Nucleophilic Addition to Linear Nitrilium Ions ($-C\equiv\overset{+}{N}-$) leading to Single Isomers. Isolation of Relatively Stable Isoimides and their Rearrangement to Imides limited by Substrate *Z–E* Isomerisation [1]

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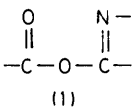
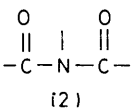
The *N*-anilinonitrilium ions formed by solvolysis of halides (5) and (10) react with acetate or methanol to give a single isomer (20) or (23) in which the entering nucleophile and the forming lone pair on nitrogen are *trans*. The reaction is kinetically (rather than thermodynamically) controlled since the *Z*-isomer, which is formed exclusively in the initial reaction, undergoes isomerisation to the *E*-isomer at elevated temperatures. The observed stereospecificity is not due to selective solvation of the nitrilium ion by the departing halide ion since (5; R = Bu^t), which has the *Z*-configuration gives (20) or (23) with *retention* of configuration. The rate determining step for the O ⟶ N acyl group migration [(12) ⟶ (11)] is inversion of the configuration at nitrogen (*Z–E* isomerisation); in the *E*-isomer the nucleophilic lone pair on nitrogen and the acyl group are adjacent. Stable *O*-acylisoimides can be isolated by slowing the rate of *Z–E* isomerisation. Substituent effects on *Z–E* isomerisation have been measured and contrast with those observed for simple imine systems.

THE Mumm rearrangement,[2,3] which involves a rapid 1,3-acyl group migration from oxygen to nitrogen [(1) ⟶ (2)] accounts for the fact that *O*-acylisoimides (1) have rarely been isolated. The exceptions are cyclic materials such as 2-methyl-3,1-benzoxazin-4-one [4] (3) or *N*-methylphthalisoimide [5] (4) in which the



(1)



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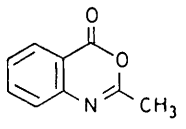

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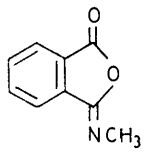


(4)

carbonyl group is sterically inaccessible to the nucleophilic nitrogen and one report [6] in which the stability of the isoimide form (1) was attributed to the reduced nucleophilicity of the nitrogen due to the presence of a dinitrophenyl group.

In spite of their tendency to rearrange to the imide form, isoimides have been proposed as intermediates in several reactions, including carbodi-imide-mediated condensations,[7-9] and have been proposed as models in active CO_2 transfer by the coenzyme biotin.[10] More recently an attempt has been made, with limited success, to isolate and use *O*-acylisoimides as active acyl transfer agents useful in peptide synthesis.[11] This latter approach is attractive since when (1) undergoes intermolecular attack at the acyl carbon site by an external nucleophile the leaving ability of the amide group can be greatly enhanced by acid catalysis through protonation on the basic nitrogen.

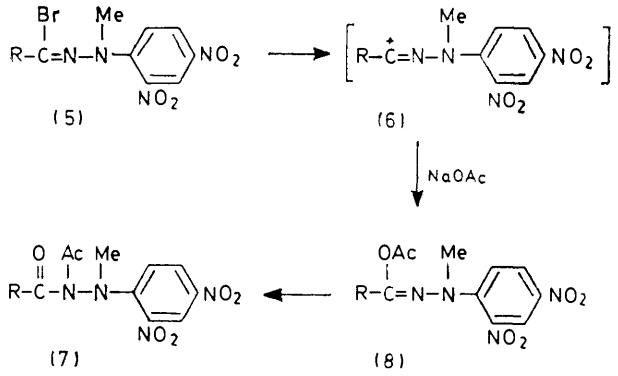
We have carried out a study to identify the structural features which might minimize the wasteful O ⟶ N acyl group migration in acylic isoimides (1) without reducing the nucleophilicity (and basicity) of the adjacent nitrogen, and we now report, *inter alia*, on three novel features of compounds containing the carbon–nitrogen double bond. (a) *O*-Acylisoimides which are stable for extended periods at ambient temperatures have been isolated for the first time; their stability is attributed to a slow rate of isomerisation about the C=N bond. (b) The route used to form the isoimides implies that nucleophilic attack on the $-C\equiv\overset{+}{N}-$ ion is stereospecific giving only the isomer in which the entering nucleophile and lone pair on the adjacent nitrogen are *trans*. (c) Since the isoimide to imide migration is limited by *Z–E* isomerisation about the C=N bond we have used this technique to study the effect of substituents on this process.

RESULTS AND DISCUSSION

When the hydrazonyl bromides (5; R = Me or Bu^t) were solvolysed in the presence of sodium acetate at 30°, the *O*-acylisoimides (8; R = Me, Bu^t) were obtained in quantitative yield. The isoimide structure (8) rather than the imide (7) is indicated by the strong carbonyl absorption in the i.r. at 1 770—1 750 cm^{-1} and the absence of absorptions in the region 1 680—1 710 cm^{-1} [characteristic of imides (7)]. We have previously reported [12] that under these conditions the solvolysis of (5; R = Bu^t) occurs *via* rate-determining formation of the stabilized azocarbonium ion (6); the formation of

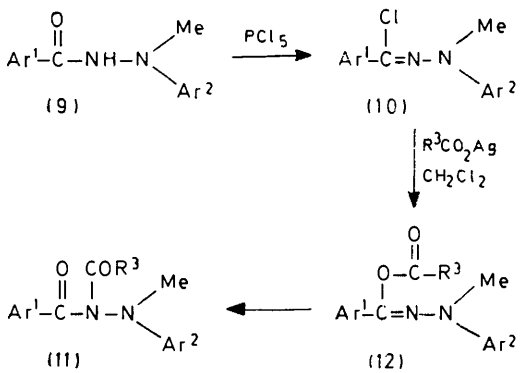
[1] Preliminary account, A. F. Hegarty and M. T. McCormack, *J.C.S. Chem. Comm.*, 1975, 168.
[2] O. Mumm, H. Hesse, and H. Volquartz, *Chem. Ber.*, 1915, **48**, 379.
[3] J. W. Shubenberg and S. Archer, *Org. React.*, 1965, **14**, 31; *J. Amer. Chem. Soc.*, 1967, **89**, 760.
[4] F. A. Anet and A. J. Brown, *J. Amer. Chem. Soc.*, 1967, **89**, 760.
[5] H. Kessler, *Angew. Chem. Internat. Edn.*, 1970, **9**, 219.
[6] D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, 1967, **89**, 637.
[7] F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, 1967, **67**, 107.
[8] H. G. Khorana, 'Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest,' Wiley, New York, 1961.
[9] J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067.
[10] A. F. Hegarty and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 6568; T. C. Bruice and A. F. Hegarty, *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **65**, 805.
[11] J. S. P. Schwarz, *J. Org. Chem.*, 1972, **37**, 2906.
[12] A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J.C.S. Perkin II*, 1972, 44.

(8) therefore involves the selective trapping of this ion by acetate.



