Condensation of 2-Methylquinoline with Benzaldehydes in Acetic Anhydride

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Condensation of 2-methylquinoline with benzaldehydes to give *trans*-β-(2-quinolyl)styrenes has been studied kinetically in acetic anhydride containing acetic acid at 130°. The reaction proceeds *via* addition (k *ca.* 10^{-4} l mol^{-1} s^{-1} at 130°), esterification (k *ca.* 10^{-4} l mol^{-1} s^{-1} at 55°), and elimination (k *ca.* 10^{-4} s^{-1} at 30°). The intermediates, four 1-aryl-2-(2-quinolyl)ethanols and one acetate, were isolated and their rates of elimination were measured separately at 55 and 30°. The addition is rate-determining and the elimination is the most rapid step in the presence of acetic acid. The acetic acid-catalysed addition is promoted by electron-withdrawing groups on the aldehyde, with a Hammett ρ value of +1·42. The esterification of the intermediate alcohols with acetic anhydride is also accelerated slightly by electron-withdrawing groups, with a ρ value of +0·4. The elimination of the acetate is catalysed by carboxylic acids in the order chloroacetic > benzoic > acetic acid. The dependence of the rate of elimination on concentration of acetic acid changes from first order at lower concentrations to zero order at higher concentrations. A plausible mechanism involving 2-methylene-1,2-dihydroquinoline as an intermediate is suggested and discussed.

THE methyl group of aza-aromatic compounds is weakly acidic because of the electron-withdrawing nature of the pyridine ring. Thus, base-catalysed hydrogen–deuterium exchange[1] or condensations[2] of the methyl group with carbonyl compounds to give the corresponding olefins are possible.

In a previous paper[3] on the condensation of 2-picoline with aldehydes, we proposed a mechanism which involved the rate-determining addition of 2-methylene-1,2-dihydropyridine to a carbonyl group, with carboxylic acids as catalysts. However, the mode of catalysis by carboxylic acids and the mechanism of the dehydration are as yet unknown. We therefore selected 2-methylquinoline as a substrate, which reacts much faster than 2-picoline (as in H–D exchange[1]) to discover more precisely the mechanism involving the intermediate alcohol and its acetate.

RESULTS AND DISCUSSION

Substituted quinolylstyrenes were prepared by refluxing a mixture of the appropriate benzaldehyde and 2-methylquinoline in acetic acid–acetic anhydride (1 : 1, v/v). The products were identified by m.p.s and u.v. and i.r. spectra (see Table 1) as *trans*-olefins. Virtually no by-products were detected. As reported previously with 2-(4-nitrostyryl)pyridine, the *trans–cis* photoisomerisation was prevented by carrying out reactions in the dark.

TABLE 1

Physical properties of β-(2-quinolyl)styrenes

Aryl substituent	M.p. (°C)	Solvent for recrystallisation	$\lambda_{max.}$/nm (log ε)[a]
p-MeO	125—126	EtOH	346 (4·49)
H	98—100	EtOH	338 (4·40)
p-Cl	143—145	EtOH	340 (4·45)
m-NO_2	147—149	EtOH-$CHCl_3$	336 (4·37)
p-NO_2	173—175	EtOH-$CHCl_3$	351 (4·52)

[a] In methanol. Kinetic experiments were done by following the extinctions at these wavelengths.

Additions.—The rates of the reaction were measured by u.v. spectrophotometry, and fit second-order kinetics (Table 2) which shows a catalysis by acetic acid as reported with 2-picoline.[3] As shown in Figure 1, the apparent second-order rate constant, k_a, shows a first-order dependence on acetic acid at its lower concentra-

TABLE 2

Second-order rate constants, k_a in equation (6), for the reaction of 2-methylquinoline with benzaldehydes in acetic anhydride at 130°

