HETEROCYCLES, Vol 15, No 2, 1981

SUBSTITUENT EFFECTS ON ACIDITIES AND TAUTOMERIC STRUCTURES OF 1-ARYL-3-ETHOXYCARBONYL-4-PYRAZOLONES AND THEIR 5-ARYLAZO DERIVATIVES.

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Abstract - Two series of 1-aryl-3-ethoxycarbonyl-4-hydroxypyrazoles (1) and 1-(m-chlorophenyl)-3-ethoxycarbonyl-4-hydroxy-5-arylazopyrazoles (2) have been prepared and their acidities determined spectrophotometrically at 25°C and ionic strength of 0.1 in 60 vol.% ethanol-water medium. The pK_a data were correlated with the simple and extended Hammett equations. The regression lines are: $pK_a(1) = 9.34 - 0.794\,\sigma_X$; $pK_a(1) = 9.78 - 0.794\,\sigma^*_{XC_6H_4}$; $pK_a(2) = 7.49 - 1.158\,\sigma_X$; and $pK_a(2) = 7.49 - 1.245\,\sigma_{I,X} - 1.075\,\sigma_{R,X}$. It is concluded that such linear relations exclude the presence of the keto tautomers (1A) and (2A) in equilibrium with the hydroxy tautomers (1B) and (2B) respectively, in agreement with the spectral data of the compounds investigated. The electrical effect, E, of value 0.86 determined for series (2) indicates that such compounds exist in the cis-chelated hydroxyazo structure (2B).

INTRODUCTION

The applicability of the Hammett equation to the effective ionization constants, pK_a, of tautomeric substances has been investigated[1,2]. The results indicate that a good linear dependence of pK_a on substituent constant, σ_X, is observed when the tautomeric equilibrium is shifted toward one of the forms. When at particular σ_X values the second tautomeric form makes its appearance in equilibrium to a noticeable extent, one observes deviation from linearity.

In the present report, the simple and extended Hammett equations [1] and [2] respectively were used to investigate the keto-enol tautomerism of 1-substituted phenyl-3-ethoxycarbonyl-4-pyrazolones (1), and the azo-hydrazone tautomerism of their 5-arylazo derivatives (2) (Scheme 1). The tautomerism of

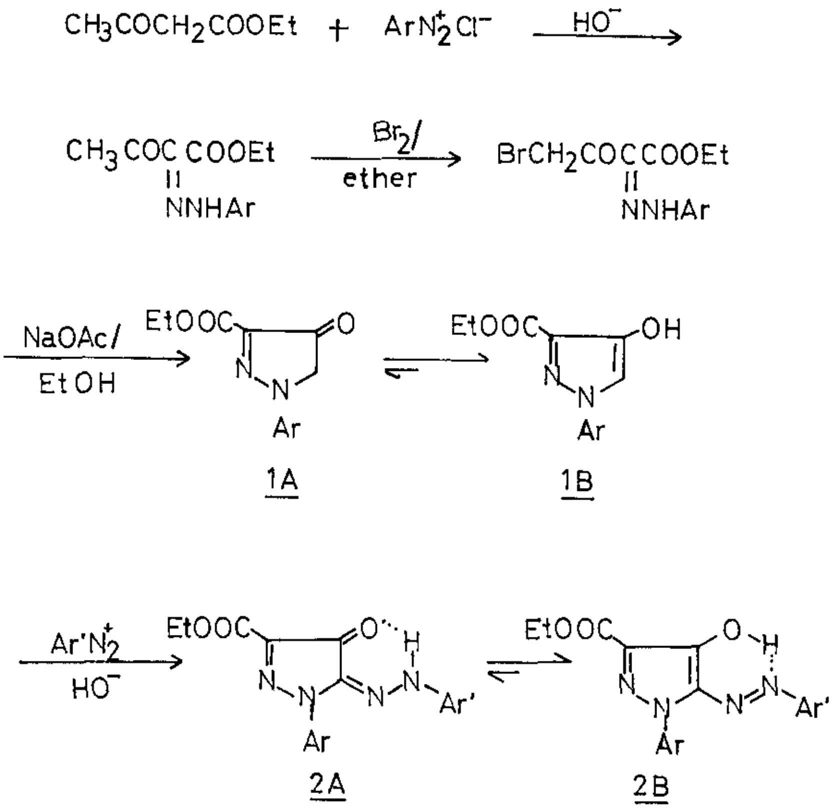
(1) and (2) is less studied than the corresponding derivatives of 3- and 5-pyrazolones[3]. Snavely and coworkers[4,5] have reported that 4-hydroxy-5-phenylazo-1-phenyl-3-ethoxycarbonylpyrazole (1, Ar = Ar' = C_6H_5) exists as such on the basis of spectral data. Nye and Tang[6] reported that 3,5-diphenyl- and 1-methyl-