As a route to isoimides this method is limited by the availability of the hydrazonyl bromides (5), whose formation is subject to severe limitations. The most direct method involves bromination of the corresponding *NN*-disubstituted hydrazones;[13] this reaction is slow and competitive bromination may occur in the *N*-aryl ring or the aliphatic group R unless these are deactivated or blocked [*e.g.* (5; R = Bu^t)].

In a search for a more general procedure which would allow substituent variation at each position, the reaction Scheme 1 was developed. The *NN*-disubstituted hydrazides (9) were treated with phosphorus pentachloride to give the hydrazonyl chlorides (10);[14] under these conditions the *N*-aryl ring was not chlorinated even when unsubstituted (Ar^2 = Ph). The hydrazonyl chlorides (10) solvolysed slowly in acetone–water and the formation of (12) was best catalysed by Ag^+. Thus, good yields of (12) were obtained in all cases by treating



SCHEME 1

(10) at 25—40° in methylene chloride with silver salts of substituted benzoic or acetic acids. T.l.c. indicated that the products obtained were pure single materials (12), uncontaminated by the isomeric (11).

Rearrangement of Isoimides.—(a) *Substituent effects.* On refluxing the isoimides (8) and (12) in chlorobenzene for 1 h rearrangement to the imides (7) and (11) occurred smoothly in all cases. The i.r. spectra of (7) and (11) showed carbonyl absorptions at *ca.* 1 710 cm^{-1} and there was a characteristic downfield shift in the acyl group proton signals in the n.m.r. spectrum of (7; R = CH_3) and (11; R^3 = CH_3) relative to the isoimide.

The rate of rearrangement of (8) ⟶ (7) and of (12; R^3 = CH_3) ⟶ (11; R^3 = CH_3) was conveniently followed by n.m.r.; four determinations were possible on these compounds *e.g.* for (8) the rate of disappearance of the NCH_3 and $COCH_3$ peaks were followed while concomitantly the appearance of the NCH_3 and $COCH_3$ peaks in (7) were measured. The results are summarised in Table 1 for substituent variation in the *N*-aryl ring.

TABLE 1

First-order rate constants for the rearrangement of the *O*-acylisoimides (12; R^3 = CH_3) to *N*-acylhydrazides (11; R^3 = Me) [a]

Ar^1	Ar^2	t/°C	10^4k_{obs}/s^{-1} [b]
Bu^t	2,4-$(NO_2)_2C_6H_3$	80	2.4
Me	2,4-$(NO_2)_2C_6H_3$	80	2.5
Ph	2,4-$(NO_2)_2C_6H_3$	55	0.13 [c]
		70	0.63
		80	2.35
		85	4.7
		90	10.5
Ph	4-$NO_2C_6H_4$	55	1.8
Ph	Ph	40	0.81 [d]
		45	1.65
		50	3.3
		55	10.0

[a] Solvent, chlorobenzene. [b] Average of four values. [c] Extrapolated values using E_a 27.3 (±2.0) kcal mol^{-1}. [d] E_a = 20.1 (±2.0) kcal mol^{-1}.

TABLE 2

First-order rate constants for the rearrangement of (12; Ar^1 = Ar^2 = Ph) to (11; Ar^1 = Ar^2 = Ph) at 56° in acetonitrile

R^3	10^4k_{obs}/s^{-1}
4-$MeOC_6H_4$	0.25
Ph	0.38
4-ClC_6H_4	0.67
3-$NO_2C_6H_4$	1.35
4-$NO_2C_6H_4$	1.7

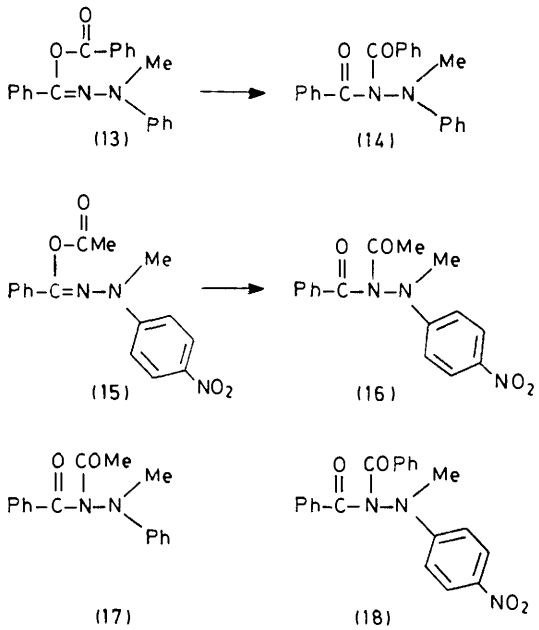
In Table 2 are summarised the rate constants for isomerisation of the isoimides (12) in which the acyl group (R^{3}CO) was systematically varied. The rates of reaction were followed in these cases at 56° in acetonitrile by monitoring the decrease in optical density in the u.v. spectrum at 350 nm.

(b) *Intramolecularity.* The O ⟶ N acyl group rearrangement was shown to be intramolecular by heating a mixture of (13) and (15) together at 55° in chlorobenzene. As can be seen from Tables 1 and 2, these isoimides are of comparable reactivity. The only two products detected were (14) and (16) in a series of experiments run at different concentrations. The possible 'cross-over' products (17) and (18) were prepared independently and preliminary experiments showed that ⩾5% of (17) or (18) would have been detected by t.l.c.

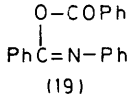
(c) *Mechanism of* O ⟶ N *acyl migration.* That isoimides of type (8) or (12), particularly those without an

[13] A. F. Hegarty and F. L. Scott, *J. Org. Chem.*, 1968, **33**, 753.
[14] An alternative procedure has recently been described using triphenylphosphine–CCl_4, P. Wolkoff, *Canad. J. Chem.*, 1975, **53**, 1333.

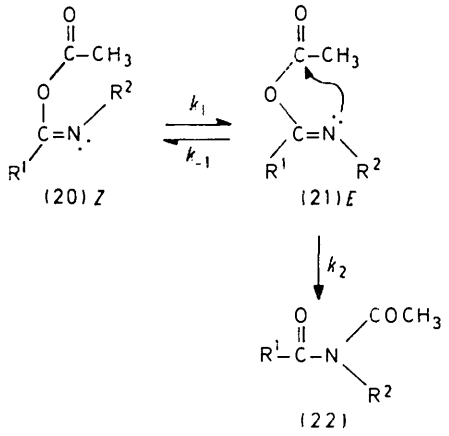
electron-withdrawing Ar^2 group, can actually be isolated and rearrange only at elevated temperatures is certainly



unexpected from previous work. Thus Curtin and Miller [6] failed to isolate *N*-phenylbenzimidoyl benzoates (19) while more recently Schwarz reported [11] that such materials, if formed, have a very limited lifetime, even at 0°. The essential difference between (12; Ar^2 = Ph) and (19) is the interpolation of the NMe group and this must be taken into account in any mechanism of isomerisation.


