THE ALKYLATION AND ACYLATION

OF

SOME 1,3 AMBIDENT NUCLEOPHILES

BY

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ABSTRACT

The behaviour of amides and phenols towards electrophilic reagents is reviewed, with particular regard to alkylation and acylation in which their apparent 1,3 ambident character is observed. The relevance of rearrangement reactions *via* 1,3 migrations in these systems is also outlined.

Results for the alkylation of phenol by alkyl halides are reported which identify the pH of the reaction medium as an important factor in determining the site of alkylation. This result is interpreted in terms of kinetically- and thermodynamically-controlled alkylation.

An investigation of the acylation of neutral N-alkoxyamides shows the formation of amide oxygen substituted products at low temperatures, but the N-acyl product at high temperatures. This difference is explained in terms of kinetic *versus* thermodynamic product.

From a kinetic study the rearrangement of O-acylisoimides was found to occur thermally and, in the case of N-alkoxyamides, by a catalysed pathway. The rearrangement of N-benzyloxybenzimidoyl acetates was found to be catalysed by both nucleophilic and electrophilic entities. The relevance of this catalysed rearrangement to the site of acylation of amides under neutral conditions is discussed.

It is proposed that neutral amides and phenols do not react as 1,3 ambident nucleophiles but their behaviour towards alkylating and acylating agents may be interpreted in terms of the formation of kinetic and thermodynamic products.

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I would like to thank my supervisor, Dr.B.C.Challis, for the inspiration behind the work described here and the encouragement which enabled it to be completed.

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My sincerest thanks also go to the many people who provided their services and friendship during my stay here.

Finally I would like to thank Miss P.A. Greenwood for the typing of this manuscript.

DEDICATION

To my wife, Margaret

and

my Mother and Father.

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PART THREE - THE EXPERIMENTAL DETAILS

P A R T O N E

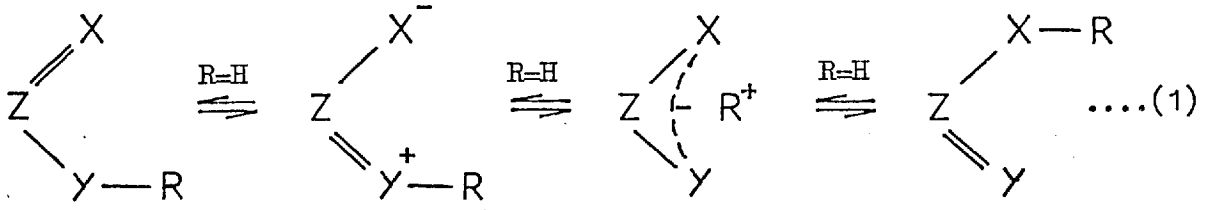
INTRODUCTION

CHAPTER I

1.1 AMBIDENT NUCLEOPHILES : GENERAL CONSIDERATIONS

An ambident [1] nucleophilic compound may be described as a compound possessing the capability for covalent bond formation at either of two positions. The ambident character is of great significance from both the preparative and theoretical points of view.

Systematic investigations [1,2,3,4] carried out over the past few years, have revealed that the relative proportions of products resulting from the two possible reaction paths depend on numerous, frequently still unclarified, factors. Typical ambident systems are amides, amide anions, enols, enol anions, allyl anions and nitrosamines.



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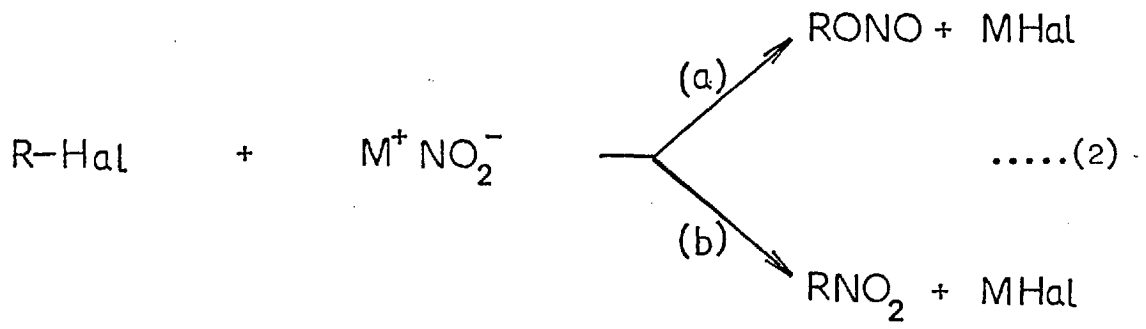
In Equation (1), a 1,3 ambident system is illustrated, demonstrating that electrophilic substitution may occur at either the X or Y atoms of this particular compound.

Perhaps the first general theory regarding the reactivity of ambident nucleophiles was that proposed by Kornblum,[1] who suggested that, in general, S_N1-type substitution proceeds more readily at the more electronegative atom of the ambident nucleophile, whereas S_N2-type reactions are found to favour the site of lower electronegativity. These deductions were based on examination of several ambident nucleophiles.

Some of the strongest evidence for the basic principles advanced by Kornblum, was obtained in his investigations [1] into the reaction of alkyl halides with metal nitrites (Equation (2)).



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The extent to which a given reaction proceeds along pathway (a) (giving rise to O-attack), or (b) (leading to N-attack), was found [1] to depend significantly on the nature of the metallic cation, M^+. In reactions where silver nitrite was used, and where silver ion would be expected to enhance the unimolecular nature of the reaction by polarization of the alkyl halide bond, alkyl nitrites were found to be the major reaction products. Conversely, with potassium nitrite high yields of the nitroalkane were observed.

The alkyl halide also plays an important part in determining the course of the reaction, as shown in Table 1.1 [1].

TABLE 1.1

R-Hal	MNO_2	Yield (%) RONO	RNO_2
$4\text{-}NO_2PhCH_2Br$	$AgNO_2$	16	84
$PhCH_2Br$	$AgNO_2$	30	70
$4\text{-}CH_3PhCH_2Br$	$AgNO_2$	48	52
$4\text{-}CH_3OPhCH_2Br$	$AgNO_2$	61	39

The increased stability of the developing carbonium ion with an electron-donating para-substituent on the aryl ring was proposed [1] to account for the observed results.

Kornblum [1] cited similar arguments [5,6,7] for the alkyl halide alkylation of silver and potassium amide salts, where the presence of silver ion is known [5,6] to promote the formation of an O-alkylated product in preference to the N-alkylamide product observed when potassium salts [7] are used.

The chief drawback of Kornblum's theory, however, is that it is valid only for the reaction of anions with alkylating agents and cannot, for example, be used to explain the reaction of the neutral molecule with an alkylating agent. It can, nevertheless, explain the alkylation of the cyanide, amide and nitrosamine anions. It agrees only in part with the results obtained with enolate and phenoxide anions (Section 1.2) and largely fails with the anions of nitroalkanes and oximes.

An attempt has also been made to explain ambident reactivity in terms of "hard" and "soft" acids and bases [8,9]. Pearson and Songstad [10] explained the ambident reactivity of enols in terms of a "soft" nucleophilic centre (the carbon atom) and a "hard" centre (the oxygen atom). Using this theory they correctly predicted that alkyl sulphates and tosylates (which are "hard" centres) react with an enolate anion [11,12] to give O-alkylation, whereas alkyl bromides and iodides [13,14] react to give predominantly C-alkylation. It was shown by Kornblum [15] that the C/O alkylation ratio rises steadily on changing from RCl to RBr to RI. These results are also explicable in terms of "hard" and "soft" acid and base theory, as the observed order is also the order of increasing "softness" of the leaving group.

The "hard" and "soft" acid and base theory, and the ideas expressed by Kornblum, find some theoretical justification in the perturbation treatment [16] of chemical reactivity. The theoretical basis for the perturbation theory will not be discussed in detail as a recent paper by Hudson [16] provides a convenient summary.

In the perturbation theory, the energy change in the initial stages of a chemical reaction as the orbitals of the reactants mutually interact (i.e. perturb each other) is calculated. The orbitals may interact in various ways depending on their symmetry and relative energies. The derived equation for the energy change on perturbation, therefore, contains two terms, one relating to the symmetry interaction, the other to the Coulombic attraction and interelectronic repulsion.

In reactions of non-polar π-systems and molecules of weak polarity, orbital interactions normally determine the course of the reaction. For polar molecules, the Coulombic energy term may become important, and in these cases, the symmetry and energy terms may be in opposition.

If the Coulombic energy or orbital terms change in the same direction with a change in structure of the nucleophile, the nucleophiles show the same relative reactivity order to all electrophilic centres as required by the Brönsted relation (Equation (3)).