Aryl substituent	Initial concentration (M) [Aldehyde]	[2-Methylquinoline]	[Acetic acid]	10^4k_a/l mol^{-1} s^{-1} [a]
H	0·100	0·750	0	0·182 [b]
	0·100	0·750	0·875	0·646
	0·100	0·750	1·75	0·983
	0·100	0·750	3·50	1·49
	0·100	1·50	3·50	1·44
	0·200	0·750	3·50	1·43
	0·100	0·750	5·25	1·45
m-NO_2	0·0909	0·136	0	0·88 [b]
	0·100	0·150	0·875	6·95
	0·100	0·150	1·75	9·45
	0·111	0·167	1·96	10·3
	0·100	0·150	3·50	13·0
	0·100	0·150	5·25	12·5

[a] Second-order rate constant for $v = k_a$[Aldehyde] × [2-methylquinoline]. Errors were within 3%. [b] Initial rate constant.

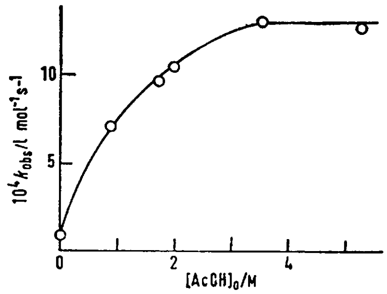

FIGURE 1 Plot of the apparent second-order rate constant, k_{obs}, *vs.* the initial concentration of acetic acid for the reaction of 2-methylquinoline with *m*-nitrobenzaldehyde in acetic anhydride at 130°

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[1] W. N. White and D. Lazine, *J. Org. Chem.*, 1969, **34**, 2756.

[2] G. Jones, *Org. Reactions*, 1967, **15**, 204.

[3] Y. Ogata, A. Kawasaki, and H. Hirata, *J. Org. Chem.*, 1970, **35**, 2199.

tions, but becomes independent of acetic acid for higher concentrations; this is different from the behaviour of 2-picoline and may be owing to the combined effects of the activation of the carbonyl group of the aromatic aldehyde and deactivation of 2-methylquinoline by protonation with acetic acid.

The effect of substituents in benzaldehyde was measured in the presence of 3·50M-acetic acid, where k_a is practically independent of the concentration of acetic acid (Table 3). The rates correlate well with the Hammett σ values (correlation coefficient $r = 0·999$), giving a ρ value of $+1·42$, which indicates a rate-determining nucleophilic attack of 2-methylquinoline on benzaldehydes.

1-(*p*-Nitrophenyl)-2-(2-pyridyl)ethanol was prepared by the acetic acid-catalysed reaction of 2-picoline with *p*-nitrobenzaldehyde in dimethylformamide or dimethyl sulphoxide at 135° for 4—5 h.[3] Although Tipson[4] reported the preparation of 1-nitrophenyl-2-(2-quinolyl)-ethanol in the absence of acids, we treated 2-methylquinoline with substituted benzaldehydes in refluxing ethanol as a protic solvent in expectation of acid catalysis (Table 4). The product from this process is much purer than that formed without solvent. The yield varies with the substituent in the order m-NO$_2$ > p-Cl > p-H, in agreement with the rate data ($\rho > 0$). An attempt to prepare an intermediate alcohol with an electron-releasing group such as *p*-methoxy was unsuccessful, probably because of slower addition of the aldehyde and subsequent faster dehydration. The observed higher yield in ethanol than in benzene suggests acid catalysis by ethanol.

TABLE 3

Substituent effect on the condensation in acetic anhydride at 130° [a]

Aryl substituent	Initial concentration (M) [Aldehyde]	[2-Methylquinoline]	10^4k_a/l mol^{-1} s^{-1} [b]
p-MeO	0·750	0·750	0·53
H	0·100	0·750	1·45
	1·000	0·750	1·35
p-Cl	0·593	0·593	2·92
m-NO$_2$	0·100	0·150	13·0
	0·100	0·750	13·6
p-NO$_2$	0·100	0·150	18·0
	0·100	0·750	18·9

[a] Initial concentration of acetic acid = 3·50M. [b] Errors were within 5%.

