289. *The Hydrolysis of Acetic Anhydride. Part III.* The Catalytic Efficiency of a Series of Tertiary Amines.*

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The catalytic effect of a series of heterocyclic tertiary amines on the hydrolysis of acetic anhydride in water at 0° has been studied, and comparative catalytic coefficients have been evaluated for several amines. α-Substituents in the amine decrease the catalytic activity. There was no evidence of formation of an intermediate by interaction of the amine and the anhydride. The experimental facts are consistent with the mechanism proposed, in which the transfer of an acetylium group ($CH_3{\cdot}CO^+$) from acetic anhydride to the catalyst is rate-determining, hydrolysis of the resulting cation being rapid. The low frequency factor generally found in bimolecular heterolytic reactions between neutral molecules (of which the uncatalysed acylation reactions are examples) is explained in terms of entropies of solvation. The rôle of amine catalysts in some preparative acylation reactions is briefly discussed.

IN view of the remarkable catalysis of the hydrolysis of acetic anhydride by pyridine (Part II *) the effect of other tertiary amines has been examined. The catalytic coefficients were evaluated on the basis of the analysis given in Part II. In order to remove the uncertainties consequent upon the use of a mixed solvent the measurements now reported relate to water at 0° as solvent.

More reliable dissociation constants, at 25°, of several of the amines used have recently been reported (Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26; cf. Gero and Markham, *J. Org.*

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* Part II, preceding paper.

Chem., 1951, **16**, 1835) and therefore comparative catalytic coefficients may be deduced from the kinetic data. A slight gap remains in the complete evaluation of catalytic coefficients through lack of knowledge of the temperature dependence of basic dissociation constants.

EXPERIMENTAL

Acetic anhydride was allowed to reflux over magnesium turnings for several days and then fractionally distilled.

Benzoic anhydride was redistilled under reduced pressure and largely freed from benzoic acid by this treatment. Acetone (" AnalaR ") was dried over silica gel and fractionally distilled.

FIG. 1. *Illustration of graphical evaluation of* k_{HL}.

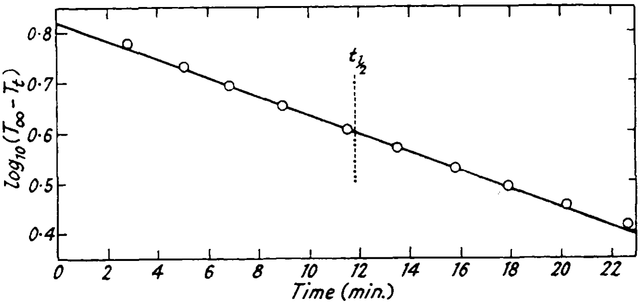
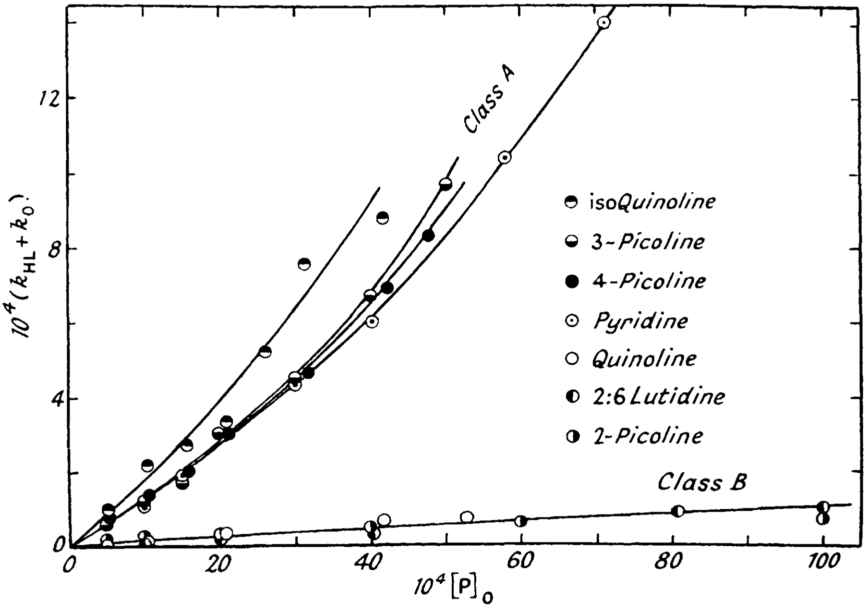


FIG. 2. *Catalytic effect of tertiary amines on the hydrolysis of acetic anhydride.*



For conductivity measurements it was allowed to pass down a column of finely ground silica gel and then fractionally distilled.

