCTURE OF 5-ARYL-2-MERCAPTO-1,3,4-OXADIAZOLES

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Abstract - The acidity constants of a series of substituted 5-phenyl-2-mercapto-1,3,4-oxadiazoles were determined by potentiometric and spectrophotometric methods in 80% (vol.) ethanol-water at 25°C. The data obtained by the two methods are in good agreement. The pK_a values correlate with the $\sigma^*_{XC_6H_4}$ constants of the substituted phenyl group (ρ = -0.985, r = 0.936), however, a better correlation of the pK_a data with the Hammett substituent constants σ_X (ρ = -0.983, r = 0.959) was obtained. These linear correlations exclude the possibility of the presence of the thiol tautomer 1 in equilibrium with the thioamide tautomer 2 and indicate that the ionization of the compounds takes place in the form of the thioamide tautomer 2. According to the results of the HMO calculations, the thioamide form 2 is more stable than the thiol tautomer 1. A satisfactory correlation between the observed pK_a values and the difference between the π-electronic energies (ΔE_π) of the thioamide tautomer and of the common resonance-stabilized anion was obtained, thus supporting the assigned tautomeric structure 2 for the series under study.

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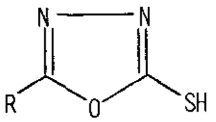
INTRODUCTION

Although several studies concerning the transmission of substituent effects by heterocyclic rings have been reported,[1-3] the 1,3,4-oxadiazole ring, to our knowledge, has not been investigated from this point of view so far.

In the present contribution, the acid dissociation constants of a series of 5-aryl-2-mercapto-1,3,4-oxadiazoles 1a-1j (R = XC_6H_4) have been determined in 80% (vol.) ethanol-water at 25°C and the results have been correlated by using the Hammett equation. The pK_a values for only three compounds, 1a (R = Ph), 1k (R = H), and 1ℓ (R = Me) have been reported in the literature.[4,5]



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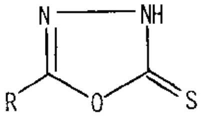

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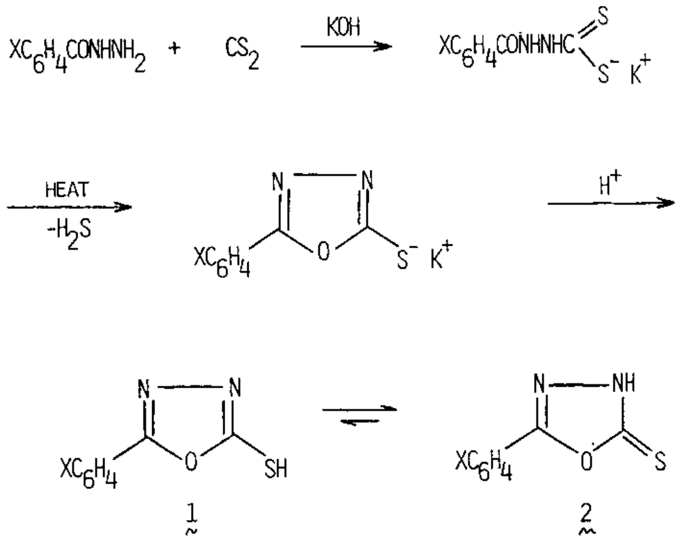
The test of the applicability of the Hammett equation to the effective ionization constants of 1 is also of interest because it will help to obtain further insight into the possible tautomerism between 1 and 2. On the basis of the spectral data, these compounds were reported to exist in their thioamide form 2 in solution.[4,5]

Furthermore, it seemed worthwhile to study the acidity of a systematic series of compounds of type 1 from a quantum-chemical viewpoint. In the present work, the HMO π-electronic energies of the two tautomers 1 and 2 and of their common anion 3, $E_\pi(1)$, $E_\pi(2)$, and $E_\pi(3)$, respectively, have been calculated[6] and correlations between the pK_a data and each of the energy differences $[E_\pi(3) - E_\pi(1)$ and $E_\pi(3) - E_\pi(2)]$ were examined.

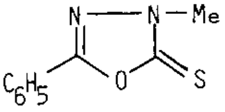
RESULTS AND DISCUSSION

The reaction sequence followed in the synthesis of the compounds 1a-1j is shown in Scheme 1.[7] Five of the 1,3,4-oxadiazoles prepared are new compounds and their structures have been confirmed on the basis of their elemental and spectral analyses (see Experimental).