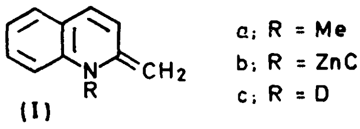
TABLE 4

Reaction of 2-methylquinoline with substituted benzaldehydes in boiling ethanol or without solvent

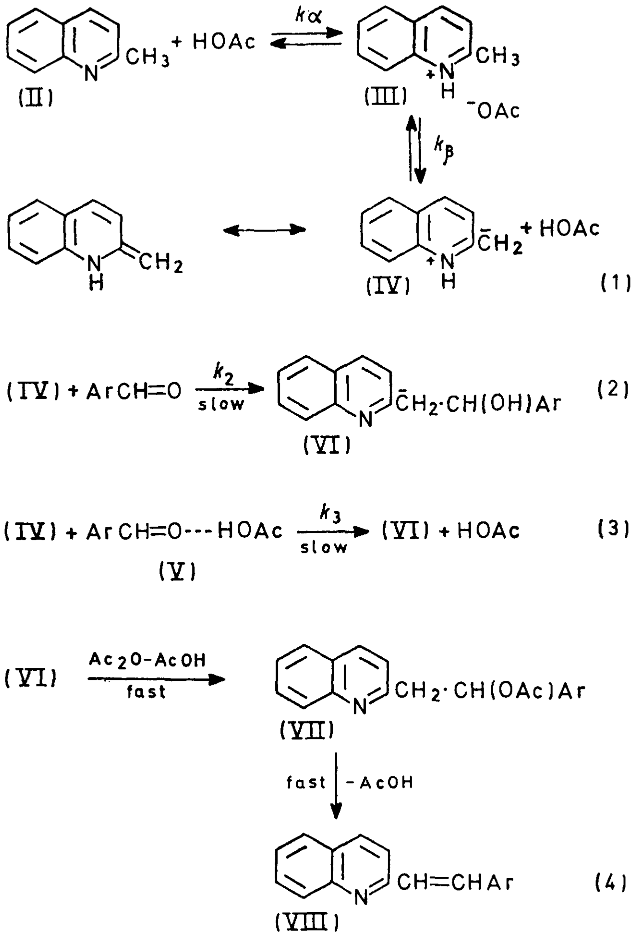
Aryl substituent	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield (%) Alcohol [a]	Olefin [b]
m-NO$_2$	EtOH	80	18	50	0
	PhH	80	24	0	0
	None	120	4	45 [c]	
p-NO$_2$	None	120	3	50	Trace
p-Cl	None	120	6·5	0	48
	EtOH	80	21	20	*d*
H	EtOH	80	24	5	*d*
p-MeO	EtOH	80	24	0	Trace

[a] 1-Aryl-2-(2-quinolyl)ethanol. [b] *trans*-β-(2-quinolyl)styrene, determined by u.v. method. [c] Total yield of alcohol and olefin. [d] Trace of olefin, contaminated by alcohol.

For the base-catalysed condensation of 2-methylquinoline methiodide with benzaldehydes, the reactive species may be the tautomer (Ia) whose highly reactive nature is known.[5] Similar species have been postulated for the $ZnCl_2$-catalysed condensation[6] (Ib) and hydrogen–deuterium exchange in protic solvents (Ic).[7] Thus, species (IV) may function as the nucleophile for the condensation. Since the approximate third-order rate constant for the acetic acid-catalysed condensation of *p*-nitrobenzaldehyde is estimated to be 5×10^{-4} for 2-methylquinoline at 130° and 2×10^{-5} l^2 mol^{-2} s^{-1} for 2-picoline at 135°,[3] 2-methylquinoline is *ca.* 30 times more reactive than 2-picoline. This figure



(I)



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[4] A. F. Walter, R. S. Tipson, and L. H. Cretch, *J. Amer. Chem. Soc.*, 1945, **67**, 1501.

[5] F. Bergstrom, *Chem. Rev.*, 1944, **35**, 77.