Pyridine (" AnalaR ") was purified by the method of Heap, Jones, and Speakman (*J. Amer. Chem. Soc.*, 1921, **43**, 1936), fractionally distilled, and stored over barium oxide.

The picolines (B.D.H.) and 2 : 6-lutidine (Light and Co.) were dried (NaOH) and fractionally distilled. Quinoline (B.D.H.) was also dried over metallic calcium, and *iso*quinoline (Light and Co.) was fractionally frozen. These purification procedures are less stringent than that used for pyridine, and the presence of minor amounts of isomers, homologues, and hydrocarbons in the purified compounds cannot be ruled out. This possibility cannot, however, introduce an error into our measurements large enough to change the major conclusion.

The procedure for rate measurements and evaluation of rate coefficients was described in Part II. As in the previous experiments, the first-order rate coefficients decreased during the reaction (Fig. 1), and the first-order rate coefficients quoted (k_{HL}) are those after one half-life of reaction. In view of the large heat of hydrolysis of acetic anhydride it was verified that the temperature of the reaction mixture did not differ from that of the thermostat bath by more than 0·01°.

The evaluation of catalytic coefficients was based on equation (6) of Part II. For each catalyst the dependence of k_{HL} on the stoicheiometric concentration of catalyst ($[P]_0$) was studied for a fixed initial concentration of anhydride ($[Ac_2O]_0$). This dependence was found to be linear only at the lowest concentrations of catalyst. Since equation (6) was derived on the assumption that $[P]_0$ is small, the slope of the initial low-concentration portion of the curve was used in the evaluation of R (Fig. 2). R is related to the catalytic coefficient k_p by equation (7) of Part II, and the following assumptions were made regarding the other factors occurring in that equation : (i) The ratio $f_I^2 : f_{II}$ was evaluated from the Debye–Hückel limiting law for activity coefficients; at the ionic strength of 0·05M-acetic acid ($\mu \sim 0{\cdot}001$), this ratio is calculated to have the value 0·96. (ii) The constants K_w and K_{AcOH} are accurately known for water at 0° ($K_w = 1{\cdot}14 \times 10^{-15}$ mole^{-2} l.$^{-2}$; $K_{AcOH} = 1{\cdot}66 \times 10^{-5}$ mole l.$^{-1}$). (iii) The recent basic dissociation constants (*locc. cit.*), at 25°, of some of the amines studied by us differ by a factor of 2—3 from those accepted hitherto. There is, however, no information on the values at 0° or the temperature dependence of the dissociation constants. We preferred not to correct for this temperature variation by some arbitrary procedure based on analogies, but we substituted for K_p in equation (7) the experimental value at 25°. In this way we do not obtain the true catalytic coefficient (k_p) at 0°, but the coefficient k'_p which is related to k_p by the equation $k'_p = k_p(K_p)^0/(K_p)^{25}$, where the superscripts indicate the temperatures to which the dissociation constants refer. For comparisons of the catalytic efficiency of different amines, k'_p is probably almost as useful as k_p since the factor $(K_p)^0/(K_p)^{25}$ would not be expected to depend very markedly on the nature of the amine for the particular series considered.

The conductivity apparatus used has previously been described (Gold, *Trans. Faraday Soc.*, 1948, **44**, 506).

Ultra-violet absorption spectra were measured on a Hilger " Uvispek " Spectrophotometer. Infra-red absorption measurements were carried out with a Grubb–Parsons single-beam instrument.

The results are tabulated.

TABLE 1. *Rate coefficients for amine-catalysed hydrolyses of acetic anhydride in water at 0°.*

