953. *The Electrophilic Reactivity of Pyridine, Deduced from the Pyrolysis of* 1-*Arylethyl Acetates.*

By R. Taylor.

The electrophilic reactivities of the 2-, 3-, and 4-positions in pyridine have been determined by comparing the effects of pyridyl substituents with that of the phenyl substituent, on the stability of adjacent carbonium ions in the gas-phase pyrolysis of 1-arylethyl acetates. The rates of pyrolysis of 1-phenyl-, and 1-2′-, 1-3′-, and 1-4′-pyridyl-ethyl acetate were each measured at four temperatures between 319·8° and 387·7°. The relative reactivities are phenyl- $\gg$ 3-pyridyl- $\gg$ 2-pyridyl- $>$ 4-pyridyl-ethyl acetate, and a plot of the values of log k/k_0 (log $k_{\text{Py}}/k_{\text{Ph}}$) against π-electron densities of pyridine, calculated by the Hückel molecular-orbital method, with the parameters previously found satisfactory for quinoline and isoquinoline is linear. Analysis of the results in terms of localisation energies indicates that the auxiliary inductive effect is only partially operative at localised centres.

The electrophilic reactivity of pyridine cannot be determined by measuring the rate at which it reacts with external electrophiles, since the latter seem only to be found in acidic media; protonation to a different species, the very unreactive pyridinium ion, therefore occurs, and reaction only takes place under extreme conditions, *e.g.*, pyridine (as pyridinium ion) is sulphonated (in the 3-position) only after being heated with fuming sulphuric acid at 320—330° for many days,[1] whereas H. C. Brown and Kanner showed [2] that 2,6-di-t-butylpyridine (in which protonation of the nitrogen atom is sterically hindered) could be sulphonated in 4 hr. by sulphur trioxide in liquid sulphur dioxide at $-10°$. Qualitative measures of the electron-donating ability of pyridine, which is related to its electrophilic reactivity, have been obtained [3] from a study of the C=O stretching frequencies of substituted pyridines of the type Py·COR, which indicates an electron-donating order Ph $>$ 3-Py $>$ 4-Py.

The gas-phase pyrolysis of esters is a unimolecular first-order reaction of stoicheiometry two.[4] The reaction requires partial formation of a carbonium ion which develops on the carbon atom to which the acyl group is initially attached; this has been shown from a study of the pyrolysis rates of 1,2-diaryl- and 1-aryl-ethyl acetates.[5,6] Plots of log k/k_0 values for the effects of substituents in the 1-aryl ring against Hammett's σ-constants were unsatisfactory in each series, whereas plots of log k/k_0 values against σ^+-constants

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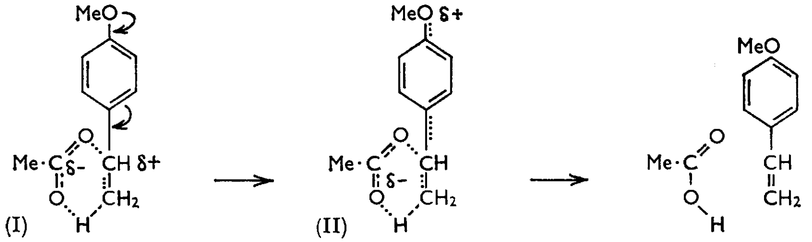
[1] Fischer, *Chem. Ber.*, 1882, **15**, 62.
[2] H. C. Brown and Kanner, *J. Amer. Chem. Soc.*, 1953, **75**, 3865.
[3] Katritzky, *Quart. Rev.*, 1959, **13**, 353.
[4] DePuy and King, *Chem. Rev.*, 1960, **59**, 431.
[5] Smith, Bagley, and Taylor, *J. Amer. Chem. Soc.*, 1961, **83**, 3647.
[6] Taylor, Smith, and Wetzel, *J. Amer. Chem. Soc.*, in the press.