The compounds 1a - 1j behave as weak acids in 80% (vol.) ethanol-water at 25°C. If the prototropic tautomerism is taken into account, the ionization of 1a-1j can be represented by Scheme 2. The effective ionization constants, pK_a, of these compounds were determined both by spectroscopic and by potentiometric titration methods. The uv spectra of 1, in each case, vary with increasing pH of the medium (Fig. 1). For all the compounds under study, the dependence of the absorbance on the pH value gives sigmoid curves. Similarly, the potentiometric titration curves were sigmoid as well. Typical plots are shown in Fig. 2.



a, X = H
b, X = *p*-MeO
c, X = *p*-Me
d, X = *m*-Me
e, X = *p*-Cl
f, X = *m*-Cl
g, X = *p*-Br
h, X = *m*-Br
i, X = *m*-NO_2
j, X = *p*-NO_2



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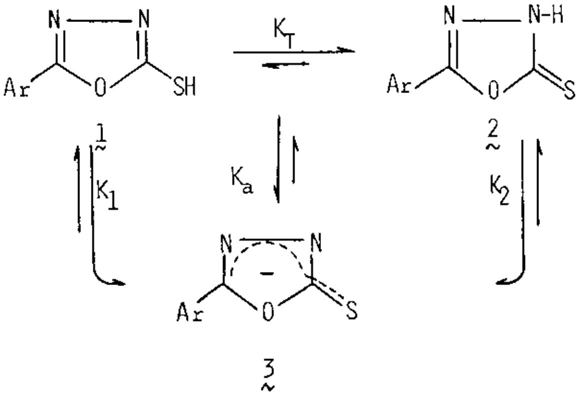
Scheme 1