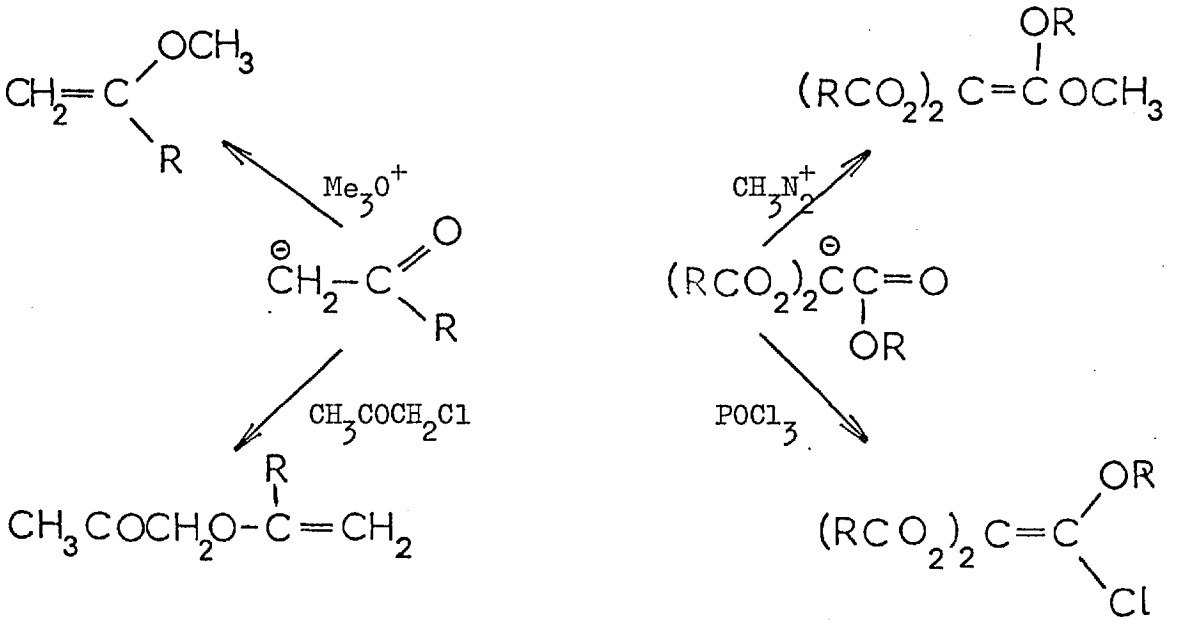
$$\log \left|\frac{k}{k'}\right| = \beta\,(pK_a - pK'_a) \qquad \text{.....(3)}$$

The nucleophilic order may change, however, with the nature of the electrophile. In alkylations using alkyl halides, for example, the Coulombic term is small, and the reactivity order follows the dominant orbital term, i.e. $I^- > Br^- > Cl^- > F^-$, and hence alkylation is orbital controlled.

In acylation, the Coulombic term is large owing to the high positive charge on the carbonyl carbon, and although the orbital term is also increased, the first term is dominant, resulting in a reversed nucleophilic order. Acylation is therefore charge controlled. The change in the relative acid and base strengths with the nature of the electrophile has been extensively discussed by Pearson [8,9,10] in terms of the "hard" and "soft" acid and base theory and it can be seen therefore that the perturbation theory gives the "hard" and "soft" acid and base theory [8] some theoretical basis. The reactions of "hard" acids and bases are those in which the Coulombic charge term is dominant, and orbital symmetry is most important in the reactions of "soft" acids and bases.

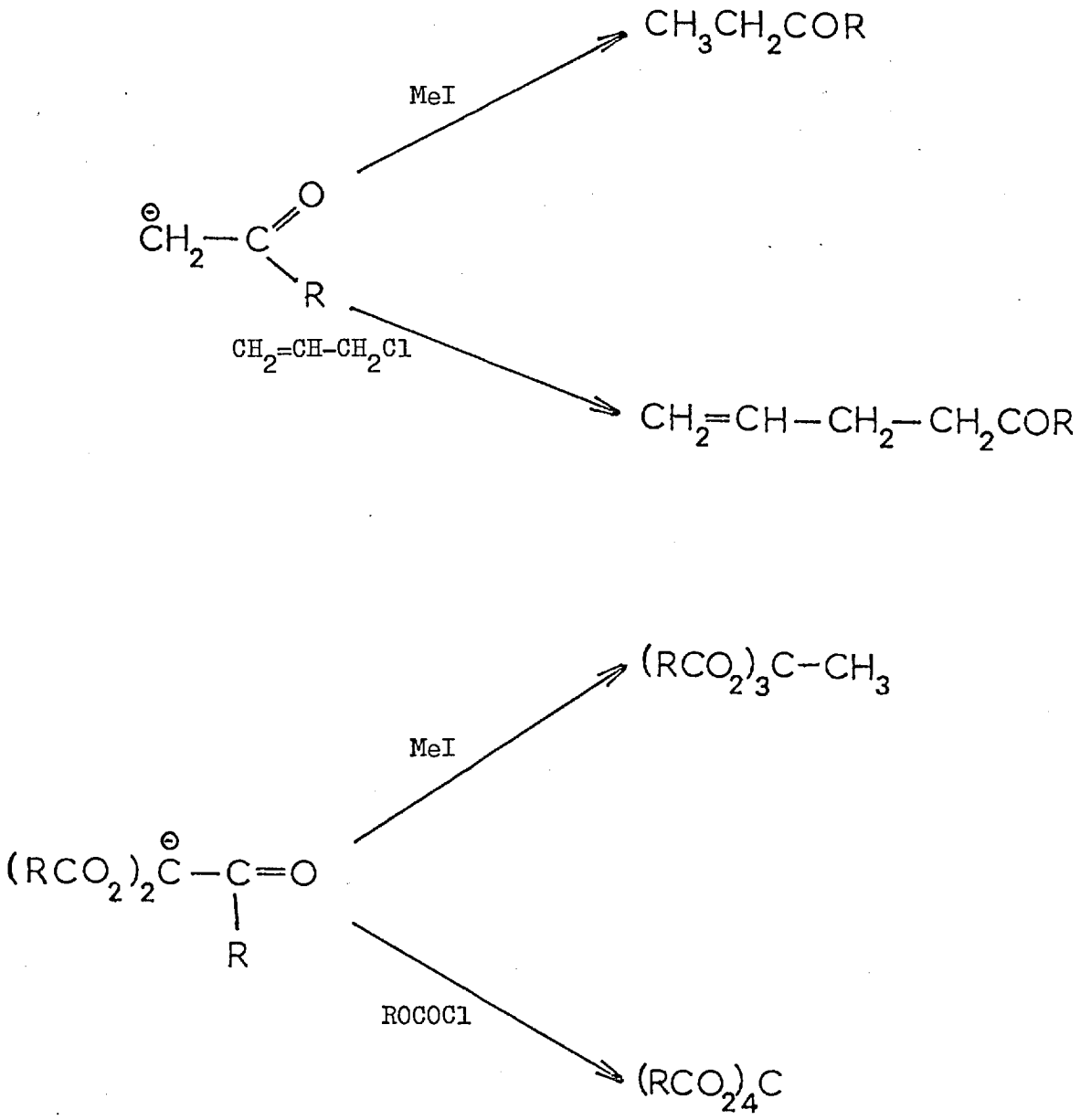
The perturbation treatment [16] may also be used to predict the reactive site of an ambident nucleophile. In the reactions of ambident enolate ions where the charge term is large (e.g. reactions with cations or incipient carbonium ions), the reactions are charge controlled and substitution occurs on oxygen (Scheme 1.1).

Scheme 1.1



As the charge decreases, the reactions of enolate ions become orbital controlled, and substitution in this case occurs at carbon (Scheme 1.2).

Scheme 1.2



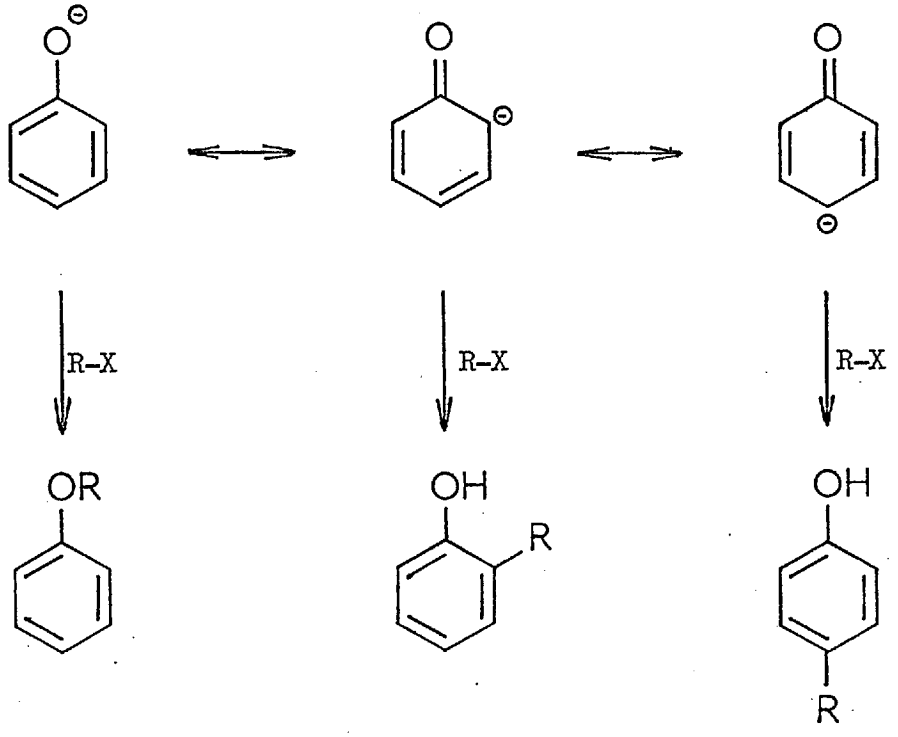
It can be seen that the observed behaviour for electrophilic substitution at ambident anionic nucleophiles may be successfully explained in terms of the perturbation theory. In addition, the perturbation theory gives a theoretical basis for the ideas expressed by Kornblum [1] and Pearson [9,10] to explain ambident reactivity.

The generality of the theories considered above have only rarely been studied, and it is upon this aspect that the present work is focussed.

