The Mechanism of Acylation of Neutral *O*-Alkyl Benzohydroxamates. The Formation of (*Z*)-Acetic *O*-Benzylarylhydroximic Anhydrides and their Conversion to *O*-Benzyl *N*-Acetylarylhydroxamates

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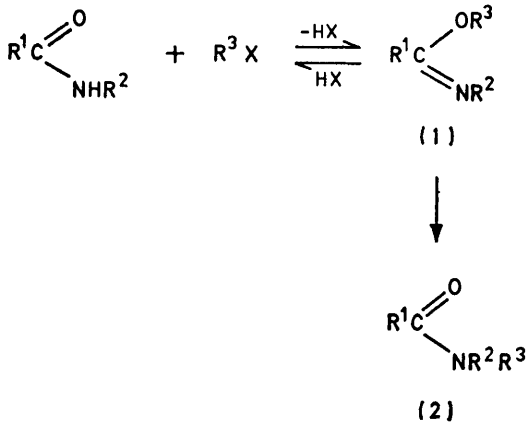
The acetylation of *O*-benzyl benzohydroxamates by acetic anhydride and pyridine in organic solvents is shown to proceed by the primary formation of (*Z*)-acetic *O*-benzylhydroximic anhydrides which rearrange, either in the presence of the acetylation reagent or in the presence of tertiary nitrogen bases, AcO^-, or Br^-, to the more stable *O*-benzyl *N*-acetylbenzohydroxamate isomers: AcO^- is a better catalyst than pyridine for this reaction by a factor of *ca.* 1 300.

The formation of (*Z*)-acetic *O*-benzylbenzohydroximic anhydrides follows the equation Rate = k_3[hydroxamate]-[Ac_2O][pyridine], and probably involves S_N2 attack of the hydroxamate on the acylpyridinium ion. The nucleophilic catalysed conversion of the (*Z*)-acetic *O*-benzylhydroximic anhydrides to the corresponding *N*-acetyl isomers follows Rate = k_2[anhydride][nucleophile], and proceeds by a two-step intermolecular S_N2 process involving *O*-benzyl benzohydroxamate anions and an acetylation reagent as intermediates. The corresponding conversion in the presence of the acetic anhydride–pyridine acetylation reagent results principally from catalysis by the pyridine component, but for (*Z*)-acetic *O*-benzylhydroximic anhydrides bearing electron-donating substituents in the benzene ring electrophilic catalysis by the acetylating agent is also apparent. The (*Z*)-acetic *O*-benzylbenzohydroximic anhydride obtained from the acetylation of *O*-benzyl benzohydroxamate is considered to be the kinetically controlled product and the *N*-acetyl isomer the thermodynamically controlled product.

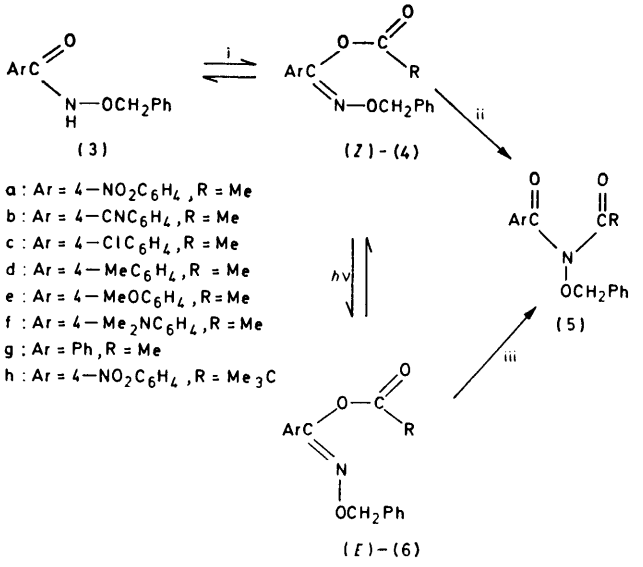
In connection with our interest in the nucleophilic reactivity of amides,[1] we have recently shown [2] that the alkylation of *neutral* amides can best be understood in terms of the formation of a kinetic *O*-alkyl product (1)



Scheme 1

which, under suitable conditions, rearranges to the thermodynamic *N*-alkyl product (2) (Scheme 1).

We wished to extend our investigations to the mechanism of acylation of neutral amides, which, by analogy, should form the kinetic *O*-acyl product (1; R^3 = RC=O) and, under favourable conditions, the thermodynamic *N*-acyl isomer (2; R^3 = RC=O). Unfortunately, *O*-acylimidates (*i.e.* isoimides) (1; R^3 = RC=O) are generally too unstable to be isolated, unless they either form part of a ring (*e.g.* as in isophthalimide) or they bear a strongly electron-withdrawing substituent on the nitrogen atom {*e.g.* [1; R^2 = 2,4-$(NO_2)_2C_6H_3$]}. We therefore turned our attention to the *O*-benzyl arylhydroxamates (3), whose (*Z*)-*O*-acyl derivatives (4) are relatively stable and suitable for kinetic investigation. After our studies on the formation of the (*Z*)-anhydride (4) [by acylation of the neutral hydroxamate (3)] and its catalytic conversion to the imide (5) were complete, the results of complementary studies by McCarthy and Hegarty,[3] were published: these concerned the formation of the (*Z*)-anhydride (4) and its photolytic conversion to the (*E*)-anhydride (6) which then thermally rearranged to the imide (5) (Scheme 2). This type of thermal rearrangement [(6) ⟶ (5)] has been observed for other *O*-acylimidates [(1) ⟶ (2)] both by Curtin and Miller [4] [(1; R^1 = Ph, R^2 = 2,4-$(NO_2)_2$-C_6H_3, R^3 = 4-X-C_6H_4)] and by Schwarz [5] [(1; R^1 = 4-X-C_6H_4, R^2 = 4-X-C_6H_4, R^3 = Ph)], although for these compounds no *E*- and *Z*-isomers have so far been detected, possibly because their interconversion is more facile than that of the hydroxamate analogues.



Scheme 2 Reagents: i, RC(O)X; ii, catalyst; iii, heat

The present paper deals with the formation of (*Z*)-

anhydride (4) using pyridine–Ac_2O as the acylating agent and its conversion to the imide (5) under the reaction conditions, or in the presence of nucleophilic catalysts.