Scheme 2

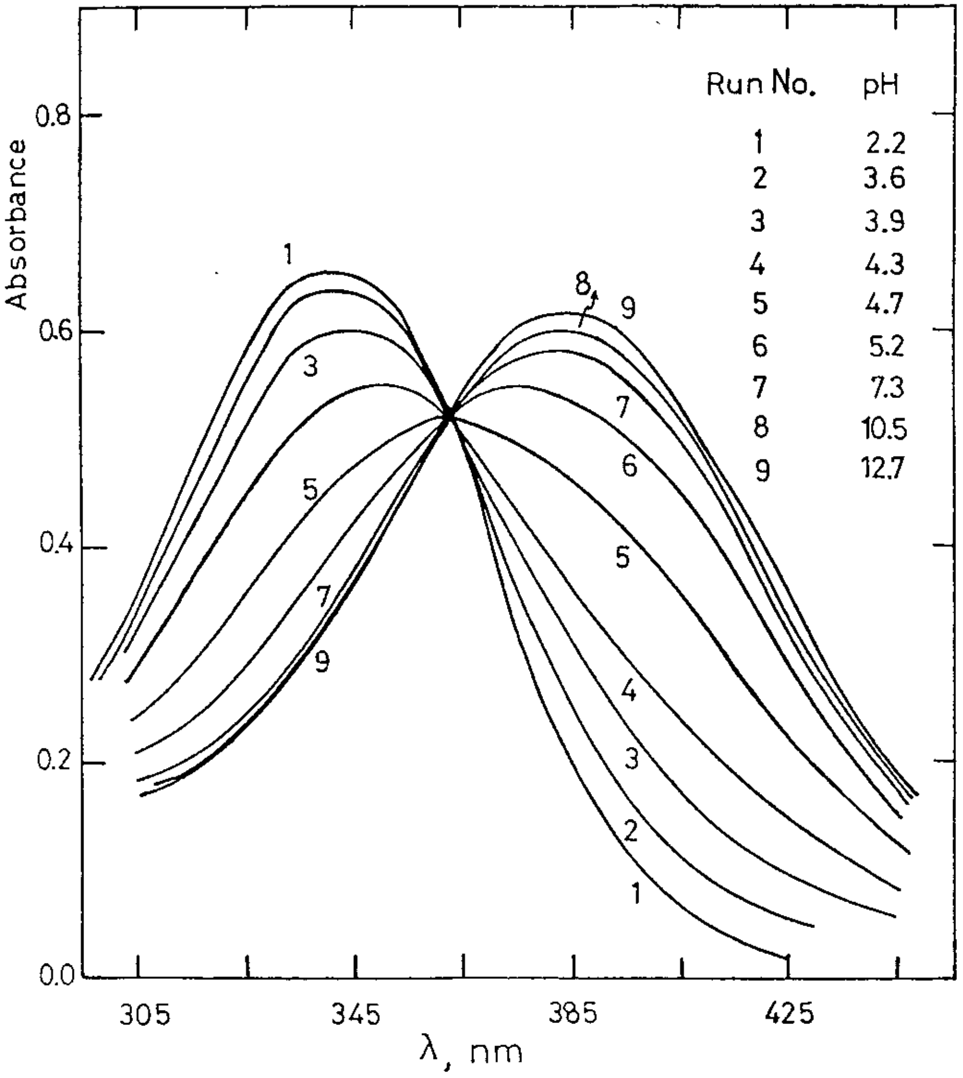


Fig.1. Ultraviolet absorption spectra of 5-(p-nitrophenyl)-2-mercapto-1,3,4-oxadiazole **1j** at different pH values; c = 5.0 x 10^{-5}M, in 80% (vol.) ethanol-water at 25°C and μ = 0.10.