1.2 AMBIDENT NUCLEOPHILIC PROPERTIES OF PHENOLS

Phenols and their anions can be regarded as 1,3 or 1,5 ambident nucleophiles with the possibility of reaction at either the oxygen or ortho and para carbon atoms of the benzene nucleus (Scheme 1.3). Generally reaction on the aromatic nucleus predominates mainly

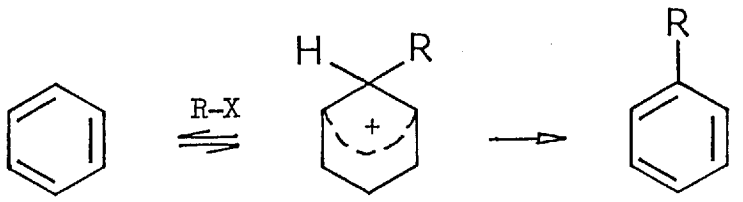
Scheme 1.3



because the O-substituted product is formed reversibly, but examples of mixed O-substituted and ring-substituted products are well known, particularly for alkylation reactions.

Reaction at the aromatic carbon atoms is an example of electrophilic aromatic substitution for which the generally accepted mechanism [17] is a two-step process involving an intermediate sigma complex, 1(Wheland intermediate). There is no evidence against a

Wheland intermediate in the substitution of phenol, but there is considerable support for the opinion that the actual mechanism is more complex than that shown in Equation (4). It has been established [18,19] that, in certain halogenations of phenol, dienone



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intermediates may participate and that weakening or breaking of the O-H bond may be significant in the rate determining step.

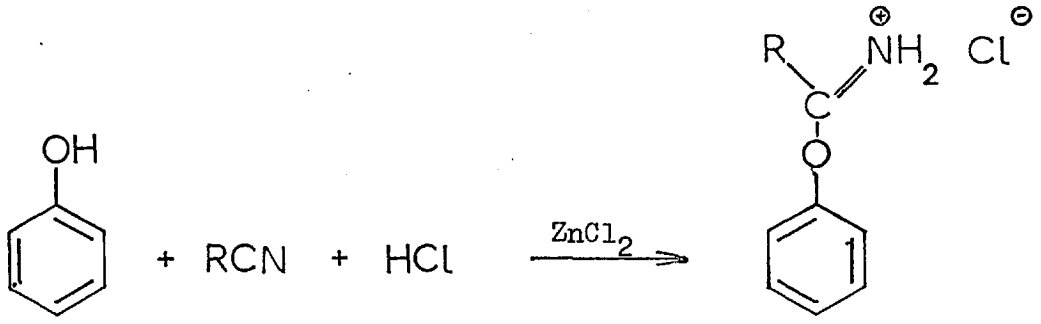
In a monosubstituted benzene derivative the steric effect of the substituent normally decreases the accessibility of the ortho positions. Further, for phenols, the -I and +R electronic characteristics of the hydroxyl group combine to favour para-substitution. In principle therefore an ortho:para ratio less than the statistical 2:1 is expected for phenols. Electrophilic attack at the ortho position of phenols, however, may be complicated by interaction of the reagent with the hydroxyl group. In some cases the electrophile attacks oxygen first, and then migrates; in others, some bonding between the attacking electrophile and the phenolic oxygen results in abnormally high ortho:para ratios.

For most electrophilic substitution reactions (e.g. nitration, halogenation) no evidence is available to demonstrate attack at the phenolic oxygen atom, although in alkaline solutions the phenoxide ion must be the reacting species. As noted above, it is possible that attack at this site does occur, but the inherent instability of the O-substituted product precludes isolation.

In the alkylation and acylation of phenol, however, both the O- and C-substituted products are relatively stable, and in these cases, the ambident nucleophilic properties of phenol and its anion may become apparent.

1.2.1 ACYLATION OF PHENOLS

In the Hoesch [20] acylation of phenol, reaction is found to occur mainly at oxygen to give imido-esters [21], 2(Equation (5)).



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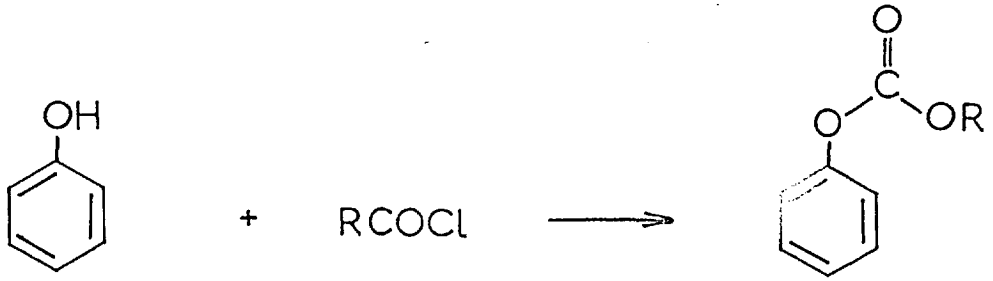
The precise nature of the attacking electrophile is unknown but it is believed to be a complex of $R-C=\overset{+}{N}H$ with HCl. Acylation of phenol or phenoxide ion using either acyl halides or acid anhydrides leads to the formation of the phenol ester [22], 3(Equation (6)). The reaction of phenol with acetic anhydride is catalysed by both strong mineral acids (protonation of the anhydride) and base (formation of phenoxide anion).



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In the acylation of phenols using aromatic acid chlorides in aqueous alkali (Schotten-Baumann reaction) O-acylation is again observed.

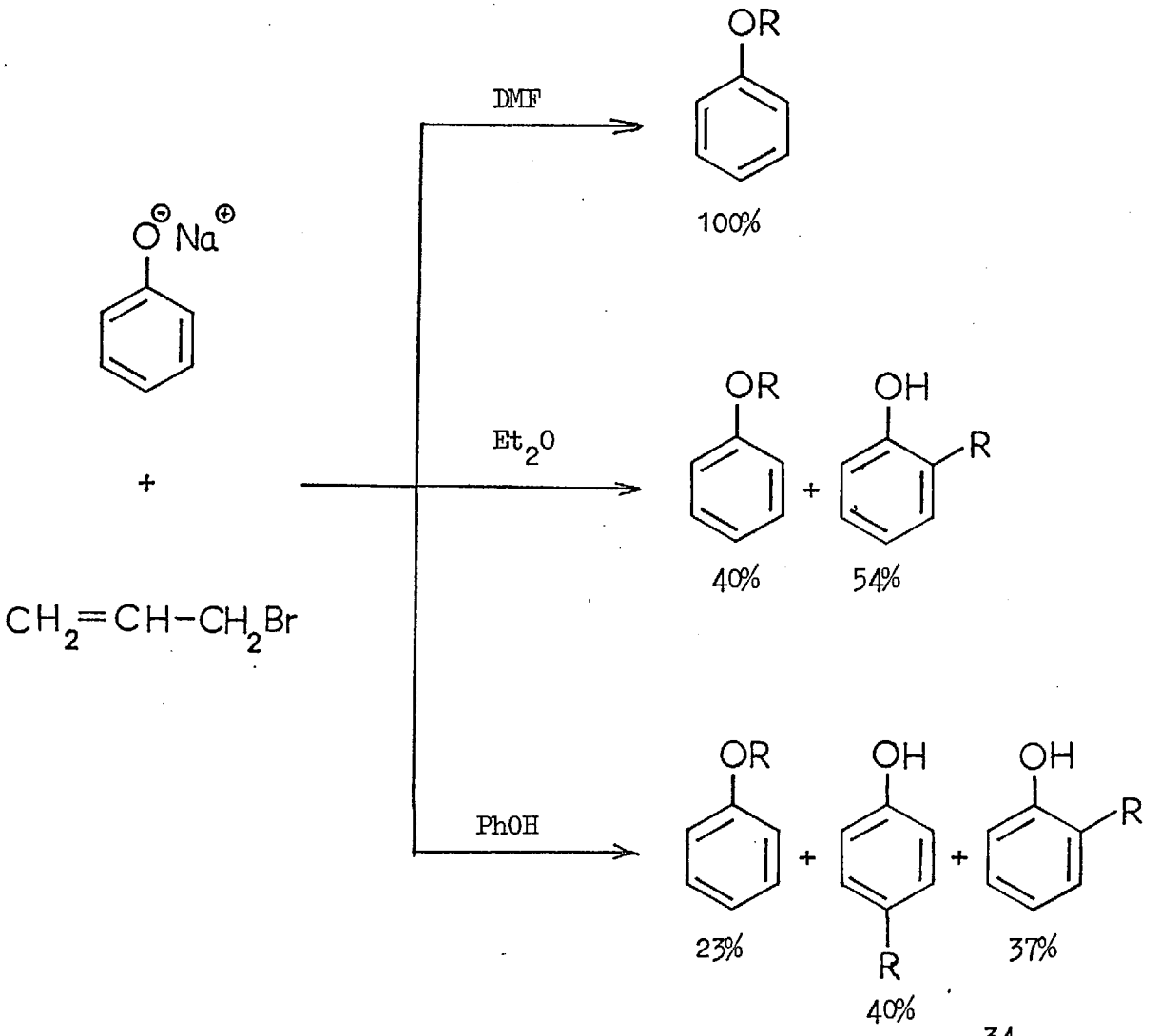
The Friedel-Crafts acylation of phenol is also relevant, but will not be considered in detail since exhaustive reviews of this and other reactions of the Friedel-Crafts type are given in the treatise edited by Olah [23]. In general, however, acylation under mild conditions appears to give O-acylation rather than C-acylation which is observed under more forcing conditions (i.e. higher temperature). By suitable selection of reaction conditions, therefore, the kinetic O-acyl product or the thermodynamic C-acyl product may be favoured. The O-acyl product is unstable under the more forcing Friedel-Crafts reaction conditions, and rearranges to give ortho- and para-acylphenols via the Fries rearrangement. The para product is formed by an intermolecular deacylation-reacylation reaction [24], but, in the cases so far investigated, the ortho product appears to be formed by an intramolecular reaction [24], although no definitive evidence to support this conclusion has been found.