$$[1] \qquad pK_a = \rho\sigma_X + pK_o$$

$$[2] \qquad pK_a = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + pK_o$$

3,5-diphenyl- derivatives of 4-pyrazolone exist predominantly in the enolic form. As the tautomeric equilibrium of some heterocyclic compounds[7] and azophenols[8] has been reported to be affected by substituents, it was thought interesting to examine the substituent effects on the acid dissociation constants of (1) and (2) in order to obtain further insight into this substituent effect on their tautomeric structures.

SCHEME 1.



RESULTS AND DISCUSSION

The reaction sequence followed in synthesis of the two series examined is shown in Scheme 1. In agreement with literature report on 1-methyl-3,5-diphenyl-4-hydroxypyrazole[6] , the compounds in series (1) appear to exist mainly in the hydroxy structure (1B). This conclusion is based on the following spectral data. The ultraviolet spectra of (1)(Table 1) are typical of pyrazole derivatives exhibiting two intense maxima near 300 and 250 nm[6]. Their infrared spectra in the solid state or in chloroform solution reveal only one carbonyl band near 1700 cm^{-1} assignable to the 4-ethoxycarbonyl group. Both free and bonded OH bands were observed near 3450 and 3210 cm^{-1} respectively in the solution phase whereas only bands due to bonded OH group appear in the spectra of the solid samples. The ketonic band near 1680 cm^{-1} characteristic of the fixed keto structure (3)[8] was absent in the spectra of (1). The pmr spectra of (1) exhibit one exchangable proton signal in the region 7.5 - 8.5 ppm.

The 4-hydroxypyrazoles (1a-1g) prepared behave as weak acids in 60 vol. per cent ethanol-water medium. The ultraviolet absorption maxima shifted by ca. 45 nm toward longer wavelengths on anion formation. This bathochromic shift is similar to that in case of 4-hydroxypyrazole[9] but is considerable greater than that encountered for most phenols[10]. Spectra recorded for (1) at different pH values showed, in each case, two isobestic points near 315 and 275 nm. A typical spectrophotometric titration curve is shown in Fig. 1. The pK_a values of (1a-1g) at ionic strength of 0.1 and 25°C, determined from such titration curves are listed in Table 2.

The pK_a data obtained show that the acidity of (1) is influenced to some extent by the substituent in the 1-phenyl moiety. Two ways were followed in correlating these pK_a values with the simple Hammett equation [1] . In the first case, the pK_a values were plotted versus the Hammett substituent constant, σ_X , (Fig. 2), whereas in the second, we include the phenyl group with the substituent and correlated the pK_a values with the polar substituent constant, $\sigma^*_{XC_6H_4}$ for the substituted phenyl group[11]. The regression lines expressing such correlations follow equations [3] and [4] respectively.

