239. *The Kinetics of Alkaline Hydrolysis of 2-, 3-, and 4-Ethoxycarbonylpyridines and their 1-Oxides.*

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Rates of alkaline hydrolysis, in 70% (w/w) ethanol–water, of the esters named in the title have been measured in the temperature range 15—35°. All six are hydrolysed more rapidly than ethyl benzoate; for the pyridine esters the order is $4 > 2 > 3$, but for the 1-oxides it is $3 \approx 2 > 4$. The electronic interpretation of the latter order is discussed.

Recent studies of substituted pyridine 1-oxides, as summarized by Katritzky, Randall, and Sutton,[1] show that the *N*-oxide group may act as an electron-donor or -acceptor, depending on the requirements of any group attached to the carbon atom considered. This duality is observed also in reactivities; *e.g.*, the 4-position is activated to both nucleophilic and electrophilic attack.[2] The theoretical interpretation of these facts has been considered by Jaffé,[3] and more recently by Barnes.[4]

The object of the present investigation is to obtain quantitative information concerning the rates of reaction of pyridine 1-oxides. As a first step we have studied the alkaline hydrolysis of ethoxycarbonylpyridine 1-oxides in ethanol–water (70% w/w). We have also measured rates of hydrolysis of the ethoxycarbonylpyridines, since the only previous determinations were at one temperature only.[5] A kinetic study of the hydrolysis of amides of the pyridine series has recently been reported.[6]

Experimental

Esters.—Ethoxycarbonylpyridines were prepared from the acids by use of ethanol–sulphuric acid and purified by fractional distillation: 2-, b. p. 125°/12 mm., n_D^{20} 1·5105 (lit.,[7] 1·5104); 3-, b. p. 105°/11—12 mm., n_D^{20} 1·5040 (lit.,[7] 1·5038); 4-, b. p. 100—101°/11 mm., n_D^{20} 1·5016 (lit.,[7] 1·5017). 3- and 4-Ethoxycarbonylpyridine 1-oxides were prepared by Katritzky's method [8] and had m. p. 99·5—101·5° and 68—70° respectively (lit.,[8] 100·5—102·5° and 63·5—65°), $\lambda_{\max.}$ 224, 272 mμ (ε 24,700, 12,500) and $\lambda_{\max.}$ 223, 293·5 mμ (ε 11,100, 19,700) respectively in 95% EtOH. 2-Ethoxycarbonylpyridine 1-oxide was obtained by the method of Katritzky *et al.*[9] except that the yield was increased from 3% to 30% by using sodium hydrogen carbonate in place of sodium carbonate in the working up. The ester, which darkened considerably when kept, had b. p. 152—160°/1·1—1·2 mm., n_D^{20} 1·5570, $\lambda_{\max.}$ 217, 272 mμ (ε 13,500, 10,300) in 95% ethanol (Found: N, 8·0. Calc. for $C_8H_9NO_3$: N, 8·4%).

Acids.—For the p*K* measurements, pure samples of pyridine-3- and -4-carboxylic acid were crystallised three times from water, and pyridine-2-carboxylic acid from benzene. The 1-oxide of the last formed needles, m. p. 159—160° (lit.,[10] 160°), from methanol.

Solvent.—The solvent used throughout was aqueous ethanol d_{25}^{25} 0·8646 (70·55% w/w).

[1] Katritzky, Randall, and Sutton, *J.*, 1957, 1769.
[2] Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[3] Jaffé, *J. Chem. Phys.*, 1952, **20**, 1554.
[4] Barnes, *J. Amer. Chem. Soc.*, 1959, **81**, 1935.
[5] Kindler, *Ber.*, 1936, **69**, 2806.
[6] Favini, *Rend. Ist. Lombardi Sci.*, 1957, **91**, 162.
[7] Mena and Nunez, *Ciencia*, 1954, **14**, 156.
[8] Katritzky, *J.*, 1956, 2404.
[9] Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182.
[10] Hata, *Bull. Chem. Soc. Japan*, 1958, **31**, 255.

Hydrolysis Rates.—(a) *Ethoxycarbonylpyridines.* A standard titration procedure was employed as described by Elderfield and Siegel.[11] Solutions were approx. 0·04M-sodium hydroxide and 0·02M-ester in 70% aqueous ethanol. The thermostat bath was maintained within ±0·01° of the required temperature.