(19)

Two plausible reasons can be proposed for the stability of the isoimide (12) and these are summarised in terms


(20) *Z* (21) *E* (22)

SCHEME 2

of the mechanistic Scheme 2. In this the isoimide is assumed to exist in two isomeric forms and only one form, the *E* isomer in which the nucleophilic lone pair and the acyl group are adjacent, can lead to the isoimide (22). Now either of the steps, *Z*–*E* isomerisation or the acyl transfer [(21) ⟶ (22)], can be rate determining. The latter was the mechanism proposed by Curtin and Miller [6] for *N*-(2,4-dinitrophenyl)isoimides; it was assumed that the *E*- and *Z*-isomers were in rapid equilibrium and that the nucleophilic step determined the overall reaction rate.

The substituent effects are equivocal as to which step is rate determining. Thus a Hammett plot of log k_{obs} *versus* the σ value for *m*- and *p*-substituents in the migrating benzoyl group of (12; $R^3 = XC_6H_4$) (see Figure 1) gives a Hammett ρ value of +0.77. Sensitivity constants of this order of magnitude have previously been reported for the effect of *C*-aryl substituents [such as R^1 in (20)] in rates of *E*–*Z* isomerisation (where ρ is usually in the region +0.1 to +0.6).[15] Models for the effect of substituents on an intramolecular nucleophilic attack on an acyl function *via* a four-membered ring [(21) ⟶ (22)] are not available; however, intermolecular nucleophilic attack by amines on phenyl-substituted benzoates are generally characterised by

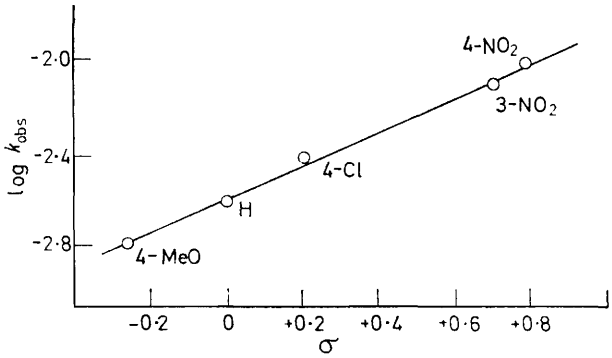


FIGURE 1 Hammett plot for the rearrangement of *O*-aroylisoimides (12; $R^3 = XC_6H_4$; $Ar^1 = Ar^2$ = Ph) to isoimides (11; $R^3 = XC_6H_4$; $Ar^1 = Ar^2$ = Ph) in acetonitrile at 56° (k_{obs}/min^{-1})

larger ρ values (*e.g.* ρ +1.81 for nucleophilic attack of semicarbazide on substituted benzaldehydes [16]).

Electron-withdrawing substituents in Ar^2 have a strongly deactivating effect on the rate of isomerisation (Table 1). This is expected for rate-determining nucleophilic attack since the introduction of nitro-groups in the *N*-aryl ring should reduce the nucleophilicity of the imine nitrogen. Moreover it has previously been reported that *E*–*Z* isomerisation of imines is *aided* by a simple electron-withdrawing substituent on nitrogen (ρ for *N*-aryl variation in benzylideneaniline is reported as +1.5 to +2.0).[17,18] Although this evidence would appear to support the conversion of (21) into (22) as rate determining (and consequently attribute the stability of the isoimide to the reduced nucleophilicity of the adjacent nitrogen) it

[15] C. G. McCarty in ' The Chemistry of the Carbon–Nitrogen Double Bond,' ed. S. Patai, Wiley, New York, 1970.

[16] B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.*, 1960, **82**, 1773.

[17] G. Wettermark, *Arkiv. Kemi*, 1967, **27**, 159.

[18] H. Kessler, *Tetrahedron*, 1974, **30**, 1861.

must be stressed that no data is available for *N*-aryl substituent variation in hydrazone (as opposed to imine) systems.[19]

Isomerisation of Hydrazonyl Ethers.—In order to identify the rate-determining step therefore an indirect method was used. As models for the *Z*–*E* isomerisation step the ethers (23) and (24) were prepared. In the

(23) *Z* (24) *E*

ethers the basic –O–C=N–N– structure present in (12) is maintained thus minimizing any differences due to dipole interactions or interorbital effects.[20,21] The hydrazonyl ethers were prepared by the same general procedure used for the synthesis of the acetates except that methanol was used in place of sodium acetate. Again a single isomer was obtained in each case. On heating partial rearrangement took place and the equilibration of the isomers could be followed by n.m.r. The two isomers were separated on preparative scale t.l.c. or by dry column chromatography and spectral characteristics are consistent with their being the *Z*- and *E*-isomers [23 and 24; R^1 = Ph; R^2 = N(Me)Ph, N(Me)-4-$NO_2C_6H_4$, or N(Me)-2,4-$(NO_2)_2C_6H_3$].* The rearrangement followed by n.m.r. therefore represents *E*–*Z* equilibration rather than, say, methyl group migration to the adjacent nitrogen. The latter reaction, known as the Chapman rearrangement,[3] would produce a carbonyl group in the product and moreover only takes place at much higher (>200°) temperatures.

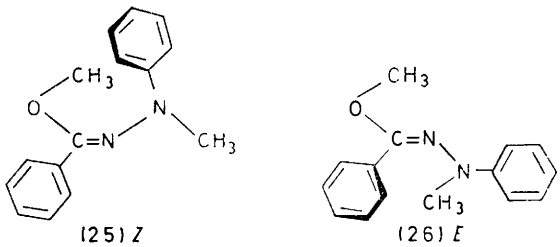
Assignment of the thermodynamically more stable isomer to the *E*-configuration in each case follows from n.m.r. interpretations. Inspection of molecular models suggests an upfield chemical shift for the NCH_3 protons in the *E*- relative to the *Z*-isomer due to the strong shielding effect of the *C*-phenyl ring [see (26)]. By the same reasoning, the OCH_3 protons in the *Z*-isomer should experience an upfield chemical shift relative to the *E*-isomer [see (25)]. The results are summarised in Table 3; in each case the ether isolated initially is assigned the *Z* (25) configuration on this basis. Similar type shielding effects have been observed previously for *ortho*-substituted acetophenone *NN*-dimethylhydrazones [22] and in alkyl *O*-alkylbenzohydroximates.[23] Moreover the assignment of (26) as the thermodynamically most stable isomer is consistent with previous estimations of the relative stabilities of the *E*- and *Z*-isomers of alkyl- and aryl-benzimidates.[24]

The rates of *Z*–*E* isomerisation of the ethers (23) were examined at various temperatures in chlorobenzene as solvent (Table 4). These results show clearly that the

TABLE 3

Chemical shifts for the methyl hydrazonates (23) and (24)

Hydrazonate (23, 24; R^1 = Ph) R^2	NCH_3	OCH_3	NCH_3	OCH_3	*Z* : *E* Isomer ratios
N(Me)C_6H_5	3.02	3.55	2.50	3.85	20 : 80
N(Me)$C_6H_4NO_2$-*p*	3.08	3.47	2.62	3.85	43 : 57
N(Me)$C_6H_3(NO_2)_2$-2,4	3.05	3.60	2.55	3.70	22 : 78
Assignment		*Z*		*E*	