EXPERIMENTAL

Solvents and Reagents.—AnalaR solvents were dried as follows: benzene and diethyl ether were stored over sodium, and light petroleum (b.p. 40—60°) and n-hexane over calcium chloride; carbon tetrachloride was distilled from P_2O_5 and nitrobenzene from calcium hydride. Deuteriochloroform (Merck, Sharp, and Dohme) was dried over molecular sieve (Linde 4A). Tertiary nitrogen bases were distilled from either KOH or CaH_2 and stored over molecular sieve (Linde 4A). *N*-Acetylimidazole (Aldrich) was recrystallized from benzene and dried over P_2O_5. Tetramethylammonium acetate was prepared by neutralizing a solution of tetramethylammonium hydroxide with acetic acid followed by removal of solvent and drying under reduced pressure over P_2O_5. Tetraethylammonium bromide was precipitated by addition of hydrobromic acid to an aqueous solution of tetraethylammonium hydroxide, recrystallized from ethanol–ether and dried at 110° under reduced pressure. Acetic anhydride was twice distilled from P_2O_5. [1-^{14}C]Acetic anhydride (New England Nuclear) was used as supplied.

Substrates and Products.—1. *O-Benzyl arylhydroxamates* (3a—g). These were prepared by the method of Hearn and Ward [6] from the appropriate aroyl chloride, benzyloxyamine, and triethylamine in benzene at 10°. These compounds had m.p.s. and u.v. spectra in close agreement with those recorded by Hearn and Ward.[6]

2. (*Z*)-*Acetic O-benzylarylhydroxymic anhydrides* (4a—g). These were prepared by dissolving the appropriate *O*-benzyl arylhydroxamate (3a—g) (0.5 g) in a solution of acetic anhydride (3 ml) and pyridine (3 ml) at room temperature. The reaction was monitored by recording the n.m.r. spectrum of the reaction solution. When all the starting hydroxamate (3) had reacted [shift of the OCH_2Ph signal (δ 5.0—5.1) downfield by 6—10 Hz] after *ca.* ½ h the mixture was poured into ice–water and the product extracted with chloroform (3 × 30 ml). After the chloroform solution had been washed with sodium hydrogencarbonate (2 × 50 ml of a saturated aqueous solution), hydrochloric acid (2 × 50 ml of 10%), and water (2 × 50 ml), it was dried ($MgSO_4$) and the solvent was removed under reduced pressure at *ca.* 30°. Recrystallization of the solid residue from ether–n-hexane gave the (*Z*)-anhydrides (4a—g) in 91—96% yield. The (*Z*)-anhydrides (4a—f) had m.p.s and i.r., u.v., and ^{1}H n.m.r. spectra (Table 1) in close agreement with those recorded by Hearn and Ward,[6] but in some cases [*e.g.* (4a)] the present procedure provided a considerable improvement in yield over that obtained by Hearn and Ward,[6] presumably because their longer reaction times (*ca.* 24 h) allowed some rearrangement of the (*Z*)-anhydride (4) to the imide (5) to occur. (*Z*)-*Acetic O-benzyl-4-dimethylaminobenzohydroximic anhydride* (4g) had, after recrystallization from ether-n-hexane, m.p. 98—99°; $\nu_{max.}$(Nujol) 1 765 cm^{-1} (C=O); $\lambda_{max.}$(MeOH) 316 nm (log ε, 4.38); ^{1}H n.m.r. spectrum in Table 1 (Found: C, 69.3; H, 6.3; N, 8.85. $C_{18}H_{20}N_2O_3$ requires C, 69.2; H, 6.45; N, 9.0%).

3. (*Z*)-*Pivalic O-benzyl-4-nitrobenzohydroximic anhydride* (4h). Pivaloyl chloride (0.24 g) in dichloromethane (5 ml) was added dropwise to a stirred solution of hydroxamate (3a) (0.54 g) in pyridine (3 ml) and dichloromethane (20 ml) at −70° and then the mixture was allowed to warm to room temperature. The anhydride was isolated as above and after recrystallization from ether–light petroleum (b.p. 60—80°) gave (*Z*)-*pivalic O-benzyl-4-nitrobenzohydroximic anhydride* (4h) (93%) as needles, m.p. 92—93°; $\nu_{max.}$ (Nujol) 1 760 cm^{-1} (C=O); δ($CDCl_3$) 1.35 (9 H, s), 5.25 (2 H, s), 7.42 (5 H, m), and 7.86 and 7.94 (4 H, ABq) (Found: C, 64.0; H, 5.7; N, 7.8. $C_{19}H_{20}N_2O_5$ requires C, 64.0; H, 5.7; N, 7.9%).

4. *O-Benzyl N-acetylarylhydroxamates* (5a—g). These were prepared by heating a solution of the appropriate *O*-benzyl arylhydroxamate (3a—g) (1.0 g) in benzene (50 ml) with a mixture of acetic anhydride (3 ml) and acetyl chloride (1 ml) under reflux. The reaction was monitored by t.l.c. (silica plates using chloroform solvent) until both starting hydroxamate (3a—g) and intermediate (*Z*)-acetic arylhydroximic anhydride (4a—g) were absent. The mixture was cooled and poured into ice–water and the crude product isolated as above. Recrystallization of the solid residue from chloroform–n-hexane or ether–n-hexane gave the *O*-benzyl *N*-acetylarylhydroxamates (5a—g) in 85—93% yield. Compounds (5a, c—e, and g) had m.p.s, and i.r., u.v., and ^{1}H n.m.r. spectra in close agreement with those recorded by Hearn and Ward.[6] *O-Benzyl N-acetyl-4-cyanobenzohydroxamate* (5b) had m.p. 152—153°; $\nu_{max.}$ (Nujol), 1 728 and 1 690 (C=O) cm^{-1} (Found: C, 69.3; H, 5.0; N, 9.45. $C_{17}H_{14}N_2O_2$ requires C, 69.4; H, 4.8; N,

TABLE 1

^{1}H N.m.r. chemical shifts (δ) relative to tetramethylsilane for *p*-X-$C_6H_4C(OCOMe)=NOCH_2Ph$ (4) and for *p*-X-$C_6H_4C(O)N(COMe)OCH_2Ph$ (5) in $CDCl_3$ solution (0.4M)

