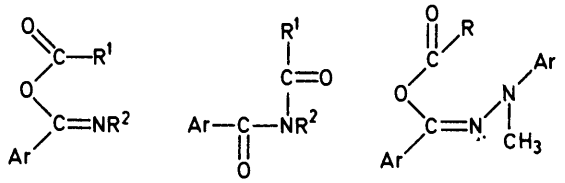
Isomerisation of (*E*)-*O*-Acyl Isoamides to *N*-Acyl Amides. Mechanism of an Intramolecular [1,3] Acyl Group Migration *via* a Four-membered Transition State

By **Daniel G. McCarthy** and **Anthony F. Hegarty,*** Chemistry Department, University College, Cork, Ireland

The (*Z*)-*O*-acyl isoamides (7) (which do not themselves thermally rearrange) may be photoisomerised to the (*E*)-isomers (8) which undergo a ready thermal rearrangement to the more stable *N*-acyl isomers (9). The mechanism of this rearrangement was investigated using solvent effects (a linear free energy correlation with dielectric constant was observed but with an overall low sensitivity to solvent) and substituent effects in the migrating aroyl group (8: R^2 = Ar) (ρ +0.65) and the aryl group attached to carbon (ρ −0.49) and to nitrogen (ρ −0.91). The mechanisms discussed include a sigmatropic $_{\pi}2_s + {}_{\sigma}2_a$ pathway, but that favoured is rate-determining nucleophilic attack by the nitrogen lone pair on the carbonyl carbon with an early transition state. Intermolecular acylation of water by (7) and (8) (which is acid and base catalysed) and of piperidine were examined as analogues of the intramolecular process. In general, the rates of intermolecular reactions of the (*Z*)- and (*E*)-*O*-acyl isoamide isomers (7) and (8) are similar to one another and show the same sensitivity to substituent effects.

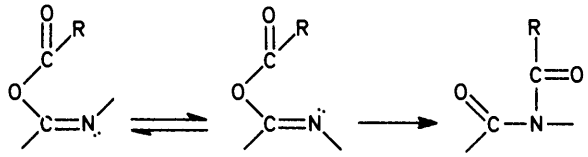
THE rearrangement of isoimides (1) to imides (2) occurs through a [1,3] O ⟶ N acyl migration. This was first described by Mumm [1] who failed to isolate simple iso-



(1) (2) (3)

imides from the reactions of imidoyl chlorides with carboxylate ions, the only products being imides (2). Later, Curtin and Miller,[2] by depressing the nucleophilicity of the imino-nitrogen atom, in (1), isolated *N*-(2,4-dinitrophenyl)benzimidoyl benzoates, and measured their rates of conversion into imides. The work of Schwarz [3] showed that electron-withdrawing substituents on the imino-nitrogen atom are not necessary for the transitory generation of isoimides in solution. Carbodi-imides [4] and heterocumulenes [5] react with carboxylic acids to give *O*-acyl isoamide type intermediates which, in the absence of an external nucleophile, undergo [1,3] acyl shifts to give *N*-acyl compounds. Diazomethane trapping experiments with the coenzyme biotin give *N'*-methoxycarbonylbiotin, and it has been suggested that this arises through a [1,3] O ⟶ N shift of the methoxycarbonyl group initially in the *O*-acyl form.[6] Model studies by Bruice and Pratt have established that acyl migrations in this system are rapid.[7]

Curtin and Miller attribute the stability (to rearrangement) of their materials to their existence in equilibrium largely as the *Z*-isomers, *i.e.* where the lone pair of electrons on the imino-nitrogen and the acetate group are *trans*.[2] Conversion of the *O*-acyl material to the *N*-acyl form requires initial *Z* ⟶ *E* isomerisation of the substrate, followed by O ⟶ N acyl transfer, and either step can be rate determining in the overall process (Scheme 1). A recent study in these laboratories using a hydrazone substrate (3) has shown that the *Z* ⟶ *E* isomerism is rate limiting in this case,[8] and while Curtin and Miller concluded that the acyl transfer step was the



(4) (5) (6)

SCHEME 1

slow step for their system, they were unable to unequivocally assign configuration or to detect both the *E*- and *Z*-isomers of their isoimides. Rate-limiting acyl transfer reactions have been observed with *O*-acyl derivatives of cyclic amides (2-pyridone and 6-phenanthridone), where, due to the configuration of the substrate, *Z* ⟶ *E* isomerism is precluded. With these systems an equilibrium between the *O*- and *N*-acyl forms has been observed [9] and moreover it is difficult to obtain systematic data for the effect of substituent variation on the rate of rearrangement.

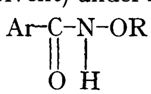
Thus to establish the kinetic and mechanistic requirements of a pure O ⟶ N acyl migration in an acyclic system we have chosen the oxime derivatives (7) and (8). This was prompted by the configurational stability of oxime derivatives and by the isolation of *E*- and *Z*-isomers of a range of oximes.[10] In this paper we report

[1] O. Mumm, H. Hesse, and H. Volquartz, *Chem. Ber.*, 1915, **48**, 379.
[2] D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, 1967, **89**, 637.
[3] J. S. P. Schwarz, *J. Org. Chem.*, 1972, **37**, 2906.
[4] H. G. Khorana, *Chem. and Ind.*, 1955, 1087.
[5] C. L. Stevens and M. E. Munk, *J. Amer. Chem. Soc.*, 1958, **80**, 4069.
[6] J. Knappe, B. Wenger, and U. Wiegard, *Biochem. Z.*, 1963, **337**, 232; T. C. Bruice and A. F. Hegarty, *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **65**, 805.
[7] R. F. Pratt and T. C. Bruice, *Biochemistry*, 1971, **10** (17), 3178.
[8] A. F. Hegarty and M. T. McCormack, *J.C.S. Perkin II*, 1976, 1701.
[9] D. Y. Curtin and J. H. Engelmann, *J. Org. Chem.*, 1972, **37**, 3439; *Tetrahedron Letters*, 1968, 3911.
[10] J. E. Johnson, E. A. Nalley, and C. Weidig, *J. Amer. Chem. Soc.*, 1973, **95**, 2051; A. Padwa and F. Albrecht, *ibid.*, 1974, **96**, 4849; O. Exner, V. Jehlicka, and A. Reiser, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3207.

the preparation of the E- and Z-isomers of further groups of isoimides and the kinetics of their conversion to the N-acyl compounds.

RESULTS AND DISCUSSION

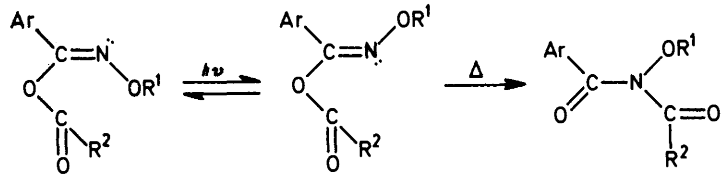
Synthesis of Substrates.—Acylation of the silver salts of O-alkyl benzohydroxamic acids (10) with alkanoyl or aroyl chlorides gave the Z-isomers (7) of the isoimides; * acylations with aroyl halides were slower and required up to 48 h to go to completion. Direct irradiation of the acetates (7a and b) in hexane or benzene with u.v. light produced a photostationary equilibrium of the Z-(7) and E-(8) isomers. With the benzoates (7c; R^2 = aryl) this method produced a complex mixture of products including the initial Z-isomer, some E-isomer, the N-benzoyl material (9), and other unidentified materials. Triplet sensitisers (acetophenone, 1-acetonaphthone, and biacetyl) were successfully used to promote the Z-E equilibrium. T.l.c. indicated that it would be difficult to remove acetophenone and acetonaphthone from the reaction mixture by column chromatography, so biacetyl which, because of its low b.p. (88°), could be removed (with the solvent) under reduced pressure at the



(10)

end of the photochemical reactions, was used subsequently. The E-isomers could be detected, and separated from the reaction mixture by t.l.c. (or dry column chromatography), and these isomers had lower R_F values than the Z-isomers with a wide range of solvent mixtures. For the acetates, the n.m.r. spectra were also useful for detecting the E-isomers using both the acetyl and $NOCH_2$ protons (Figure 1).