$$[3] \qquad pK_a = 9.34 - 0.794\,\sigma_X \; ; \; r = 0.996 \; ; \; s = \pm\,0.031$$

$$[4] \qquad pK_a = 9.78 - 0.794\,\sigma^*_{XC_6H_4} \; ; \; r = 0.956 \; ; \; s = \pm\,0.140$$

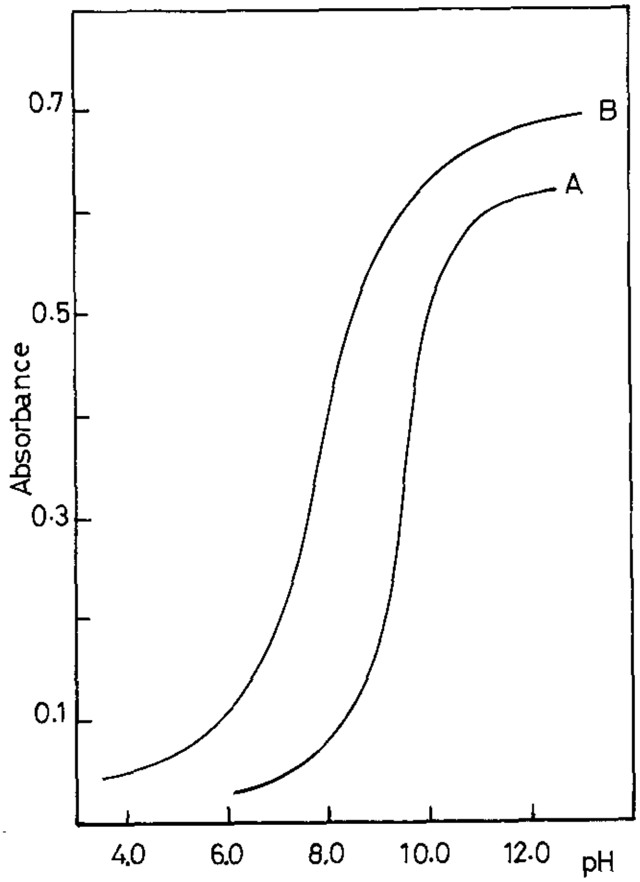


Fig. 1. Spectrophotometric titration curves of (1b) at 335 nm (A) and (2a) at 480 nm in 60 vol.% ethanol-water medium at 25°C and ionic strength of 0.1 .

From the values of the correlation coefficient ,r, and the standard deviation, s, it is obvious that the pK_a values of (1) are better correlated by the Hammett substituent constant, σ_X , rather than the inductive effect, $\sigma^*_{XC_6H_4}$ of the substituted phenyl group. This observation indicates the involvement of the lone pair of electrons on the nitrogen atom in the transmission of the substituent effects. Both linear relations substantiate, however, the previous conclusion that the compounds in series (1) exist predominantly in one tautomeric form,