Compound	X	$CH_3C=O$ (3 H, s)	$PhCH_2ON$ (2 H, s)	$PhCH_2O$ (5 H, m)	*p*-XC_6H_4	X
(4a)	O_2N	2.34	5.28	7.43	7.91, 8.29 [a]	
(4b)	NC	2.33	5.26	7.43	7.76 [b]	
(4c)	Cl	2.30	5.23	7.43	7.38, 7.69 [a]	
(4d)	Me	2.36	5.18	7.38	7.22, 7.62 [a]	2.29 (3 H, s)
(4e)	MeO	2.26	5.19	7.36	6.87, 7.67 [a]	3.76 (3 H, s)
(4f)	Me_2N	2.26	5.17	7.37	6.64, 7.56 [a]	2.98 (6 H, s)
(4g)	H	2.30	5.23	7.4	7.27—7.83 [c]	
(5a)	O_2N	2.50	4.87	7.03—7.73 [d]		
(5b)	NC	2.53	4.92	7.72	7.1—7.8 [e]	
(5c)	Cl	2.52	4.88	7.03—7.70 [d]		
(5d)	Me	2.53	4.85	7.13—7.72 [d]		2.43 (3 H, s)
(5e)	MeO	2.48	4.87	6.86—7.87 [d]		3.90 (3 H, s)
(5f)	Me_2N	2.43	4.88	7.32	6.65, 7.81 [a]	3.08 (6 H, s)
(5g)	H	2.50	4.83	7.27—7.90 [f]		

[a] 4 H, ABq (*J* 9.0 Hz). [b] 4 H, d. [c] 5 H, m. [d] 9 H, m. [e] 4 H, m. [f] 10 H, m.

9.5%). *O-Benzyl N-acetyl-4-dimethylaminobenzohydroxamate* (5f) had m.p. 90—91°; $\nu_{max.}$ (Nujol) 1 705 and 1 660 (C=O) cm^{-1} (Found: C, 69.4; H, 6.6; N, 8.8. $C_{18}H_{20}N_2O_3$ requires C, 69.2; H, 6.45; N, 9.0%).

^1H N.m.r. data for the anhydrides (4a—g) and the corresponding imide isomers (5a—g) are recorded in Table 1.

5. (Z)-[1-^{14}C]*Acetic O-benzyl-4-cyanobenzohydroximic anhydride* (4b). To a solution of *O*-benzyl 4-cyanobenzohydroxamate (3b) (0.45 g) in pyridine (3 ml) was added [1-^{14}C]-acetic anhydride (0.185 g). The reaction was monitored by n.m.r. and the product (*Z*)-anhydride (4b) was isolated and purified as above. The m.p. and i.r. and n.m.r. spectra of the ^{14}C-labelled anhydride were identical with those of unlabelled (*Z*)-anhydride (4b).

Rearrangement of (Z)-[1-^{14}C]*acetic 4-cyanobenzohydroximic anhydride* (4b) *in the presence of unlabelled* (4a). A solution of (*Z*)-[1-^{14}C]-acetic 4-cyanobenzohydroximic anhydride (4b) (0.09 g) and (*Z*)-acetic 4-nitrobenzohydroximic anhydride (4a) (0.09 g) and pyridine (0.03 ml) in $CDCl_3$ (0.5 ml) was heated at 60° and monitored by n.m.r. as above until rearrangement was complete. The solution was poured into water (10 ml) and extracted with $CHCl_3$. After washing the chloroform solution with dilute HCl and water and drying over $MgSO_4$, solvent was removed to give a solid. Pure *N*-acetyl products (5a and b) were isolated by preparative t.l.c. (silica plates with chloroform solvent) and characterized by comparison of their m.p.s and i.r. spectra with authentic material. Each product was radioassayed by scintillation counting of the product (*ca.* 3—15 mg) dissolved in xylene.

Kinetics.—Acetylation of O-benzyl 4-nitrobenzohydroxamate (3a). Kinetic measurements were carried out on a solution of hydroxamate (3a) (10^{-3}M) in CCl_4 containing varying amounts of acetic anhydride (0.2—1M) and pyridine (0.2—1M) in a temperature controlled spectrophotometric cell at 30°. The reaction rate was measured by monitoring the increase in the absorption at λ 300 nm, resulting from the product (*Z*)-acetic *O*-benzyl-4-nitrobenzohydroximic anhydride (4a), $\lambda_{max.}$ 300 nm (log ε 4.20). Pseudo-first-order rate coefficients {Rate = k_0 [(3a)]}, calculated in the usual way and constant for >90% reaction, are recorded in Table 2.

TABLE 2

Variation of pseudo-first-order rate coefficients (k_0) with [Ac_2O] and [pyridine] for the acetylation of (3a) to (4a) in CCl_4 at 30 °C; initial [(3a)] *ca.* 10^{-3}M

[Pyridine]/M	[Ac_2O]/M	$10^4k_0/s^{-1}$
0.2	1.0	6.94
0.4	1.0	14.9
0.6	1.0	21.8
0.8	1.0	29.5
1.0	1.0	37.7
1.0	0.8	28.7
1.0	0.6	20.9
1.0	0.4	14.9
1.0	0.2	7.24

Catalytic rearrangement of (Z)-*anhydrides* (4a—g) *to imides* (5a—g). The rearrangement of (4) to (5) in nitrobenzene, $CDCl_3$, or CCl_4 was followed by the n.m.r. method previously described.[2] Typically, kinetic measurements were carried out on a solution of the (*Z*)-anhydride (4) (0.2 mmol) and catalyst (0.1—0.5 mmol) in solvent (0.5 ml) contained in a sealed n.m.r. tube. Reactions were monitored by following the decrease in either the $NOCH_2Ph$ signal (δ 5.17—5.28) or the CH_3CO signal (δ 2.26—2.36) of (4) relative to the total $NOCH_2Ph$ or CH_3CO signal of (4) and (5) [for (5), δ_{NOCH_2Ph} 4.82—4.92; δ_{CH_3CO} 2.43—2.53], respectively, each spectrum being integrated three times to minimise errors arising from fluctuations in the n.m.r. signal. Pseudo-first-order rate coefficients (Rate = k'_0 [(4)]) were calculated from equation (1), where a = total area of

$$k'_0t = 2.303\log[a/(a - x)] \quad (1)$$

either the $NOCH_2Ph$ or CH_3CO signal for (4) and (5) and a_x = area of the $NOCH_2Ph$ or CH_3CO signal for (4) only, at time t. Results for a typical run are given in Figure 1.