(H. C. Brown and Okamoto [7]) were linear for a number of *meta-* and *para*-substituents. This shows that the reaction proceeds by partial formation of a carbonium ion (I) which can be stabilised (or destabilised) in the transition state by substituents in the 1-aryl ring, as for example in (II).



Yukawa and Tsuno [8] showed that substituent effects in a number of reactions involving the formation (in the rate-determining stage) of carbonium ions in the aryl ring (pure electrophilic substitutions) or in the side chain could be correlated with considerable precision by means of the equation, log $k/k_0 = \rho[\sigma + r(\sigma^+ - \sigma)]$, where r is a measure of the amount of resonance interaction between the substituent in the aryl ring and the incipient carbonium ion.* The *precise* correlation of log k/k_0 values with σ^+-constants in the pyrolysis of 1,2-diaryl- and 1-aryl-ethyl acetates is therefore fortuitous and arises because the amount of resonance stabilisation of the incipient carbonium ion by the substituents in the pyrolysis reaction is approximately the same as in the solvolysis of αα-dimethylbenzyl chlorides, σ^+-constants being derived from the latter reaction. Thus the pyrolysis of 1-arylethyl acetates is allied to electrophilic aromatic substitution, and it follows that substituent effects in the former reaction can be related to those observed in reactions of the latter type. The ρ-factor for the pyrolysis reaction is only —0·66 (at 600°K) and the reaction is therefore particularly suitable for determining the effects of strongly activating or deactivating substituents since relative-rate measurements can generally all be carried out under the same set of conditions. Hence it appeared that this reaction could be used to determine, quantitatively, the electrophilic reactivity of pyridine under conditions whereby protonation of the nitrogen atom could not occur.

RESULTS AND DISCUSSION

The rates of pyrolysis of the esters at various temperatures are given in Table 1 together with the values of log k/k_0 (log $k_{\mathrm{Py}}/k_{\mathrm{Ph}}$), the energies, and entropies of activation, determined at 625°K. Rate constants were reproducible to within ±2% for 1-phenylethyl acetate, ±3% for 1-3′-pyridylethyl acetate, and ±4% for the 1-2′- and 1-4′-pyridylethyl acetate (see Experimental section). The maximum errors arising from calculating the values of E and $\Delta S^{\ddagger}$ from rate constants obtained over a 50° range are 0·3 kcal./mole and 0·5 e.u., respectively, for each percentage error in the rate constants at a given temperature. Thus, within the limits of experimental error, both E and $\Delta S^{\ddagger}$ could be considered constant. However, previous work has indicated that the pyrolysis of 1-arylethyl acetates is a reaction controlled by variations in the activation energy,[6] and the present results are in agreement with this observation since the activation energy decreases as the reactivity of the esters increases.

The Arrhenius diagram of the results is given in Fig. 1. Although individual rate

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* Van Bekkum, Verkade, and Wepster,[9] and Taft,[10] have proposed rather more rigorous treatments which take account of the fact that σ-constants are themselves derived in a system in which resonance interaction between the substituent and the reaction site is finite.

[7] H. C. Brown and Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.

[8] Yukawa and Tsuno, *Bull. Chem. Soc. Japan*, 1959, **32**, 971.

[9] Van Bekkum, Verkade, and Wepster, *Rec. Trav. chim.*, 1959, **78**, 816.

[10] Taft, *J. Phys. Chem.*, 1961, **64**, 1805.

TABLE 1.

Pyrolysis of compounds $CH_3{\cdot}CHR{\cdot}OAc$.