1.2.2 THE ALKYLATION OF PHENOLS

The potential ambident properties of phenoxide ions with respect to alkylating agents have also been widely examined [1,4,25,26,27]. Both allyl and benzyl halides react at the ortho carbon of phenoxide ions as well as at the oxygen atom, when the sodium salt of the phenol is suspended in aromatic hydrocarbons [28,29,30] (i.e. under heterogeneous conditions). Alkyl halides, under similar conditions, react almost entirely at oxygen [31], except when attack at the oxygen atom is severely inhibited by bulky, ortho-substituents [32]. The observation that para-alkylation occurs when alkylating agents such as diphenylmethyl chloride and trityl chloride [33] are used, led to the suggestion that para-alkylation was "diagnostic of the intermediacy of carbonium ions" [29].

A different product ratio can be obtained by conducting the alkylation reaction in homogeneous conditions. Thus Kornblum [34] obtained the ether in 100% yield in dimethylformamide (DMF), but in diethyl ether the yield of the O-alkyl product decreased to 40%, and the ortho-alkylphenol was obtained in 54% yield, when allyl bromide was reacted with sodium phenoxide (Scheme 1.4).

Scheme 1.4



Kornblum, in his study of the alkylation of phenoxide [34] and 2-naphthoxide ions [35] by allyl and benzyl bromide explained the apparent ambident reactivity under homogeneous conditions in terms of solvation,

with particular reference to the hydrogen-bonding capacity [34] and the dielectric constant [35] of the solvent. The results are summarised in Table 1.2 [34].

Table 1.2

EFFECT OF SOLVENT UPON THE HOMOGENEOUS ALKYLATION OF SODIUM PHENOXIDE

SOLVENT	T(°C)	ALKYLATING AGENT	PRODUCT (%) O-ALKYL	C-ALKYL
tert-Butanol	27	Allyl Bromide	100	
Dimethylformamide	27	Allyl Bromide	91	
	27	Benzyl Chloride	100	
Dioxane	27	Allyl Bromide	93	
	27	Benzyl Chloride	100	
Ethanol	27	Allyl Chloride	100	
Methanol	27	Allyl Bromide	96	
	27	Benzyl Chloride	100	
Water	27	Allyl Chloride	49	41
	27	Allyl Bromide	51	38
	27	Benzyl Chloride	65	24
Phenol	43	Allyl Chloride	22	78
	43	Allyl Bromide	23	77
	43	Benzyl Chloride	22	69
2,2,2,-Trifluoro-ethanol	27	Allyl Bromide	37	42
	27	Benzyl Chloride	62	26

The possibility that the reactions in water, phenol and trifluoroethanol proceeded via a carbonium ion (S_N1) process was rejected on the grounds of the high overall yield of O- and C-alkyl

products with little or no hydrolysis of the alkyl halide to give the corresponding alcohol. In addition, Kornblum [34] demonstrated that the reaction rate depended upon the phenoxide concentration, a dependency which was not attributable to a salt effect (Table 1.3).

Table 1.3

ALKYLATION OF SODIUM PHENOXIDE IN PHENOL AT 43°C

REACTANTS	REACTION TIME (hrs)	% REACTION
$PhOH+PhCH_2Br$	20.0	43
$PhOH+PhCH_2Br+LiClO_4$	20.5	50
$PhOH+PhCH_2Br+PhONa$	21.0	88

It was therefore concluded that alkylation, independent of the solvent, was a bimolecular (S_N2) process. In order to explain the change in product ratio in water, phenol and trifluoroethanol (Table 1.2), Kornblum [34] proposed that the transition states of reactions conducted in these solvents are significantly different from those in the other solvents in Table 1.2. This difference in the transition state was attributed to (a) 'selective solvation' of the phenoxide ion, and (b) enhanced solvation of the leaving group of the alkylating agent. The term 'selective solvation' referred to the intensive solvation of the oxygen atom of the phenoxide ion by solvents such as water and phenol able to form strong hydrogen bonds [36]. Owing to this 'selective solvation' the availability of the oxygen atom for reaction is greatly

decreased, and as a result, the C-alkylation pathway can compete successfully. A similar argument was used by Zook and Russo [37] to explain the change in the site of alkylation of the sodium salt of diphenylacetophenone in various solvents.

In the case of sodium-2-naphthoxide, the O- and C- alkylation pathways are much more evenly balanced, as can be seen from Table 1.4 [35]. The formation of relatively large amounts of C-alkylated product (36%) in THF was not explicable by 'selective solvation' and, Kornblum [35] postulated the dielectric constant of the solvent was also important.

Table 1.4

EFFECT OF SOLVENT UPON THE REACTION OF BENZYL BROMIDE WITH SODIUM-2-NAPHTHOXIDE

SOLVENT	T(°C)	YIELD (%) O-CH_2Ph	C-CH_2Ph
Dimethylformamide (DMF)	10-15	97	
Dimethylsulphoxide (DMSO)	20	95	
Tetrahydrofuran (THF)	20	60	36
Methanol	20	57	34
Ethanol	20	52	28
2,2,2-Trifluoroethanol	20	7	85
Water	20	10	84

In aprotic solvents of high dielectric constant (e.g. DMF, DMSO), the departing bromide ion in the linear transition state was thought to be shielded from the sodium ion (Fig 1.1). In THF, an aprotic solvent of

low dielectric constant, no such shielding was possible and thus C-alkylation was favoured at the expense of O-alkylation (Fig 1.2).

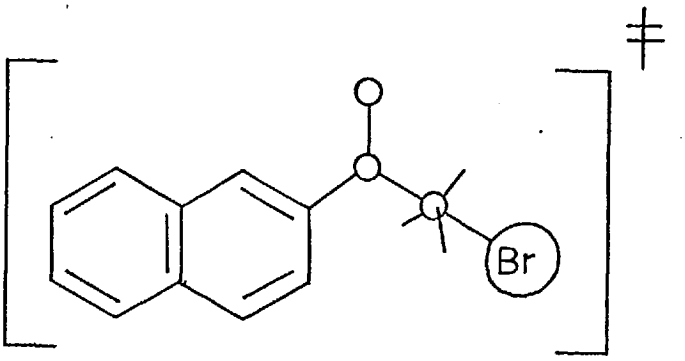


Fig 1.1

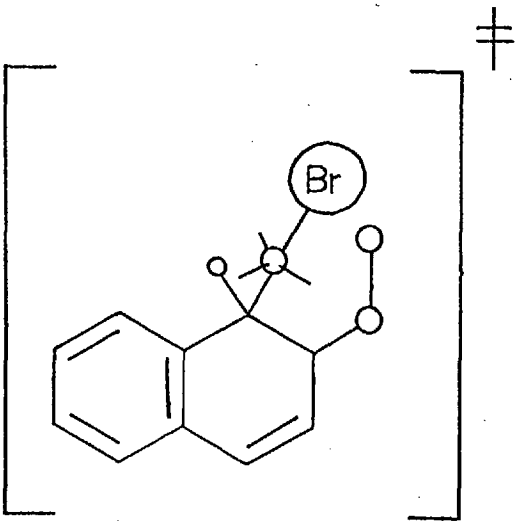


Fig 1.2

Kornblum [35] found further evidence for this argument in the dependence of the product ratio on the cation present. In methanol or ethanol, there was little variation in the product ratio for various cations, but in diethyl ether, THF, benzene or toluene, the percentage of carbon alkylation decreased along the sequence Li^+,Na^+,K^+ and R_4N^+, i.e. a phenoxide ion strongly paired within a small cation reacted preferentially at carbon. Similar cation effects on the alkylation of phenoxides had been observed earlier by Zagorevsky [33].

Neutral phenol is also a potential ambident nucleophile but less work has been carried out to investigate this, probably because phenol is

less reactive than the phenoxide ion. Hart [38,39] has studied the kinetics of alkylation of phenol by various reactive alkyl halides in the absence of solvent, following the evolution of hydrogen chloride manometrically. With t-butyl chloride [39], the only product obtained was the para-t-butylphenol. Triphenylmethyl (trityl) chloride [38] also gave solely the para-alkyl phenol, and, further when performed in dilute solution in an inert solvent, the reaction was found to be catalysed by hydrogen chloride [38]. This observation was interpreted as evidence of a carbonium ion mechanism (Equation (7)), in which formation of the trityl carbonium ion was catalysed both by the hydrogen chloride and by

$$Ph_3C\text{-}Cl \rightleftharpoons Ph_3C^+ + Cl^-$$

$$PhOH + Ph_3C^+ \longrightarrow 4\text{-}Ph_3C\text{-}PhOH \qquad \text{.....(7)}$$

the phenol. The phenol catalysis in the ionisation step was invoked to explain the lack of reactivity of anisole [38,39] under similar reaction conditions. Hart [38] derived a rate expression (Equation (8)) for the autocatalytic reaction containing terms representing the S_N1 and S_N2

$$\text{Rate} = k_2(PhOH)(Ph_3CCl) + k_3(PhOH)(Ph_3CCl)(HCl) \qquad \text{.....(8)}$$

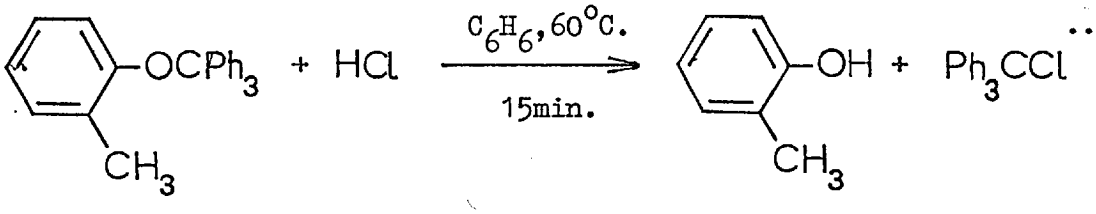
processes. Prior saturation of the phenol with hydrogen chloride gave kinetics which fitted the rate expression given in Equation (9).

$$\text{Rate} = k_3(PhOH)(Ph_3CCl)(HCl) \qquad \text{.....(9)}$$

Although Brönsted acid catalysis of the reaction is not without precedents [40,41], the proof of involvement of phenol in the ionisation

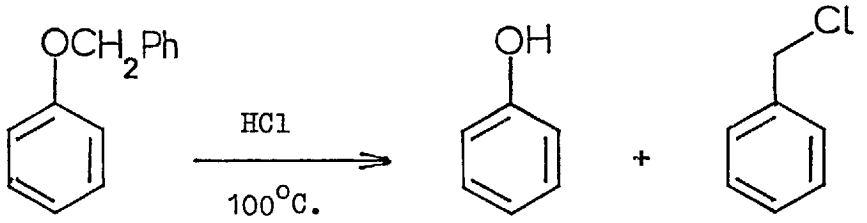
step is rather tenuous since electrophilic substitution of phenol is invariably faster than anisole.