However, the methylene protons of the latter were equivalent for the benzoates (7c) and (8c). In the E-isomer the resonance of the OCH_2 group is shifted upfield from that of the Z-isomer due to the shielding effect of the C-aryl ring in (11a), which is twisted out of the plane of the azo-vinyl linkage.[12] In the Z-isomer this shift could be compensated for by an equivalent shielding of the CH_2 group due to the aromatic ring of the benzoate portion of the molecule (11b). A similar result was obtained when the benzyl group was replaced by an n-propyl group.



(7) (8) (9)

a; $R^1=R^2=CH_3$
b; Ar = Ph, $R^2=CH_3$
c; Ar = Ph, $R^1=CH_2Ph$
d; Ar = R^2 = Ph

SCHEME 2

Kinetics of Rearrangement.—On heating in a wide variety of solvents ranging from carbon tetrachloride to 1 : 4 dioxan–water (v/v) (phosphate buffer, pH 6.6),

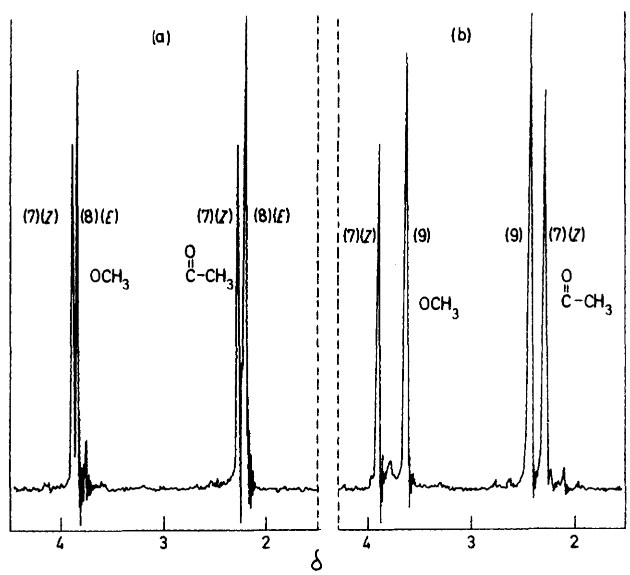


FIGURE 1 [1]H N.m.r. spectra (60 MHz) in $CDCl_3$ of (a) a mixture of Z- and E-isomers (7a and 8a; Ar = p-$NO_2C_6H_4$) obtained by photoisomerisation of (7a; Ar = p-$NO_2C_6H_4$) and (b) the reaction products obtained on refluxing the materials in (a) in toluene for 30 min; unchanged (7a; Ar = p-$NO_2C_6H_4$) and the isomerised (9a; Ar = p-$NO_2C_6H_4$) are present, while the E-isomer (8a; Ar = p-$NO_2C_6H_4$) is absent

the E-isomers (8a—d) were converted quantitatively into the N-acetyl or N-benzoyl compounds (9). Under the same conditions the Z-isomers, with the exception of the O-phenyl compound (7b; R^1 = Ph), were unchanged (i.r. and t.l.c.). The O-phenyl compound underwent

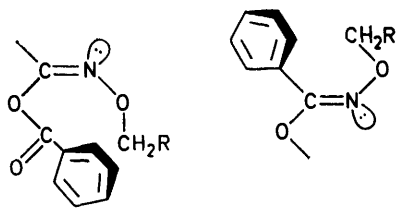
* A more detailed description of the syntheses, interconversion, and configurational assignment of the E- and Z-isomers is given in ref. 11.

[11] D. G. McCarthy and A. F. Hegarty, *J.C.S. Perkin I*, preceding paper.

[12] J. Bjorgo, D. R. Boyd, C. G. Watson, and W. B. Jennings, *Tetrahedron Letters*, 1972, 1747; J. Bjorgo, D. R. Boyd, C. G. Watson, W. B. Jennings, and D. M. Jerina, *J.C.S. Perkin II*, 1974, 1081.

reaction when refluxed in toluene or chlorobenzene, as evidenced by the disappearance of the ester carbonyl absorption at 1 770 cm^{-1} and the simultaneous appearance of absorptions in the region 1 670—1 700 cm^{-1}. The nature of the reaction is not yet clear, but the possibility of thermally induced sequential aryl and acetyl group migrations to give (12) exists.

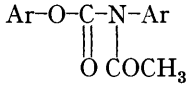
A number of techniques were used to observe the conversion of (8) into (9). Thus the i.r. spectrum shows a decrease in the carbonyl stretching frequency above



(11a) (11b)

1 750 cm^{-1} accompanied by one or two new carbonyl bands at 1 720—1 690 cm^{-1} (Figure 2). Similarly the ^1H n.m.r. spectra show the disappearance of the $NOCH_2$ and the *O*-acetyl group resonances, these being replaced by the corresponding resonances in the *N*-acyl material (Figure 1). For the kinetic data reported here u.v. spectrophotometry was used, and acetonitrile was the common solvent employed.

Over the temperature range 50—80°, the rearrangement of the acetates (8b; $R^1 = CH_3$, CH_2Ph, or



(12)

Pr^n) obey the Arrhenius equation and the kinetic and thermodynamic data obtained are summarized in Table 1. As can be seen, the activation energies are *ca.* 26 kcal mol^{-1} and the entropies of activation are positive and small, the latter being consistent with the occurrence of an intramolecular process involving little solvent reorganization in the transition state.[13]

The rate of rearrangement of (8a; Ar = Ph) in acetonitrile was insensitive to the addition of small quantities (10^{-4}M) of acetic acid and calcium hydride. In addition no rate change was observed in the presence of small quantities of free radical initiators (benzoyl peroxide and azobisisobutyronitrile). Furthermore a free radical inhibitor bis-(4-hydroxy-5-methyl-3-t-butylphenyl) sulphide did not change the rate of reaction. Thus, it is unlikely that the reaction takes place by a free radical mechanism. Ionic reactions involving formation of an acylium cation and *O*-methylbenzohydroxamate anion followed by recombination of these to give the *N*-acylated material or initial hydrolysis of the ester followed by *N*-acylation were not considered to be important reactions as a result of crossing experiments. When the benzoate (8c; R^2 = Ph) was rearranged in the presence of acetic acid the only product observed (by t.l.c.) was the *N*-benzoyl compound (9c; R^2 = Ph). In another experiment a mixture of the acetate (8b; $R^1 = Pr^n$) and benzoate (8c; R^2 = Ph) was rearranged, and the only products detected were those resulting from the intramolecular reaction [(9c; R^2 = Ph) and

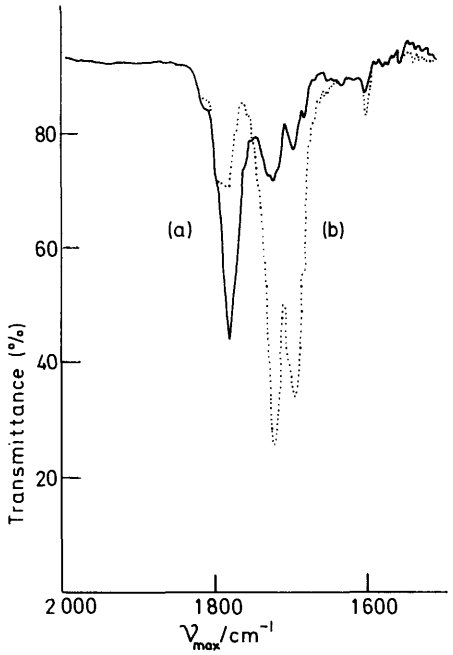


FIGURE 2 Time dependence of the carbonyl stretching region of the i.r. spectrum for the rearrangement of (8b; $R^1 = Pr^n$) in carbon tetrachloride at 65°: (a) *t* 2 min; (*b*) *t* 30 min

(9b; $R^1 = Pr^n$)]. T.l.c. showed that the cross-over products (9d; $R^1 = Pr^n$) and (9c; $R^2 = CH_3$) were not present. Dilution experiments showed that small quantities of these (*ca.* 5%) could be observed by t.l.c. analysis. Although the acetate and benzoate used in this experiment have an approximately four-fold difference in reactivity, sufficient quantities of both compounds would have rearranged during the experiment to enable any cross-over products to be detected.