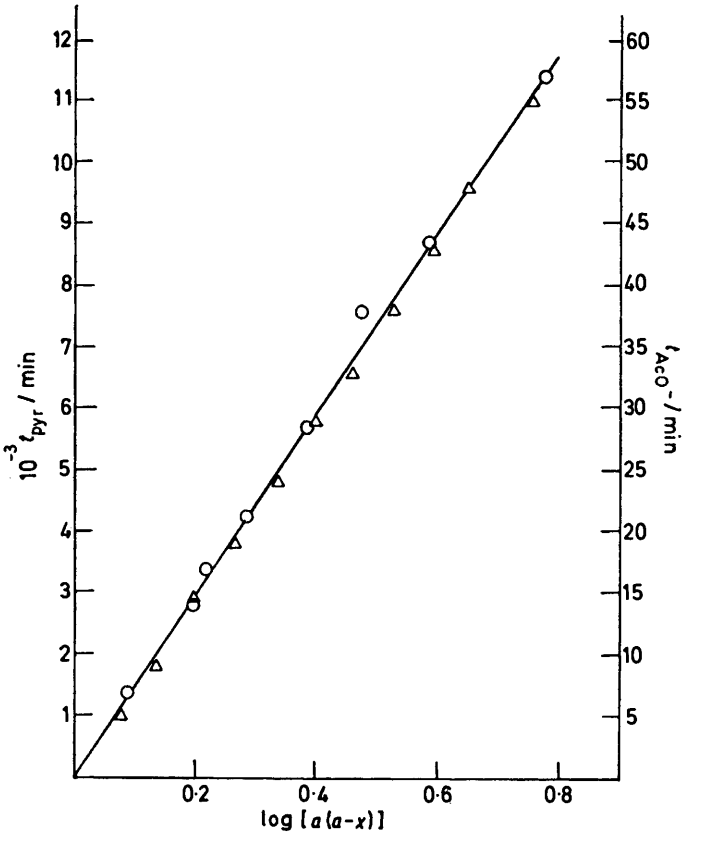


FIGURE 1 Typical first-order plots for the nucleophilic catalysed rearrangement of (4) to (5) in $CDCl_3$ at 60 °C; ○ initial [(4a)] *ca.* 0.4M, [pyridine] = 0.8M; △ initial [(4b)] *ca.* 0.4M, $[Me_4N^+AcO^-]$ = 0.15M

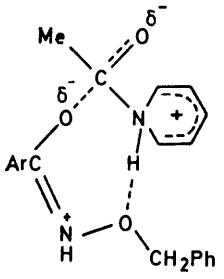
Linear plots were obtained up to 80% reaction when the insensitivity of the n.m.r. procedure produced significant errors in the measurement of small integrals. Rate coefficients obtained by this method were reproducible to ±20%.

Product Analysis.—The n.m.r. spectra of the rearrangement reactions after 10 half-lives compared favourably with those of authentic *N*-acetyl products (5).

RESULTS AND DISCUSSION

Acetylation of O-Benzyl Arylhydroxamates.—*O*-Benzyl arylhydroxamates (3a—g) were monoacylated by treatment with a mixture of acetic anhydride and pyridine at room temperature until the n.m.r. spectrum of the mixture showed that all the starting hydroxamate had reacted (*ca.* ½ h). At this stage only one of the three possible monoacetyl products [(4)—(6); R = Me] was

evident in the spectrum [McCarthy and Hegarty [3] have shown that the signal for the CH_3CO protons of (*E*)-(6) is upfield by 3—5 Hz from that for (*Z*)-(4) and the corresponding signal for (5) is downfield by *ca.* 9—13 Hz from that for (*Z*)-(4) (*cf.* Table 1)]. This monoacetyl product was isolated from the reaction mixture in >90% yield and shown, in each case, by comparison of its m.p., and i.r. and ^1H n.m.r. spectra with that recorded by Hearn and Ward,[6] to be the *O*-acetyl product (4a—g; R = Me) or (6a—g; R = Me) and not the *N*-acetyl isomers (5a—g; R = Me). These *O*-acetyl products were stable in inert solvents at 60° for >4 weeks and therefore must be the (*Z*)-*O*-acetyl products (4) and not the *E*-isomers (6) which rapidly rearrange ($t_{\frac{1}{2}}$ *ca.* 15 min) to (5) under such conditions.[3] The stereospecificity of this acetylation reaction [like that of the reaction of the silver salt of (3) with acetyl chloride [3]] may well arise from co-ordination of the hydroxamate (3) with reagent prior to reaction [*e.g.* as in (7)].



(7)

The rate of acetylation of hydroxamate (3a) to (*Z*)-anhydride (4a) (step i, Scheme 2) by acetic anhydride–pyridine in CCl_4 at 30° was proportional to [(3a)]. The pseudo-first-order rate coefficients (k_0) depended on both [Ac_2O] and [pyridine] (Table 2) and the full rate expression for the reaction is given by equation (2) with k_3 = 3.6×10^{-3} l^2 mol^{-2} s^{-1} at 30 °C. This expression is comparable with other acetylation reactions by acetic

$$\text{Rate} = k_3[Ac_2O][\text{pyridine}][(3a)] \qquad (2)$$

anhydride–pyridine (*e.g.* in ref. 7) and is consistent with a rapid pre-equilibrium formation of acetylpyridinium ion followed by slow reaction with hydroxamate (3a) [equation (3)]. The kinetically equivalent slow reaction of acetic anhydride with the pyridinium salt of (3a) [equation (4)] can probably be ruled out by the absence of any *N*-acetyl product (5a), since Hearn and Ward [6] have shown that other similar hydroxamate salts (K^+ or Ag^+) have ambident properties, and therefore, detectable amounts (>4%) of the *N*-acetyl isomer (5a) would be expected from an ionic intermediate such as (8).

Conversion of (Z)-*Acetic* O-*Benzylarylhydroximic Anhydrides* (4a—g) *to the Corresponding Imides* (5a—g).—In the absence of added electrophiles or nucleophiles, solutions of the (*Z*)-anhydrides (4a—g) in either nitrobenzene, $CDCl_3$, or CCl_4 were stable at 60 °C for periods >4 weeks. This is in marked contrast to the (*E*)-anhydrides (6) which have been shown [3] to rearrange intramolecularly to imides (5) (step iii, Scheme 2) when heated in a range of solvents at 50—80 °C [*e.g.* $t_{\frac{1}{2}}$ (6g) in MeCN at 70° *ca.* 15 min.]. The mechanism of this thermal rearrangement is thought [3] to involve attack by the suitably placed nitrogen lone pair electrons on the carbonyl carbon in an 'early' transition state. The contrasting stability of the (*Z*)-anhydrides (4) is attributable to the *trans*-disposition of the nitrogen lone pair electrons relative to the carbonyl group thus prohibiting intramolecular attack.