(b) *Ethoxycarbonylpyridine* 1-*oxides.* The titration procedure was replaced by a conductometric method on account of the very rapid hydrolysis of these esters. Conductances were measured on a direct-reading conductivity bridge (Cambridge Instruments) with an accuracy of ±0·2%. The conductivity cell was of the type described by Evans and Hamann.[12] The ester solution (20 ml.; approx. 0·005M) was placed in the electrode compartment, and sodium hydroxide (20 ml.; approx. 0·01M) in the smaller compartment. After the whole had reached temperature equilibrium with the bath, the solutions were rapidly mixed and conductance readings were taken after suitable intervals of time (generally 15—30 sec.). The reactions were followed to about 70% hydrolysis and 15—20 readings were taken. A linear relation being assumed between conductance and hydroxyl-ion concentration, the concentration of unchanged ester at time t is given by $c_t = c_0 (\kappa_t - \kappa_\infty)/(\kappa_0 - \kappa_\infty)$, where c_0 is the initial concentration of ester, κ_0 the initial conductance, κ_∞ that when hydrolysis is complete, and κ_t that at time t. κ_0 was determined from the conductance of a mixture of equal volumes of the sodium hydroxide solution and solvent, with a correction ($\not>$0·5% of the total) for the conductance due to the ester itself. κ_∞ was determined when the conductance had attained a constant value (usually 1—2 hr.). Blank runs with alkali alone gave no detectable change in conductance over this time. At least two runs were carried out on each ester at each temperature. The complete series included sets of runs in which both ester concentration and alkali concentration were varied. Good agreement with second-order kinetics was obtained in all cases. Table 1 gives the mean rate constants obtained together with the derived values of $\log_{10} A$ and E for the Arrhenius equation $\log_{10} k = \log_{10} A - E/2{\cdot}303RT$.

TABLE 1. *Rates of hydrolysis of* $R{\cdot}CO_2Et$ *as* $\log_{10}k$ (k *in l. mole*$^{-1}$ *sec.*$^{-1}$).

R	15°	17°	20°	25°	30°	35°	log A	E (kcal. mole^{-1})
2-Pyridyl		−1·488		−1·189		−0·858	9·3	14·4
3-Pyridyl		−1·701		−1·416		−1·101	8·6	13·7
4-Pyridyl		−0·939		−0·692		−0·415	8·0	12·0
2-Pyridyl 1-oxide	−0·053		+0·121	+0·277	+0·425	+0·587	9·7	13·0
3-Pyridyl 1-oxide	−0·112		+0·083	+0·258	+0·412	+0·587	10·5	14·1
4-Pyridyl 1-oxide	−0·378		−0·186	−0·026	+0·143	+0·272	9·7	13·3
Phenyl		−3·355		−3·031		−2·650	8·7	16·1

p*K Values.*—These were obtained by a simple potentiometric method using 0·005M-solutions of the acid and its sodium salt.

DISCUSSION

No great significance can be given to small differences in log A or E values since these quantities are very sensitive to experimental error. However, the values of log A for 3- and 4-ethoxycarbonylpyridine appear to be approximately the same as for ethyl benzoate. The 2-isomer may be abnormal owing to the proximity of the nitrogen atom (cf. Simonetta and Favini [13]). All three ethoxycarbonylpyridines and their 1-oxides have lower activation energies than ethyl benzoate. The very rapid hydrolysis of the 1-oxides, however, is not associated with abnormally low activation energies, but rather with log A values which are about 1 unit higher than for the other esters studied.

Under the conditions of hydrolysis used, a mechanism other than $B_{AC}2$ is unlikely. It has been established by studies of substituted ethyl benzoates that the activation energy in such reactions is decreased by an increase in the electron-attracting power of the attached residue. The observed order 4-pyridyl < 3-pyridyl is thus in agreement with the conclusion from other evidence that the ring nitrogen atom withdraws electrons more effectively from the 4- than from the 3-position. For the 2-ester, steric effects may be an interfering factor. It is interesting that, whilst in the series studied here the 2-ester

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[11] Elderfield and Siegel, *J. Amer. Chem. Soc.*, 1951, **73**, 5622.