$10^2[Ac_2O]_0$ (M)	$10^4[P]_0$ (M)	10^4k_{HL} (sec.$^{-1}$)
5·01	—	4·48
	Pyridine	
5·03	5·02	5·22
5·10	10·04	5·60
5·08	15·06	6·44
5·06	20·1	7·10
5·11	30·1	8·81
5·09	40·2	10·52
5·36	58·0	14·9
5·37	71·3	18·5
	2-Picoline	
5·06	5·0	4·69
5·08	10·0	4·78
5·01	20·0	4·84
5·03	40·0	5·01
5·08	60·0	5·12
5·03	100·0	5·23
	3-*Picoline*	
5·01	5·0	5·11
5·20	10·0	5·76
5·45	15·0	6·22
5·34	20·0	7·54
5·35	30·0	9·00
5·35	40·0	11·20
5·34	50·0	14·2
	4-Picoline	
5·25	5·29	5·28
5·12	10·6	5·89
5·21	15·9	6·52
5·09	21·2	7·52
5·26	31·7	8·82
5·31	42·3	11·43
5·20	47·7	12·80
	2 : 6-*Lutidine*	
5·09	5·1	4·57
5·10	10·1	4·61
4·98	20·2	4·70
5·12	40·4	4·84
5·07	80·8	5·40
5·20	100·1	5·51
	Quinoline	
4·97	5·2	4·63
5·02	10·4	4·66
4·96	20·8	4·86
5·05	41·6	5·18
5·11	52·6	5·23
	*iso*Quinoline	
5·10	5·2	5·52
5·26	10·5	6·70
5·08	15·6	7·21
5·32	20·9	7·87
5·19	26·0	9·70
5·22	31·4	12·1
5·31	41·8	13·3

TABLE 2. *Catalytic coefficients for different amines.*

Catalyst	10^3R sec.$^{-1}$ (mole l.$^{-1}$)$^{-\frac{1}{2}}$	$10^{-10}k_p/K_p$ (sec.$^{-1}$)	$10^9(K_p)^{25°}$ (mole l.$^{-1}$)	$10^{-1}k'_p$ (sec.$^{-1}$ mole^{-1} l.)
Pyridine	$28{\cdot}_2$	9·7	1·44 [a]	14
3-Picoline...........	$25{\cdot}_1$	8·6	4·54 [a]	39
4-Picoline	$25{\cdot}_7$	8·8	10·6 [a]	93
*iso*Quinoline	39	13·3	2·5 [b]	33
2-Picoline	$3{\cdot}_4$	1·2	8·77 [a]	11
2 : 6-Lutidine	$2{\cdot}_3$	0·8	38·4 [a]	33
Quinoline	$3{\cdot}_3$	1·1	0·87 [c]	1

[a] Herington, *loc. cit.* [b] Golumbic and Orchin, *J. Amer. Chem. Soc.*, 1950, **72**, 4145. [c] Albert and Goldacre, *Nature*, 1944, **153**, 407.

TABLE 3. *Catalysis of the hydrolysis of benzoic anhydride by pyridine.*

Temp. = 30·02°. Solvent = 50% aqueous acetone (w/w). $[Bz_2O]_0$ = 0·0221M.

$10^4[P]_0$ (M)	—	8·68	17·4	34·8
10^6k_{HL} (sec.$^{-1}$)	4·26	8·67	11·1	14·2

DISCUSSION

The amines examined can be divided into two groups according to their catalytic efficiency. At a given stoicheiometric concentration of amine, pyridine, 3- and 4-picoline, and *iso*quinoline (group *A*) are about ten times more effective catalysts than the members of group *B*, made up of 2-picoline, 2 : 6-lutidine and quinoline (cf. values of *R* in Table 2). On evaluation of the catalytic coefficients k'_p this division seems to disappear but it again comes into evidence if we attempt to relate the catalytic coefficient to the basic dissociation constant of the amine (Table 4). The members of group *A* follow the Brönsted catalysis law: those of the group *B* appear to have catalytic coefficients only about one-tenth of those to be expected from their basic strengths. The effect may in reality be still more pronounced. It is not impossible (see p. 1411) that some of the feeble catalysis found with amines of group *B* may in fact be due to small amounts of impurities of group *A* amines.

TABLE 4. *Test of catalysis law*, $\log k'_p = 10{\cdot}36 + 0{\cdot}92_5 \log K_p$.

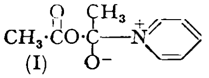
Base	$\log K_p$	$\log k'_p$ (calc.)	$\log k'_p$ (expt.)	Difference	Base	$\log K_p$	$\log k'_p$ (calc.)	$\log k'_p$ (expt.)	Difference
Class A.					*Class* B.				
Pyridine ...	$\bar{9}{\cdot}16$	2·18	2·15	−0·03	2-Picoline ...	$\bar{9}{\cdot}94$	2·90	2·04	−0·86
3-Picoline ...	$\bar{9}{\cdot}66$	2·64	2·59	−0·05	2 : 6-Lutidine	$\bar{8}{\cdot}58$	3·50	2·52	−0·98
4-Picoline ...	$\bar{8}{\cdot}03$	2·99	2·97	−0·02	Quinoline ...	$\overline{10}{\cdot}94$	1·98	1·00	−0·98
*iso*Quinoline	$\bar{9}{\cdot}40$	2·41	2·52	+0·11					