[6] R. C. Elderfield, 'Heterocyclic Compounds,' Wiley, New York, 1952, vol. 4, p. 1.

[7] A. I. Shatenshtein, *Adv. Phys. Org. Chem.*, 1963, **1**, 169.

corresponds to the relative reactivity (*ca.* 40) in the base-catalysed hydrogen–tritium exchange,[1] where reactivity is roughly correlated with the π-energy difference for carbanion formation ($ArCH_3 \longrightarrow ArCH_2^-$).[1,8] Similar arguments based on resonance stabilisation may be partially applied to the condensation of methyl-quinolines or -pyridines, since the suggested reactive species (I) or (IV) have π-systems isoelectronic with the carbanion of methylquinolines. However, the equilibrium concentration of (IV) may be too low to be detected by n.m.r. spectroscopy,[9,10] since it has no stabilising substituent in the side chain. The above observations suggest the mechanism (1)—(4). Here, (III) may be an ion-pair rather than dissociated ions in acetic acid–acetic anhydride, since acetates have low dissociation constants in acetic acid.[11,12]

If steps (2) and (3) are rate determining, the rate is expressed by equation (5), where k and K represent rate and equilibrium constants, respectively, a and b are the

$$\mathrm{d}[(\mathrm{VIII})]/\mathrm{d}t = \mathrm{d}x/\mathrm{d}t = (k_2 + k_2[\mathrm{HOAc}])(a - x)(b - x)/(1 + 1/K_\alpha K_\beta + [\mathrm{HOAc}]/K_\beta) \quad (5)$$

initial concentrations of benzaldehyde and 2-methylquinoline respectively, and x is the concentration of product at time t. Since $[\mathrm{IV}] \ll ([\mathrm{II}] + [\mathrm{III}])$, or $1 \ll (1/K_\alpha K_\beta + [\mathrm{HOAc}]/K_\beta)$, the apparent second-order rate constant, k_a, can be expressed by equation (6).

$$k_a = \{K_\alpha K_\beta(k_2 + k_3[\mathrm{HOAc}])\}/\{1 + K_\alpha[\mathrm{HOAc}]\} \quad (6)$$

If $k_3[\mathrm{HOAc}] \gg k_2$ and $1/K_\alpha \ll [\mathrm{HOAc}]$ at high concentration of acetic acid, $k_a = k_3K_\beta =$ constant. If $1/K_\beta \gg [\mathrm{HOAc}]$ at the low concentration of acetic acid, $k_a = K_\alpha K_\beta(k_2 + k_3[\mathrm{HOAc}])$. This agrees with the result in Figure 1 in which the apparent second-order rate constant increases linearly at first and is then independent of the concentration of acetic acid at higher concentrations.

Esterification.—The rate of elimination from 1-(*m*-nitrophenyl)-2-(2-quinolyl)ethyl acetate (VII) was found to be much faster than that of the esterification of the ethanol (VI) in acetic acid. Therefore, the rate of esterification can be followed by the formation of the final product, *trans*-3-nitro-β-(2-quinolyl)styrene (VIII). The rate for added acetic anhydride is expressed by equation (7).

$$\mathrm{d}[(\mathrm{VIII})]/\mathrm{d}t = k_a'\,[\mathrm{VI}] = (k_0 + k_1[\mathrm{Ac_2O}]_0)\,[\mathrm{VI}] \quad (7)$$

The kinetic data are shown in Table 5. The values of k_0 and k_1 are calculated from the plot of k_a' *vs.* initial concentration of acetic anhydride as $0{\cdot}21 \times 10^{-4}$ s^{-1} and $1{\cdot}98 \times 10^{-4}$ l mol^{-1} s^{-1}, which correspond to esterification with acetic acid and acetic anhydride, respectively. The value of k_0 is very small compared with that of $k_1[\mathrm{Ac_2O}]$.