[12] Evans and Hamann, *Trans. Faraday Soc.*, 1951, **47**, 31.

[13] Simonetta and Favini, *Gazzetta*, 1954, **84**, 566; 1955, **85**, 1025.

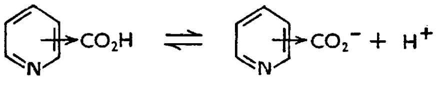
is hydrolysed faster than its 3-isomer, the reverse is the case for the alkaline hydrolysis of the acetates of the pyridylmethanols.[13]

For the 1-oxides, all three esters are hydrolysed about 1000 times more rapidly than ethyl benzoate. Hence very powerful electron-withdrawal must be affecting all positions of the ring and being relayed to the attached ethoxycarbonyl groups. This cannot be a conjugative process since the 3- is affected more than the 4-position. Instead, we suggest that the dominant factor is electron-withdrawal by a " direct " effect as discussed by Ingold [14] or by a normal inductive effect through the σ-electrons of the ring. The latter effect would diminish with increasing distance from the powerfully electron-attracting nitrogen atom which probably carries a considerable positive charge. The present example is somewhat similar to cases studied by Roberts, Clement, and Drysdale,[15] and by Rooda, Verkade, and Wepster,[16] in both of which greater electron-withdrawal from the *meta*- than from the *para*-position of a substituted benzene was observed. For the 1-oxides studied here, mesomeric effects are possible in either direction, but presumably they are too weak to alter the order of reactivity for the 3- and 4-positions. A " direct " or inductive effect as postulated above, does not explain why the 2-ester differs only slightly in rate of reaction from its 3-isomer although the ethoxycarbonyl group is much nearer to the nitrogen atom. A possible explanation is that the formation of the transition state is subject to steric hindrance in the 2-ester.

For the 4-position, conjugative electron-release to the ethoxycarbonyl group is a possible deactivating factor, but spectroscopic evidence indicates that this is unlikely in the 2-position. We have observed that, in the spectra of the esters in ethanol, the main band in the 270 mμ region is almost identical in position for the 2- and the 3-ester, but is shifted to longer wavelengths (*ca.* 20 mμ) and intensified for the 4-ester. Similar observation on the acids [10] could be a result of hydrogen bonding, but this is clearly not the case for the esters. In the latter, the ethoxycarbonyl group in the 2-position is twisted out of the plane of the ring and is hence unable to conjugate appreciably with it (cf. infrared spectra [9]). Mesomeric electron-release to the ring carbon atom is, however, still possible.

Reactions of the type studied here have been discussed in terms of the Hammett equation,[17] substituent constants being defined for the replacement of −CH= of a benzene ring by −N=. Table 2 summarizes values of these constants (σ_2, σ_3, and σ_4) derived from all available data. Where the same reaction has been studied at different temperatures, only one has been selected for the present purpose. In our view, the values do not constitute very strong evidence for the validity of the Hammett equation in this series, particularly in view of the similarity of several of the reactions involved. Poor agreement is not unexpected for the σ_2 values, but variations of, *e.g.*, 0·45—1·3 in the case of σ_3 are quite unsatisfactory.

In general, it is preferable to define σ values in terms of the thermodynamic dissociation constants of carboxylic acids [18] and to use these to determine reaction constants (ρ). In the pyridine series, the required dissociation constants cannot be measured directly because of the large proportion of zwitterion present in aqueous solutions. Of two possible indirect methods, one [19-21] uses spectrophotometric measurements to calculate the true constant for the equilibrium:



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[14] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, 1953, pp. 731, 732.
[15] Roberts, Clement, and Drysdale, *J. Amer. Chem. Soc.*, 1951, **73**, 2181.
[16] Rooda, Verkade, and Wepster, *Rec. Trav. chim.*, 1954, **73**, 849.
[17] Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 96.
[18] McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420.
[19] Green and Tong, *J. Amer. Chem. Soc.*, 1956, **78**, 4896.
[20] Stephenson and Sponer, *J. Amer. Chem. Soc.*, 1957, **79**, 2050.
[21] Lumme, *Suomen Kem.*, 1957, **30**, *B*, 168.

from observed pK values. Green and Tong [19] explain the assumptions involved in this method, and do not claim great accuracy for the results. An alternative method uses pK measurements in partially non-aqueous solvents to reduce the amount of zwitterion present (cf. Elderfield and Siegel [11]). Neither method is sufficiently reliable to define " primary " σ constants.