TABLE 1

Kinetic and thermodynamic data for the rearrangement of (*E*)-acetic *O*-alkylbenzohydroximic anhydrides (8)

R^1	$10^3 k_{obs}/s^{-1}$	T/°C	E_a/ kcal mol^{-1} [c]	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}
CH_3 [a]	1.41	77			
	1.15	75			
	0.60	70	26.1	25.5	1.1
	0.22	61			
	0.10	54			
CH_2Ph [a]	0.85	70	26.3	25.6	2.0
Pr^n [b]	2.63	70	25.8	25.1	2.65

[a] In acetonitrile. [b] In 1 : 4 dioxan–water (v/v), containing 10^{-2}M-phosphate buffer (ph 6.6; μ 1.0; $NaClO_4$). [c] ±0.5 kcal mol^{-1}, E_a calculated from kinetic measurements over the range 50—80 °C.

Substituent Effects.—On replacement of the acetyl group in (8c; $R^2 = CH_3$) by a benzoyl residue the rate

[13] R. W. Alder, R. Baker, and J. M. Brown, 'Mechanism in Organic Chemistry,' Wiley–Interscience, London, 1971.

of rearrangement (in acetonitrile) is reduced by a factor of five (k_{obs} 1.58 and 0.34 × 10^{-3} s^{-1}). This is due to the greater steric requirements of the aromatic ring in a four-membered transition state and to the normal reduction in reactivity towards nucleophiles of a benzyl group relative to an acetyl group. This difference is much less than that found in the corresponding intermolecular process. The reaction of *p*-nitrophenyl acetate with ammonia is 50 times faster than that of the corresponding benzoate ester.[14,15] The rate of [1,3] benzoyl group migration in (8c; $R^2 = C_6H_4X$) increases with the electron-withdrawing power of the substituent (Table 2).

TABLE 2

First-order rate constants (s^{-1}) for [1,3] aroyl group migrations in (*E*)-benzoic *O*-benzylbenzohydroximic anhydrides in acetonitrile at 77 °C

Substituent	$10^3 k_{obs}/s^{-1}$ (±4%)	λ/nm [a]
p-CH_3	0.235	285
H	0.34	283
p-Cl	0.45	285
m-Cl	0.56	290
m-NO_2	0.85	290
p-NO_2	1.09	300

[a] Wavelength at which kinetic measurements were performed.

A plot of log k_{obs} *versus* the δ values of McDaniel and Brown [16] is linear with slope ρ 0.65 (*r* 0.997).

O-Alkyl substituents (Me, Pr^n, CH_2Ar) do not greatly effect the rate of rearrangement of (8; $R^2 = CH_3$) but in order to estimate the extent of involvement of the imino-nitrogen in the transition state for the rearrangement a range of substituents in this position was necessary. Only a very limited range of *O*-arylhydroxylamines are known [17] and some of these (*e.g.* *O*-2,4-dinitrophenylhydroxylamine) would reduce the rate of rearrangement of (8) to such an extent that other processes (Lossen rearrangements) might take precedence over the [1,3] acyl migration. Instead *para*-substituted benzyl groups were used [(8b; $R^1 = CH_2C_6H_4X$-*p*)]. The rates of rearrangement were found to decrease with increasing electron-withdrawing power of the substituents but the overall sensitivity of the reaction to the electronic effect of substituents was small (requiring precise kinetic measurements). On going from X = *p*-CH_3 to *p*-NO_2, the rate of reaction decreased by a factor of only two. Using normal σ values a Hammett ρ of −0.26 was obtained (*r* 0.999).

The low sensitivity of the reaction to substituents is due in part to the system used. Insertion of a methylene group between the oxygen and the aryl ring reduces the ρ value by 2.2. Using this a ρ of −0.57 can be calculated for the effect of *O*-aryl substituents on the reaction. Using the data of Chapman and Shorter for the reactions of benzoic, phenylacetic, and phenoxyacetic acid with diazodiphenylmethane [18] a reduction factor of 1.6 is obtained for oxygen. Thus a ρ value of −0.91 is estimated for the effect of *N*-aryl substituents on a [1,3] acyl migration. This value is less than that found by Schwartz (−1.27),[3] and much less than the value suggested by Curtin.[2]

Introduction of electron-withdrawing substituents in the *C*-aryl ring retards the rate of rearrangement of the acetate (8a). For three substituents (Table 3) a Hammett ρ of −0.49 was obtained. The *p*-nitro-group does not deviate from a straight line through the other two points, indicating the lack of any significant ground state stabilization of the ester (8a; Ar = *p*-$NO_2C_6H_4$) through conjugation of the carbon–nitrogen double bond with the nitro-group. As there is considerable evidence [12] that in these and related systems the *C*-aryl ring is twisted out of the plane of the carbon–nitrogen double bond this type of interaction is unlikely and electron-demanding substituents in the *C*-aryl ring retard the rate of rearrangement mainly by lowering the electron density on the imino-nitrogen through an inductive effect. The negative ρ indicates the build up of positive charge on the imino-carbon in the transition state due to electron donation to the neighbouring nitrogen.

TABLE 3

Observed first-order rate constants (s^{-1}) for the rearrangement of substituted (*E*)-acetic *O*-methylbenzohydroximic and *O*-benzylbenzohydroximic anhydrides in acetonitrile at 77 °C

Substrate	Substituent	$10^3 k_{obs}/s^{-1}$
(8a; Ar = Ph)	H	1.37 [a]
(8a; Ar = *m*-ClC_6H_4)	*m*-Cl [c]	0.96
(8a; Ar = *p*-$NO_2C_6H_4$)	*p*-NO_2	0.57
(8b; R^1 = *p*-$MeC_6H_4CH_2$)	*p*-CH_3	1.76 [b]
(8c; $R^2 = CH_3$)	H	1.58
(8b; R^1 = *p*-$ClC_6H_4CH_2$)	*p*-Cl	1.37
(8b; R^1 = *p*-$NO_2C_6H_4CH_2$)	*p*-NO_2	1.01

[a] k_{obs} ±4%. [b] ±2%, mean value of four measurements for each substituent in the series. [c] Rate measured on a mixture (52 : 48) of the *E*- and *Z*-isomers.

Solvent Effects.—The variation of a reaction rate with the solvent used is an important criterion of mechanism.[19] In the present case the rate of rearrangement of the benzoate (8c; R^2 = *p*-$NO_2C_6H_4$) was studied in eight aprotic solvents. The rate of reaction showed a low sensitivity to the solvents used. On changing from methylcyclohexane (ε 2.02) to dimethyl sulphoxide (ε 48.9), a four-fold increase in the rate of reaction occurred. This small solvent sensitivity is similar to that encountered in dipolar cycloaddition reactions.[20] A linear

[14] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.

[15] J. F. Kirsch and A. Kline, *J. Amer. Chem. Soc.*, 1969, **91**, 1841.

[16] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

[17] E. C. Taylor and F. Kienzle, *J. Org. Chem.*, 1971, **36**, 233; R. L. Blakeley and B. Zerner, *Chem. and Ind.*, 1973, 133; Y. Tamura, J. Menamihowa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 1239.

[18] K. Bowden, N. B. Chapman, and J. Shorter, *Canad. J. Chem.*, 1964, **42**, 1979.

[19] S. G. Smith, A. H. Fainberg, and S. Winstein, *J. Amer. Chem. Soc.*, 1961, **83**, 618; A. H. Fainberg and S. Winstein, *ibid.*, 1956, **78**, 2770.

[20] A. Battaglia, A. Dondoni, G. Maccagnani, and G. Mazzenti, *J. Chem. Soc.* (*B*), 1971, 2096; R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.*, 1967, **100**, 2494.

relationship [equation (1); r 0.979] between log k and the dielectric constant of the solvent was obtained (Figure 3) with dimethylformamide showing a large positive deviation. A plot of log k against $(\varepsilon - 1)/(2\varepsilon + 1)$ gave a parabolic curve.

$$\log k = -3.270\,3 + 0.007\,3\varepsilon \qquad (1)$$

The linear relationship obtained must be viewed in the context of the limited range of solvents used and may represent the linear portion of a more complex relationship between log k and ε for a wider range of possible solvents and dielectric constants. Polar protic solvents were not used as with the substrate studied intermolecular acyl transfer would probably compete with the intramolecular process in alcoholic or acidic solvents. The deviation shown by dimethylformamide may be due to specific solute–solvent interactions [21a] in the ground or transition states. When the sensitivity of the rate of rearrangement (8) ⟶ (9) to the dielectric constant of the solvent is compared with that shown by the reaction of tertiary amines with alkyl halides [21b] (a reaction which involves a considerable charge separation in the transition state and consequently shows a large sensitivity to ε), the conclusion drawn is that the rearrangement proceeds through a transition state which has little charge separation.