TABLE 5

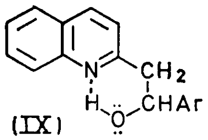
First-order rate constant, k_a', in equation (7), for the esterification of 1-(*m*-nitrophenyl)-2-(2-quinolyl)-ethanol (VI) with acetic anhydride at 55° [a]

Initial concentration (M)		
10^3[Alcohol] (VI)	[Acetic anhydride]	$10^4k_a'/s^{-1}$ [b]
10·54	0	0·08
9·72	0·29	0·71
9·09	0·54	1·21
7·73	0·75	1·81
7·00	0·99	2·26
3·97	0·99	2·26
7·80	0·99	2·28
11·66	0·99	2·24
6·80	1·08	2·56
6·61	1·39	3·07

[a] The rate was followed by observing the appearance of (VI) ($\lambda_{max.}$ 336 nm), spectrophotometrically. [b] Errors were within 5%.

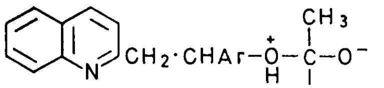
Rate equations analogous to equation (7) were obtained for other substrates. The values of 10^4k_1/l mol^{-1} s^{-1}) at 55° in acetic acid for substituents in the alcohols (VI) are H, 1·02; *p*-Cl, 1·30; *m*-NO_2, 1·98; and *p*-NO_2, 2·08, giving a satisfactory linear Hammett plot with a ρ value of +0·4.

Although the polar effect of substituents in alcohols on rates of esterification is unavailable, the positive ρ value is strange, since the reaction probably involves a nucleophilic attack of the oxygen atom of the alcohol on the carbonyl carbon atom of acetic anhydride. However, it

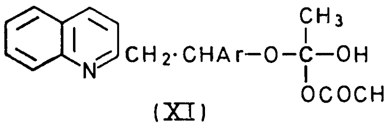


(IX)

is explicable provided that intramolecular hydrogen bonding in species (IX) can assist the nucleophilic attack of the oxygen. An electron-withdrawing substituent in the aryl group results in stronger hydrogen bonding and a weaker O–H bond. This is a kind of general base catalysis.



(X)



(XI)

Another mechanism which involves the slow proton-transfer from an oxonium ion to an oxygen anion (X) or the slow breakdown of the tetrahedral intermediate (XI) to the acetate seems impossible, since the former is

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[8] D. A. Brown and M. J. S. Dewar, *J. Chem. Soc.*, 1953, 2406.

[9] R. Mondelli and L. Merlini, *Tetrahedron*, 1966, **22**, 3252.

[10] A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1**, 426.

[11] S. Bruckenshtein and I. M. Kolthoff, *J. Amer. Chem. Soc.*, 1956, **78**, 2974.

[12] Y. Ogata, A. Kawasaki, and F. Sugiura, *J. Org. Chem.*, 1969, **34**, 3981.

generally a rapid process and the latter requires a negative ρ value.

Elimination.—The kinetic data on the elimination from 1-(*m*-nitrophenyl)-2-(2-quinolyl)ethyl acetate (VII) in acetic anhydride at 30° are shown in Table 6, which indicates a catalysis by acetic acid. The rate equation does not show the first-order dependence on the concentration of acetic acid. A plot of $1/[\mathrm{AcOH}]_0$ *vs.* $1/k_a''$, however, has a good linear correlation (Figure 2).

TABLE 6

First-order rate constants, k_a'' in equation (10), for the elimination of acetic acid from 1-(*m*-nitrophenyl)-2-(2-quinolyl)ethyl acetate (VII) in acetic anhydride at 30°

Initial concentration (M)		
10^3[Acetate (VII)]	[Acetic acid]	$10^4 k_a''/\mathrm{s}^{-1}$ [b]
7·01	0·83	0·625
6·56	1·59	1·11
6·75	1·75	1·14
5·82	2·28	1·33
5·51	2·82	1·64
6·55	3·50	1·81
6·47	5·25	2·28
6·94	7·00	2·60
6·55	8·75	2·76

[a] Pseudo-first-order rate constant. [b] Errors were within 3%.