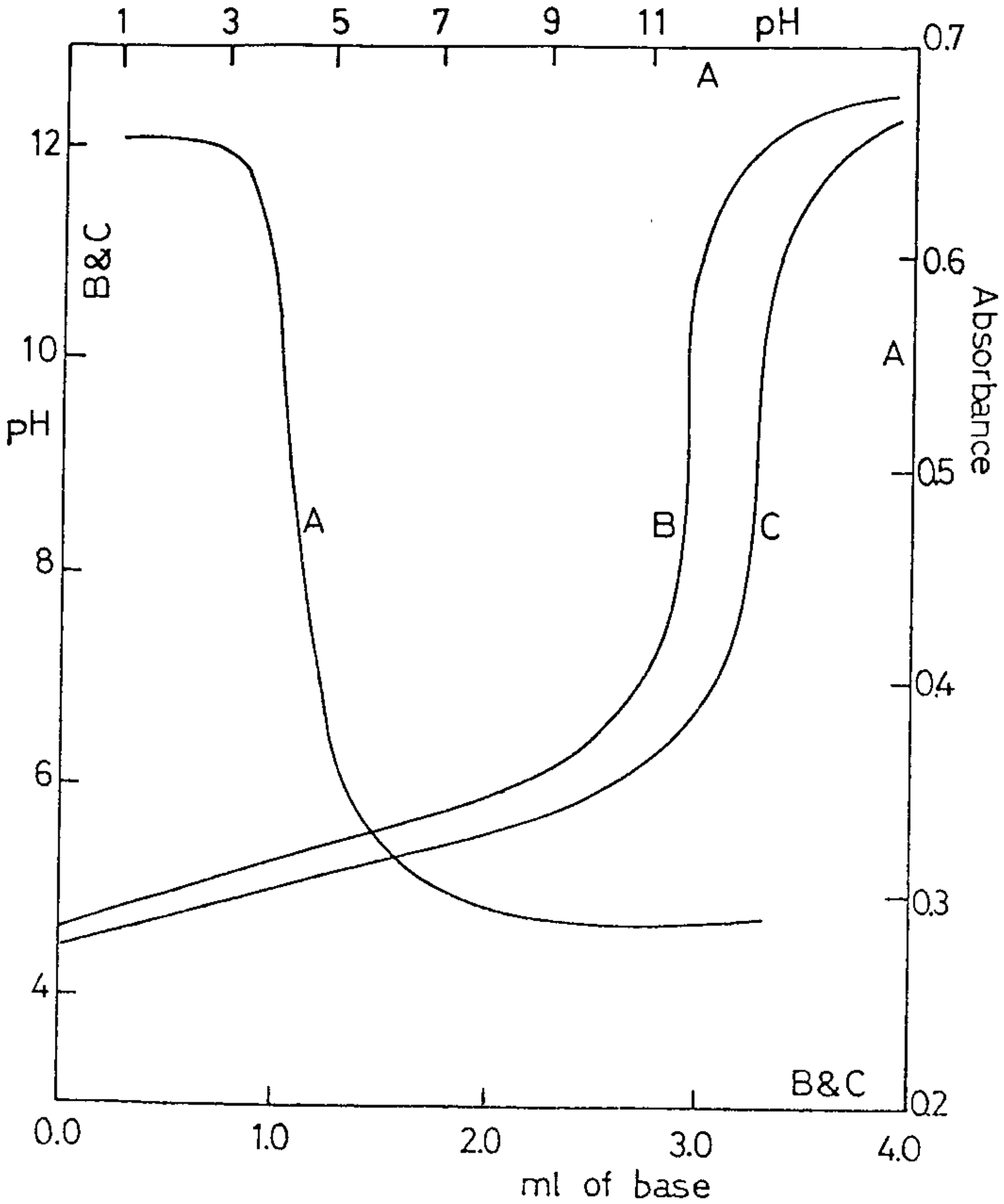


Fig. 2. Typical spectrophotometric titration curve of 1j (A) at λ = 345 nm and potentiometric titration curves of 1b (B) and 1a (C).

The pK_a values were calculated from the absorbance-pH data by eq. [1].

$$pK_a = pH_i + \log \frac{A_b - A_i}{A_i - A_a} \qquad [1]$$

where A_i is the absorbance of the test solution at pH_i, and A_b and A_a are the absorbance values of the strongly alkaline and strongly acid solutions, respectively. In the potentiometric method, the pK_a values were calculated by using eq. [2].

$$K_a = (a\,T_l + [H^+])[H^+]/T_l\,(1 - a) - [H^+] \qquad [2]$$

where a is the molar ratio of the base added to the compound, and T_l is the total acid concentration. It should be noted that the pK_a values from potentiometric titrations agree well with the data obtained spectrophotometrically. The pK_a values of the compounds studied are summarized in Table 1.

Table 1. Experimental and Calculated Quantities for Substituted 5-Aryl-2-mercapto-1,3,4-oxadiazoles, 1a-1j

Compound	Substituent	pK_a(a)	σ_X	$\sigma^*_{XC_6H_4}$	E_π (β) Form 1	 2	 3
1a	None	5.25	0.00	0.58	20.813	21.672	23.976
1b	p-MeO	5.29	-0.27	0.36	23.995	25.875	28.127
1c	p-Me	5.49	-0.17	0.47	23.516	25.393	27.673
1d	m-Me	5.40	-0.07	0.53	23.740	25.591	27.885
1e	p-Cl	5.07	0.23	0.75	23.847	25.721	28.096
1f	m-Cl	4.98	0.37	0.85	23.856	25.720	28.120
1g	p-Br	4.92	0.23	0.74	-	-	-
1h	m-Br	4.93	0.39	0.86	-	-	-
1i	m-NO_2	4.60	0.71	1.09	29.077	30.739	33.312
1j	p-NO_2	4.56	0.78	1.50	28.874	30.754	33.385

(a) Standard deviation s = ±0.02-0.04.

The results show that, to some extent, the acidity of 1 is influenced by the substituent in the 5-phenyl ring. Two correlations of the pK_a data with the simple Hammett equation[8] were attempted. In the first case, the pK_a values were plotted against the Hammett substituent constants σ_X (Fig. 3), whereas in the second plot the phenyl group is included with the substituent and the pK_a values are correlated with the polar substituent constants $\sigma^*_{XC_6H_4}$ for the substituted phenyl groups.[9]