R	Temp.	10^3k (sec.$^{-1}$)	log A	E (kcal./mole)	$\Delta S\ddagger$ (e.u.)	log k/k_0
Phenyl...............	371·7°	9·38	12·81	43·7	−1·3	0·00
	352·9	3·33				
	335·5	1·16				
	322·1	0·480				
3-Pyridyl	387·7	14·3	12·62	43·7	−2·2	−0·19
	367·7	4·93				
	349·6	1·73(5)				
	334·4	0·770				
2-Pyridyl	387·0	6·70	12·73	44·9	−1·7	$-0{\cdot}50_6$
	371·4	2·79				
	353·1	1·06				
	336·2	0·379				
4-Pyridyl	386·9	5·97	12·79	45·1	−1·4	−0·55
	371·4	2·60				
	352·9	0·935				
	335·5	0·326				

constants could be in error by as much as ±4%, the linearity of the plots indicates that the values of log k/k_0, which are obtained from the diagram at the point corresponding to 625°K, are accurate to better than this. The spread of rates decreases towards higher temperature in agreement with previous results[6] and the reactivity-selectivity principle of H. C. Brown and Nelson which predicts that the spread of rates should decrease as the reaction takes place more readily.[11]

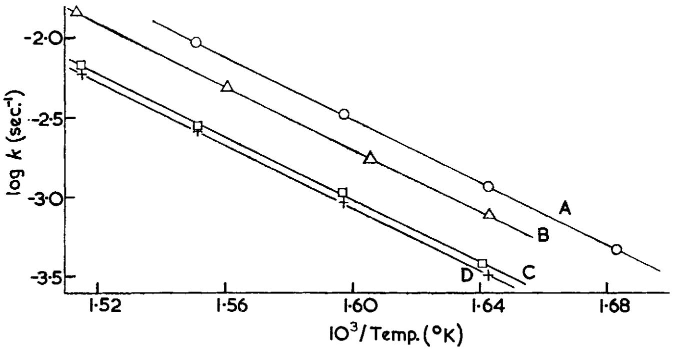

FIG. 1. Arrhenius plot for the pyrolysis of 1-arylethyl acetates. Aryl = (A) phenyl, (B) 3-pyridyl, (C) 2-pyridyl, (D) 4-pyridyl.

The main features of the results are two-fold:

(i) The ability of the aryl substituent to stabilise an adjacent carbonium ion is in the order Ph $\gg$ 3-Py $\gg$ 2-Py $>$ 4-Py, and thus all nuclear positions in pyridine will be deactivated towards electrophilic substitution, the 3-position being the least deactivated. Although this result is in accordance with the well-known reactivity of pyridine in electrophilic substitution, each of the previous reactions has involved the pyridinium ion. Hence the present results constitute the first assessment of the electrophilic reactivity of the neutral pyridine molecule.

Previous work has shown that the ρ-factor for the pyrolysis of 1-arylethyl acetates is —0·66 at 600°K and —0·63 at 625°K. From the log k/k_0 values given in Table 1 σ^+-"constants" for positions 2, 3, and 4 in pyridine of +0·80, +0·30, and +0·87, respectively, may be calculated. It is stressed that these exact values will only apply in reactions in which the amount of resonance stabilisation of the transition states is the

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[11] H. C. Brown and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 6292.

same as in the pyrolysis of 1-arylethyl acetates, *i.e.*, in reactions where r, the resonance factor, is 1·0 on the scale defined by Yukawa and Tsuno.[8] The electronegativity of the nitrogen atom (relative to carbon) in pyridine gives rise to a combination of $-I$ and $-M$ effects.* The former effect withdraws electrons from, and deactivates, all nuclear positions towards electrophilic substitution, and the latter effect further deactivates positions 2, 4, and 6. However, since neither of these effects is time-variable, it is to be expected that these σ^+-constants will describe, with considerable accuracy, the reactivity of the nuclear positions of pyridine towards electrophilic substitutions of widely varying demand for resonance stabilisation of the rate-determining transition states. It also follows that the differences between the σ^+-constants and the Hammett σ-constants will be relatively small, as they are for example for the nitro- and cyano-substituents which also give rise to $-I$ and $-M$ effects. It is instructive to note that the σ^+-constants indicate that, towards electrophilic substitution, the 3-position of pyridine will have a reactivity similar to a position in benzene *meta* to a halogen substituent, whilst the 2- and the 4-position will have reactivities similar to that of a position in benzene *para* to a nitro- or cyano-substituent.