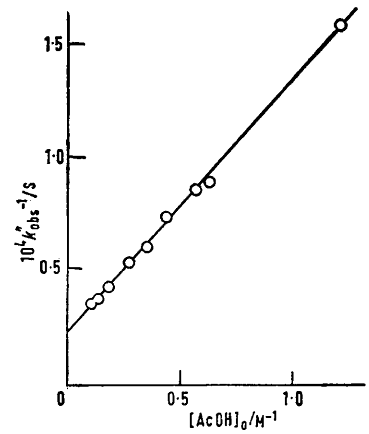
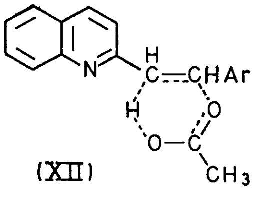


FIGURE 2 Correlation between k''_{obs} in equation (10) and the initial concentration of acetic acid for the elimination from 1-*m*-(nitrophenyl)-2-(2-quinolyl)ethyl acetate (VII) at 30°

Other carboxylic acids also catalyse the elimination (Table 7), but mineral acids inhibit the reaction. The



(XII)

*E*i mechanism or *cis*-elimination (XII) proposed by Horwitz [13] is unacceptable because of the observed acid catalysis.

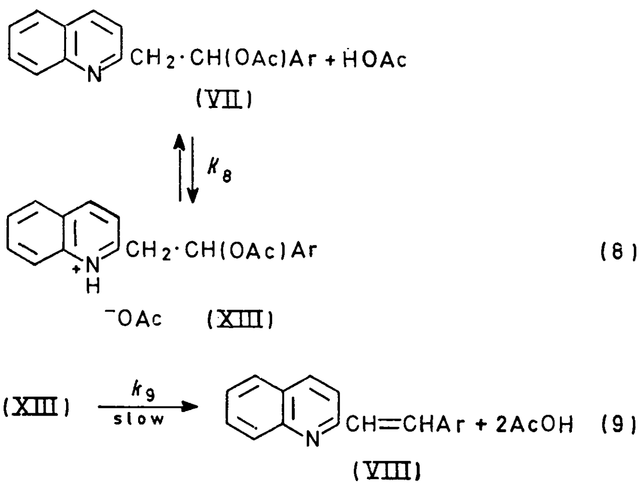
TABLE 7

Effect of acids on the elimination of acetic acid from 1-(*m*-nitrophenyl)-2-(2-quinolyl)ethyl acetate (VII) at 40°

Acid	Initial concentration of acid (M)	Solvent	$10^4 k_a''/\mathrm{s}^{-1}$ [c]
$\mathrm{ClCH_2{\cdot}CO_2H}$	0·83	Benzene	6·58
$\mathrm{PhCO_2H}$	0·83	Benzene	4·55
AcOH	0·83	Benzene	2·42
$\mathrm{H_2SO_4}$	$\sim 10^{-2}$	$\mathrm{(AcO)_2O}$	0

[a] Pseudo-first-order rate constant. [b] Data at 30°. [c] Errors were within 5%.

These observations suggest processes (8) and (9). Here again (XIII) may be an ion pair rather than dissociated ions,[11,12] and the second step may be rate-determining, hence giving the rate equation (10). Here, $[(\mathrm{VII})]_s$



$$d[(\mathrm{VIII})]/dt = k_a''[(\mathrm{VII})]_s = k_9[(\mathrm{XIII})] = \frac{k_9K_8[\mathrm{AcOH}]}{1 + K_8[\mathrm{AcOH}]}[(\mathrm{VII})]_s \quad (10)$$

denotes the stoicheiometric concentration of (VII). The rate constants in Table 6 are the values obtained for an excess of acetic acid, and the pseudo-first-order rate constant, k_a'', is expressed by equation (11). Hence equation (12) is obtained. This relation is