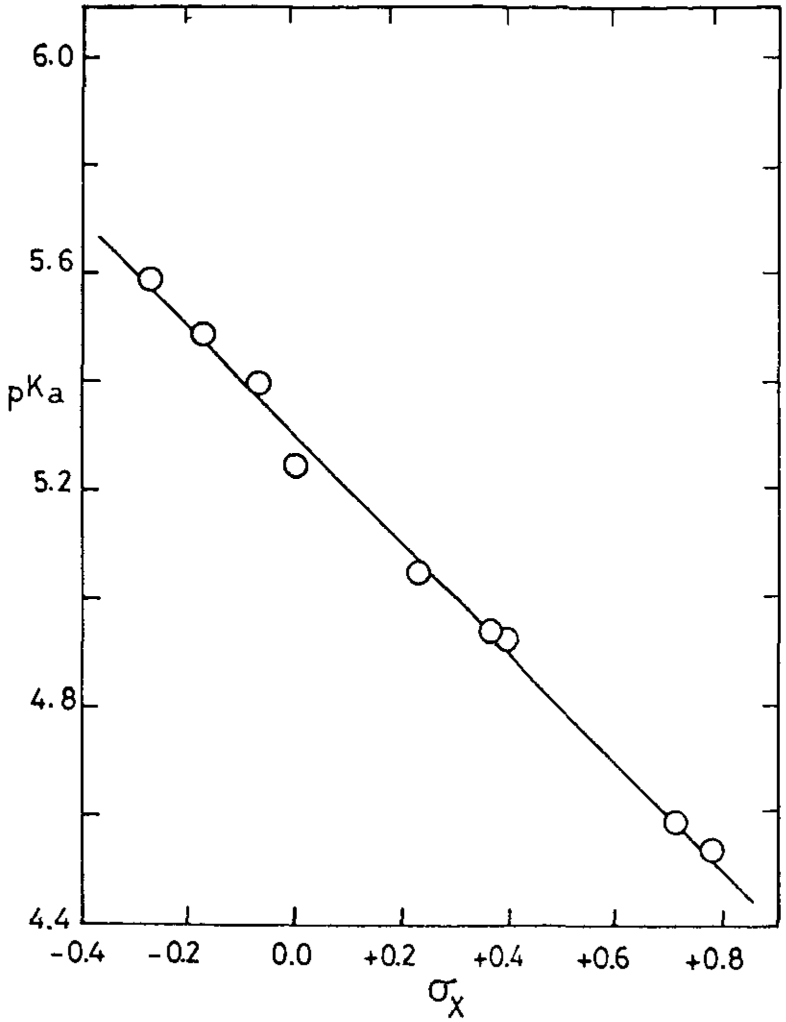


Fig. 3. Correlation of pK_a of 5-aryl-2-mercapto-1,3,4-oxadiazoles with the Hammett substituent constants.

The corresponding regression lines expressing such correlations are given by eqs. [3] and [4], respectively.

$$pK_a = 5.29 - 0.983\sigma_X \qquad r = 0.959,\ s = \pm 0.055 \qquad [3]$$

$$pK_a = 5.83 - 0.985\sigma^*_{XC_6H_4} \qquad r = 0.936,\ s = \pm 0.123 \qquad [4]$$

From the values of the correlation coefficient, r, and the standard deviation, s, it is obvious that the pK_a values of **1** are correlated better by the Hammett substituent constants σ_X than by the inductive constants $\sigma^*_{XC_6H_4}$ of the substituted phenyl group. This linear correlation between pK_a and σ_X indicates further that the compounds in question exist predominantly in one tautomeric form regardless of the nature of the substituent on the 5-phenyl group. If the two forms **1** and **2** coexisted in equilibrium, a good correlation would not be observed.[10,11] This is because for such an equilibrium (Scheme 2), the overall acid dissociation constant K_a is related to the dissociation constants K_1 and K_2 of the thiol and of the thioamide forms, respectively, and the tautomeric equilibrium constant K_T by eqs. [5] and [6]. According to these equations,

$$K_a = K_1/(1 + K_T) \qquad [5]$$

$$K_a = K_2\, K_T/(1 + K_T) \qquad [6]$$

a linear correlation between pK_a and σ_X should be observed only if $K_1 \approx K_2$. In general, because of the ionization of the SH and NH groups, respectively, the values of K_1 and K_2 are different. The data from the correlation analysis make it possible to decide which of the possible tautomeric forms of mercaptooxadiazoles should be given preference. The reaction constant ($\rho = 0.983$) agrees better with the existence of the thioamide form **2**. The absolute value of the reaction constant for the thiol tautomer **1** should be clearly much lower, because the length of the bridge between the substituent and the reaction site in **2** is shorter than in the tautomer **1**.

The assignment of the tautomeric structure **2** is compatible with the spectral data of the compounds studied. Thus, the infrared spectra of the compounds reveal no band in the 2550-2600 cm^{-1} region that could be assigned to the thiol tautomer **1**.[4] The spectra possess, however, in all cases, an absorption band close to 3100 cm^{-1} which can be assigned to an NH stretch, and a stretching frequency at 1152-1160 cm^{-1} attributable to the C=S bond. The NMR spectra do not possess a signal which would be due to a proton of an SH group; they contain signals in the 7.0-8.2 ppm range (aromatic protons) and, after exchange with D_2O, a signal appears at 4.65 ppm due to HDO and resulting from the NH → ND exchange. Furthermore, the electronic absorption pattern of **2a** is identical to that of 5-phenyl-3-methyl-1,3,4-oxadiazole-2-thione **4** (Scheme 1).[4]

To assess further the relative stabilities of the two tautomeric forms **1** and **2** and of their common resonance-stabilized anion **3**, their π-electronic energies, E_π, were calculated using the HMO method.[6] The parameters used in the calculations are listed in Tables 2 and 3 and the results of the calculations are summarized in Table 1. In all cases it has been found that the thioamide form **2** has a higher π-electronic energy than the thiol tautomer **1**. The value of 0.859β for the term $E_\pi(\mathbf{2})-E_\pi(\mathbf{1})$ found for compound **1a** is similar to that (0.908β) reported[4] for the same compound.