(ii) Numerous attempts have been made to relate the reactivities of heterocyclic compounds to π-electron densities and to localisation energies of the nuclear positions.[13] Where the transition state of a particular reaction resembles the reactants, then a correlation of electrophilic reactivity with π-electron densities would be expected, whereas, if the transition state resembles the Wheland intermediate, then the electrophilic reactivity should be correlated with localisation energies. In attempting to relate electrophilic reactivities to either of the above quantities, two difficulties arise: first, the nature of the transition state must be ascertained and, secondly, the correct parameters for the coulomb and resonance integrals of the heterocyclic atom must be chosen. Now the ρ-factor for the pyrolysis of 1-arylethyl acetates is very small, whilst the resonance factor, r, of 1·0 is not large compared with values obtainable in some reactions involving incipient carbonium ions in the rate-determining transition states.[9] Both these facts provide evidence, therefore, that the transition state in the pyrolysis of 1-arylethyl acetates will tend to resemble the reactants rather than the Wheland intermediate, so that deformation of the π-electron orbitals of the aryl rings (relative to their configuration in the ground state) will be fairly small in the transition state of the reaction; hence correlation of log k/k_0 values with π-electron densities would be expected.

The choice of parameters for the resonance and coulomb integrals of nitrogen has received considerable attention of late. It has been suggested [14,15] that the resonance integral for nitrogen, β_{CN}, is approximately the same as that for carbon, β_{CC}, so that $\beta_{CN} = \beta_{CC}$ (which has the standard value β) is a reasonable working assumption. The coulomb integral of nitrogen may be written as $\alpha_N = \alpha_C + h\beta$, where α_C is the coulomb integral of carbon. Measurements of dipole moments,[16] and the reactivity of pyridine towards free radicals,[15] have indicated a value of 0·5 for h. The carbon atoms adjacent to the nitrogen atom may not be treated as identical with the other carbon atoms in the pyridine ring, since their electronegativity will be enhanced by the proximity of

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* Pyridine cannot be activated towards electrophilic substitution by a $+E$ effect since this would involve a geometrically unfavourable (forbidden) n–π transfer of electrons from the lone pair of the nitrogen to the π-orbitals of the ring. Such a process, which is observed in absorption spectra,[12] would require a very high minimum energy before occurring and would then totally alter the character of the aromatic system. The high energy requirement means that an activation by such a process in electrophilic reactions is not only extremely unlikely, but in any event would not vary according to the perturbation, as is required for a $+E$ effect.

[12] Platt, *J. Chem. Phys.*, 1951, **19**, 101.

[13] de la Mare and Ridd, " Aromatic Substitution, Nitration and Halogenation," Butterworths Scientific Publns., 1959, contains examples in Chapter 17.

[14] R. D. Brown, *Quart. Rev.*, 1952, **6**, 63.

[15] R. D. Brown, *J.*, 1956, 272.

[16] Lowdin, *J. Chem. Phys.*, 1951, **19**, 1323.

the nitrogen atom. The coulomb integral of these carbon atoms may be written as $\alpha_{C'} = \alpha_C + h'\beta$, and R. D. Brown and Harcourt have shown[17] that the chemistry of quinoline and isoquinoline can be related to π-electron densities if a value of 0·085 is used for h'.

In the present paper, π-electron densities have been calculated for pyridine by the Hückel molecular-orbital method[18] with the parameters given above. The values are given in Table 2 along with those calculated for h' values of 0·095, 0·075, 0·050, and 0. (The values for $h' = 0{\cdot}05$ are those calculated by Barnes.[19]) Fig. 2 shows the plot of the log k/k_0 values against π-electron densities obtained for the various values of h', whence it is apparent that an extremely satisfactory linear correlation is obtained for $h' = 0{\cdot}085$, while an almost perfectly linear correlation can be obtained for $h' = 0{\cdot}08$ (when π-electron densities are those interpolated from the calculated values for $h' = 0{\cdot}075$ and 0·085). The fact that the same value of h' gives π-electron densities which describe some of the chemistry of pyridine, quinoline, and isoquinoline is most encouraging. Further work will show if the parameters chosen have the generality in describing the reactivities of heterocycles containing tertiary nitrogen that, at present, they appear to have.