(25) *Z* (26) *E*

TABLE 4

First-order rate constants for the *Z*–*E* isomerisation of hydrazonates (23) in chlorobenzene

Substrate	*t*/°C	$10^3(k_1 + k_{-1})$/ s^{-1}	10^3k_1/ s^{-1} [a]
[23; R^1 = Ph, R^2 = N(Me)Ph]	40	0.21	0.165
	45	0.60	0.46
	50	0.81	0.67
	55	1.7	1.3
	75 [b]	15	11.5
[23; R^1 = Ph, R^2 = N(Me)$C_6H_4NO_2$-*p*]	75	3.5	1.9
[23; R^1 = Ph, R^2 = N(Me)$C_6H_3(NO_2)_2$-2,4]	65	0.075	0.09
	70	0.22	0.18
	80	0.75	0.59
	85	1.7	0.13

[a] Calculated by the method of Frost and Pearson,[25] using experimental k_1/k_{-1} values. [b] Extrapolated from data at lower temperatures.

order of reactivity is R^2 = N(Me)Ph > N(Me)-4-$NO_2C_6H_4$ > N(Me)-2,4-$(NO_2)_2C_6H_3$, which is the same as that observed for the conversion of the *O*-acylisoimides (12) to (11). Moreover the absolute rate constants in both systems and the variation in rate as the substituent is changed are similar (the ethers in general react *ca.* twice as rapidly). This is shown in Figure 2 in which log k_{obs} for (12) is plotted against log k_1 for *Z*–*E*-isomerisation of similarly substituted ethers (23). This provides strong evidence that the rate-determining step for both reactions is the same and since this can only be *Z*–*E* isomerisation for the ethers, this suggests that the rate-determining step in the O ⟶ N acyl group migration is that governed by k_1 in Scheme 2.

Mechanism of E–Z Isomerisation.—The order of decreasing rates observed for isomerisation about the

* The assignment of the O-Me and N-Me signals in [23; R^1 = Ph, R^2 = N(Me)$C_6H_3(NO_2)_2$-2,4] was confirmed by the absence of the signal at δ 3.60 in the hydrazonate prepared using CD_3OD.

[19] A. F. Hegarty, P. J. Moroney, and F. L. Scott, *J.C.S. Perkin II*, 1973, 1466.
[20] C. O. Messe, W. Walker, and M. Berger, *J. Amer. Chem. Soc.*, 1974, **96**, 2259.
[21] R. M. Moriarty, C. L. Yeh, R. C. Ramey, and P. W. Whitehurst, *J. Amer. Chem. Soc.*, 1970, **92**, 6360.
[22] G. R. Newkome and W. S. Bhacca, *J. Org. Chem.*, 1971, **36**, 1719.
[23] J. E. Johnson, J. R. Springfield, J. S. Hwang, L. J. Hayes, W. C. Cunningham, and D. L. McClaugherty, *J. Org. Chem.*, 1971, **36**, 284.
[24] A. C. Satterthwait and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 7045.
[25] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1961.

C=N bond in the *O*-acyl- (20) and methyl-hydrazonates (23) [R^2 = N(Me)Ph > N(Me)-4-$NO_2C_6H_4$ > N(Me)-2,4-$(NO_2)_2C_6H_3$] is surprising when contrasted with previously reported results for systems such as (27)—(29).

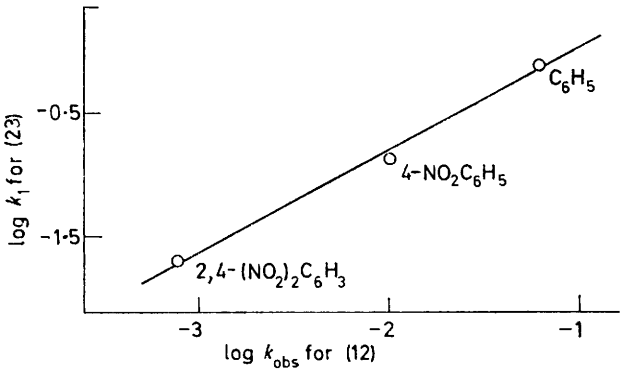
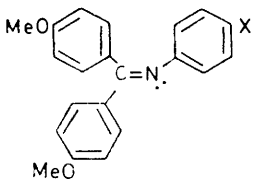


FIGURE 2 Plot of the log k_1 for the rearrangement of the hydrazonates [23; R^1 = Ph, R^2 = N(Me)Ar] at 75° *versus* log of the rate constants for the isoimide to imide rearrangement (12; Ar^1 = Ph; Ar^2 = XC_6H_4, R^3 = Me) in chlorobenzene at 55°

In the case of (27)—(29) and other related imines electron withdrawal by X aids reaction [17,26-28] and the accepted mechanism of isomerisation involves a ' lateral shift.' [29] However, there are two examples, (30) and (31), in which electron withdrawal slows reaction (as in the present instance). For (30) Roberts [30] proposed that a rotation mechanism is operative, facilitated by the strongly electron-withdrawing CF_3 groups. The



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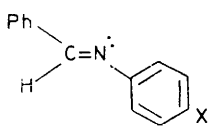

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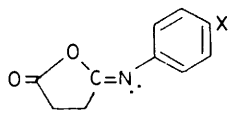

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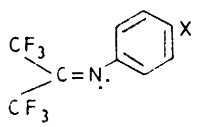
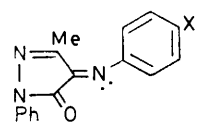


(30)



(31)

pyrazolone (31) actually gives a curved Hammett plot with ρ −2.7 for electron-donating groups and it is proposed [31] that this is due to a changeover in mechanism within the series, a rotation mechanism being operative when electron-donating substituents are present.

The possibility therefore exists that the unusual behaviour shown by (20) and (23) is due to the operation of a rotation mechanism. This was tested using the method suggested by Jeffery [32] where this effect of complex formation was used as the critical criterion for mechanism. We have found that the addition of a molar ratio of the Lewis acids $AlMe_3$ or BF_3 inhibited the isomerisation of both the isoimide [20; R^1 = Ph, R^2 = $N(Me)C_6H_3(NO_2)_2$] and the methylhydrazonate [23; R^1 = Ph, R^2 = $N(Me)C_6H_3(NO_2)_2$] in chlorobenzene at 90° (see Table 1 for the rate constant in the absence of added Lewis acid). Moreover the *E–Z* isomerisation is not acid catalysed to any appreciable extent. This was shown (a) under anhydrous conditions in chlorobenzene, where the addition of gaseous HCl or acetic acid to a