A mechanism involving the initial formation of a t-alkylaryl ether with intramolecular rearrangement by hydrogen chloride was discounted by Hart [38], who showed that under acidic conditions the alkylaryl ether was rapidly cleaved to give phenol and the tert-alkyl halide (Equation (10)).



.....(10)

Confirmation of this is to be found in the earlier work of Short and Stewart [42], who demonstrated that benzylphenyl ether was rapidly cleaved by hydrogen chloride at 100°C, to give phenol and benzyl chloride (Equation (11)).



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The phenol and benzyl chloride subsequently reacted to give ortho- and para-benzylphenol when the reaction was left at 100°C.

It can be seen that the ambident behaviour of phenol and phenoxide is clearly shown in both acylation and alkylation. An examination of the results in terms of Kornblum's theory of ambident reactivity [1] reveals several discrepancies between the observed behaviour and predictions based upon this theory. Kornblum's theory [1], relating substitution at the most electronegative atom to an S_N1-like transition state, fails in the reactions of neutral phenol, where tertiary alkyl

halides [38,39] have been found to give predominantly C-alkylated products. In addition, the basic theory does not fully explain the observed behaviour of phenoxide [34] and thus additional factors, e.g. 'selective solvation', were invoked by Kornblum [34] to explain these anomalous results.

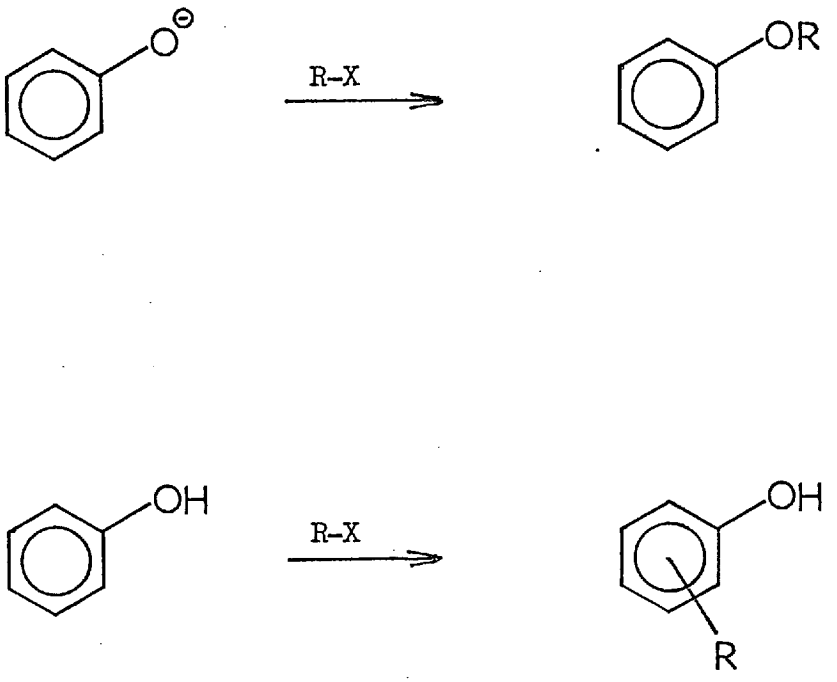
The C-alkylation pathway was particularly favoured for the reaction of phenoxide ion and benzyl chloride in phenol at 43°C, where the C-alkylation pathway accounted for 72% of the products isolated [34]. Kornblum [34] demonstrated that the reaction rate depended upon the phenoxide concentration which was not attributable to a salt effect (Table 1.3). However, examination of the data of Table 1.3 shows clearly that neutral phenol must react at a similar rate to phenoxide ion, and which substrate is reacting is therefore in doubt. Hart [39], in his studies on the uncatalysed alkylation of phenol also used benzyl chloride as the alkylating agent. The reaction half-life was estimated to be ca.27 hours, which is in good agreement with that obtained by Kornblum [34].

From the above results it would appear that the phenol may be competing with phenoxide for the benzyl halide leading to the formation of the mixed products observed. The formation of O- and C-alkylated products in hydroxylic solvents could therefore be explained by the presence of an equilibrium concentration of phenol (Equation (12)),

$$PhO^- + ROH \rightleftharpoons PhOH + RO^- \qquad \text{.....(12)}$$

assuming O-alkylation of phenoxide and C-alkylation of phenol (Scheme 1.5), i.e. the acidity of the medium is important in determining the site of substitution. It is upon this approach to ambident reactivity that the current study is focussed.

Scheme 1.5



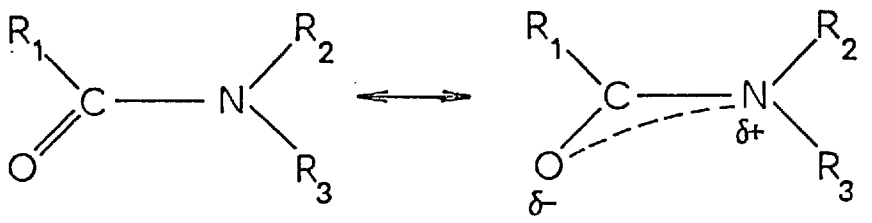
1.3 AMBIDENT NUCLEOPHILIC PROPERTIES OF AMIDES

Amides and amide anions have been described by Gompper [4] as 1,3 ambident systems with the possibility of reaction at either the oxygen or nitrogen atoms. Generally, however, it is found that reaction at the nitrogen atom predominates, mainly because the O-substituted product is either formed reversibly or rearrangement occurs to the N-substituted amide. Examples of mixed O- and N-substituted products are well known, particularly in the alkylation of amides.

In the present discussion, the alkylation and acylation of amides and N-hydroxyamides will be considered in detail. The relevance of the ambident ion theories outlined in Section 1.1 will also be discussed with reference to the observed products in these particular reactions.

1.3.1 STRUCTURE OF THE AMIDE MOIETY

Pauling [43], in 1933, predicted the heats of formation of various molecules from their constituent atoms. Comparison with experimental heats of formation showed that acetamide and formamide were more stable by approximately 83 kJ mole^{-1} than expected from their classical structures 4a. This stabilisation was ascribed to the energy of delocalisation in 4b compared to 4a [44](Equation (13)).



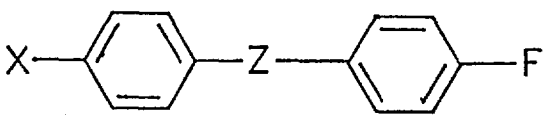
4a 4b .....(13)

The physico-chemical properties of amides are in accord with structure 4b rather than 4a. The C-N bond lengths in amides, determined by X-ray diffraction [45] and by microwave spectroscopy [46], are between those of typical C-N bonds (e.g. in triethylamine) and C=N bonds (e.g. in oximes). Although the relationship between bond length and bond order is complex [47], it may be deduced that the π-bond order of the C-N bond in structure 4b is about 0.4.

Increase in bond length causes a decrease in the stretching force constant of a bond and, therefore, the infra-red carbonyl stretching frequency of amides would be expected to be lower than that for esters, since amides have only a partial C=O bond. Experimentally, the frequency is indeed found to be lower [48]. Ramiah *et al* [49] have calculated the carbonyl frequency for both structures, 4a and 4b, and found good agreement with the observed results for structure 4b.

The availability of the lone pairs on oxygen enables amides to coordinate easily to electron acceptors. Thus amides are extremely efficient extractants for transactinide elements [50]. The adducts with BF_3 and $SbCl_5$ have been studied in solution [51,52], and coordination to lanthanide shift reagents is well-known [53,54]. All these species have been shown to coordinate *via* the oxygen atom of the amide.

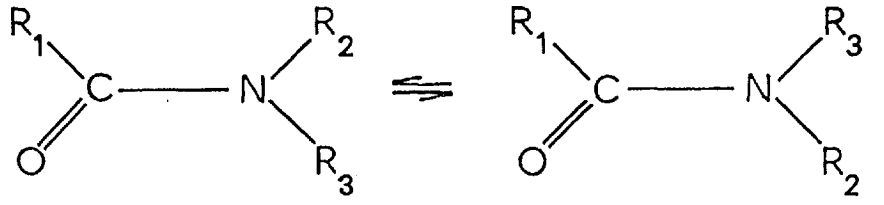
Pews [55] examined the transmission of substituent effects across various linkages in molecules. By measuring the change in the ^{19}F nuclear magnetic resonance chemical shift induced by the substitution of X for hydrogen in compounds of type 5 6 and 7, and plotting these changes against Hammett's σ parameters, it was shown [55] that the peptide linkage



5 Z=-CH=CH-
6 Z=-CONH-
7 Z=-CH_2-CH_2-

transmitted electronic effects with 40% of the efficiency of the formal double bond linkage as in 5. The transmission of the bibenzyl (7) was zero. Thus a π-bond order of 0.4 for the peptide C-N bond is again indicated.