Conversion of (Z)-*Anhydride* (4) *to Imide* (5) *by Pyridine and Acetic Anhydride.*—The isolation of less than quantitative yields of (*Z*)-anhydride (4) by Hearn and Ward [6] after relatively long reaction times suggests that the conversion of (4) into (5) is catalysed by the acetylat-

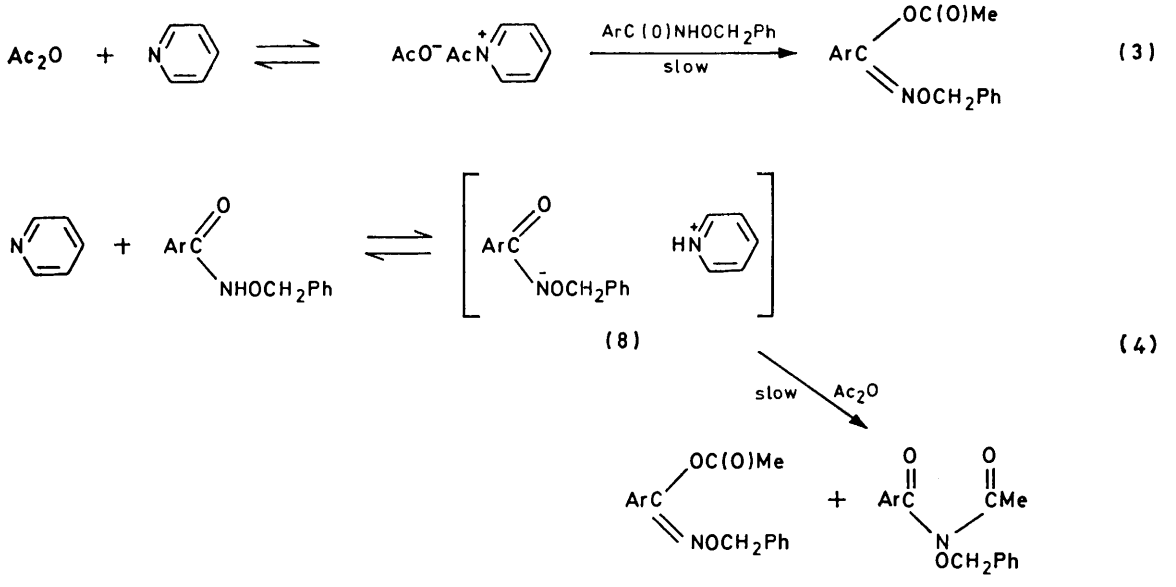


TABLE 3

Pseudo-first-order rate coefficients [equation (5)] for the conversion of (4a) to (5a) by pyridine and acetic anhydride in nitrobenzene at 60 °C

[(4a)]/M	$[Ac_2O]$/M	[pyridine]/M	$10^6k'_o/s^{-1}$
0.2	0.4	0.4	4.9
0.2	0.8	0.8	8.95
0.4	0.2	0.2	2.4
0.4	0.4	0.4	4.6
0.4	0.8	0.8	9.2
0.8	0.8	0.8	9.3

TABLE 4

Pseudo-first-order rate coefficients [equation (5)] for the conversion of (4) into (5) by equimolar amounts of pyridine and Ac_2O in nitrobenzene at 60 °C: initial [(4)] *ca.* 0.4M

Substrate	$[Ac_2O]$/M	[Pyridine]/M	$10^7k'_o/s^{-1}$
(4c)	0.2	0.2	6.7
(4c)	0.4	0.4	13
(4c)	0.8	0.8	30
(4d)	0.4	0.4	3.3
(4d)	0.8	0.8	6.5
(4e)	0.2	0.2	1.6
(4e)	0.4	0.4	3.4
(4e)	0.8	0.8	7.45
(4f)	0.8	0.8	3.6
(4g)	0.2	0.2	2.3
(4g)	0.4	0.4	4.5
(4g)	0.8	0.8	9.4

ing mixture. Evidence to this effect was obtained by heating (4a) in nitrobenzene at 60° with equimolar amounts of pyridine and acetic anhydride (Table 3). The reaction rate has a first-order dependence on [Substrate] [equation (5)] and k'_o increases with either [pyridine] or $[Ac_2O]$ but it is not proportional to the product [pyridine]$[Ac_2O]$. The latter rules out a simple third-order rate expression indicative of catalysis by the

$$\text{Rate} = k'_o[(4a)] \qquad (5)$$

acetylpyridinium ion and implies that pyridine and Ac_2O exert independent catalyses. The ability of the acetylating mixture to effect the conversion of (4) to (5) was not

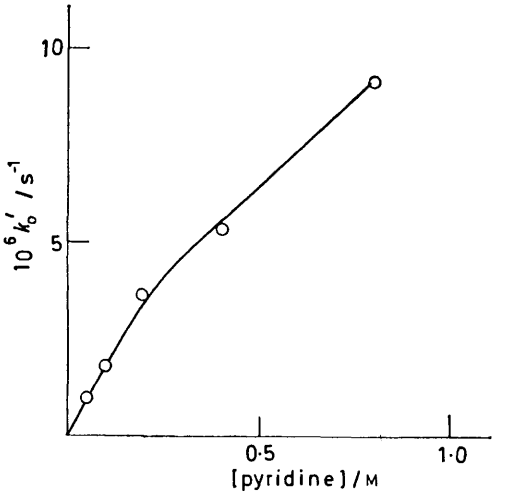


FIGURE 2 Variation of the pseudo-first-order rate coefficient [equation (5)] with [pyridine] for the conversion of (4a) into (5a) in nitrobenzene at 60 °C; initial [(4a)] *ca.* 0.4M; $[Ac_2O]$ = 0.8M

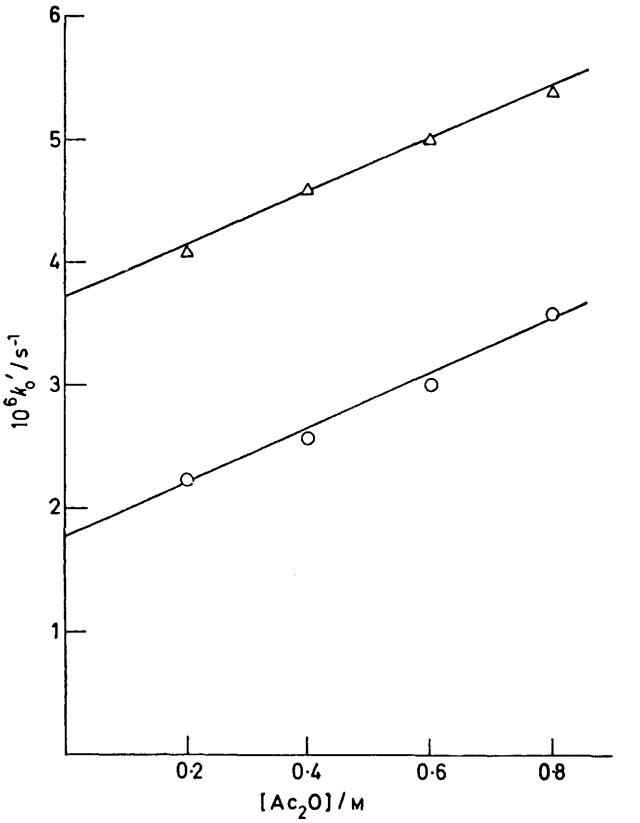


FIGURE 3 Variation of the pseudo-first-order rate coefficients [equation (5)] with $[Ac_2O]$ for the conversion of (4a) into (5a) in nitrobenzene at 60 °C; initial [(4a)] *ca.* 0.4M; [Pyridine] = 0.2M, ○; or 0.4M, △

confined to (4a) and similar results for other *para*-substituted substrates (4c—g) are given in Table 4.