Table 2. HMO Heteroatom Parameters Used in the Calculations

$\alpha_X = \alpha + h_X\beta$ (a) $\beta_{XY} = k_{XY}\beta$ (a)

SH form (1)	NH form (2)	Anion (3)
$h_{N(3)} = 0.5$	$h_{N(3)} = 1.5$	$h_{N(3)} = 1.75$
$h_{N(4)} = 0.5$	$h_{N(4)} = 0.5$	$h_{N(4)} = 1.75$
$h_S = 1.0$	$h_S = 0.6$	$h_S = 0.8$
$h_O = 2.0$	$h_O = 2.0$	$h_O = 2.0$
$k_{CN} = 1.0$	$k_{C=N} = 1.0$	$k_{CN} = 0.9$
$k_{CO} = 0.8$	$k_{C-N} = 0.8$	$k_{CO} = 0.9$
$k_{NN} = 0.8$	$k_{C-O} = 0.8$	$k_{NN} = 0.9$
$k_{CS} = 0.7$	$k_{NN} = 0.8$	$k_{CS} = 0.8$
	$k_{CS} = 0.9$	

(a) α_X is the Coulomb integral of the p_Z atomic orbital of atom X; α is the same quantity for $2p_Z$ atomic orbital of carbon; β_{XY} is the resonance integral of the XY bond and β is the same quantity for the CC bond in planar conjugated hydrocarbons.

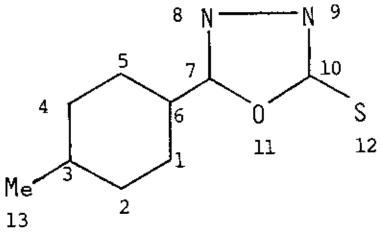
Table 3. HMO Parameters for Substituents in the Phenyl Group

Substituent, X	Coulomb integral, α_X	Resonance integral, β_{CX}
Cl	$\alpha_{Cl} = \alpha + 2.0\beta$	$\beta_{CCl} = 0.4\beta$
NO_2	$\alpha_N = \alpha + \beta$	$\beta_{CN} = \beta$
	$\alpha_{C(N)} = \alpha + 0.2\beta$	$\beta_{NO} = \beta$
	$\alpha_O = \alpha + 1.5\beta$	
Me (a)	$\alpha_{Me} = \alpha + 1.83\beta$	$\beta_{CMe} = 0.6\beta$
	$\alpha_{C(Me)} = \alpha - 0.2\beta$	
MeO	$\alpha_{MeO} = \alpha + 2\beta$	$\beta_{C-OMe} = 0.8\beta$

(a) Heteroatom model, see ref.[12]

These findings seem to substantiate the above conclusion that the compounds studied exist predominantly in the thioamide form **2**. Furthermore, the differences $[\Delta E_\pi(i) = E_\pi(\mathbf{3}) - E_\pi(i)]$ between the π-electronic energy of the anion **3** and that of the each of the two tautomers indicate that the acidity of **1** is higher than that of **2**. Because in acid-base equilibria of various tautomers the tautomer with higher acidity is considered to be less stable,[13] it is not unreasonable to conclude that the NH tautomer **2** is more stable than the SH form **1**. In all cases which we have studied, the structure of the anion **3** is intermediate between the thiol **1** and the thioamide **2** forms as it can be seen from the molecular diagrams (Table 4). Also, if it is assumed that the changes in free energy due to entropy, ΔS, and energy of solvation of the anion **3** and its conjugate

Table 4. Molecular Diagram for 5-(*p*-Tolyl)-2-mercapto-1,3,4-oxadiazole (a)