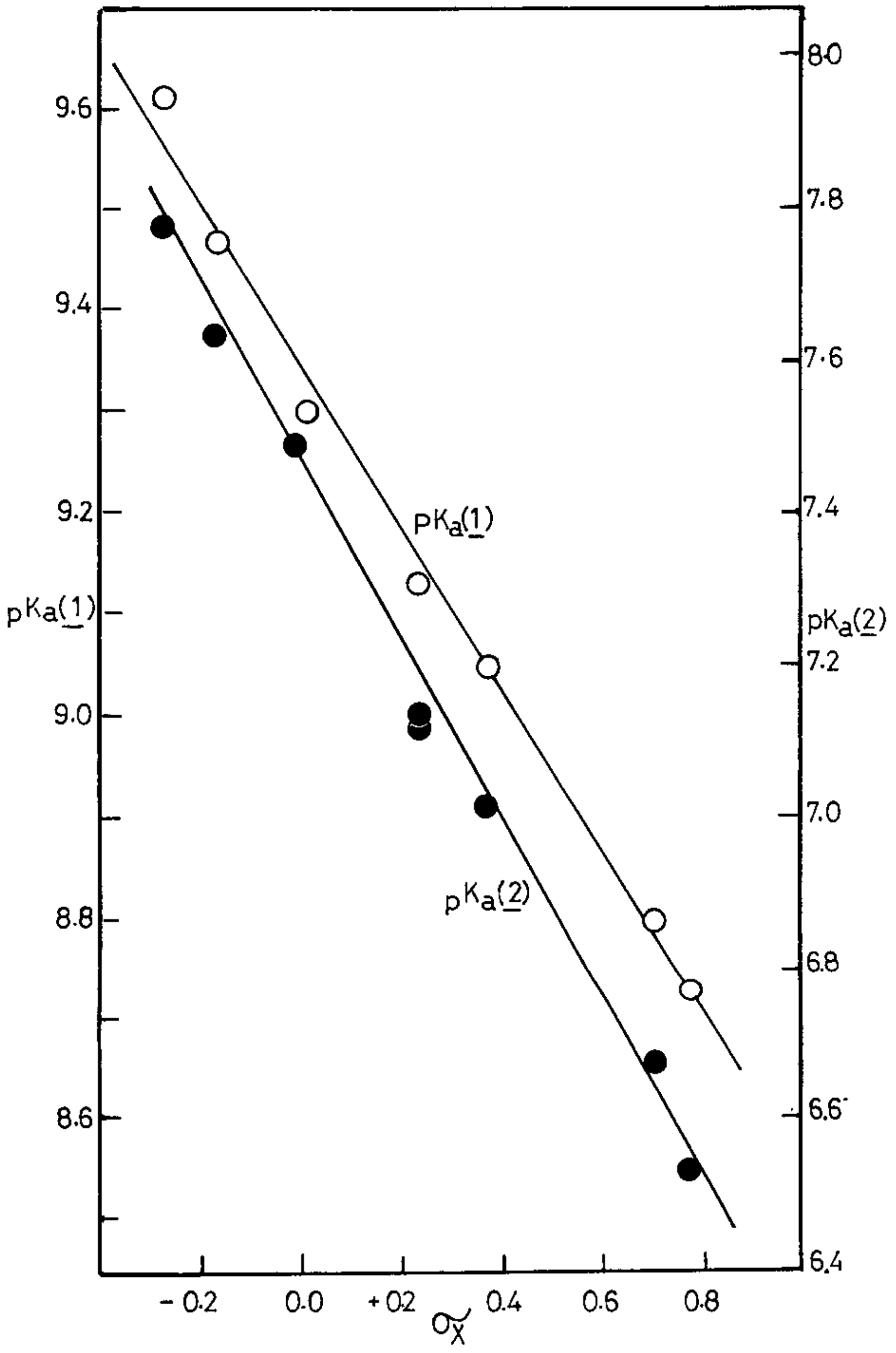


Fig. 2. Correlations of pK_a of 1-aryl-3-ethoxycarbonyl-4-hydroxypyrazoles (1),○, and of 1-(m-chlorophenyl)-3-ethoxycarbonyl-4-hydroxy-5-arylazo-pyrazoles (2), ●, with Hammett substituent constant, σ_X .

Table 1. 1-Aryl-3-ethoxycarbonyl-4-hydroxypyrazoles (1).

Compound no.	1-Ar	Mp., °C	Molecular formula	N,% Found	N,% Calcd.	λ_{max}^{EtOH} nm, (log e)
1a	p-$CH_3OC_6H_4$	110	$C_{13}H_{14}N_2O_4$	10.64	10.69	291(4.19);260(3.98)
1b	p-$CH_3C_6H_4$	119	$C_{13}H_{14}N_2O_3$	11.29	11.38	295(4.14);251(4.01)
1c	p-ClC_6H_4	135	$C_{12}H_{11}ClN_2O_3$	10.37	10.51	298(4.17);251(4.06)
1d	m-ClC_6H_4	115	$C_{12}H_{11}ClN_2O_3$	10.34	10.51	298(4.12);246(4.03)
1e	m-$NO_2C_6H_4$	195	$C_{12}H_{11}N_3O_5$	14.99	15.16	298(4.14)
1f	p-$NO_2C_6H_4$	219	$C_{12}H_{11}N_3O_5$	15.03	15.16	333(4.26);270(3.98)
1g	C_6H_5	86	$C_{12}H_{12}N_2O_3$	12.01	12.11	294(4.17);250(4.03)

Lit. Mp. 84–85°C[23] .