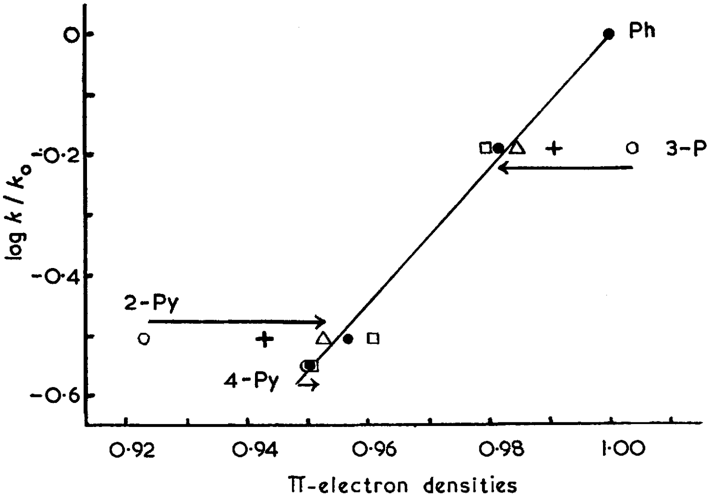

FIG. 2. Plot of log k/k_0 values against π-electron densities for pyridine for $h = 0{\cdot}5$, and various values of h'.

$h' = 0$ (○), 0·05 (+), 0·075 (△), 0·085 (●), 0·095 (□). Increase in h' indicated by the arrows.

TABLE 2.

π-Electron densities of pyridine for values of h'.

h'	0·0	0·05	0·075	0·085	0·095
2-Position	0·923	0·943	0·953	0·957	0·961
3-Position	1·004	0·991	0·985	0·982	0·980
4-Position	0·950	0·950	0·951	0·951	0·951

Because the pyridine molecule is not activated by time-variable resonance effects, it was argued above that the relative reactivities of positions 2, 3, and 4 should remain fairly constant in electrophilic and related reactions having transition states with configurations varying between the limits of the ground state and the Wheland intermediate. Thus one might expect that the reactivities of these positions in electrophilic-type reactions

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[17] R. D. Brown and Harcourt, *Tetrahedron*, 1959, **8**, 23; *J.*, 1959, 3451.

[18] Hückel, *Z. Physik*, 1931, **72**, 310.

[19] Barnes, *J. Amer. Chem. Soc.*, 1959, **81**, 1935.

for which the transition states more nearly resemble the ground states might nevertheless be correlated reasonably well with localisation energies. To test this possibility, localisation energies have been calculated for pyridine by using the parameters $j = 1{\cdot}0$, $h = 0{\cdot}5$,

TABLE 3.

Localisation energies for pyridine for values of h'.

h'	2-Position	3-Position	4-Position
0·0	2·672	2·540	2·700
0·05	2·62 * (2·72) †	2·57	2·69
0·085	2·589 * (2·759) †	2·596	2·698

* Calculated by assuming that the auxiliary inductive effect operates at the localised centre.

† Calculated by assuming that the auxiliary inductive effect does not operate at the localised centre.

and $h' = 0{\cdot}085$ (where $j = \beta_{CN}/\beta_{CC}$), which were found above to give a linear log k/k_0 *vs.* π-electron density correlation. The values are given (in units of $-\beta$) in Table 3 with, for comparison, those calculated by R. D. Brown and Heffernan[20] for $j = 1{\cdot}0$, $h = 0{\cdot}5$, $h' = 0$, and by Barnes[19] for $j = 1{\cdot}0$, $h = 0{\cdot}5$, and $h' = 0{\cdot}05$.