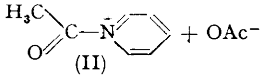
The division into the two groups may be linked with structural similarities. The less active amines are those having a substituent in one or both of the positions adjacent to the heterocyclic nitrogen atom and this suggests steric influence on the mechanism of catalysis. Chemical considerations already render it unlikely that the catalysis involves a proton transfer from anhydride to base, and the steric effect reinforces this view. Furthermore, the hydrolysis of benzoic anhydride (Table 3) is also catalysed by pyridine and in this case the anhydride molecule has no hydrogen atom that could be transferred to the catalyst.

We may also take into consideration the results of related work. It was found that the catalysis is not confined to the acetylation of water, but that pyridine will catalyse the acetylation of *o*-chloroaniline and of ethanol, and that quinoline is again inactive, at least in the former of these reactions (Gold and Jefferson, unpublished work). More significantly still the same division of catalytic amines into two groups occurs in the decomposition of acetic formic anhydride in an aprotic solvent (*idem*, *J.*, 1953, 1416) where the only possible catalytic effect of the amine is by interaction with the anhydride. We therefore suggest that in the hydrolysis too the catalysis is due to an interaction of amine and anhydride, and that it does not take the form of a proton transfer.

Whatever the nature of this interaction, it fairly certainly does not produce an appreciable equilibrium concentration of a new species. All experiments to detect such a product have had negative results : (1) The absorption spectra of pyridine and acetic anhydride in *cyclo*hexane over the range 2300 and 2800 Å (the chief absorption region of pyridine in the near ultra-violet) are strictly additive. (2) In the infra-red absorption spectra of acetic anhydride and an equimolecular mixture of acetic anhydride and pyridine in carbon tetrachloride the intensity and position of the bands due to carbonyl vibrations (at 1769 and 1936 cm.$^{-1}$) and C–O–C skeletal vibrations (at 1124 cm.$^{-1}$) of acetic anhydride are unaffected by the presence of pyridine. (3) The electrical conductivities of mixtures of acetic anhydride and pyridine in dry acetone were not significantly higher than the sum of the conductivities of solutions of acetic anhydride and of pyridine in acetone; the same result was obtained with benzoic anhydride and pyridine in 50% acetone–water at 0°, *i.e.*, under conditions where the hydrolysis is sufficiently slow to permit reliable back-extrapolation of the conductivity measurements to zero time, but otherwise in a solvent and with an anhydride for which the operation of catalysis has been established. (4) Depressions of the freezing point of benzene by acetic anhydride and pyridine are additive. Thus neither an association complex nor an ionic reaction product between an anhydride and pyridine are formed in analytically detectable amounts.

The view that the catalysis occurs *via* some association between amine and the whole or part of the anhydride molecule is strengthened by the known steric hindrance of α-substituents on the rate and equilibria of association reactions of tertiary amines. The Menschutkin reactions of alkyl chlorides (Long, *J.*, 1911, 2164) and benzyl bromide (Baker and Nathan, *J.*, 1935, 519) with heterocyclic amines proceed more slowly if the amine contains a blocked α-position. The complex of 2-picoline with trimethylboron is much less stable than the analogous complexes of pyridine or 3- and 4-picoline (Brown and Barbaras, *J. Amer. Chem. Soc.*, 1947, **69**, 1137) but more stable than the doubly substituted amine 2 : 6-lutidine; and similarly the complex of boron trifluoride with 2 : 6-lutidine is less stable than that with pyridine (Brown, Schlesinger, and Cordon, *ibid.*, 1942, **64**, 325). There are two chemically plausible interaction products between acetic anhydride and pyridine, *viz.*, (I) and (II) (the formulæ being the classical ones to represent molecules in which the real electron distribution will be such as to minimise the energy), but postulation of the complex (I) does not seem sufficient to explain all the observed catalytic effects. It is difficult to see why the bimolecular reaction of (I) with a water or amine molecule should be easier than that of acetic anhydride alone, and it is even less obvious why a structure such as (I) should be an intermediate in the decomposition of acetic formic anhydride (cf. Ingold, *Trans. Faraday Soc.*, 1941, **37**, 718). If we wish to attribute the higher reactivity of (I) than of acetic anhydride to a greater ease of unimolecular heterolysis, then we are in effect postulating the formation of (II) from (I). A consistent interpretation of the phenomena can be based on the postulate that (II) is the complex between amine and anhydride whose formation is important in the catalysis.