Table 2.† Acid Dissociation constants, pK_a, of (1) and (2) in 60 vol.% ethanol-water at ionic strength of 0.1 and 25°C, and substituent constants used in their correlation.

Compound no.	pK_a	Compound no.	pK_a	σ_X	$\sigma_{I,X}$	$\sigma_{R,X}$	$\sigma^*_{XC_6H_4}$
1a	9.61	2a	7.78	-0.27	0.27	-0.54	0.36
1b	9.47	2b	7.65	-0.17	-0.04	-0.13	0.46
1c	9.13	2c	7.11	0.23	0.46	-0.23	0.75
1d	9.05	2d	7.02	0.37	0.46	-0.09	0.85
1e	8.80	2e	6.68	0.71	0.51	0.18	1.09
1f	8.73	2f	6.54	0.78	0.64	0.14	1.50
1g	9.30	2g	7.50	0.00	0.00	0.00	0.58
1h	9.12	2h	7.14	0.23	0.44	-0.21	0.74

† Standard deviation in pK_a ±0.02 - 0.04 .

namely, the hydroxy tautomer (1B) regardless the nature of the substituent on the 1-aryl group. If the keto form (1A) exists in equilibrium with the hydroxy form, a good correlation would not be observed between pK_a and σ_X^- or $\sigma_{XC_6H_4}^{-\bullet}$ [1,12]. 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 keto and hydroxy tautomers respectively and the tautomeric equilibrium constant K_T by the equations:

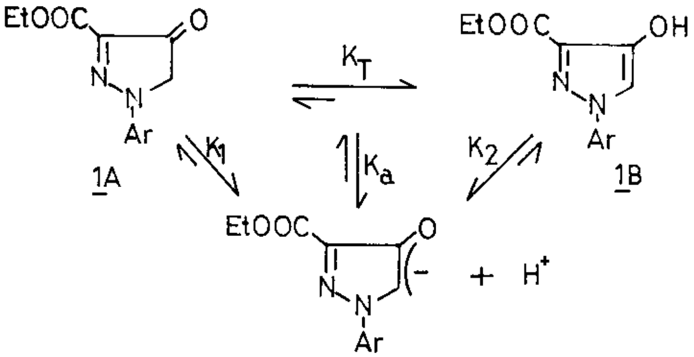
$$[5] \qquad K_a = K_2/(1 + K_T)$$

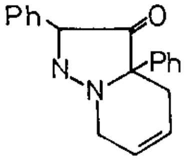
$$[6] \qquad K_a = K_T K_1 / (1 + K_T)$$

According to these relations, a linear relation between pK_a and substituent constant would be observed only if $K_1 = K_2$. In general case, the values of K_1 and K_2 constants are different.

The spectral data of the coupling products (2) (Table 3) are compatible with the hydroxyazo structure (2B). Thus, the infrared spectra of the compounds prepared exhibit in each case only one carbonyl band near 1700 cm^{-1} and a broad band due to bonded OH group in the region 3600 - 3400 cm^{-1}, both in solid and in chloroform solution. The keto-hydrazone structure (2A) requires the presence of two CO bands and weak NH band. The pmr spectra of (2) in deuterated chloroform are also in favor of structure (2B). All compounds exhibit a low-field absorption in the region δ 9.0 - 9.4 ppm, assignable to intramolecularly hydrogen bonded OH proton resonance. The NH chemical shift of the keto-hydrazone structures of type (4) appears at δ 13.3 - 13.5 ppm[4].