Position, i	Electron densities, q_i **1**	**2**	**3**	Bond, ij	Bond orders, p_{ij} **1**	**2**	**3**
1	0.967	0.983	1.053	1-2	0.801	0.682	0.707
2	1.066	1.024	1.027	1-6	0.440	0.608	0.523
3	0.973	0.960	1.051	2-3	0.468	0.644	0.619
4	1.008	1.024	1.027	3-4	0.468	0.644	0.619
5	0.993	0.983	1.054	3-13	0.196	0.203	0.182
6	1.010	1.026	1.083	4-5	0.801	0.682	0.707
7	0.897	0.884	0.982	5-6	0.440	0.608	0.523
8	1.277	1.224	1.828	6-7	0.398	0.400	0.566
9	1.360	1.757	1.790	7-8	0.766	0.806	0.371
10	0.815	0.807	0.670	7-11	0.349	0.311	0.325
11	1.805	1.820	1.774	8-9	0.419	0.291	0.114
12	1.807	1.589	1.723	9-10	0.750	0.457	0.500
13	1.961	1.958	1.963	10-11	0.380	0.376	0.436
				10-12	0.394	0.720	0.613

(a) Heteroatom model of the methyl group; see ref.[12]

acid are negligible in comparison with changes in the π-electronic energy due to dissociation, $\Delta\underline{E}_{\pi}(i)$ can be approximated as

$$p\underline{K}_a = \underline{a}\ \Delta\underline{E}_{\pi}(i) + \underline{b} \qquad [7]$$

where a and b are numerical constants. The correlation between the experimentally determined $p\underline{K}_a$ values and $\Delta\underline{E}_{\pi}(3,2)$ [i.e., $E_{\pi}(3) - E_{\pi}(2)$] appears (Fig. 4) to be quite acceptable, particularly if the heterogeneity of the substituents as a group is taken into account. The equation of the regression line shown in Fig. 4 is

$$p\underline{K}_a = 11.52 - 2.68\ \Delta\underline{E}_{\pi}(3,2);\ \underline{r} = 0.971,\ \underline{s} = \pm 0.086 \qquad [8]$$

However, the values of $\Delta\underline{E}_{\pi}(3,1)$ (i.e., $\underline{E}_{\pi}(3) - \underline{E}_{\pi}(1)$) for the thiol tautomers 1 do not correlate with the $p\underline{K}_a$ data. This result provides an additional support for the conclusion that the compounds examined in this study exist predominantly in the thioamide form 2 regardless of the nature of the substituent in the 5-phenyl group.

EXPERIMENTAL

The melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. Elemental analyses were carried out by the Microanalytical Laboratory of the University of Cairo, Giza, Egypt. Infrared spectra were recorded with a Beckman 200 infrared spectrophotometer, and the NMR spectra were taken on a Varian T60-A instrument. The δ values were obtained in $CDCl_3$ at room temperature, with TMS as the internal reference. The ultraviolet spectra of 1a-1j were measured in ethanol on Pye-Unicam AR55 and Cary 118 spectrophotometers.

5-Aryl-1,3,4-oxadiazole-2-thiones, 1a-1j

They were prepared by a previously described method.[7,14] The physical constants of the known compounds (1a, 1b, 1d, 1e) were in agreement with the data published in the literature. The remaining compounds were new. They were purified by crystallization from ethanol until a constant melting point was obtained.

The characteristics of the synthesized compounds were as follows [compound no., substituent in the 5-phenyl ring, m.p. [m.p. lit. (ref.)], uv spectrum, λ^{EtOH} (log ε), molecular formula, anal. %S, found (calc.): 1a, H, 218°C [219-220°C (15)], 250 nm (4.05), 295 nm (4.32), $C_8H_6N_2OS$, - (-); 1b, p-MeO, 203°C [204-206°C (7)], 245 nm (3.90), 296 nm (3.98), $C_9H_8N_2O_2S$, - (-); 1c, p-Me, 223°C[-],