The origin of the catalysis was investigated further for the conversion of (4a) to (5a) by measuring the effects of varying [pyridine] and $[Ac_2O]$ at constant $[Ac_2O]$ and [pyridine], respectively. The plot of k'_o *versus* [pyridine] shown in Figure 2 is clearly curved at low [pyridine] but its intercept passes through the origin. The plots of k'_o *versus* $[Ac_2O]$ (Figure 3), however, are linear, but the positive intercepts imply that pyridine effects catalysis independently of Ac_2O. Both observations, as discussed further below, suggest that the acetylating components act as nucleophilic catalysts in the conversion of (4) into (5).

Nucleophilic Catalysed Conversion of (Z)-*Anhydride* (4) *to Imide*(5).—Tertiary nitrogen bases (with the exception of 2,6-lutidine), AcO^-, and Br^- were found to catalyse the rearrangement of (4a) to (5a) in nitrobenzene or $CDCl_3$ at 60°. The rate of these reactions also followed equation (5) and k'_o varied linearly with the concentration of added catalyst (Figure 4). It follows that the reactions are bimolecular and the catalysed rates are governed by equation (6). Values of the second-order rate co-

$$\text{Rate} = k_2\ [(4a)][\text{Catalyst}] \qquad (6)$$

efficients (k_2) for these catalysts in either $CDCl_3$ or nitrobenzene are summarised in Table 5. The in-

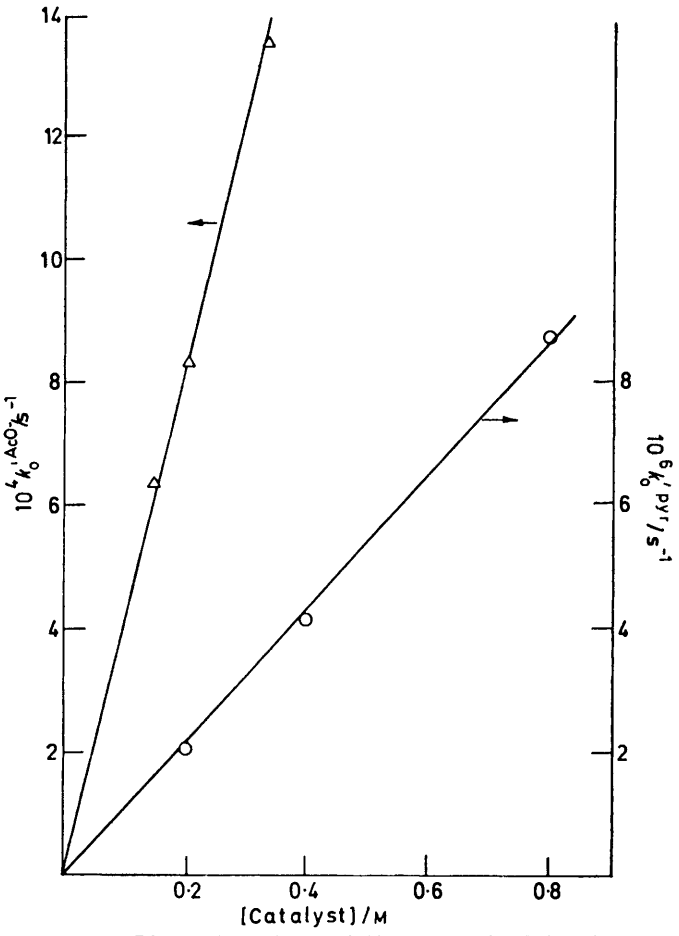


FIGURE 4 Linear dependence of k'_0 on [Catalyst] for the rearrangement of (4a) to (5a) at 60 °C; initial [(4a)] *ca.* 0.4M; ○, pyridine in nitrobenzene; △, $Me_4N^+AcO^-$ in $CDCl_3$

effectiveness of 2,6-lutidine (pK_a 6.7) compared with pyridine (pK_a 5.23) shows that the catalysis is probably nucleophilic rather than general base. Further, with the exception of AcO^-, the variation of k_2 with pK_a is that expected for nucleophilic attack at an sp^3 carbon: for example, the enhanced nucleophilicity of 1-methylimidazole is consistent with an α-effect from the second nitrogen atom. Equation (6) implies reaction *via* an S_N2 mechanism and two possible pathways can be envisaged for the nucleophilic catalysis (Scheme 3).

TABLE 5

Second-order rate coefficients [equation (6)] for the rearrangement of (4a) to (5a) catalysed by nucleophiles in nitrobenzene at 60 °C; initial [(4a)] = 0.4M, [Nucleophile] = 0.28—0.4M

Nucleophile	pK_{BH^+}	$10^6 k_2$/l mol^{-1} s^{-1}
2,6-Lutidine	6.7	No reaction
$Et_4N^+Br^-$		0.67 [a]
1-Acetylimidazole	3.6	3.9
Pyridine	5.23	10.8
Pyridine	5.23	3.2 [a]
Triethylamine	9.72	25
1-Methylimidazole	7.00	2 410
$Me_4N^+AcO^-$	4.75 (HOAc)	4 090 [a]

[a] $CDCl_3$ solvent.