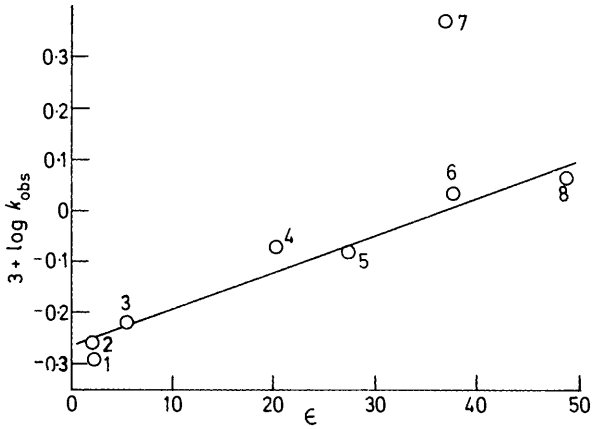


FIGURE 3 Plot of log k_{obs} *versus* the dielectric constant of the solvent used (at 25°) for the rearrangement of (8c; R^2 = *p*-$NO_2C_6H_4$) at 77°. Solvent index: 1, toluene; 2, methylcyclohexane; 3, chlorobenzene; 4, butyronitrile; 5, propionitrile; 6, acetonitrile; 7, dimethylformamide; 8, dimethyl sulphoxide. Dielectric constants are taken from ref. 21*a*

Intermolecular Acyl Transfer to Water and Amines.—Intermolecular acyl transfer was investigated with the *Z*- and *E*-isomers (7b; R^1 = Pr^n) and (8b; R^1 = Pr^n) to enable comparison to be made with the intramolecular process, and because of current interest in the acyl transfer potential of the isoimide linkage as a model for carbodi-imide mediated processes. In 1 : 4 dioxan–water (v/v) the acetates (7b; R^1 = Pr^n) and (8b; R^1 = Pr^n) hydrolysed by acid and base catalysed processes giving acetic acid and the hydroxamic acid (10; R^1 = Pr^n) as the only products.

(a) *Acid catalysed hydrolysis.* For the acid catalysed process a plot of log k_{obs} *versus* pH is linear with a slope of −1 with both isomers, indicative of specific acid catalysis. The *E*-isomer (8) reacted faster than the *Z*-isomer by a factor of *ca.* 2 (Table 4). This difference could reflect either slightly differing pK_a values for the conjugate acids of the two isomers,[22] or a steric influence on the rate-determining step. Two sites are available for pre-equilibrium protonation of the substrate, the carbonyl oxygen of the ester linkage and the imino nitrogen. The latter is more basic and is the most likely site of protonation. Rate-determining water attack on the protonated substrate (13) or (14), either at the carbonyl oxygen or at the carbon–nitrogen double bond gives the final product. Acid catalysed *E*–*Z* isomerisation of oxime derivatives is well known [23,24] and in the present case the hydrolysis product could arise either from direct displacement of acetate from the conjugate acid of each isomer [(13) and (14)] or from the conjugate acid of second isomer formed by initial *Z* ⟶ *E* isomerisation of the starting material (Scheme 3).

If this is significant then the rate difference observed for the two isomers represents a lower limit on the possible rate difference. To check if *E* ⟶ *Z* isomerism was occurring in our case, the two isomers were hydrolysed separately on a quantitative basis under the kinetic conditions at pH 1.0 and 25°. T.l.c. analysis during the reaction failed to detect any trace of a second isomer. As the equilibrium constant for *E*–*Z* isomerism in this system is not known, and if the equilibrium lies largely on the side of one isomer, detection of small quantities (<5%) of a second isomer may not be possible by t.l.c. particularly when the two isomers hydrolyse at comparable rates.

TABLE 4

Dependence of observed first-order rate constants (s^{-1}) for the hydrolysis of (*E*)- and (*Z*)-acetic *O*-n-propylbenzohydroximic anhydride on pH in 1 : 4 dioxan–water (v/v) (μ 1.0, $NaClO_4$) and at 25°

Z [b]		*E* [c]	
pH	$10^3 k_{obs}/s^{-1}$ [a]	pH	$10^3 k_{obs}/s^{-1}$ [a]
0.13	23.38	0.1	41.70
0.295	14.57	0.3	27.54
0.50	9.10	0.51	14.40
0.78	4.39	0.82	8.10
1.03	2.93	1.06	4.04
1.44	0.75	1.57	1.15
11.0	0.73	11.2	5.0
11.55	3.14	11.52	12.6
12.16	9.55	12.0	28.8
12.58	23.24	12.58	96.0
12.96	67.7	12.80	190.0

[a] ±4%. [b] At 260 nm. [c] At 257 nm.

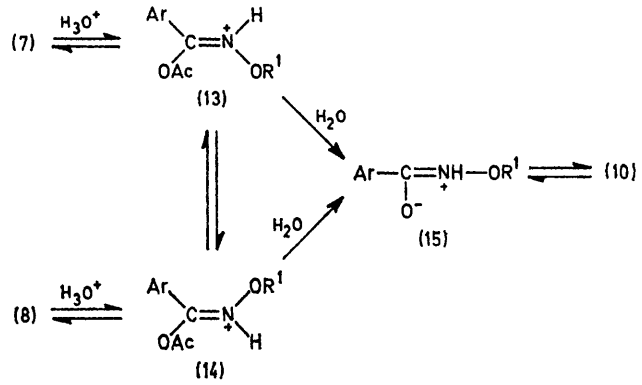
(b) *Base catalysed hydrolysis.* At high pH (>11) both isomers of the acetate (7b; R = Pr^n) and (8b; R^1 = Pr^n) hydrolyse at 25° to give the same products as the acid catalysed process. The rates of reaction in-

[21] (*a*) J. A. Koppel and V. A. Palm in 'Advances in Linear Free Energy Relationships,' eds. J. Shorter and N. B. Chapman, Plenum Press, London, 1972, ch. 5; (*b*) G. H. Grimm, H. Luff, and H. Wolff, *Z. Phys. Chem.*, 1931, **313**, 301.

[22] A. C. Satterthwait and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 7045.

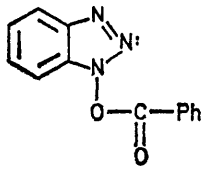
[23] J. E. Johnson, E. A. Nalley, Y. K. Kunz, and J. R. Springfield, *J. Org. Chem.*, 1976, **41**, 252.

[24] K. J. Dignam and A. F. Hegarty, *J.C.S. Chem. Comm.*, 1976, 862.



SCHEME 3

crease with pH (Table 4); plotting log k_{obs} *versus* pH for both isomers gives straight lines of unit slope. Thus a specific base catalysed process involving rate-determining hydroxide ion attack on the ester linkage of each isomer is occurring. With hydroxide ion the *E*-isomer reacts *ca.* 6 times faster than the *Z*-isomer. Molecular models indicate that isoimide linkage of the *E*-isomer is much less hindered than in the *Z*-isomer and thus is more susceptible to nucleophilic attack by hydroxide ion. We have previously reported [25] the high reactivity towards hydroxide ion of 1-benzoyloxybenzotriazole (16); in (16) the ester function and the lone pair on N-2 have similar relative positions to those in (8).



(16)

(c) *Aminolysis.*—The reactions of the benzoates (7c; $R^2 = C_6H_4X$) and (8c, $R^2 = C_6H_4X$) with piperidine in 1 : 1 dioxan–water (v/v) at 25° were investigated as a model for the intermolecular process. Kinetic measurements were made under first-order conditions using a range (10^{-2}—10^{-1}M) of buffer concentrations, and three different fractions of free base, 0.35, 0.50, and 0.75. For each fraction of free base, the first-order rate constant for disappearance of (7c) or (8c) was directly proportional to the total buffer concentration (Figure 4).