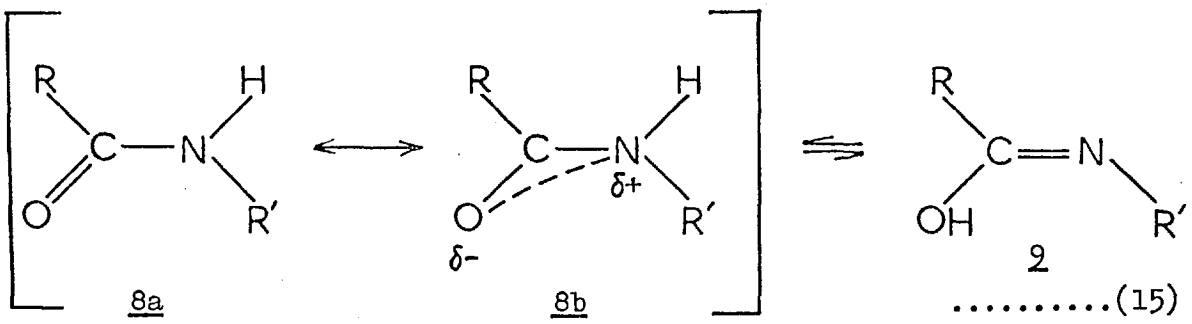
For maximum delocalisation, orbital overlap of the π-system must be maximised and this is accomplished by the amide moiety assuming a planar form with all the skeletal σ-bonds coplanar. Geometric isomerism is therefore expected to occur in amides with different N-substituents and the isolation of the two rotamers 4a and 4c may be possible where $R_2 \neq R_3$ (equation(14)) and the rate of interconversion of 4a to 4c is slow, i.e. the barrier to rotation about the C-N bond is



4a 4c .....(14)

high [56]. In practice it is found that the rotational barrier is of the order of 83.7 kJ/M.[57].

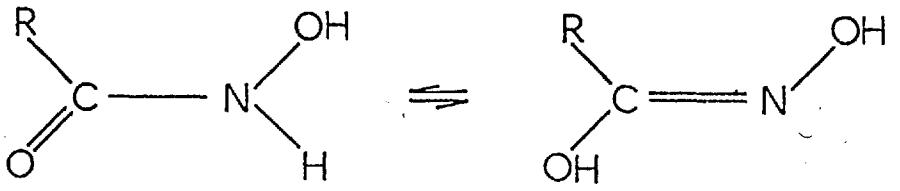
However, both in solution and solid state, amides are best represented by structures 8a and 8b and not the iminol form 9. Many



8a 8b 9 .....(15)

attempts to detect the iminol species have failed [58,59,60].

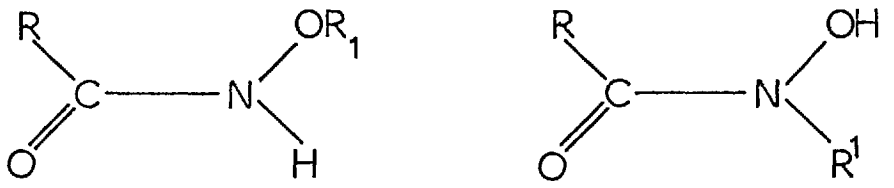
A similar situation concerning the iminol structure seems to exist for N-hydroxyamides (10), where structure 10 represents the compound in the solid state [61]. All spectral evidence indicates that 10 is the



.....(16)

10 11

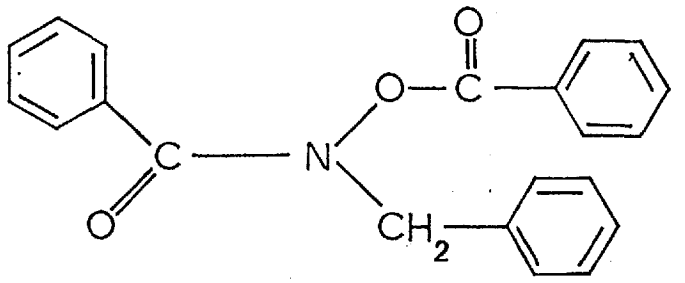
predominant species in solution, and attempts to detect even minute amounts of the tautomeric iminol form (11) in solutions have failed. Ultra-violet studies on N-hydroxyamides and their monoalkyl derivatives (12,13) support structure 10 [62,63], which is further substantiated by the



12 13

carbonyl stretching frequency in their infra-red spectra [64,65,66]. Furthermore, mass [67] and n.m.r. [68,69] spectra of N-hydroxyamides agree with structure 10.

Attempts to detect restricted rotation around the C-N bond of 10 due to partial carbon-nitrogen double bond character have been less successful [70]. However, slightly restricted rotation about the C-N bond is reported for the highly substituted compound 14 [69].



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N.m.r. spectra of N-alkyl-N-alkoxyformamide compounds ($HCON(R)OR^1$) at low temperature have also clearly revealed restricted rotation about the C-N bond [71]. The configuration of the rotamers has been established by means of long-range coupling constants [71].

In conclusion, it can be seen that the physico-chemical data which have been gathered to date suggest an amide structure containing appreciable conjugation and double-bond character in the C-N linkage. The nucleophilic reactivity of amides reflects these results, and it is in the alkylation and acylation of amides that these effects are most clearly observed.

1.3.2 NUCLEOPHILIC REACTIVITY OF AMIDES

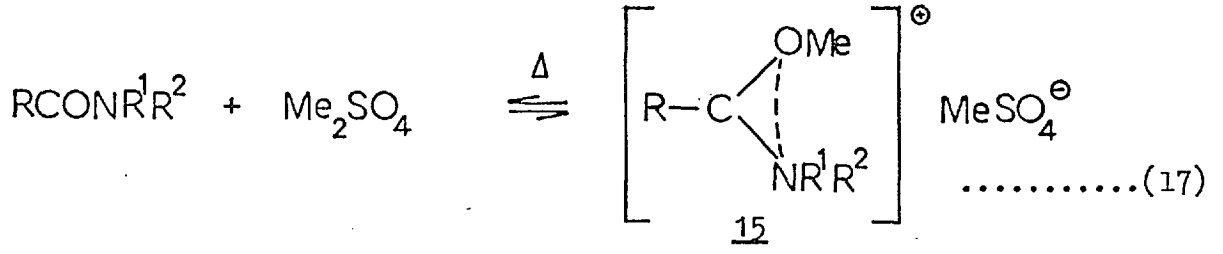
The chemistry of amides is complicated by reactivity residing in all three atoms in the O-C-N chain, but the reactions of amides may be greatly simplified by assuming that their reactions consist mainly of one of two possible processes. As described in Section 1.3.1 nucleophilic attack by the amide moiety may involve either the oxygen or nitrogen atoms attacking the electrophilic centre. The second process, of less relevance to the present discussion, involves a normal nucleophilic addition to the carbonyl entity.

The possibility of electrophilic reagents reacting at either amide oxygen or nitrogen confers ambident nucleophilic character to the amide

moiety. However, the relative reactivity of the oxygen and nitrogen atoms is difficult to assess. This is demonstrated by the fact that the site of protonation of amides is still uncertain [72]. Recently however Challis and Challis [73] have suggested that although amide anions may react as 1,3 ambident nucleophiles, the reactions of the neutral amide molecule may be interpreted in terms of kinetically- and thermodynamically-controlled reactions. They suggested [73] that in reactions of the neutral molecule, substitution at oxygen is the kinetically favourable pathway with subsequent rearrangement providing the thermodynamically stable N-substituted amide.

1.3.3 ALKYLATION OF AMIDES

In the alkylation of neutral amides it is found that both O- and N-alkylation may occur. With highly reactive alkylating agents, such as alkyl sulphates [74,75] and oxonium salts [76,77], O-alkylation predominates. Dimethyl sulphate [74,75], for example, reacts quantitatively with an equimolar proportion of either primary, secondary or tertiary amide, to give the corresponding O-alkyl imidonium salt (15)(Equation (17)). Reaction temperatures of 20-60°C are required.