SCHEME 2.





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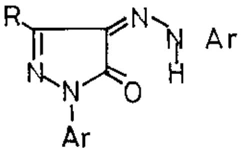

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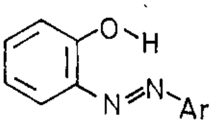

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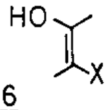

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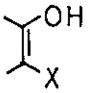

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Table 3. 1-(m-Chlorophenyl)-3-ethoxycarbonyl-4-hydroxy-5-arylazopyrazoles (2).

Compound no.	1-Ar'	Mp., °C	Molecular formula	N,% Found	N,% Calcd.	λ_{max}^{EtOH} nm, (log e)
2a	p-$CH_3OC_6H_4$	180	$C_{19}H_{17}ClN_4O_4$	13.89	13.97	525(3.59);358(4.21); 255(4.33)
2b	p-$CH_3C_6H_4$	146	$C_{19}H_{17}ClN_4O_3$	14.39	14.56	443(3.77);362(4.21); 251(4.28)
2c	p-ClC_6H_4	228	$C_{18}H_{14}Cl_2N_4O_3$	13.80	13.82	436(3.95);356(4.20) 251(4.31)
2d	m-ClC_6H_4	161	$C_{18}H_{14}Cl_2N_4O_3$	13.76	13.82	440(3.90);352(4.18) 250(4.32)
2e	m-$NO_2C_6H_4$	192	$C_{18}H_{14}ClN_5O_5$	16.71	16.84	440(3.94);345(4.11); 255(4.30)
2f	p-$NO_2C_6H_4$	237	$C_{18}H_{14}ClN_5O_5$	16.80	16.84	520(4.03);360(4.09) 246(4.28)
2g	C_6H_5	132	$C_{18}H_{15}ClN_4O_3$	14.95	15.11	440(3.94);349(4.19); 246(4.28)
2h	p-BrC_6H_4	140	$C_{18}H_{14}BrClN_4O_3$	12.50	12.45	440(4.04);355(4.20); 253(4.32)

The ultraviolet spectra of (2) in aqueous-ethanol solution vary with increase in the pH of the medium. At pH $\langle$ 3 each compound exhibits an intense $\pi - \pi^*$ band near 375 nm and in alkaline medium the ambident anion absorbs in the region 420 - 550 nm. Spectra recorded at different pH values showed two isobestic points near 420 and 525 nm. The absorbance values of freshly prepared solutions measured at λ_{max} of the anion, plotted against pH showed a dependence in the shape of a dissociation curve of a monobasic acid (Fig. 1). From the pH-absorbance data, the overall pK_a values for (2a - 2h) were determined. The results are listed in Table 2. Inspection of these data reveals that both inductive and conjugative effects of the substituents examined are operative. For a deeper insight, the fitness of the data in the simple and extended Hammett equations [1] and [2] respectively was tested.

The pK_a data for (2) agree with the simple Hammett equation [1] (Fig.2). The equation of the straight line obtained follows equation [7] :

$$[7] \qquad pK_a = 7.49 - 1.158\,\sigma_X \quad ; r = 0.995 \; ; s = \pm\, 0.036$$

Following the foregoing arguement, the linearity observed between pK_a values and σ_X constants can be taken as an evidence that the diazonium coupling products (2) exist in one tautomeric structure namely (2B). The value of the reaction constant, ρ, of -1.158 is similar to -1.223 found for the acid dissociation of 2-arylazophenols (5) in 50% ethanol-water medium[13]. This similarity suggests that the transmission of electronic effects in (2B) , like in (5), occurs through the hydrogen bond, and in the mean time substantiates the assignment of the o-hydroxyazo structure (2B).