General base catalysis of the aminolysis reaction by a second molecule of amine was not evident and a plot of $k_{obs}/[B]_T$ (where $[B]_T$ is the total buffer concentration) *versus* the fraction of free base was linear with an intercept at the origin, indicating the absence of any general acid catalysis of the reaction by piperidinium ion. Both isomers showed the same general behaviour except that the *E*-isomer reacted faster than the *Z*-isomer by a factor of 1.3, the second-order rate constants being 0.297 ± 0.004 and 0.240 ± 0.007 l mol^{-1} s^{-1} respectively.

Electron-withdrawing substituents in the benzoyl portion of the molecule increase the rate of the piperidine reaction (Table 5). For the *Z*-isomers five esters gave

[25] D. G. McCarthy, A. F. Hegarty, and B. J. Hathaway, *J.C.S. Perkin II*, 1977, 224.

TABLE 5

Observed first-order rate constants (s^{-1}) for reaction of (*Z*)-Benzoic *O*-benzylbenzohydroximic anhydrides (7c; $R^2 = C_6H_4X$) with 0.04M-piperidine (fraction free base 0.5) in 1 : 1 dioxan–water (v/v) at 25° (μ = 1.0, NaCl)

Substituent	*p*-CH_3	H	*p*-Cl	*m*-Cl	*m*-NO_2
10^3k_{obs}/s^{-1} [a]	2.9 (3.27) [b]	5.1 (5.9) [b]	9.35 (12.2) [b]	15.8	53.6

[a] Measured at 260 nm. [b] Observed first-order rate constants for reaction of the corresponding *E*-isomers under the same conditions.

ρ +1.3 (*r* 0.998). Using three substituted *E*-isomers under the same conditions ρ +1.44 was found. The ρ values obtained here are of the same order of magnitude as those reported (1.1—1.4) for the reaction of amines with phenyl benzoates in aqueous media [15] and are

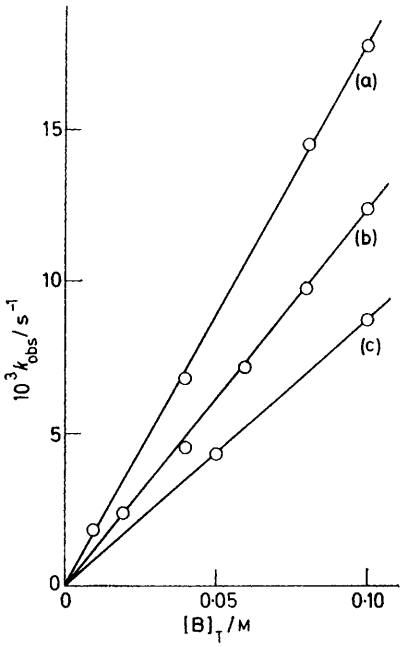
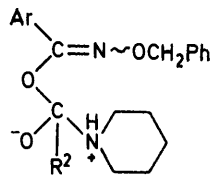


FIGURE 4 Dependence of the pseudo-first-order rate constants on the total buffer concentration ($[B]_T$) for the reaction of (8c; R^2 = Ph) with piperidine at various fractions of free base: (a) 0.75; (b) 0.50; (c) 0.35; at 25°. Solvent 1 : 1 dioxan–water (v/v) (μ 1.0; NaCl)

consistent with initial rapid attack of the amine on the ester (7) or (8) to form the tetrahedral intermediate $T^{\pm}$ (17) followed by rate-determining loss of the leaving group (hydroxamate ion).

Mechanism of Intramolecular Acyl Transfer.—Two extreme mechanisms may be considered for the [1,3] acyl migration described here. The first (as described by Curtin [2]) involves initial nucleophilic attack by the lone pair of electrons on the imino-nitrogen atom at the ester carbonyl carbon to give a zwitterionic four-membered intermediate (18), followed by breakdown of this to give the product (9) (Scheme 4). This mechanism is the intramolecular analogue of a normal ester aminolysis reaction.

The second mechanism involves considering the [1,3] acyl migration as a concerted sigmatropic rearrangement and describing the mechanism in terms of the

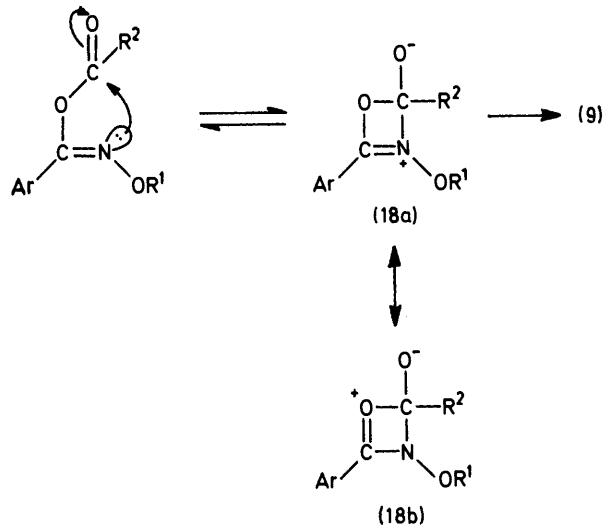


T±

(17)

principle of conservation of orbital symmetry.[26] However, this treatment would have to explain why the *E*-isomer rearranges while the *Z*-isomer is thermally stable to rearrangement.

In this latter mechanism the orbital containing the lone pair of electrons on the nitrogen and the π orbitals of the



(18a)

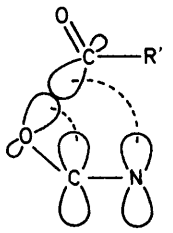
(18b)

(9)

SCHEME 4

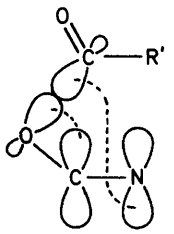
carbonyl group do not take part in the reaction, the only orbitals which are involved being the σ bonding orbitals of the C–O σ bond and the π bonding orbitals of the carbon–nitrogen double bond. The suprafacial process (19) is thermally forbidden but the rearrangement can take place in a suprafacial manner with formal 'inversion' of the configuration at the carbonyl carbon (21). While the antarafacial process (20) whereby the acetyl group migrates across the face of the π system is thermally allowed, it is unlikely for steric reasons, particularly since it is not observed in [1,3] hydrogen migrations [27] where steric requirements are much less. Under photochemical conditions the $_{\pi}2_s + _{\sigma}2_s$ process would be allowed and with the direct irradiation methods we used to isomerize the acetates (7a and b) traces (*ca.* 5%) of the *N*-acyl material (9) were detected at the end of the reaction by t.l.c. However we feel that these resulted from some thermal isomerization of the *E*-isomer (8) during the reaction rather than a direct photoinduced O ⟶ N acyl migration in the *E*- and *Z*-isomers. It is difficult to visualize why the thermally induced suprafacial process (21) would only occur in the *E*-isomer, since the extra steric constraints of the OR^1 group when *cis* to the acyl function should not be very great (as judged from molecular models).

For the stepwise mechanism either step can be rate



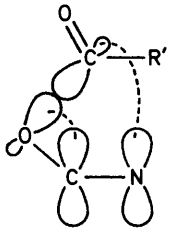
$\pi 2_s + \sigma 2_s$

(19)



$\pi 2_a + \sigma 2_s$

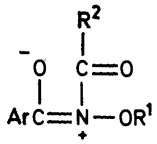
(20)



$\pi 2_s + \sigma 2_a$

(21)

determining. Rate-limiting nucleophilic attack at the carbonyl group in the benzoates (8c; R^2 = Ar) would show a reasonably large sensitivity to acyl substituents ($\rho > 1$), while a slow breakdown of a tetrahedral intermediate would show a lower sensitivity. Thus Menger has observed ρ values of 1.02—1.4 for the uncatalysed addition of pyrrolidine to acyl-substituted phenyl benzoates [28] in acetonitrile under conditions where collapse of the tetrahedral intermediate is rate determining, ($\rho_{1.gr.}$ −6.24). The ρ values found for the intermolecular reaction of piperidine with the *E*- and *Z*-isomers (7c) and (8c) are in agreement with those found by Menger and by Kirsch [15] for the reaction of phenyl benzoates with ammonia in 1 : 2 acetonitrile–water, and thus in accord with a rate-limiting breakdown of the tetrahedral intermediate (17).