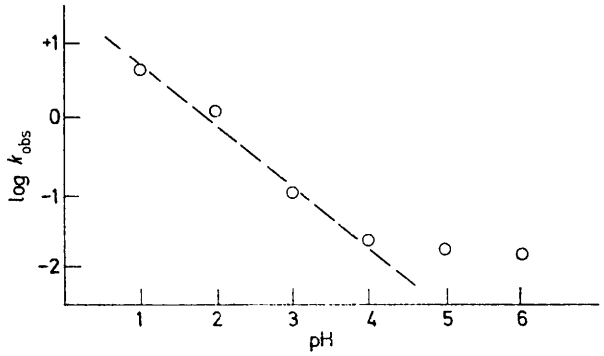


FIGURE 3 Plot of the log of the first-order rate constants (k_{obs}/min^{-1}) for the reaction of (12; R^3 = Ar^1 = Ar^2 = Ph) in 1 : 1 methanol–water at 45° (μ 0.5) as a function of pH

solution of [20; R^1 = Ph, R^2 = $N(Me)C_6H_3(NO_2)_2$] had no effect on the rate of isomerisation and (b) in 1 : 1 methanol–water. In this case the substrate used was [20; R^1 = Ph, R^2 = N(Me)Ph] and the course of the reaction was followed spectrophotometrically at 340 nm. At high pH, the rate of reaction is independent of pH (Figure 3) but increases with hydrogen ion concentration at low pH (see Figure 3). This changeover is accompanied by a change in product: at pH >4, the product formed is the *N*-acylhydrazide (11 ; Ar^1 = Ar^2 = Ph, R^3 = Me) while at low pH *N*-methyl-*N*-phenylbenzohydrazide is the only product formed. Although acid catalysis of the reaction of the isoimide is therefore observed this is due, not to catalysis of *E–Z* isomerism, but to a changeover in mechanism to intermolecular hydrolysis of the ester function.

On these criteria (inhibition by complex formation, absence of acidic catalysis) a rotation mechanism involving the buildup of substantial negative charge on nitrogen is ruled out. A rotation mechanism similar to

[26] D. Y. Curtin, E. J. Grubbs, and C.G. McCarty, *J. Amer. Chem. Soc.*, 1966, **88**, 2775.
[27] A. Reiber and H. Kessler, *Tetrahedron*, 1967, **23**, 3723.
[28] C. K. Sauers and H. M. Relles, *J. Amer. Chem. Soc.*, 1973, **95**, 7731.
[29] M. Raban and E. Carlson, *J. Amer. Chem. Soc.*, 1970, **93**, 685.
[30] G. E. Hall, W. J. Middleton, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 4778.
[31] W. C. Herkstroeter, *J. Amer. Chem. Soc.*, 1973, **95**, 8686.
[32] E. A. Jeffery, A. Meisters, and T. Mole, *Tetrahedron*, 1969, **25**, 741; see also W. B. Jennings, S. Al-Showiman, M. S. Tolley, and D. R. Boyd, *J.C.S. Perkin II*, 1975, 1535 and references cited therein.

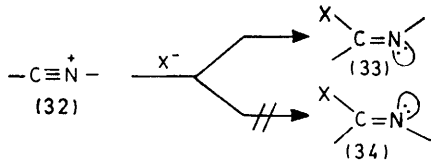
that proposed for (30) and (31) is also unlikely due to the absence of strongly electron-withdrawing groups on carbon.

A possible explanation for this dilemma comes from the special nature of the imine systems under study. In each case the substrates have an N(Me)Ar group attached to the imine nitrogen. It is well recognised that such substituents with lone pair electrons can dramatically slow the rate of *E*–*Z*-isomerisation (by a nitrogen inversion mechanism) as shown by the configurational stability of oximes, thio-oximes, hydrazones, and halogenoimines relative to simple (*N*-aryl- or *N*-alkyl-) imines.[15,33] Both increasing electron withdrawal by a non-conjugative mechanism as well as the presence of the non-bonded pair are expected to lead to increased inversion barriers.[33d] Thus the more electronegative the group attached to nitrogen then the slower the isomerization rate (*i.e.* OR ≪ SR < NR_2); the substituent effects which we have observed are consistent with this since as the amino-substituent is made more electronegative the configurational stability of the hydrazonate or isoimide is increased.

A recent theoretical study on the lateral shift mechanism using extended Hückel calculations has shown [34] that the net energy of isomerisation is composed of two separate terms (a) the energy required to promote the two non-bonded electrons from an sp^2 hybrid orbital to a pure p orbital and (b) the energy released in the simultaneous $sp^2 \longrightarrow sp$ hybridization of the imine nitrogen in the transition state. Both processes are influenced in opposite directions by inductive and resonance effects of a substituent on nitrogen. Thus electron withdrawal from the imine nitrogen by resonance aids isomerisation while electron withdrawal by induction [which effectively reduces the electron density in the N–N bond in (12)] is expected to slow isomerisation.

We propose that in the hydrazonates [20 and 23; R^2 = N(Me)Ar], the inductive effect is dominant and there is little resonance interaction between the *N*-aryl ring and the C=N bond. Some support from this comes from the *X*-ray crystallographic study of the hydrazonyl bromide (5; R = Me_3C).[35] The $N(Me)C_6H_3(NO_2)_2$ group is twisted by an angle of 54° out of the plane of the C=N bond, minimizing extended conjugation. Moreover the N–C(aryl) bond length (1.40 Å) is close to a C=N double bond length (1.36 Å) suggesting a strong mesomeric effect between the sp^3 nitrogen lone pair and the aryl group in the ground state. The aryl group is therefore incorrectly oriented for stabilization of the transition state of the lateral shift through resonance stabilization of the p-orbital on the imino nitrogen. The inductive effect is however independent of coplanarity of the C=N bond and the aryl group so that the introduction of nitro groups into the *N*-aryl ring slows the overall rate of *E*–*Z*-isomerisation.

Stereospecificity of Nitrilium Ion Reactions.—The quantitative formation of a single *O*-acylhydrazonate (20) or methylhydrazonate (23) isomer has important implications for the stereochemical course of the reactions leading to their formation. In both cases substitution of halide from (6) or (10) occurs *via* an S_N1 mechanism and the product-forming step involves reaction of the intermediate nitrilium ion (32) with the nucleophile X^-. The results already presented imply



SCHEME 3

that the formation of (33), in which the incoming nucleophile (AcO^- or MeOH) and the forming lone pair on nitrogen are *trans*, is favoured over (34).

The reaction of [10; Ar^1 = Ph, Ar^2 = 2,4-$(NO_2)_2$-C_6H_3] in methanol–water solution actually gives two products, the *Z*-hydrazonate [23; R^1 = Ph, R^2 = $N(Me)C_6H_3(NO_2)_2$] and the hydrazide [9; Ar^1 = Ph; Ar^2 = 2,4-$(NO_2)_2C_6H_3$]. The possibility arises that the hydrazonate was formed by small concentrations of methoxide ion reacting *via* a $B_{AC}2$ mechanism. The data presented in Table 5 show that this is clearly not so, since the relative percentages of hydrazonate and hydrazide formed do not vary with pH.