Next , the ionization constants for (2) were correlated with the extended Hammett equation [2] using multiple regression analysis[14]. The data used in the correlation are given in Table 2. For the para substituents, the $\sigma_{I,X}$ were taken from the collection of Taft and coworkers[15]; the $\sigma_{R,X}$ constants were obtained from the relation:

$$[8] \qquad \sigma_{R,X} = \sigma_{p-X} - \sigma_{I,X}$$

For the meta-substituents, the $\sigma_{R,X}$ constants were estimated by the method of Charton[16] using the relation:

$$[9] \qquad \sigma_{R,X} = 0.25\,\sigma_{m-X}$$

The σ_{p-X} and σ_{m-X} constants were taken from the copilation of Ritchie and Sager[17]. The results of the correlation with equation [2] are presented in

Table 4. The value of the multiple correlation coefficient of 0.997 indicates an excellent correlation. The Values of α and β, thus obtained, indicate that for series (2) the composition of the electrical effect, E, defined as the ratio β/α has a value of 0.86. This value substantiates the cis-chelated structure (2B). This is because for reaction series in which the substituent X has anti configuration (6), the E value is 0.37, whereas for series with syn-configuration (7), the E value is close to unity[18].

Table 4. Results of correlation with Eq. [2] .

Parameter	Value	Parameter	Value
α	-1.245	s_α^b	0.191
β	-1.075	s_β^b	0.132
pK_o	7.49	s_o^b	0.030
R^a	0.997	n	8

a, Multiple correlation coefficient.

b, Standard errors of the estimates : α, β and pK_o

n, number of points .

EXPERIMENTAL

Melting points are uncorrected. Infrared and electronic absorption spectra were recorded on Unicam SP1000 and Unicam SP8000 spectrophotometers respectively. Proton magnetic resonance spectra were obtained on Varian T60A spectrometer with tetramethylsilane as an internal reference.

Ethyl 2,3-dioxobutyrate 2-arylhydrazones were prepared by coupling ethyl acetoacetate with diazotized anilines as previously described[19]. Conversion of these coupling products into ethyl 4-bromo-2,3-dioxobutyrate 2-arylhydrazones was effected by bromination in ether following the method of Garg and Sing[20]. The physical constants of both series of compounds agreed with literature values[19,20].

1-Aryl-3-ethoxycarbonyl-4-hydroxypyrazoles (1). General Procedure - A mixture of the appropriate 4-bromo-2,3-dioxobutyrate 2-arylhydrazone (0.005 mole) and sodium acetate (3.0 g) in 40 ml ethanol was refluxed for 2-3 hr, then cooled. The product separated was collected, washed with water and crystallized from ethanol. The compounds prepared together with their physical constants are given in Table 1.

1-(m-Chlorophenyl)-3-ethoxycarbonyl-4-hydroxy-5-arylazopyrazoles (2). General Procedure - A mixture of (1d) (0.8 g, 0.003 mole) and sodium acetate (1 g.) in ethanol (50 ml) was cooled to 0°C. To this was added portionwise the appropriate arenediazonium chloride (0.003 mole) over a period of 30 min. while stirring. The solid that separated was collected, washed with water and crystallized from ethanol or acetic acid to give (2) in 60-75% yield, Table 3.

Determination of pK_a - The acid dissociation constants of (1) and (2) were determined spectrophotometrically in 60 vol.% ethanol-water medium at 25°C and an ionic strength of 0.10 . A Radiometer pH type 63 fitted with a combined glass electrode type GK2310C was used to record the pH values. The pH meter reading correction factor $(\log U_H)^{23}$ in 60vol.% ethanol-water medium was -0.25. The procedure followed in the determination of the pK_a constants and their calculation from the absorbance-pH data has already been described[21]. Typical titration curves are given in Fig. 1 . The pK_a values obtained were reproducible to within ±0.03 pK_a unit. The results are summarized in Table 2.

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Received, 6th August, 1980