(22)

The ρ value for the [1,3] benzoyl migration (0.65) is much lower.* If a tetrahedral intermediate is present for the rearrangement (8) ⟶ (9), the low ρ value would indicate that the relative magnitudes of the

* No correction is necessary for the difference in dielectric constants of the solvents used for the rearrangement and the piperidinolysis reaction, as both are essentially the same, [ε(CH_3CN) 37.5, ε (1 : 1 dioxan–water) 35).[29]

[26] R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Academic Press, New York, 1970.

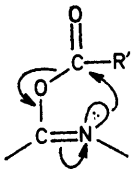
[27] Ref. 26, p. 120.

[28] F. M. Menger and J. H. Smith, *J. Amer. Chem. Soc.*, 1972, **94**, 3824.

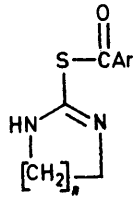
[29] F. E. Critchfield, J. A. Gibson, and J. L. Hall, *J. Amer. Chem. Soc.*, 1953, **75**, 1991.

absolute values for the formation and breakdown of (17) are much closer than in an intermolecular process. Breakdown of a tetrahedral intermediate is unlikely to be rate determining for the [1,3] acyl migration as a very good leaving group [essentially the *N*-acyl species (22)] is present. Furthermore a considerable driving force would be present for the breakdown of a four-membered ring. Rate-determining formation of the tetrahedral intermediate (18) is more likely. The ρ values for the migrating group and for the imino-nitrogen atom indicate that if this is the case a very early transition state is necessary. This would agree with the solvent effect observed. A useful comparison for this is data for the reactions of anilines with aroyl chlorides (which have good leaving groups) in benzene giving ρ −3.21 for the substituted anilines and 1.18 for substituents in the aroyl chlorides.[30]

A synchronous mechanism incorporating partial cleavage of the C–O bond and partial C–N bond formation in the transition state (23) would also accommodate



(23)



(24)

the substituent effects. This mechanism would not have the same transition state as a concerted sigmatropic reaction as in the latter the lone pair on nitrogen is not involved. A transition state like (23) would avoid the unfavourable steric effects associated with the formation of a four-membered ring.

Whichever mechanism is present for the rearrangement of (8), the necessity for the correct orientation of the lone pair on the nitrogen and the carbonyl group so to minimize the strain associated with the transition state for the rearrangement is evident from the data on the rearrangement of cyclic *S*-acylisothioureas (24).[7] The derivative with the six-membered ring (24; $n = 3$) rearranged *ca.* 200 times faster than the five-membered ring compound (24; $n = 2$). Thus while we cannot rule out the presence of a tetrahedral intermediate [such as (8)] on the reaction pathway for the conversion of (8) into (9), the transition state is reached very early on the reaction co-ordinate. In these circumstances, the relief of steric strain brought about by the concerted C–O bond cleavage [as shown in (23)] would be advantageous.

[30] J. Shorter, 'Correlation Analysis in Organic Chemistry,' Clarendon Press, Oxford, 1973, p. 10.

EXPERIMENTAL

The general experimental procedures are as previously described.[11] For t.l.c. and dry column chromatography the following solvents were used: A and B, chloroform–cyclohexane in the ratios 3 : 1 and 1 : 1 respectively; C, 1 : 5 (v/v) ethyl acetate–light petroleum; D—F, ether–light petroleum (<40°) in the proportions 1 : 15, 1 : 6, and 1 : 3.

Substrates.—Some of the *O*-alkylbenzohydroxamic acids used have been described previously.[11] *O*-(4-Nitrobenzyl)-benzohydroxamic acid (prepared by the method of Brady and Klein [31]) had m.p. 154—156° (lit.,[32] 161°). Reaction of the corresponding benzyl chloride with potassium benzohydroxamate gave *O*-(4-chlorobenzyl)benzohydroxamate. For this compound stirring at 45° for 7 days was required to give a negative hydroxamic acid test with $FeCl_3$. The *hydroxamate* had m.p. 156—158° [chloroform–light petroleum (b.p. 60—80°) 1 : 5], $\nu_{max.}$ (KBr) 3 225 (NH) (C=O) 1 640 cm^{-1} (Found: C, 64.6; H, 4.9; N, 5.3; Cl, 13.8. $C_{14}H_{12}ClNO_2$ requires C, 64.25; H, 4.6; N, 5.35; Cl, 13.55%). Also prepared was O-(*4-methylbenzyl*)*benzohydroxamate*, m.p. 101—103°, $\nu_{max.}$ 3 390 and 3 215 (NH) and 1 670 cm^{-1} (C=O), δ($CDCl_3$) 2.3 (3 H, s), 4.9 (2 H, s), and 7.2—7.6 (9 H, m) (Found: C, 74.2; H, 5.9; N, 5.8. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%). *O*-Phenylbenzohydroxamate was obtained by the procedure of Taylor [17] and had m.p. 136° (lit.,[17] 136—137°).

(Z)-*Acetic* O-*Benzylbenzohydroximic Anhydrides.*—These were prepared by acylation of the silver salts of *O*-benzylbenzohydroxamic acids with acetyl chloride in ether. Thus obtained were (*Z*)-acetic *O*-(4-methylbenzyl)benzohydroximic anhydride. The crude product from this reaction was contaminated (as shown by i.r. and t.l.c.) with some of the hydroxamic acid. This was removed by swirling the product with cold carbon tetrachloride, filtering the undissolved hydroxamic acid, and evaporating the solvent to give the pure *anhydride* (Found: C, 72.45; H, 6.2; N, 4.7. $C_{17}H_{17}NO_3$ requires C, 72.1; H, 6.05; N, 4.9%). Similarly prepared were (Z)-*acetic* O-(*4-chlorobenzyl*)*benzohydroximic anhydride* (Found: C, 62.9; H, 4.8; N, 4.5; Cl, 11.7. $C_{16}H_{14}ClNO_3$ requires C, 63.3; H, 4.65; N, 4.6; Cl, 11.7%) and (Z)-*acetic* O-(*4-nitrobenzyl*)-*benzohydroximic anhydride* (Found: C, 6.15; H, 4.7; N, 8.9. $C_{16}H_{14}N_2O_5$ requires C, 61.1; H, 4.5; N, 8.8%). Also prepared was (Z)-*acetic* O-*phenylbenzohydroximic anhydride*, m.p. 86—87.5° [light petroleum (b.p. 40—60°)], $\nu_{max.}$ (KBr) 1 768 (C=O) cm^{-1}, δ 2.3 (3 H, s), 7.6 (2 H, q), 7.2 (2 H, m), 7.1 (6 H, m) (Found: C, 70.9; H, 5.6; N, 5.45. $C_{15}H_{13}NO_3$ requires C, 70.6; H, 5.1; N, 5.5%).

(Z)-*Benzoic* O-*Benzylbenzohydroximic Anhydride.*—The silver salt of *O*-benzylbenzohydroxamic acid (2.01 g, 6 mmol) was suspended in dry ether (50 ml). To this was added dropwise freshly distilled benzoyl chloride (0.88 g, 6.2 mmol) in dry ether (10 ml). The reaction was protected from light and stirred at ambient temperature for 48 h. Filtration of the silver chloride, followed by evaporation of the ether under reduced pressure gave an oil. On addition of low boiling light petroleum and cooling the solution in an ice–salt-bath, a *solid* resulted (1.6 g, 80%) (Found: C, 76.3; H, 5.6; N, 4.3. $C_{21}H_{17}NO_3$ requires C, 76.1; H, 5.2; N, 4.2%). Table 6 gives physical data for this and the other compounds in the series: O-p-*methylbenzoic* (Found: C, 76.4; H, 5.4; N, 3.9. $C_{22}H_{19}NO_3$ requires C, 76.5; H, 5.5; N, 3.9%); O-p-*chlorobenzoic* (Found: C, 69.3; H, 4.4; N,

[31] O. L. Brady and K. Klein, *J. Chem. Soc.*, 1927, 874.
[32] A. Werner, *Ber.*, 1892, **25**, 44.