The first is an intermolecular pathway initiated by attack of the nucleophile on the acyl carbon atom of (4) to give an acylium ion which then reacts at the nitrogen atom. The second is an intramolecular pathway where nucleophilic attack at the imino carbon atom of (4) promotes either formation of an ' early ' cyclic transition state or isomerization to the (*E*)-anhydride (6) which then rearranges thermally in the way already described.[3]

To distinguish between these mechanisms for the pyridine catalyst, two further studies were made. The first concerned the effect of 4-substituents on the rate of rearrangement of the (*Z*)-anhydride (4). These results, summarized in Table 6, show that electron-withdrawing

TABLE 6

Variation of second-order rate coefficients [equation (6)] for the nucleophilic catalysed rearrangement of *p*-XC_6H_4-C(OCOMe)=$NOCH_2Ph$ at 60 °C with *p*-substituent X; initial [(4)] *ca.* 0.4M; [Catalyst] = 0.15—0.8M

X	Substrate	$10^6 k_2^{pyr}$/ l mol^{-1} s^{-1} [a]	$10^3 k_2^{AcO^-}$/ l mol^{-1} s^{-1} [b]
NO_2	(4a)	3.2 [b]	
NO_2	(4a)	10.8	3.0
CN	(4b)	6.1	3.7
Cl	(4c)	2.5	1.3
Me	(4d)	0.54	
MeO	(4e)	0.54	0.41
Me_2N	(4f)	0.16	0.13

[a] Nitrobenzene. [b] $CDCl_3$.

4-substituents moderately increase k_2: further, log k_2 correlates better with σ^0 (ρ +1.49, r 0.996) than with Hammett σ parameters (r 0.989), which suggests that pyridine attacks the acyl carbon atom not in direct conjugation with the *para*-substituent. The second experiment enquired into the formation of cross-products when ^{14}C-labelled (*Z*)-anhydride (4b) reacted with pyridine in the presence of unlabelled (4a). Table 7 shows that *ca.* 60% of the ^{14}C-label is found in product

TABLE 7

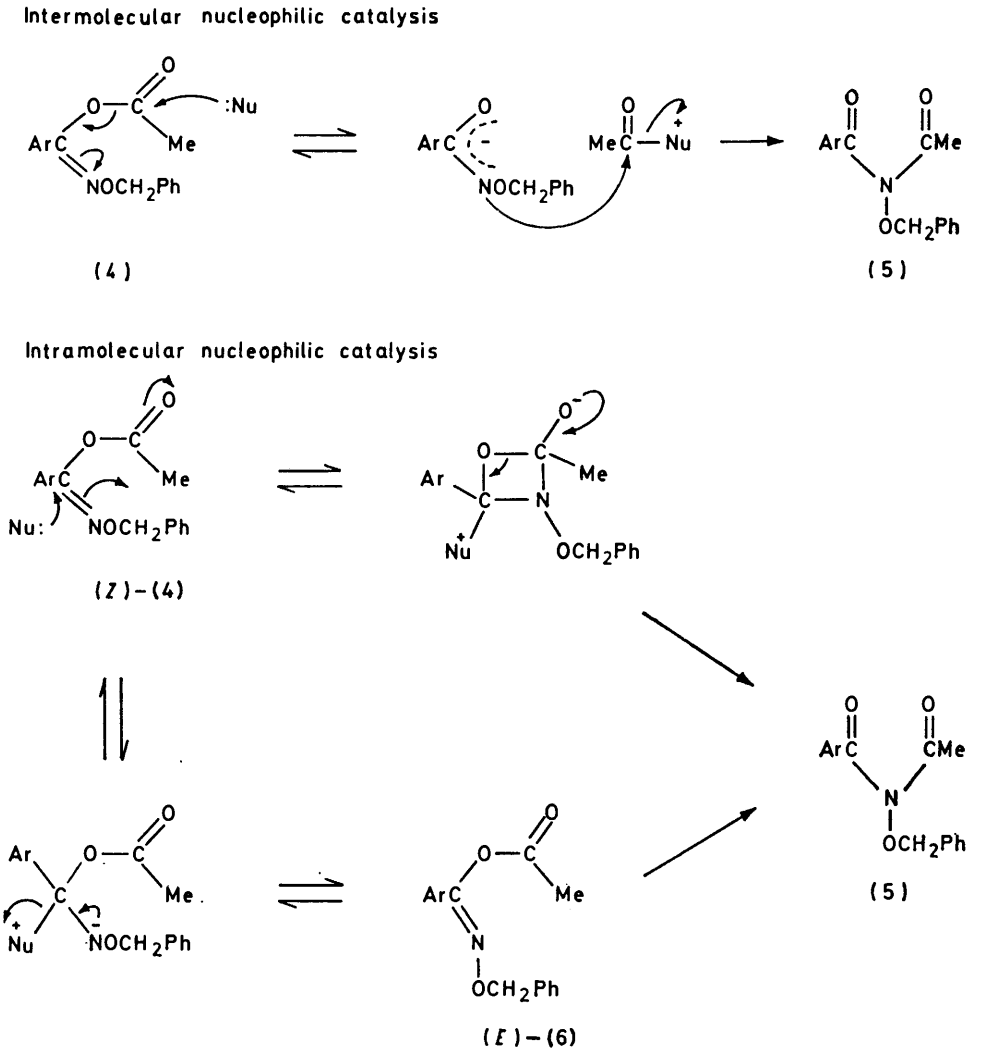
Pyridine catalysed rearrangement of *p*-$NCC_6H_4C(O-^{14}COMe)$=$NOCH_2Ph$ (4b) to (5b) in $CDCl_3$ at 60 °C in the presence of (4a); initial [(4a)] *ca.* 0.57M; initial [(4b)] *ca.* 0.61M

Compound	10^{-10} Specific activity/counts min^{-1} mol^{-1}
p-$NCC_6H_4C(O^{14}COMe)$=$NOCH_2Ph$ (4b)	2.68
p-$NCC_6H_4C(O)N(O^{14}COMe)OCH_2Ph$ (5b)	1.60
p-$O_2NC_6H_4C(O)N(O^{14}COMe)OCH_2Ph$ (5a)	0.93

(5a) and *ca.* 30% in (5b). As complete equilibration of the ^{14}C-label is precluded by the different rates for (4a and b) ($10^5 k_2$ 1.08 and 0.61 l mol^{-1} s^{-1}, respectively), this suggests that the ^{14}C-acyl fragment becomes relatively free during rearrangement. Thus both experiments are consistent with reaction *via* the intermolecular pathway with the acetylpyridinium ion and the hydroximate anion as intermediates. This conclusion is supported by the absence of significant conversion of (4h) into (5h) over 350 h on heating at 60° with 0.8M-pyridine in $CDCl_3$.

The data in Table 5 show that $Me_4N^+AcO^-$ in $CDCl_3$ is a very much better catalyst than pyridine in either

$CDCl_3$ or nitrobenzene. Since a similar intermolecular pathway (Scheme 3) is expected for both catalysts, this difference must reflect an enhanced nucleophilic reactivity for AcO^- in $CDCl_3$ similar to that noted previously [8] in dipolar aprotic solvents. The effect of 4-substituents on the rate of the AcO^--catalysed reaction was examined briefly and these results are also given in Table 6.