Generally, higher temperatures (≈150-200°C) [78,79] or heavy metal catalysts such as silver salts [80] are necessary to induce reaction with alkyl halides, and under these conditions the ambident nucleophilic

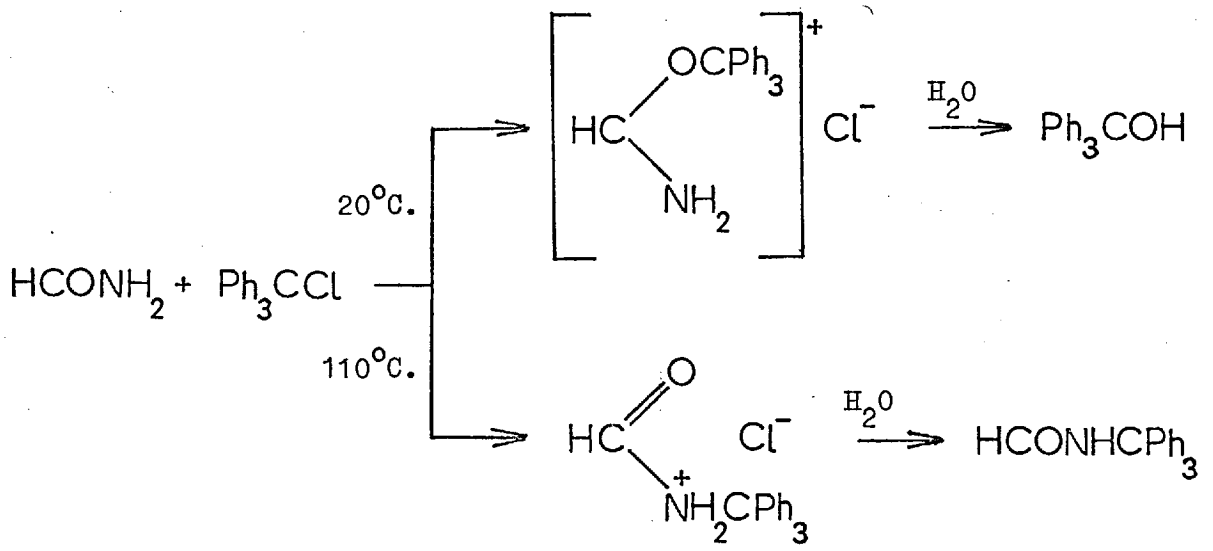
behaviour of the amide moiety becomes important. Thus either O- or N-substituted products, or a mixture of both, are commonly formed. The alkylation of amides under neutral conditions by alkyl halides has been examined by Gompper and Christmann [81] at temperatures above 110°C and the results were discussed in terms of Kornblum's general hypothesis [1], relating the tendency towards O- and N-substitution to the transition state structure. However, it was experimentally found [81] that N-substituted amides were favoured with those alkyl halides forming relatively stable carbonium ions, whereas less polarisable reagents gave rise to O-substituted derivatives. The overall reactivity of these alkyl halides towards formamide was also studied [81] and found to parallel the carbonium ion stability of the reagents. For example, the relative rates of alkylation of formamide [81] by the different butyl bromides is t -BuBr> s-BuBr> n -BuBr. This suggests that the alkylation of amides by alkyl halides has a good deal of S_N1 character. On the basis of Kornblum's predictions [1], this should lead to substitution predominantly at oxygen, which is contrary to the experimental findings usually observed.

In general, O-alkylated products seem to be favoured by lower reaction temperatures, whereas with weaker alkylating agents (e.g alkyl chlorides and bromides), which require high reaction temperatures, there is a marked tendency towards mixed O- and N-alkylated products. Other evidence suggests that the tendency towards O- and N-alkylation is governed by the temperature required for reaction. This comes from studies of both the highly reactive trityl chloride [81] and the effect of silver ion catalysis [80]. Trityl chloride is sufficiently powerful to alkylate formamide at temperatures as low as 20°C. Under these conditions the conductivity of the mixture composed of equimolar concentrations of the reactants was found to reach a maximum value almost instantaneously, and hydrolysis of this solution results in the isolation of triphenylcarbinol but not

N-triphenylmethylformamide (Scheme 1.6) [81]. When the same reaction is carried out at 110°C, however, the latter is the sole hydrolysis product [82]. Alkylation by methyl and ethyl iodide can also be effected under mild

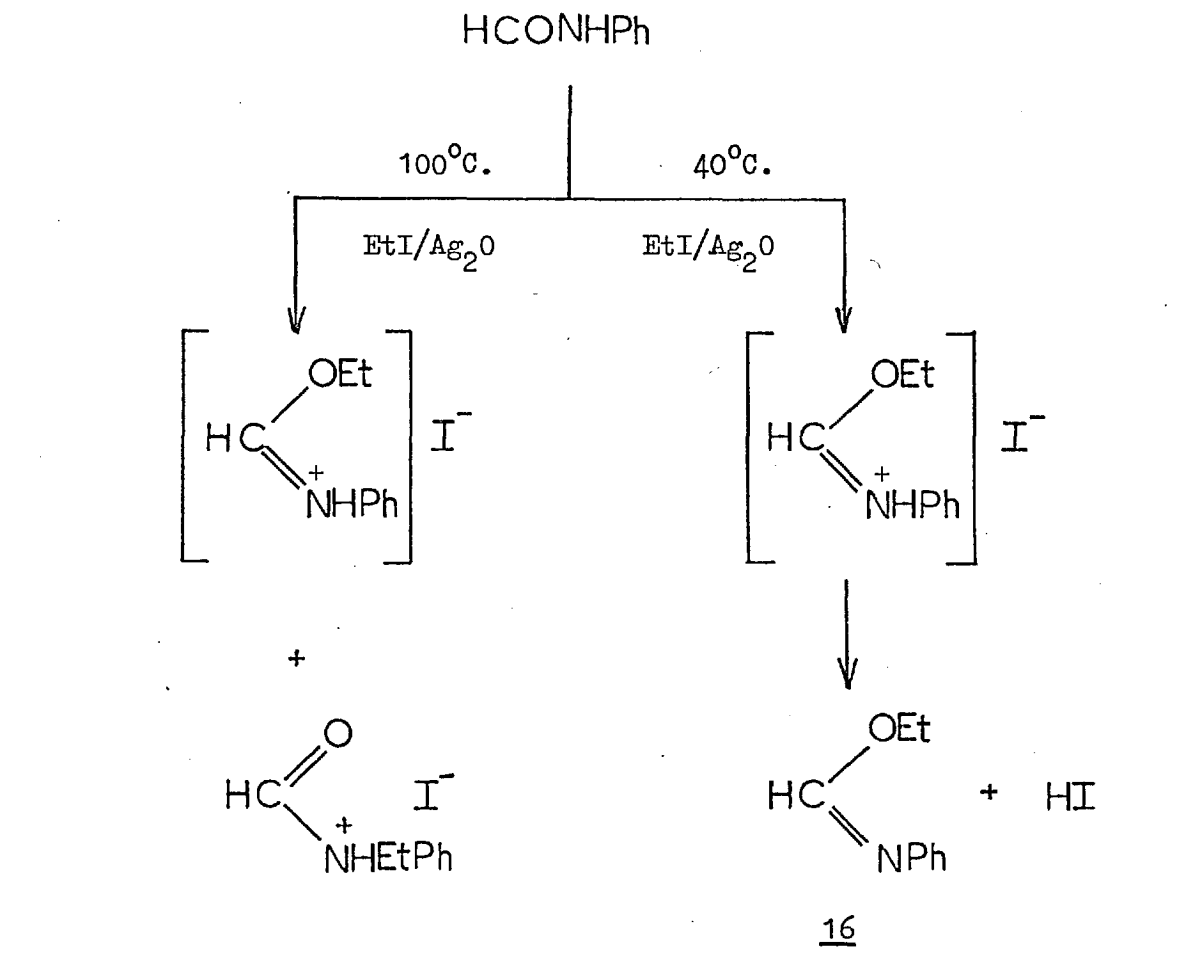
Scheme 1.6

REACTION OF FORMAMIDE WITH TRITYL CHLORIDE



conditions in the presence of silveroxide catalysts [80]. The silver ion promotes polarisation of the alkyl halide, thereby increasing its reactivity. In this way the same temperature-dependent substitution pattern emerges as that for trityl chloride. Thus the reaction of N-phenylformamide with ethyl iodide in the presence of silver oxide at 40°C produces only the O-ethylimidate (16), whereas mixed O- and N-alkylated products are obtained at 100°C [80](Scheme 1.7). Both these results point to a mechanism in which at least some of the N-alkylated product arises from a thermal rearrangement of the O-alkyl imidate salt. It is known that O-alkyl and O-aryl imidates rearrange readily on heating to give the corresponding N-alkyl- or N-arylamide. The rearrangement of O-aryl imidates (the Chapman rearrangement) is intramolecular [83,84], consistent with the formation of a tetrahedral intermediate (17) stabilised by electron delocalisation throughout the aromatic nucleus (Equation (18)).

Scheme 1.7



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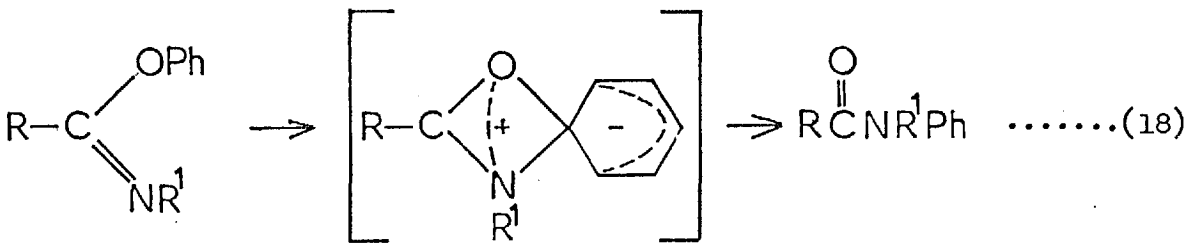
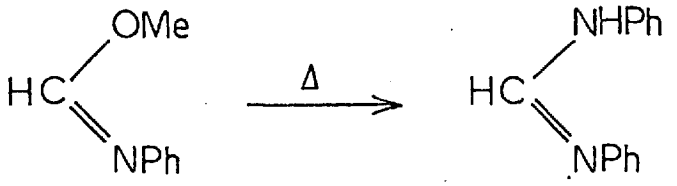


18 17

With O-alkyl imidates, however, the rearrangement is at least partly intermolecular as cross-products are obtained in experiments with mixed O-alkyl compounds [85]. The catalysis of these reactions by benzoyl peroxide, has been interpreted as evidence for a free-radical mechanism [85]. The rearrangement of O-alkyl formimidates is further

complicated by the formation of formamidine [85] (Equation (19)).