Cavill, Gibson, and Nyholm [22] determined pK values in water for sparingly soluble substituted benzoic acids by making pH measurements in aqueous acetone and extrapolating them to 100% water by use of an empirical function of solvent composition which gave a linear plot. A preliminary study of pyridine-3-carboxylic acid revealed, however, that the same function gave a curved plot even at 70% of acetone. Hence, this method was also regarded as unsuitable for definition of accurate σ values.

In view of these difficulties, for the various reactions and equilibria in Table 2 we have evaluated the expression $(1/\rho)\ \log_{10}(k_4/k_3)$, where k_4 and k_3 are the rate or equilibrium constants for the 4- and the 3-isomers respectively. The ρ values are those obtained from measurements on benzene derivatives and tabulated by Jaffé.[23] The values of the above expression in cols. 1, 3, 4, and possibly 5 agree well with each other, as expected if the Hammett equation were applicable (these would be values of $\sigma_4 - \sigma_3$) although the individual values of σ_4 and σ_3 differ greatly. This suggests an equation of the type, $\log_{10} k = \chi + \rho\sigma$, in which the constant χ is determined by both the reaction considered and the series (benzene, pyridine). The Hammett equation uses the value $\log_{10} k_0$ (k_0 is the rate or equilibrium constant for the unsubstituted benzene) throughout. If σ is a measure of the electron density at a particular ring-carbon atom, and ρ indicates the extent to which the rate of a reaction is affected by changes in this electron density, the same value of ρ might be expected to hold in different series. We intend to carry out further measurements to test the validity of the modified equation suggested above, and to determine whether ρ values measured in the benzene series are in fact applicable to the pyridine series.

TABLE 2. *Hammett substituent constants for replacement of* –C= *by* –N=.

	(1)	(2)	(3)	(4)	(5)
σ_2	0·08	0·08	0·81	1·1	0·37
σ_3	0·45	0·59	0·62	1·3	0·55
σ_4	0·76	0·70	0·93	1·6	0·95
$\log_{10}(k_4/k_3)$	0·31	0·15	0·76	0·076	0·47
$(1/\rho)\ \log_{10}(k_4/k_3)$	0·31	0·09	0·31	0·30	0·39

(1) From dissociation constants of acids in water.[19] (2) From dissociation constants of acids in 50% ethanol [values determined by present authors: pK = 5·53 (2-acid), 4·81 (3-acid), 4·66 (4-acid)]: poor agreement of the $(1/\rho)\ \log_{10} k_4/k_3$ values with those in other column ssuggests that considerable amounts of zwitterion form are present. (3) From rates of alkaline hydrolysis of ethoxycarbonylpyridines at 30°.[5] (4) From rates of alkaline hydrolysis of pyridylmethyl acetates at 20°.[13] (5) From rates of alkaline hydrolysis of pyridine-carboxyamides at 64·5°.[6]

If we take $\sigma_4 - \sigma_3 = 0{\cdot}31$, our rate measurements give the value $\rho = 2{\cdot}3$ for the alkaline hydrolysis of pyridine esters in 70% ethanol at 25°. For the 1-oxides, values of σ_4 and σ_3 from dissociation constants in water or 50% ethanol agree well [3] (zwitterion formation is relatively unimportant) and along with our rate measurements give similarly a value $\rho = 2{\cdot}2$, of the order observed for substituted benzoic esters in similar solvent mixtures. The pK values of pyridine-2-carboxylic acid 1-oxide (3·55 in water, 4·72 in 50% ethanol) give $\sigma_2 = 0{\cdot}65$, quite different from the value (1·5) expected from the rate of hydrolysis of the corresponding ester. Clearly, the 2-isomers are anomalous in both the pyridines and their 1-oxides as far as the Hammett-type treatment is concerned.

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[22] Cavill, Gibson, and Nyholm, *J.*, 1949, 2466.

[23] Jaffé, *Chem. Rev.*, 1953, **53**, 191.