TABLE 6

Physical data for (*Z*)-acetic and benzoic *O*-alkylbenzohydroximic anhydrides

Compound	M.p. (°C)	$\nu_{max.}$/cm^{-1}	Chemical shift δ [d]
(7b; R^1 = CH_2-*p*-$CH_3C_6H_4$)	48—50 [a]	1 778	7.5 (2 H, m), 7.2 (7 H, m), 5.01 (2 H, s), 2.29 (3 H, s), 2.18 (3 H, s)
(7b; R^1 = CH_2-*p*-ClC_6H_4)	59—60 [b]	1 768 [c]	7.52 (2 H, m), 7.23 (7 H, m), 5.02 (2 H, s), 2.22 (3 H, s) [c]
(7b; R^1 = CH_2-*p*-$NO_2C_6H_4$)	87—89 [b]	1 773 [c]	8.14 (2 H, d), 7.45 (7 H, m), 5.22 (2 H, s), 2.33 (3 H, s) [c]
(7c; R^2 = Ph)	74—75.5 [a]	1 755	8.1 (2 H, q), 7.75—7.21 (13 H, m), 5.14 (2 H, s) [c]
(7c; R^2 = *p*-$CH_3C_6H_4$)	77—78 [a]	1 745 [c]	7.9 (2 H, d), 7.2 (12 H, m), 5.08 (2 H, s), 2.39 (3 H, s)
(7c; R^2 = *p*-ClC_6H_4)	75—76 [a]	1 750 [c]	8.0 (2 H, d), 7.18 (12 H, m), 5.07 (2 H, s)
(7c; R^2 = *m*-ClC_6H_4)	85—87 [a]	1 753	7.8 (4 H, m), 7.2 (10 H, m), 5.09 (2 H, s)
(7c; R^2 = *m*-$NO_2C_6H_4$)	79—80 [b]	1 759	7.75 (2 H, m), 7.28 (12 H, m), 5.14 (2 H, s)
(7c; R^2 = *p*-$NO_2C_6H_4$)	85—86 [b]	1 755 [c]	8.2 (2 H, d), 7.7 (2 H, m), 7.25 (10 H, m) [c]
(7d; R^1 = Pr^n)	47—49 [a]	1 753	8.1 (2 H, q), 7.3—7.7 (8 H, m), 4.01 (2 H, t *J* 7 Hz), 1.65 (2 H, sextet *J* 7 Hz), 0.9 (3 H, t, *J* 7.5 Hz)

[a] From light petroleum b.p. 60—80°. [b] From 1 : 5 chloroform–light petroleum. [c] I.r. and n.m.r. spectra obtained in $CHCl_3$ and $CDCl_3$ respectively, all other spectra were taken with CCl_4 as solvent. [d] At 60 MHz with Me_3Si as internal standard.

3.6; Cl, 10.1. $C_{21}H_{16}ClNO_3$ requires C, 68.95; H, 4.4; N, 3.8; Cl, 907%); O-m-*chlorobenzoic* (Found: C, 69.0; H, 4.2; N, 3.7; Cl, 9.9%); O-m-*nitrobenzoic* (Found: C, 67.4; H, 4.4; N, 7.15. $C_{21}H_{16}N_2O_5$ requires C, 67.0; H, 4.3; N, 7.45%); O-p-*nitrobenzoic* (Found: C, 67.2; H, 4.55; N, 7.2%). Also prepared was (Z)-*benzoic* O-*n-propylbenzohydroximic anhydride* (Found: C, 72.4; H, 6.2; N, 4.4. $C_{17}H_{17}NO_3$ requires C, 72.1; H, 6.3; N, 4.25%).

Attempted Rearrangement of (Z)-*Benzoic* O-*Benzylbenzohydroximic Anhydride*.—In a typical experiment compound (7c; R^2 = Ph) (100 mg) was refluxed in dry toluene (10 ml) for 8 h. I.r. and t.l.c. (solvent B) showed that no rearrangement had taken place.

Photoisomerisation of (Z)-*Acetic* O-*Benzylbenzohydroximic Anhydride* (7b; R = $CH_2C_6H_4X$).—The anhydrides (0.3 g) in dry benzene (200 ml) were irradiated as previously described.[11] Removal of the solvent in vacuum without heating gave an oil or a yellow solid. N.m.r. analysis ($CDCl_3$) gave the following *Z* : *E* ratios: X = *p*-CH_3, *Z* : *E* = 49 : 51, R_F 0.64 and 0.49 (solvent A), δ 5.02 ($NOCH_2$) and 2.07 ($COCH_3$) (*E* isomer); X = *p*-Cl, *Z* : *E* = 48 : 52, R_F 0.5 and 0.3 (A), δ 4.97 and 2.02; X = *p*-NO_2, *Z* : *E* = 67 : 33, R_F 0.48 and 0.21 (A), δ 5.15 and 2.17. Small quantities (*ca.* 50 mg) of the *E*-isomers were separated from the mixtures for kinetic studies by preparative t.l.c.

Rearrangement of (E)-*Acetic* O-*Benzylbenzohydroximic Anhydrides* (8b).—Mixtures of *E*- and *Z*-isomers from the above photoisomerizations were refluxed in dry CCl_4 for 2 h, giving the *N*-acetyl-*N*-benzoyl-*O*-benzylhydroxylamines (9b; R = $CH_2C_6H_4X$): X = *p*-CH_3, ν($CHCl_3$) 1 720 and 1 698 (C=O) cm^{-1}, δ 4.71 ($NOCH_2$) and δ 2.46 ($COCH_3$); X = *p*-Cl, ν 1 720 and 1 695 (C=O) cm^{-1}, δ 4.68 (3 H, s), and 2.46 (3 H, s); X = *p*-NO_2, 1 723 and 1 695 (C=O) cm^{-1}; δ 4.7 and 2.52.

Photoisomerisation of (Z)-*Benzoic* O-*Benzylbenzohydroximic Anhydrides* (7c; R^2 = C_6H_4X).—The *Z*-isomer (X = H) (0.3 g) was irradiated with freshly distilled biacetyl (0.7 g) in dry degassed benzene (150 ml) under nitrogen for 2 h using Pyrex filtered radiation. Removal of the solvent and biacetyl on a rotary evaporator without heating gave a yellow viscous liquid. T.l.c. (solvent D) showed that the *Z*- (R_F 0.4) and *E*-isomer (R_F 0.28) were present. A pure sample of the *E*-isomer was obtained by preparative t.l.c. on silica using the above solvent, m.p. 80—81° (Found: C, 75.8; H, 5.3; N, 4.1. $C_{21}H_{17}NO_3$ requires C, 76.1; H, 5.2; N, 4.2%). Similar procedures were used for the other compounds: X = *p*-CH_3, R_F 0.38 and 0.26, the E-*isomer* had m.p. 69—71° (Found: C, 76.7; H, 5.7; N. 3.9. $C_{22}H_{19}NO_3$ requires C, 76.5; H, 5.5; N, 3.9%); X = *p*-Cl, R_F 0.4 and 0.3, the E-*isomer* had m.p. 92—93° (Found: C, 68.8; H, 4.8; N, 3.5; Cl, 9.7. $C_{21}H_{16}ClNO_3$ requires C, 68.95; H, 4.4; N, 3.8; Cl, 9.7%); X = *m*-Cl, R_F 0·23 and 0.2, the *E*-isomer had m.p. 84—85°; X = *m*-NO_2, R_F 0.5 and 0.4 (solvent F), m.p. 79—80°; X = *p*-NO_2, R_F 0.51 and 0.38 (solvent E), the *E*-isomer had m.p. 87—88°.

Acetophenone and 1-acetonaphthone were also used as sensitizers for the above isomerizations but it was found difficult to remove these from the mixtures of *E*- and *Z*-isomers.