$$k_a'' = k_9K_8[\mathrm{AcOH}]_0/(1 + K_8[\mathrm{AcOH}]_0) \quad (11)$$

$$1/k_a'' = 1/k_9 + 1/k_9K_8[\mathrm{AcOH}] \quad (12)$$

confirmed by the observed straight line (Figure 2). The values of k_9 and K_8 can be obtained from the intercept and the slope of the line as $4{\cdot}5 \times 10^{-4}$ l mol⁻¹ s⁻¹ and 0·19 l mol⁻¹, respectively. The value of K_8 seems to be reasonable, since the pK_a value in aqueous solution at 25° is *ca.* 5 for acetic acid and *ca.* 5 for the quinolinium ion. The mechanism of sequences (8) and (9) may be of the *E*2-type which is characterised by acid catalysis rather than by ordinary catalysis, but the precise transition state (*E*lcB like or *E*l-like) cannot be discussed from the present data.

Although a mechanism involving (XIV) agrees with the kinetics, it is less plausible, since 1-(*p*-nitrophenyl)-2-(4-quinolyl)ethyl acetate which cannot have such a cyclic

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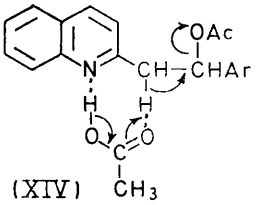
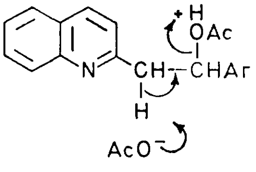
[13] L. Horwitz, *J. Amer. Chem. Soc.*, 1955, **77**, 1687.

form as (XIV) is also subject to acetic acid catalysis. An alternative mechanism involving (XV) is ruled out, since (XV) would give first-order dependence of the rate on the acetic acid concentration because of the lower basicity of the acetate oxygen atom, which differs from observation.



(XIV)



(XV)

EXPERIMENTAL

Materials.—Liquids were purified by distillation under nitrogen and crystals by recrystallisation from an appropriate solvent. Ordinary purification methods were applied to solvents.

Products.—β-(2-*Quinolyl*)*styrenes*. After refluxing a mixture of 2-methylquinoline and an aromatic aldehyde in acetic acid–acetic anhydride (1 : 1, v/v), the mixture was poured into ethanol. The crystalline product was filtered off, washed with a small amount of cold ethanol, and recrystallised from an appropriate solvent. Yield was >70% in all cases. All products have $\nu_{max.}$ (KBr) at 960—970 cm^{-1} characteristic of a *trans*-olefin (Table 1).

1-*Aryl*-2-(2-*quinolyl*)*ethanols*. A mixture of 2-methylquinoline and an aromatic aldehyde in ethanol was refluxed for 18—19 h. The mixture was then cooled to room temperature, the crystalline product being precipitated; otherwise, the mixture was concentrated to give a crystalline precipitate. Filtration, washing with a small amount of cold ethanol, and recrystallisation gave pure products (Table 4).

1-(m-*Nitrophenyl*)-2-(2-*quinolyl*)*ethyl acetate*. A mixture of 1-(*m*-nitrophenyl)-2-(2-quinolyl)ethanol (1 g), pyridine (10 ml), and acetic anhydride (10 ml) was kept at room temperature for 12—16 h. The solution was poured into ice–water (150 ml) with stirring. Neutralisation with sodium hydrogen carbonate gave a precipitate (96—100%), which was filtered, washed with cold water, and recrystallised from ethanol, m.p. 102—103°, $\nu_{max.}$ 1745 cm^{-1} (C=O).

1-(*p*-Nitrophenyl)-2-(4-quinolyl)ethyl acetate was similarly prepared.

Kinetics.—The method of ref. 3 was followed. The reaction was followed by measuring the extinction at the maximum wavelength of *trans*-β-(2-quinolyl)styrenes (Table 1). The rate constants were calculated by the ordinary equations.

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