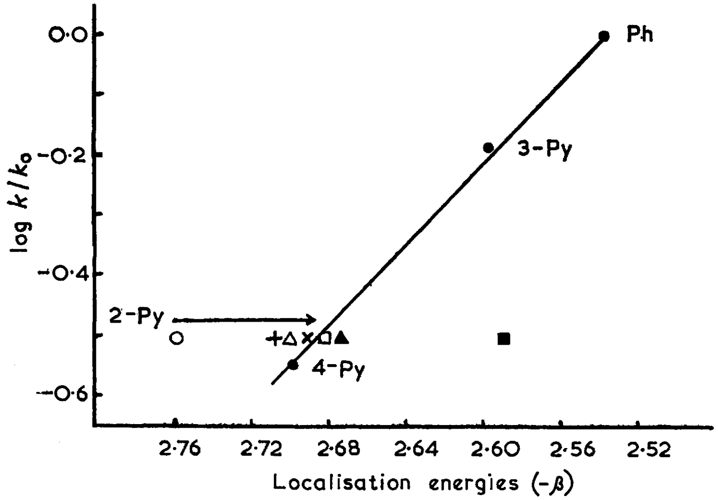

FIG. 3. Plot of log k/k_0 values against localisation energies for pyridine for $h = 0{\cdot}5$, $h' = 0{\cdot}085$, and various values of δ.

δ = 0 (○), 0·30 (+), 0·35 (△), 0·40 (×), 0·45 (□), 0·50 (▲), 1·0 (■). Increase in δ indicated by the arrow.

Uncertainty arises in the calculation of the localisation energy of the 2-position when an auxiliary inductive parameter is used because it is not then clear what energy should be assigned to the electrons localised at the position of attack. As R. D. Brown and Harcourt have pointed out,[17] if the auxiliary inductive effect is still fully operative at localised centres then $\alpha_C + h'\beta$ is appropriate, whereas, if it is no longer operative, the value α_C is appropriate; the localisation energies given in Table 3 have therefore been calculated for both these possibilities. In order to decide which of the values of h' gives localisation energies that best describe the experimental results, consider for the moment the localisation energies of the 3- and the 4-position only, since these are not affected by the decision whether or not the auxiliary inductive effect operates at localised centres. It is seen that with $h' = 0{\cdot}085$, the localisation energies are correlated almost linearly with the

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[20] R. D. Brown and Heffernan, *Austral. J. Chem.*, 1956, **9**, 83.

log k/k_0 values (see Fig. 3), whereas for the other values no correlation is obtained. However, even for $h' = 0{\cdot}085$, neither of the localisation-energy values for the 2-position is very reasonable, nor do they correlate with the observed reactivity. Now Wheland suggested that the auxiliary inductive effect should be only partially operative at the position of attack[21] and recommended that the energy of each localised electron be given by $\alpha_C + \delta h'\beta$, where $\delta = 0{\cdot}375$. R. D. Brown and Harcourt[17] showed that the chemical properties of quinoline and isoquinoline could be related to localisation energies if $1 > \delta > 0$ and from the electrophilic reactivity of isoquinoline (presumed to be in the form of the isoquinolinium ion) a value of $\delta < 0{\cdot}43$ was indicated. The localisation energies for the 2-position of pyridine have therefore been calculated for various δ-values and are given (in units of $-\beta$) in Table 4. Fig. 3 shows the plot of the experimental log k/k_0 values against localisation energies for positions 2, 3, and 4 of pyridine for the various values of δ. It is apparent from the plot that a good linear correlation is obtained if the value of δ lies between 0·4 and 0·45; by interpolation a value of 0·43 is found to give the best fit. The similarity of this value with those determined in other work provides grounds for speculating that it may eventually be possible to correlate, with reasonable precision, the chemical properties of nitrogen heterocycles with localisation energies calculated from a consistent set of parameters. This is unlikely to obtain, however, in systems where steric effects are important.