(I)


(II)

A structure to which the approximate formula (I) can be assigned would, of course, be the transition state in the formation of (II) from acetic anhydride and pyridine. It does not seem very important for our present purposes to decide whether—with a certain set of equilibrium internuclear distances—a structure (I) also corresponds to a minimum in the potential energy profile, *i.e.*, whether it is a reaction intermediate.

The reaction scheme of the hydrolysis may then be formulated

$$Ac_2O + P \underset{-1}{\overset{1}{\rightleftharpoons}} PAc^+ \text{ (II)} + OAc^-$$

$$PAc^+ + H_2O \xrightarrow[2]{} AcOH + PH^+$$

where steps 1 and 2 may also be composite (involving the transient formation of free acetylium cations), without experimentally significant consequences. Since no detectable amounts of intermediates are formed we may apply the stationary-state hypothesis,

$$v = -\frac{d[Ac_2O]}{dt} = \frac{\kappa_1\kappa_2[Ac_2O][P]}{\kappa_{-1}[OAc^-] + \kappa_2}$$

where the κ's are the rate coefficients of the individual steps of the scheme. Since the concentration of the reagent water is large and invariant, κ_2 is defined to incorporate the function of the concentration of water upon which the velocity of this step depends. If we may set

$$\kappa_2 \gg \kappa_{-1}[\text{OAc}^-] \text{ or } \kappa_2 \ll \kappa_{-1}[\text{OAc}]^-$$

simplified forms of this equation are obtained, *viz.*,

$$v = \kappa_1[\text{Ac}_2\text{O}][\text{P}]$$

i.e., a rate-determining acetylium-ion transfer from acetic anhydride to pyridine, or

$$v = \frac{\kappa_1\kappa_2}{\kappa_{-1}} \cdot \frac{[\text{Ac}_2\text{O}][\text{P}]}{[\text{OAc}^-]}$$

which implies the establishment of a rapid pre-equilibrium made up of reactions 1 and −1. The second simplified equation is not in agreement with experimental facts. The effect of added acetate ion (as sodium or potassium acetate) on the hydrolysis velocity in 50% acetone–water is quantitatively consistent with the assumption that its functions are (*a*) to exert the known catalytic influence of its own, and (*b*) to affect the equilibrium $\text{P} + \text{AcOH} \rightleftharpoons \text{PH}^+ + \text{OAc}^-$ by a mass-law effect. There is no indication that the apparent catalytic coefficient bears an inverse relation to the concentration of acetate ion. The catalysis is therefore thought to operate through the rate-determining heterolysis of the acetic anhydride molecule in a reaction closely analogous to a Menschutkin reaction, followed by rapid attack of water on the cation formed. It is intelligible that, in the absence of steric hindrance, the rate of the slow step should be related to the basic dissociation constant of the amine (Table 4).

The activation energy for the unimolecular heterolysis of acetic anhydride appears to be too unfavourable for such a mechanism to operate in the absence of catalyst. On the other hand, the considerable resonance energy to be expected for PAc^+ allows the rate of this step to become comparable with the bimolecular hydrolysis. The amount of resonance energy is reduced by α-substitution which prevents coplanarity of the C=O bond and the aromatic ring of PAc^+. This inhibition of resonance may be responsible for the strict steric requirements for catalytic efficiency in the amine.

It might be thought that hydrolysis of PAc^+ should still only proceed at a speed comparable to that of hydrolysis of acetic anhydride itself since the two molecules are combinations of acetylium cations with bases of almost identical strength (acetate ion and pyridine). The postulated higher reactivity of PAc^+ is ascribed to a more favourable entropy of activation. The hydrolysis of PAc^+ does not involve a change in the total electrical charge of the reagents and would not require significant reorientation of the solvation shell, whereas the bimolecular hydrolysis of acetic anhydride involves an electrical-charge separation (cf. Gold, *loc. cit.*) requiring the creation of order in the solvent and hence a low entropy of activation.