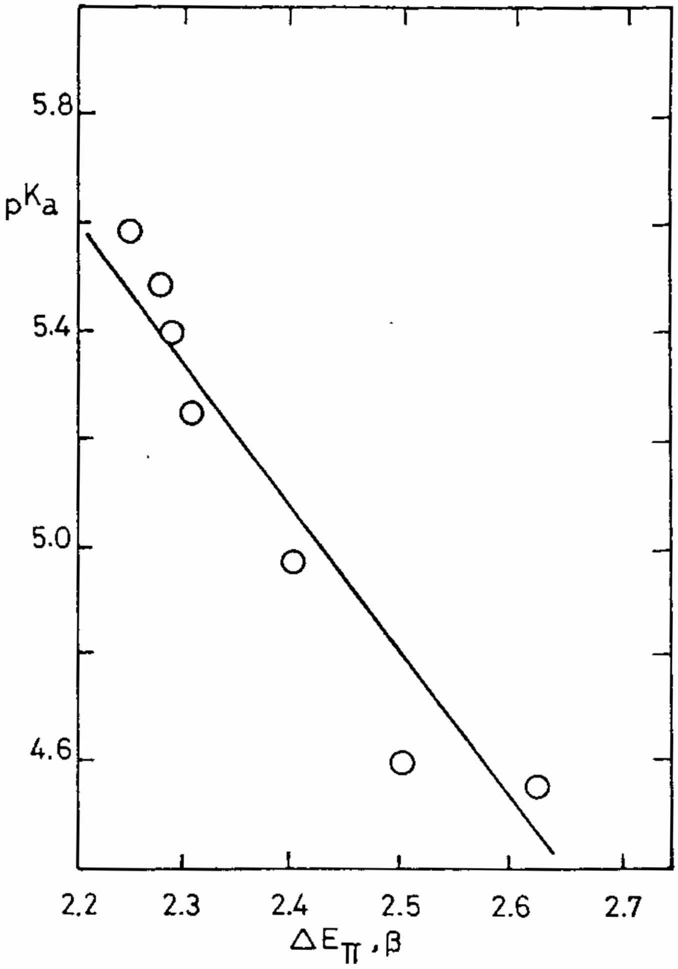


Fig. 4. Correlation of pK_a's of 5-aryl-2-mercapto-1,3,4-oxadiazoles with ΔE_π.

240 nm (4.26), 300 (4.27), $C_9H_8N_2OS$, 16.59 (16.66); **1d**, *m*-Me, 160°C[158-160°C (16)], 247 nm (4.17), 295 nm (4.46), $C_9H_8N_2OS$, - (-); **1e**, *p*-Cl; 174°C [176-178°C (7)], 248 nm (4.50), 340 nm (4.16), $C_8H_5ClN_2OS$, - (-); **1f**, *m*-Cl, 179°C [-], 257 nm (4.11), 310 nm (4.17), $C_8H_5ClN_2OS$, 14.95 (15.06); **1g**, *p*-Br, 189°C [-], 240 nm (4.13), 305 nm (4.18), $C_8H_5BrN_2OS$, 12.35 (12.45); **1h**, *m*-Br, 212°C [-], 255 nm (4.12), 305 nm (4.17), $C_8H_5BrN_2OS$, 12.37 (12.45); **1i**, *m*-NO_2, 150°C [-], 224 nm (4.40), 330 nm (4.10), $C_8H_5N_3O_3S$, 14.25 (14.35); **1j**, *p*-NO_2, 200°C [-], 257 nm (4.35), 340 nm (4.16), $C_8H_5N_3O_3S$, 14.29 (14.35).

All compounds exhibit $\tilde{\nu}_{NH}$ (3031-3175 cm^{-1}) and $\tilde{\nu}_{CS}$ (1152-1160 cm^{-1}) bands in their ir spectra, and there is no $\tilde{\nu}_{SH}$ absorption at 2550-2600 cm^{-1}. The NMR spectra do not possess a signal due to an SH proton; they contain signals at 7.0-8.2 ppm (aromatic protons). After exchange with D_2O, a signal appears at 4.65 ppm (HDO; NH → ND exchange).

Determination of pK_a

The acid dissociation constants of 1a-1j were determined by both the potentiometric and the spectrophotometric methods in 80% (vol.) ethanol-water at 25°C. An Extech digital pH-meter type 671 fitted with an Orion combination glass electrode type 91-06 was used to measure the pH values. The instrument was calibrated by two standard Beckman buffer solutions with pH 4.01 and 10.00, respectively. The pH-meter readings B were converted to hydrogen ion concentration, [H^+], by means of eq. [9].[16]

$$-\log[H^+] = B + \log U_H \qquad [9]$$

where log U_H = -0.4 is the correction factor for the solvent composition and ionic strength for which B is read off at 25°C.

The procedures followed in the determination of the pK_a constants and their calculation from the spectrophotometric and potentiometric data have already been described.[17,18] The pK_a values obtained by the two methods were in good agreement and were reproducible to within ±0.03 pK_a unit. The results are summarized in Table 1.

HMO Calculations

The HMO calculations were carried out in the usual way on an IBM 360/65 computer.[6] The values of the semiempirical parameters adopted in this work are given in Tables 2 and 3 along with those used for the corresponding anions.

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