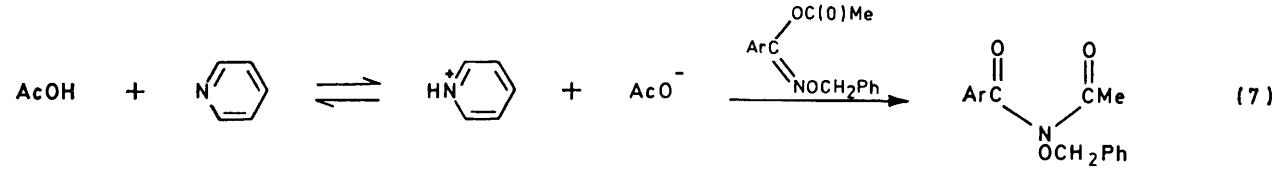
SCHEME 3

Although it is clear that electron-withdrawing substituents increase k_2, there is little to choose between the plots of log k_2 *versus* σ^0 (ρ +1.20, r 0.986) and Hammett σ parameters (ρ +0.91, r 0.992).

Conclusions.—The reaction of *O*-benzyl 4-nitrobenzohydroxamate (3a) with 0.8M-pyridine and 0.8M-acetic anhydride to give (*Z*)-acetic *O*-benzyl-4-nitrobenzohydroximic anhydride (4a) proceeds in CCl_4 at 30 °C with a half-life of *ca.* 5 min. The conversion of (4a) to *O*-benzyl *N*-acetyl-4-nitrobenzohydroxamate (5a) with the same concentrations of pyridine and acetic anhydride in nitrobenzene at 60° proceeds with a half-life of *ca.* 1 880 min. Allowing for differences of both temperature and solvent, formation of (4a) therefore proceeds *ca.* 4 000 times more rapidly than the conversion of (4a) into (5a). This demonstrates unequivocally that product orientation for the acylation of *neutral O*-benzyl hydroxamates relates to conditions of either kinetic, or thermodynamic, control as suggested recently [1] from much less substantial evidence for the acylation of neutral amides.

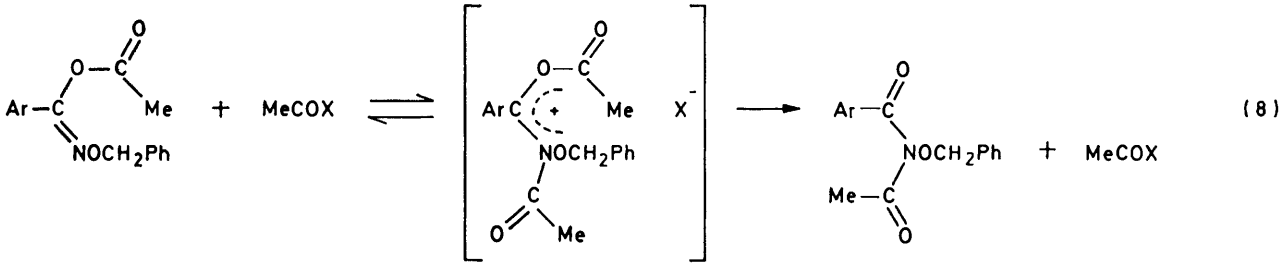
The mechanism by which the kinetically controlled *O*-acylated product (4) is converted to the thermodynamically stable *N*-acylated product (5) in the presence of pyridine and acetic anhydride requires further comment, particularly in regard to the non-linearity of Figure 2. The conversion of (4) into (5) is readily brought about by nucleophilic entities and catalysis by pyridine is obviously important with the acylating mixture. The

much stronger nucleophilic catalysis by AcO^-, however, is probably responsible for the non-linearity of Figure 2. A very low (*ca.* 0.01%) HOAc impurity in the acetic anhydride would produce this effect on conversion to AcO^- by the addition of pyridine [equation (7)]. The adventitious AcO^- catalysis would be dependent on the pyridine concentration until all the HOAc had been neutralized, and this point appears to be reached with *ca.* 0.2M-pyridine. Thereafter, further increases in reaction rate should refer to catalysis by pyridine, itself, and, significantly, the slope of Figure 2 above 0.2M-pyridine is very similar to that obtained from the addition of pyridine in the absence of acetic anhydride. The explanation also implies that the low dependency of k_0' on $[Ac_2O]$ evident in Figure 3 results from catalysis by the HOAc impurity.



(7)

Thus the acylating properties of the acetic anhydride–pyridine reagent appear to have an unsubstantial influence on the conversion of the 4-nitro-substituted substrate (4a) into (5a). This must reflect the very low electron density on the imide nitrogen-atom of (4a) occasioned by the presence of the 4-nitro substituent.



(8)

Other work, however, to be reported later,[9] shows that more powerful acylating agents are effective electrophilic catalysts for this reaction [equation (8)]. It follows that the corresponding conversion of (4) into (5) for substrates bearing electron-donating 4-substituents *e.g.* (4d—g) by acetic anhydride and pyridine probably involves electrophilic catalysis by acetylpyridinium ion as well as nucleophilic catalysis by pyridine. Direct evidence to this effect comes from a comparison of rearrangement rates in the presence of pyridine alone and pyridine plus acetic anhydride (Table 8): for compound (4f) (4-dimethylamino substituent) 0.8M-acetic anhydride increases k_1 by *ca.* 180% whereas for compound (4a) (4-nitro-substituent) k_1 increases by only 3%.

It is apparent that neutral *O*-benzyl benzohydroxamates react with the acetylpyridinium ion preferentially at the amide oxygen-atom whereas *O*-benzyl benzohydroximate anions react at amide nitrogen [*cf.* pyridine catalysed conversion of (4) into (5)]. This behaviour parallels that observed previously [1,2] for the alkylation of simple amides and supports our assertion [1] that the nucleophilic properties of the amide moiety are primarily dependent on the reaction conditions.

TABLE 8

Comparison of rates of conversion of (4) to (5) by 0.8M-pyridine and by 0.8M-pyridine plus 0.8M-acetic anhydride in nitrobenzene at 60 °C; initial [(4)] *ca.* 0.4M

	$10^6k'_0/s^{-1}$	
Substrate	Pyridine	Pyridine $+Ac_2O$
(4a)	8.9	9.2
(4c)	2.0	3.0
(4d)	0.43	0.65
(4e)	0.43	0.76
(4f)	0.13	0.36

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