On this argument an unfavourable entropy of activation would generally be expected for bimolecular heterolytic reactions between unchanged molecules since these must involve highly dipolar transition states and proceed to form two ionic primary reaction products of opposite charges. (These primary products may quickly lose their charges, *e.g.*, by proton transfers involving the solvent.) It is indeed generally found that bimolecular heterolytic reactions between neutral molecules are "slow" reactions (Moelwyn-Hughes, "The Kinetics of Reactions in Solution," Oxford, 1947, 2nd edn., p. 73), *i.e.*, they are characterised by low frequency factors.

It may at first sight appear strange that unimolecular ionisation reactions, such as the ionisation of alkyl halides, do not have such low frequency factors although here too a pair of opposite ionic charges is generated. This apparent inconsistency may be resolved by the following considerations. In the bimolecular reactions considered the charges are generated at positions which are some distance apart and therefore each of them can independently function as a focus for the orientation of solvent molecules. In the unimolecular ionisations, on the other hand, the charge separation in the transition state barely exceeds the equilibrium length of the severed bond and the sphere of influence of the two charges generated will largely overlap. At distances of the order of magnitude of the distance of closest approach of the solvent dipoles the two opposing orientation effects will already largely nullify each other, and consequently the degree of solvent orientation induced by the formation of the transition state will be less than for the generation of well separated charges. This argument is based on the same physical picture which underlies the theory of the solvent influence on energies of activation (Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," New York, 1941, chapter VIII; cf. Gripenberg, Hughes, and Ingold, *Nature*, 1948, **161**, 480).

The mechanism of the catalysis proposed is specific to the tertiary amines although certain anions may effect catalysis in a similar way. The catalytic action of hydroxide ions (if this term may be used) may again be pictured as being an acetylium-ion transfer analogous to the first step of the pyridine catalysis, *viz.*,

$$Ac_2O + OH^- \longrightarrow AcOH + OAc^-$$

but this first step now constitutes the complete hydrolysis. It has not as yet been established by kinetic measurements whether hydroxide ions will catalyse the acylation of amines and alcohols. It they do—as preparative rules would lead one to suppose—then it seems likely that this catalysis is of a different type and probably involves a proton transfer from the molecule undergoing acylation, *i.e.*,

$$ROH + OH^- \rightleftharpoons RO^- + H_2O$$
$$RO^- + Ac_2O \longrightarrow ROAc + OAc^-$$

The catalysis of the hydrolysis by acetate ions can also not be explained on the same lines as the amine catalysis since acetylium-ion transfer to the acetate ion

$$Ac_2O + OAc^- \longrightarrow OAc^- + Ac_2O$$

does not produce a net chemical change. However, since the catalysis by acetate ions is several thousand times weaker than that by pyridine, in spite of the similar basic dissociation constants of the catalysts, it seems reasonable that an explanation along different lines should be sought in this case.

It has sometimes been reported that the use of quinoline as solvent is favourable to acylation reactions and, in some cases, preferable to pyridine. In view of our conclusion that quinoline is a much poorer catalyst, if it is one at all, in the cases we have examined, we tentatively infer that the advantages of quinoline may be (*a*) its high boiling point (which permits heating of the reaction mixture to a high temperature) and (*b*) the presence of catalytically active impurities.

It has been shown (Searles and Cvejanovich, *J. Amer. Chem. Soc.*, 1950, **72**, 3200) that 2-substituted pyridines are much less active than other cyclic amines in catalysing the formation of α-acylamino-ketones from α-amino-acids and acetic anhydride, sometimes known as the Dakin–West reaction (*J. Biol. Chem.*, 1928, **78**, 91, 745). It was suggested by these authors that the function of the tertiary amine was abstraction of a proton from one of the intermediates and that this abstraction was sterically unfavourable in the case of 2-substituted pyridines, although steric hindrance is not usually thought to play such an important rôle in proton-transfer reactions. The observations in the Dakin–West reaction seem analogous to the catalytic effects discovered by us for acylation reactions. While we have no experimental results to disprove the explanation given, we suggest that catalysis of the Dakin–West reaction may be at least equally plausibly attributed to catalysis of one or both of the acylation reactions which seem to make up two of the steps of its mechanism.

Some of the preliminary measurements for this investigation were performed by Dr. S. L. Bafna, whom we thank for his co-operation. We are also indebted to Dr. W. C. Price for allowing us the use of the infra-red spectrometer and his helpful advice. This work has been supported through the award of a maintenance allowance (to E. G. J.) by the D.S.I.R., and through grants towards the cost of apparatus and chemicals from the Royal Society and the Chemical Society respectively.

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[*Received, January 7th*, 1953.]