TABLE 4.

$\delta =$	0·3	0·35	0·4	0·45	0·5
$\Delta E_{2\text{-Py}} =$	2·708	$2{\cdot}699_5$	2·691	$2{\cdot}682_5$	2·674

In conclusion, it appears that calculations of π-electron densities and atom localisation energies may have greater significance in predicting the chemical properties of heterocyclic compounds than has previously been considered.

EXPERIMENTAL

Materials.—Acetylpyridines were obtained from the Aldrich Chemical Co. and were reduced by sodium borohydride in the usual manner to the corresponding 1-pyridylethanols. Continuous liquid–liquid extraction was carried out on each highly water-soluble product with ether during 6 hr.; the resulting ethereal solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude alcohol was acetylated with pyridine and acetic anhydride, and the mixture was fractionated through an efficient 40 cm. Vigreux column,[22] to give 1-2′- (28·2 g., 83% overall), b. p. 94°/2·9 mm., n_D^{25} 1·4936 (Found: C, 65·2; H, 6·75. $C_9H_{11}NO_2$ requires C, 65·45; H, 6·7%), 1-3′- (32·0 g., 94%), b. p. 86°/1·8 mm., n_D^{25} 1·4932 (Found: C, 65·3; H, 6·6%), and 1-4′-*pyridylethyl acetate* (32·1 g., 94%), b. p. 76°/1·2 mm., n_D^{25} 1·4906 (Found: C, 65·65; H, 6·8%).

Preparation of 1-phenylethyl acetate has been described.[6]

Apparatus.—The pyrolysis reactor was essentially that described by Smith and Bagley,[23] and was kindly provided by Professor G. G. Smith.

Calculations of π-electron densities and atom localisation energies were carried out on the Ferranti Mercury Computer of the Oxford University Computing Laboratory.

Method of Pyrolysis.—The general method has been described.[5] The rate of pyrolysis of each ester was determined from single runs carried out at four different temperatures and over a temperature range of not less than 50°. As observed in the pyrolysis of 1,2-diaryl-[5] and 2-aryl-ethyl acetates,[6] the pyrolysis of 1-arylethyl acetates is accompanied by a much slower secondary reaction manifested by a continuing pressure increase after ~10 reaction half-lives. The secondary reaction is assumed to be decarboxylation of acetic acid since this is known to occur under the reaction conditions.[24] Acetic acid is the common product in each reaction series,

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[21] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.

[22] Ray, *Rev. Sci. Instr.*, 1957, **28**, 200.

[23] Smith and Bagley, *Rev. Sci. Instr.*, 1961, **32**, 703.

[24] Taylor, unpublished work.

and the extent of the reaction is more marked the less reactive the series of esters and the less reactive an ester within a given series, *i.e.*, the rate of decarboxylation relative to the rate of ester pyrolysis becomes more important as the rate of the latter decreases. Thus, in the present work a secondary reaction, which became more marked the less reactive the ester, was observed, and the stoicheiometry became correspondingly slightly greater than two after 10 half-lives of reaction. The P_∞ value for the elimination of acetic acid from the esters was therefore taken as twice the initial reaction pressure P_0, and reaction rates were calculated from the initial slopes of the plots of log $(P_\infty - P_t)$ against time. For 1-phenylethyl acetate, these plots were linear to beyond 95% of reaction, whereas for the most unreactive 4-pyridylethyl acetate the plots were linear to *ca.* 80% of reaction. Preliminary runs at one temperature indicated that reaction rates could be duplicated to ±2% for 1-phenylethyl acetate, ±3% for 1-3′-pyridylethyl acetate, and ±4% for 1-2′- and 1-4′-pyridylethyl acetate, so that errors introduced by the secondary reaction are very small.

The author is indebted to Mr. B. A. W. Coller for valuable discussion, and to Mr. M. D. Poole for computing some of the atom localisation energies and π-electron densities.

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