TABLE 5

Rate constants and products of reaction of [10; Ar^1 = Ph, Ar^2 = 2,4-$(NO_2)_2C_6H_3$] in methanol–water at 55°

Methanol–water	pH	$10^4k_{obs}/s^{-1}$	% Hydrazide [9; Ar^1 = Ph, Ar^2 = $(NO_2)_2C_6H_3$] [a]
80 : 20	3.2	1.8	49.8
80 : 20	7.0	0.8	49.0
70 : 30	3.4	3.15	59.0
70 : 30	7.0	1.16	57.5

[a] Estimated spectrophotometrically at 460 nm in basic solution.

Evidence is presented elsewhere, from *X*-ray crystallographic and n.m.r. data,[35] that the starting bromides (5) and chlorides (10) have the *Z*-configuration in which the halide and lone pair on the adjacent nitrogen are *trans*. Overall therefore the displacement (*via* ionization) is stereospecific giving retention of configuration. This result is very surprising since it contrasts with that reported for solvolytic displacements in vinyl chlorides shown to occur *via* vinyl cation intermediates.[36] For example Rappoport [37] reports a 1 : 1 mixture of *cis*- and

[33] (*a*) R. L. Layer, *Chem. Rev.*, 1963, **63**, 489; (*b*) H. Kalinowski, H. Kessler, D. Leibfritz, and A. Pfeffer, *Ber.*, 1973, **106**, 1023; (*c*) A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem. Internat. Edn.*, 1970, **9**, 400; (*d*) H. A. Bent, *Chem. Rev.*, 1961, **61**, 275.

[34] F. Kerek, G. Ostrogovich, and Z. Simon, *J. Chem. Soc.* (*B*), 1971, 541.

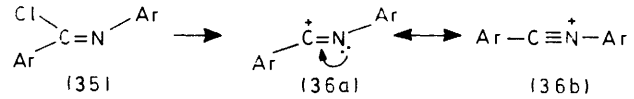
[35] A. F. Hegarty, M. T. McCormack, and B. J. Hathaway, to be published.

[36] Z. Rappoport and Y. Apeloig, *J. Amer. Chem. Soc.*, 1969, **91**, 6734; D. R. Kelsey and R. G. Bergman, *ibid.*, 1970, **92**, 228; D. R. Kelsey and R. G. Bergman, *ibid.*, 1971, **93**, 1941; Z. Rappoport and A. Gal, *J. Org. Chem.*, 1972, **37**, 1174; Z. Rappoport and A. Gal, *J.C.S. Perkin II*, 1973, 301.

[37] Z. Rappoport and Y. Apeloig, *J. Amer. Chem. Soc.*, 1974, **96**, 6428.

trans-products in the reaction of 1,2-bis-*p*-methoxyphenyl-2-phenylvinyl chloride with nucleophiles (*via* a free vinyl cation). Significant amounts of inversion have been reported for vinyl trifluoromethanesulphonates,[38] but this has been explained by the intermediacy of ion pairs which shield the side of the molecule from which the leaving group is departing. Since the displacement reactions for hydrazonyl halides involve *retention* of configuration the observed stereospecificity of the displacements cannot be explained by such a mechanism.

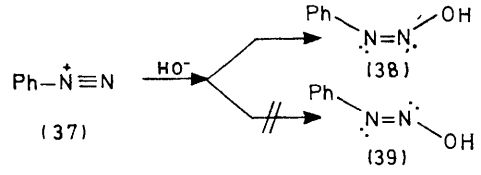
There is some evidence that in nitrilium ions (32) most of the charge is located on the nitrogen (which is then *sp* hybridized) rather than on carbon. Thus substituents in Ar^2 of the imidoyl chloride (35) have a larger



effect (ρ −3.0) in stabilizing the formation of (36) than do substituents in Ar^1 (ρ −2.0), reflecting the importance of form (36b).[39] This was confirmed by calculating the optimised geometry of the $[HCNH]^+$ ion by the *ab initio* method which show that the ion is linear.[40]

Such a free linear ion in a vinyl system would lead to equal amounts of *E*- and *Z*-isomers on reaction with a nucleophile. Clearly then the forming lone pair on nitrogen plays a vital role in determining the stereospecificity of the addition to (32), presumably the repulsions are minimized by the *trans*-arrangement of nucleophile and electron pair in the transition state for the formation of (33).

The linear benzenediazonium ion (37) appears to undergo similar stereospecific reactions with strong nucleophiles (*e.g.* HO^-) (Scheme 4). The *syn*-diazo-



SCHEME 4

hydroxide (38) (in which the OH group and the lone pair on the β-nitrogen are *trans*) is formed preferentially.[41] Interestingly, the *anti*-isomer (39) is thermodynamically more stable and isomerisation to this form occurs in time; similarly the *E*-isomer of the methylhydrazonate (24) is also the thermodynamically most stable isomer.

Since the lowest energy pathway for the addition of a nucleophile to a nitrilium ion leads to just one isomer it follows that in the reverse reaction one of the two imidoyl isomers will also react more rapidly. Thus, for example, the *Z*-isomer (23) should lose MeO^- more rapidly than (24), to give a nitrilium ion. We have been unable to confirm this as yet since the methylhydrazonates (23) and (24) do not undergo unimolecular solvolysis because of the poor leaving group (MeO^-) involved; substrates with better leaving groups [*e.g.* (5) and (10)] have not been successfully converted to *E*-isomers. However, the *syn*-diazotate (38) is rapidly converted to the diazonium ion (37) in acid solution whereas the *anti*-isomer (38) does not undergo elimination under these conditions.[41] The reverse reaction is also analogous to an *E*2 elimination facilitated by the *trans*-arrangement of the lone pair on the adjacent nitrogen; in *E*2 eliminations an antiperiplanar arrangement of the hydrogen removed and the leaving group is generally favoured.[42,43]

The stereospecificity observed in the present work demonstrates the importance of nucleophile (or leaving group) repulsions in the transition state in determining the structure of the product formed. Recent work by Deslongchamps,[44] who suggests that the breakdown of tetrahedral intermediates depends on the orientation of lone pair orbitals of the heteroatoms involved, supports this conclusion.

EXPERIMENTAL

General.—U.v. spectra were measured using a Perkin-Elmer model 124 or Unicam 800B spectrophotometer. A Perkin-Elmer model R20A was used for n.m.r. spectra using deuteriochloroform as solvent unless otherwise stated. M.p.s were measured on an Electrothermal apparatus and are uncorrected. I.r. spectra were measured (usually as KBr discs) using a Perkin-Elmer 257 spectrophotometer. All inorganic materials were AnalaR grade. Methanol was AnalaR grade and used without further purification. Chlorobenzene and acetonitrile were distilled from phosphorus pentaoxide before use. The water used was deionized and then twice distilled from alkaline potassium permanganate.