Rearrangement of (E)-*Benzoic* O-*Benzylbenzohydroximic Anhydride*.—A mixture of the *E*- and *Z*-isomers from isomerization of (7c; R^2 = Ph) (0.85 g) was dissolved in dry toluene (10 ml) and refluxed for 5 h. Removal of the toluene gave a yellow solid. Dry column chromatography on silica (activity III; 30 mm) using solvent B gave NN-dibenzoyl-*O*-benzylhydroxylamine, m.p. 90—92° (CH_2Cl_2–hexane, 1 : 10); ν 1 685 (C=O) cm^{-1} ($CHCl_3$), δ (CCl_4) 4.9 ($NOCH_2$), R_F 0.55. (Found: C, 75.8; H, 5.0; N, 4.0. $C_{21}H_{17}NO_3$ requires C, 76.1; H, 5.2; N, 4.2%). The following members of the series were generated in solution but not isolated: R^2 = *p*-$CH_3C_6H_4$, 1 698 (C=O) cm^{-1}, δ (CCl_4) 4.91 and 2.35, R_F 0.25 (solvent A); R^2 *p*-ClC_6H_4, ν (CCl_4) 1 700 and 1 710 (C=O) cm^{-1}, δ 4.9, R_F 0.1 (solvent D); R^2 = *m*-ClC_6H_4, ν (CCl_4) 1 695 and 1 705 cm^{-1}, δ 4.91, R_F 0.09 (solvent D); R^2 = *m*-$NO_2C_6H_4$, ν 1 690 and 1 710 (C=O) cm^{-1}, δ 4.93, R_F 0.2 (solvent F); R^2 = *p*-$NO_2C_6H_4$, ν ($CHCl_3$) 1 695 and 1 710 (C=O) cm^{-1}, δ 4.95 ($CDCl_3$), R_F 0.1 (solvent E). Also prepared was NN-*dibenzoyl*-O-*n-propylhydroxylamine* [from photoisomerization of (7d; R^1 = Pr^n) (0.55 g) followed by heating the product in toluene for 5 h, and dry column chromatography (solvent B)] as a yellow oil which solidified on cooling in an ice-bath, m.p. 65—66° (hexane), ν (CCl_4) 1 690 (C=O) cm^{-1}, R_F 0.36, δ 7.65 (4 H, q), 7.35 (6 H, m), 4.89 (2 H, t), 1.45 (2 H, sextet), and 0.75 (3 H, t) (Found C, 71.7; H, 6.1; N, 4.6. $C_{17}H_{17}NO_3$ requires C, 72.1; H, 6.3; N, 4.25%).

Cross-over Experiments.—(a) *Rearrangement of* (E)-*benzoic* O-*benzylbenzohydroximic anhydride* (8c; R^2 = Ph) *in the presence of acetic acid*. The *E*-isomer (20 mg) was dissolved in dry CCl_4 (1 ml) containing dry AnalaR acetic acid (0.1 ml) and refluxed for 2 h. Monitoring the reaction by t.l.c. (solvent A) showed that the only product was (9c; R^2 = Ph). The cross-over product (9c; R^2 = CH_3) was not detected.

(b) *Rearrangement of a mixture of* (E)-*acetic* O-*n-propylbenzohydroximic anhydride and* (E)-*benzoic* O-*benzylbenzohydroximic anhydride*. The two esters (8b; R^1 = Pr^n) and (8c; R^2 = Ph) (20 mg) each were refluxed in dry CCl_4 (1 ml). Again t.l.c. (solvent C) showed that the only products were (9b; R^1 = Pr^n) and (9c; R^2 = Ph). No cross-over products (9d; R^1 = Pr^n) and (9c; R^2 = CH_3) could be detected in the reaction mixture.

Product Analysis.—(a) *Rearrangement of* (8). The products from the rearrangement of isoimides were identified by comparing the u.v. spectrum of the reaction mixture at the end of a kinetic run with that containing an authentic sample of the products under the reaction conditions, and at the same concentration. In addition, in several cases preparative scale reactions were carried out and the products characterized by microanalysis and spectroscopic methods.

(b) *Rearrangement of* (8) *in aqueous dioxan.* The *E*-isomer (8b; $R^1 = Pr^n$) in dioxan (0.5 ml) was added to 10^{-2}M-phosphate buffer (5 ml) in 1 : 4 dioxan–water (μ 1; $NaClO_4$) at pH 6.65, and the reaction was heated at 65° for 1 h. Extraction with ether (10 ml) followed by t.l.c. analysis of the dried ether extract showed that the *N*-acyl species (9b; $R^1 = Pr^n$) was the only product present.

(c) *Acid catalysed hydrolysis of* (7b; $R^1 = Pr^n$). The anhydride (0.4 g) in dioxan (4 ml) was added dropwise to 1M-$NaClO_4$ (16 ml) at pH 1.0, and the mixture stirred at room temperature. T.l.c. analysis (solvent A) showed the *E*-isomer (8b; $R^1 = Pr^n$) or *N*-acyl material was not present. After 1 h the mixture was extracted with ether (3 × 25 ml). The ether was dried ($MgSO_4$) and evaporated leaving a yellow oil (0.3 g). This was identical with the hydroxamic acid (as shown by i.r. and t.l.c.). Likewise the *E*-isomer (8b; $R^1 = Pr^n$) (50 mg) gave the hydroxamic acid (10; $R^1 = Pr^n$) and t.l.c. analysis during the reaction failed to detect acid catalysed $E \longrightarrow Z$ isomerism.

(d) *Hydroxide ion catalysed hydrolysis of* (Z)-*acetic* O-*n-propylbenzohydroxamic anhydride.* The anhydride (7b; $R^1 = Pr^n$) (0.2 g) in dioxan (1 ml) was added to 1M-$NaClO_4$ in 1 : 4 dioxan–water at pH 12. Initially the solution became turbid but cleared after stirring for 5 min. Stirring was continued for 1 h (*ca.* $10t_{\frac{1}{2}}$). The solution was then adjusted to pH 2, with dilute perchloric acid and then extracted with ether (3 × 25 ml). Evaporation of the dried ether extracts ($MgSO_4$) gave a yellow oil (0.12 g). This was identical with (10; $R^1 = Pr^n$) by t.l.c. and i.r.

A similar experiment was conducted using the *E*-isomer (8b; $R^1 = Pr^n$). At the end of each kinetic run the hydroxamic acid (10; $R^1 = Pr^n$) was confirmed as the product by adjusting the pH of the solution to 14 and observing the u.v. spectrum of the anion of the hydroxamic acid ($\lambda_{max.}$ 265 nm).

Kinetic Method.—(a) Kinetic data for the rearrangement of (8) were obtained by following changes in the u.v. spectra of the substrates at wavelengths chosen from repetitive scans of the spectra of the reaction mixtures. First-order rate constants were calculated using the experimental infinity value and were reproducible to within 2—4% of the mean value. A Cary 14 spectrophotometer was used throughout. This was equipped with a brass thermostatted cell block through which water was circulated. Prior to each kinetic run the quartz cuvette containing the solvent was equilibrated in the cell block for 30 min. The temperature of the reaction solution was checked before and after each reaction using a thermocouple attached to a Pye spot-galvanometer; the latter was calibrated with the external water-bath. In addition, tight-fitting Teflon stoppers were used for the cuvettes and to prevent any solvent loss they were maintained in position using adhesive tape. Reactions were initiated by adding 50—100 μl of a stock solution of the substrate (10^{-2}M) in acetonitrile to the equilibrated solvent in the spectrophotometer cell block. All solvents were purified by established literature methods,[33] and dimethylformamide was redistilled immediately before use.

(b) *Hydrolysis and aminolysis of* (7, 8b, *and* 8c; $R^1 = Pr^n$ *and* $R^2 = Ar$). Inorganic materials were AnalaR grade and used as received. Deionized water was distilled twice from alkaline potassium permanganate, and reagent grade dioxan was purified by the method of Vogel.[33] The solvent mixtures were prepared by mixing appropriate volumes of the component solvents at room temperature. Piperidine was distilled from KOH before use. Buffer dilutions were made immediately before the kinetic runs which were carried out on a Perkin-Elmer 124 or Cary 14 spectrophotometer. First-order rate constants were calculated graphically using the experimental infinity value. The pH values quoted are those measured for the 1 : 4 dioxan–water solutions using a Radiometer model (PHM 26) pH meter and a Metrohm EA 125U glass electrode, which was standardized using Radiometer aqueous buffer solutions.

We are grateful for a State Maintenance Allowance for Research (to D. G. McC.).

[6/1683 *Received*, 3*rd September*, 1976]

[33] S. G. Smith, A. H. Fainberg, and S. Winstein, *J. Amer. Chem. Soc.*, 1961, **83**, 618; S. G. Smith, *ibid.*, p. 4285; A. I. Vogel, 'Practical Organic Chemistry,' Longman, London, 3rd edn., 1967.