Substrates.—N-*Aryl*-N-*methylbenzohydrazides*. *N*-Methyl-*N*-(*p*-nitrophenyl)hydrazine was prepared from the reaction of equimolar amounts of 1-chloro-4-nitrobenzene and methylhydrazine at 140°, and had m.p. 160—161° (lit.,[45] 160—161°). To the hydrazine (5×10^{-2} mol), dissolved in benzene (50 ml), benzoyl chloride (5×10^{-2} mol), and dry triethylamine (5×10^{-2} mol) also dissolved in benzene (50 ml) was added. The mixture was refluxed for 3 h, the precipitated triethylamine hydrochloride was filtered off to give, on evaporation of the solvent, N-*methyl*-N-(p-*nitrophenyl*)*benzohydrazide*, m.p. 158—159° (from 95% ethanol) (Found: C, 62.2; H, 4.7; N, 15.3. $C_{14}H_{13}N_3O_3$ requires C, 62.0; H, 4.8; N, 15.5%).

N-*Methyl*-N-(2,4-*dinitrophenyl*)*benzohydrazide* was similarly prepared and had m.p. 201—201.5° (Found: C, 53.0;

[38] T. C. Clarke, D. R. Kelsey, and R. G. Bergman, *J. Amer. Chem. Soc.*, 1972, **94**, 3626; R. H. Summerville and P. v. R. Schleyer, *ibid.*, 3629.

[39] A. F. Hegarty, J. D. Cronin, and F. L. Scott, *J.C.S. Perkin II*, 1975, 429.

[40] A. F. Hegarty, M. T. McCormack, and N. J. Fitzpatrick, unpublished results.

[41] H. Zollinger, *Accounts Chem. Res.*, 1973, **6**, 335.

[42] R. W. Alder, R. Baker, and J. M. Brown, 'Mechanism in Organic Chemistry,' Wiley, New York, 1971.

[43] K. Fukui and H. Fugimoto, *Tetrahedron Letters*, 1965, 4303; *Bull. Chem. Soc. Japan*, 1966, **39**, 2116; 1967, **40**, 2018.

[44] P. Deslongchamps, *Tetrahedron*, 1975, **31**, 2463.

[45] Z. Rappoport and T. Sheladsley, *J. Chem. Soc.* (*B*), 1968, 277.

H, 3.9; N, 17.2. $C_{14}H_{13}N_3O_3$ requires C, 53.2; H, 3.8; N, 17.7%). N-*Methyl*-N-*phenylbenzohydrazide* was prepared using commercially available *N*-methyl-*N*-phenylhydrazine and had m.p. 145—146° (Found: C, 74.1; H, 6.9; N, 11.9. $C_{14}H_{14}N_2O$ requires C, 74.3; H, 6.4; N, 12.4%).

N-*Methyl*-N-*arylbenzohydrazonyl chlorides*. Finely ground phosphorus pentachloride (6×10^{-2} mol) was added over 2—3 min to a stirred solution of *N*-methyl-*N*-phenylbenzohydrazide (5×10^{-2} mol) in dry benzene (150 ml). The mixture was stirred at room temperature until the evolution of HCl had ceased and t.l.c. indicated the absence of starting hydrazide [R_F 0.40; silica gel; 7 : 3 chloroform–light petroleum (60—80°) as eluant]. The solution was concentrated at 25° by the removal of benzene and phosphoryl chloride *in vacuo*. Attempted distillation of the residual oil, b.p. 30° at 0.02 mmHg, resulted in appreciable decomposition. N-*Methyl*-N-*phenylbenzohydrazonyl chloride* was therefore purified by dry column chromatography on silica gel activity III, using 7 : 3 chloroform–light petroleum (60—80°) as eluant (R_F 0.84) (Found: C, 68.7; H, 5.5; Cl, 14.5; N, 11.7. $C_{14}H_{10}ClN_2$ requires C, 69.0; H, 5.4; Cl, 14.1; N, 11.5%); n.m.r. and i.r. spectra are consistent with the hydrazonyl chloride structure.

The following hydrazonyl chlorides were prepared by the same general procedure; being solids they were purified by recrystallisation from benzene. N-*Methyl*-N-(4-*nitrophenyl*)*benzohydrazonyl chloride* had m.p. 138° (Found: C, 58.3; H, 4.4; Cl, 13.0; N, 14.4. $C_{14}H_{12}ClN_3O_2$ requires C, 58.0; H, 4.2; Cl, 12.3; N, 14.5%). N-*Methyl*-N-(2,4-*dinitrophenyl*)*benzohydrazonyl chloride* had m.p. 116—117° (Found: C, 50.0; H, 3.7; Cl, 10.1; N, 16.2. $C_{14}H_{11}ClN_4O_4$ requires C, 50.2; H, 3.3; Cl, 10.6; N, 16.7%).

N-*Methyl*-N-(2,4-*dinitrophenyl*)*pivalohydrazonyl bromide* (5; R = Me_3C). Pivalaldehyde *N*-methyl-*N*-(2,4-dinitrophenyl)hydrazone (1.0 g) was suspended in acetic acid (2.0 ml) containing 30% acetic anhydride. The slurry was stirred vigorously while bromine (0.20 ml) was added rapidly. The solution which was formed heated considerably and after *ca.* 7 min a yellow solid precipitated. The hydrazonyl bromide was collected after a further 5 min and had m.p. 107° (lit.,[13] 108°). The quantity of solvent used in this preparation was critical. With acetic acid (3.0 ml) containing 10% acetic anhydride no solid precipitated within 10 min; after 1 h the corresponding hydrazide, *N*-methyl-*N*-(2,4-dinitrophenyl)pivalohydrazide, was obtained.

N-*Methyl*-N-(2,4-*dinitrophenyl*)*acetohydrazonyl bromide*. Acetaldehyde *N*-methyl-*N*-(2,4-dinitrophenyl)hydrazone (1.0 g) was dissolved in carbon tetrachloride (120 ml) at reflux and *N*-bromosuccinimide (1.2 g) was added over 5 min. The solution was refluxed for a further 30 min and on cooling the succinimide filtered off. The solid obtained showed some contamination from succinimide, *N*-bromosuccinimide, *N*-methyl-*N*-(2,4-dinitrophenyl)acetohydrazide as well as the required hydrazonyl bromide [R_F 0.50, 0.25, 0.15, and 0.65 respectively using 3 : 2 ethyl acetate–light petroleum (b.p. 60—80°) as eluant on silica gel]. Three recrystallisations from chloroform–hexane gave the *hydrazonyl bromide*, m.p. 84—85° (Found: C, 34.3; H, 2.7; Br, 25.5; N, 17.0. $C_9H_9BrN_4O_4$ requires C, 34.1; H, 2.9; Br, 25.2; N, 17.6%), δ 2.55 (3 H, s, C–Me) and 3.25 (3 H, s, NMe). It was readily converted (in aqueous acetone) into *N*-methyl-*N*-(2,4-dinitrophenyl)acetohydrazide, m.p. 158° (lit.,[46] 158°). Attempted bromination using molecular bromine in acetic acid containing 30% acetic anhydride (as above) gave *bromoacetaldehyde* N-*methyl*-N-(2,4-*dinitrophenyl*)*hydrazone*, m.p. 95° (Found: C, 33.5; H, 2.7; Br, 25.4; N, 17.6. $C_9H_9BrN_4O_4$ requires C, 34.1; H, 2.9; Br, 25.2: N, 17.6%).

O-*Acetyl*-N-*methyl*-N-(2,4-*dinitrophenyl*)*pivalohydrazide* (8; R = Me_3C). Sodium acetate (6.0 g) was dissolved in 1 : 1 acetone–water (60 ml) containing acetic acid (1.0 ml). The hydrazonyl bromide (5; R = Me_3C) (1.0 g), dissolved in the minimum amount of acetone, was added. The mixture was maintained at 35° for 6—8 min, when t.l.c. indicated that reaction was complete (R_F 0.82 for hydrazonyl bromide, R_F 0.71 for *O*-acetylhydrazide, using 7 : 3 ethyl acetate–light petroleum as eluant on silica gel). Addition of water precipitated the O-*acetylhydrazide* in quantitative yield, m.p. 112—113° (from ethanol) (Found: C, 50.0; H, 5.6; N, 16.9. $C_{14}H_{18}N_4O_4$ requires C, 49.7; H, 5.4; N, 16.6%). The following compounds were similarly prepared: O-*acetyl*-N-*methyl*-N-(2,4-*dinitrophenyl*)*acetohydrazide* (8; R = Me), m.p. 94—95° (87%) (from ethanol) (Found: C, 44.7; H, 4.5; N, 19.0. $C_{11}H_{12}N_4O_6$ requires: C, 44.6; H, 4.1; N, 18.9%); O-*acetyl*-N-*methyl*-N-(2,4-*dinitrophenyl*)*benzohydrazide*, m.p. 122° (60%) [from benzene–hexane (4 : 1)] (Found: C, 53.2; H, 3.8; N, 15.1. $C_{16}H_{14}N_4O_6$ requires C, 53.6; H, 3.9; N, 15.6%).

O-*Acetyl*-N-*methyl*-N-(4-*nitrophenyl*)*benzohydrazide* (12; Ar^1 = Ph, Ar^2 = 4-$NO_2C_6H_4$; R^3 = Me). *N*-Methyl-*N*-(4-nitrophenyl)benzohydrazonyl chloride (1.0 g) was added to a slurry of finely ground silver acetate (3.0 g) in dry methylene chloride (40 ml). The mixture was refluxed for 6 h and the precipitated silver salts filtered off. The O-*acetylhydrazide* was recovered by evaporation of the solvent and on recrystallisation (three times) from benzene–hexane had m.p. 129—130° (Found: C, 60.9; H, 4.6; N, 13.8. $C_{16}H_5N_3O_4$ requires C, 61.3; H, 4.8; N, 13.4%).

O-Acetyl-*N*-methyl-*N*-phenylbenzohydrazide (12; Ar^1 = Ar^2 = Ph, R^3 = Me) was similarly prepared except that the mixture was not refluxed; t.l.c. indicated that reaction was complete in 15 min at room temperature. The light yellow oil isolated on filtration and evaporation of the solvent had the characteristic ester absorption in the i.r. at 1 770 cm^{-1}, the n.m.r. showed a singlet at δ 3.48 (3 H, NMe). The other *O*-aroyl-*N*-methyl-*N*-phenylbenzohydrazides (12; Ar^1 = Ar^2 = Ph) were similarly prepared at room temperature using substituted silver benzoates. All were yellow oils and had the following carbonyl stretching frequencies in the i.r. (CH_2Cl_2 solution): R^3 = Ph, 1 750; 4-ClC_6H_4, 1 750; 3-ClC_6H_4, 1 750; 4-$NO_2C_6H_4$, 1 755; 3-$NO_2C_6H_4$, 1 755; 4-MeC_6H_4, 1 740 cm^{-1}.

Z-*Methyl* N-*methyl*-N-(4-*nitrophenyl*)*benzohydrazonate* [23; R^1 = Ph, R^2 = N(Me)$C_6H_4NO_2$]. *N*-Methyl-*N*-(4-nitrophenyl)benzohydrazonyl chloride (1.0 g) was dissolved in methanol (300 ml) at room temperature containing 1.0M-sodium methoxide and stirred at room temperature for 30 min. Water was added to precipitate the *hydrazonate* in quantitative yield, m.p. 105°, R_F 0.33 on silica gel using 2 : 3 chloroform–light petroleum ether (b.p. 60—80°) as eluant (Found: C, 61.7; H, 5.4; N, 14.3. $C_{15}H_{15}N_3O_3$ requires: C, 62.1; H, 5.3; N, 14.7%). Z-*Methyl* N-*methyl*-N-(2,4-*dinitrophenyl*)*benzohydrazonate* was similarly prepared, m.p. 126°, R_F 0.31 (Found: C, 54.7; H, 4.4; N, 16.8. $C_{15}H_{14}N_4O_5$ requires C, 54.4; H, 4.3; N, 17.0%). The corresponding *E*-methyl *N*-methyl-*N*-(2,4-dinitro-

[46] J. J. Blanksma and M. L. Wackers, *Rec. Trav. chim.*, 1936, **55**, 655.

phenyl)benzohydrazonate was prepared by thermal rearrangement of the *Z*-isomer to a mixture containing 78% *E*-isomer in chlorobenzene at 130°. The isomers were separated using preparative t.l.c. on silica gel with 2 : 3 chloroform–light petroleum (b.p. 60—80°) as eluant. The E-*isomer* had m.p. 117°, R_F 0.49 (Found: C, 54.3; H, 4.4; N, 17.2. $C_{15}H_{14}N_4O_5$ requires C, 54.4; H, 4.3; N, 17.0%).

Kinetic Studies.—In the experiments using the n.m.r. technique, the neat substrate was added to the temperature equilibrated solvent to make a final solution *ca.* 0.25M in substrate. Trial experiments showed that a constant temperature was reached in 2 min, so that the amount of rearrangement that occurred during equilibration was minimal. In most cases integrated peak areas were used to estimate concentration except that in some of the faster reactions peak heights were used (the signals were in all cases sharp singlets and did not overlap). Up to four determinations were possible on each substrate involving the appearance and disappearance of peaks and the first-order rate constants calculated were in agreement, ruling out the existence of intermediates with a significant lifetime. The values quoted in the Tables represent an average of several (usually four) separate kinetic runs. In experiments where an equilibrium mixture of products was formed, the rate constants for the forward and reverse reactions were calculated by the method described by Frost and Pearson.[25]

In experiments using the u.v. method, the substrate was made up (*ca.* 10^{-2}M) in acetonitrile and reaction was initiated by the addition of 1—2 drops of this stock solution to the solvent (which had been pre-equilibrated at the desired temperature) in a 3.0 ml cuvette. Initial repetitive scans of the u.v. region established a suitable wavelength, where the change in optical density was large. These repetitive scans were characterised by tight isosbestic points, indicating the absence of long-lived intermediates. Optical density *versus* time plots at constant wavelength were then analysed to give the first-order rate constants.

M. T. McC. is grateful to the Irish Government for a State Maintenance Grant for Research.

[6/241 *Received, 4th February,* 1976]