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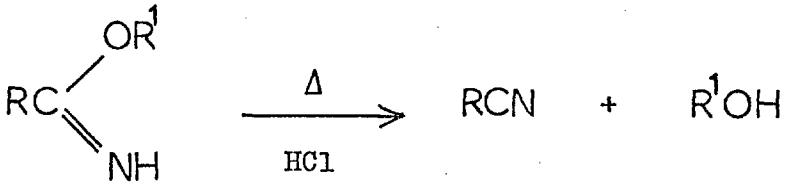
Another complication with primary imidates is the formation of nitriles when both O-alkyl and O-aryl imidates are thermally rearranged [80](Equation (20)).



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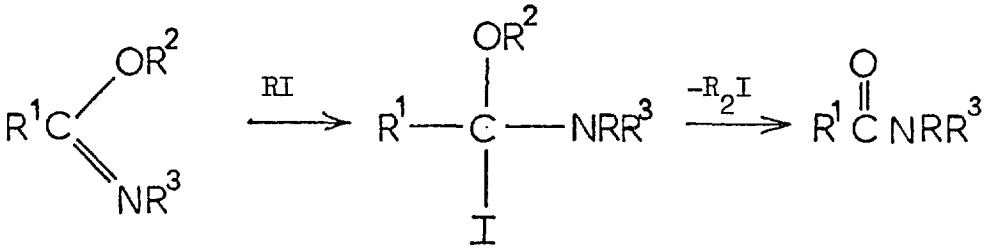
The rather forcing conditions required for the rearrangement of O-alkyl imidates may be effectively overcome by catalysis of the reaction with a variety of electrophilic species. Alkyl halides have been by far the most frequently studied catalysts. Lander [86] found that addition of alkyl halides to O-alkyl imidates made rearrangement possible at 160°C or less, compared to 300°C or greater required for the thermal rearrangement. Lander [86] concluded that the mechanism of this rearrangement must involve addition followed by elimination (Equation (21)).



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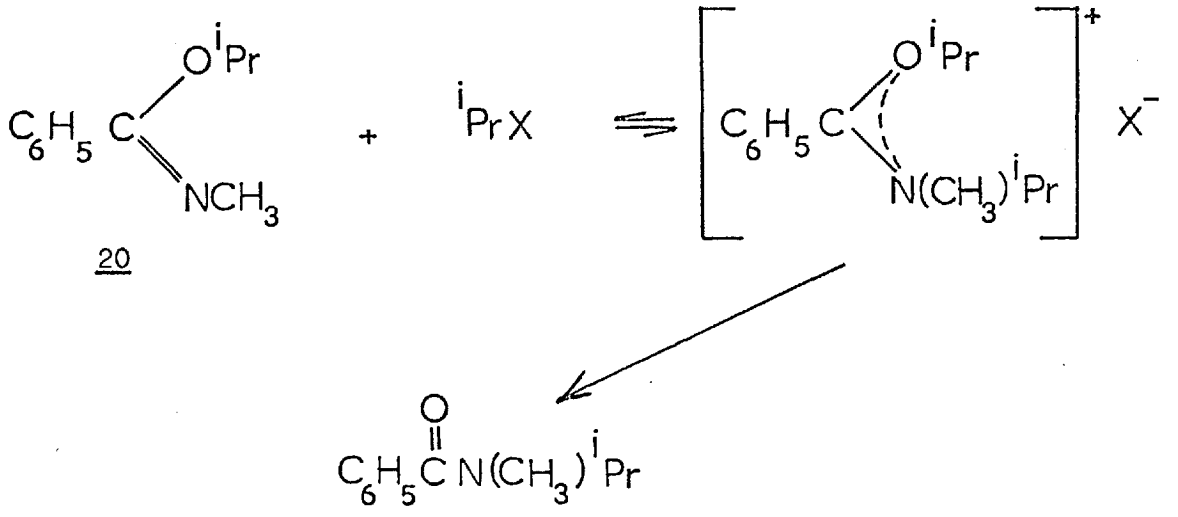
Arbuzov and Shishkin [87,88], agreed in principle with the Lander mechanism. From the results of their studies they concluded that the alkyl halide catalysed rearrangement of alkyl imidates proceeds in two steps, of which the first involves the addition of alkyl halide to form an ionic adduct (a halide salt rather than 19) which undergoes cleavage to give the final products.

A more quantitative and recent study was carried out by Challis and Frenkel [89], on the catalysed rearrangement of isopropyl N-methylbenzimidate (20) at 138°C in nitrobenzene. The data for this reaction catalysed by isopropyl iodide show that overall second-order kinetics are observed, first-order in both substrate and catalyst, implying an S_N2 mechanism. Catalysis by the various isopropyl halides decreased sharply in the order i-PrI > i-PrBr > i-PrCl for the rearrangement of 20, which is consistent with an S_N2 mechanism with either the first or second step being rate determining (Scheme 1.8).

Scheme 1.8



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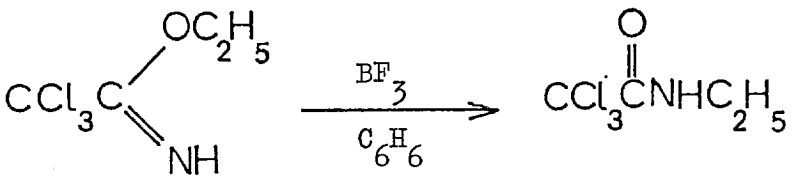
The further observation [89] that catalysis decreased with increased branching of the alkyl halide (CH_3I > i-PrI), regardless of the O-alkyl substituent in other N-methyl benzimidates, established the first step as being the slow step in these rearrangements (Scheme 1.8).

Catalysis by Lewis and Brönsted acids has also been observed. Cramer and Hennrich [90] showed that imidate 21 could be rearranged

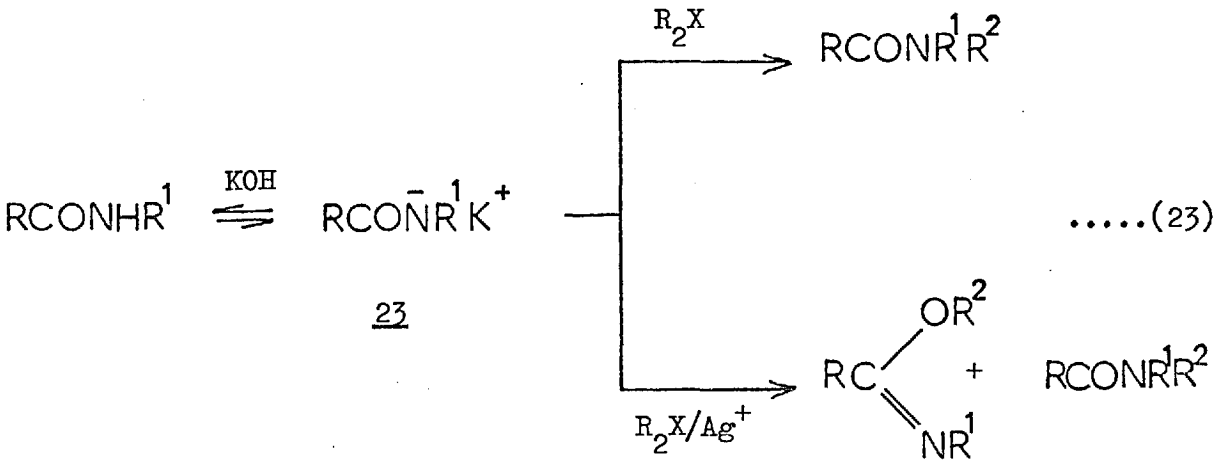


.....(22)

21 22

to amide 22 in 96% yield in refluxing benzene with catalytic amounts of BF_3 added (Equation (22)). Challis and Frenkel [89] also found BF_3 to be very effective in catalysing the rearrangement of isopropyl N-methylbenzimidate (20). The work of Roberts and Vogt [91] showed that sulphuric acid can serve as a catalyst but the concentration is critical; since too low a concentration limits the rate of rearrangement and excess results in the formation of charred products. The 'catalytic quantities' of sulphuric acid used by Challis and Frenkel [89] with 20 were apparently too little since they found no rearrangement at 138°C in nitrobenzene. The concentration of hydrogen bromide added as a catalyst is also critical. When HBr was added to 20 in 0.22 molar equivalent, the catalytic effect was the same as that found for isopropyl bromide (which is presumably formed from the addition of HBr)[89]. However, when HBr was added in equimolar quantities with 20, no rearrangement was observed at 138°C in nitrobenzene [89]. Lander [86] reported iodine to be an effective catalyst for alkyl imidate rearrangements and this was confirmed by Challis and Frenkel [89]. Their results showed iodine to be much more effective than isopropyl iodide in catalysing the rearrangement of 20 [89].

Greater control over the site of alkylation can be exercised under alkaline conditions, and these reactions are more useful from a synthetic standpoint. Primary and secondary amides in the presence of a strong base normally react at the nitrogen atom, with only small amounts of other products being formed [92]. The selectivity observed in this reaction can be interpreted in terms of formation of a carboxamide anion, 23 which is alkylated directly on the nitrogen atom (Equation (23)).



.....(23)

O-alkylated products are obtained, however, in the presence of silver salts [5,6], and in this respect the reactions are similar to those of a neutral amide molecule.

Hopkins et al [6] have studied the effect of the alkylating agent and the cation on the alkylation of salts of 2-pyridone in dimethylformamide.

The results are illustrated in Table 1.5.

The effect of solvent upon the silver salt reaction was also investigated by Hopkins [6] and the reported reaction results are given in Table 1.6.

It can be seen that only on those solvents, in which the silver salt reaction is truly heterogeneous does O-alkylation predominate. Hopkins [6] proposed that the major factor determining the

site of substitution using silver salts is the homogeneity or heterogeneity of the reaction.

Table 1.5

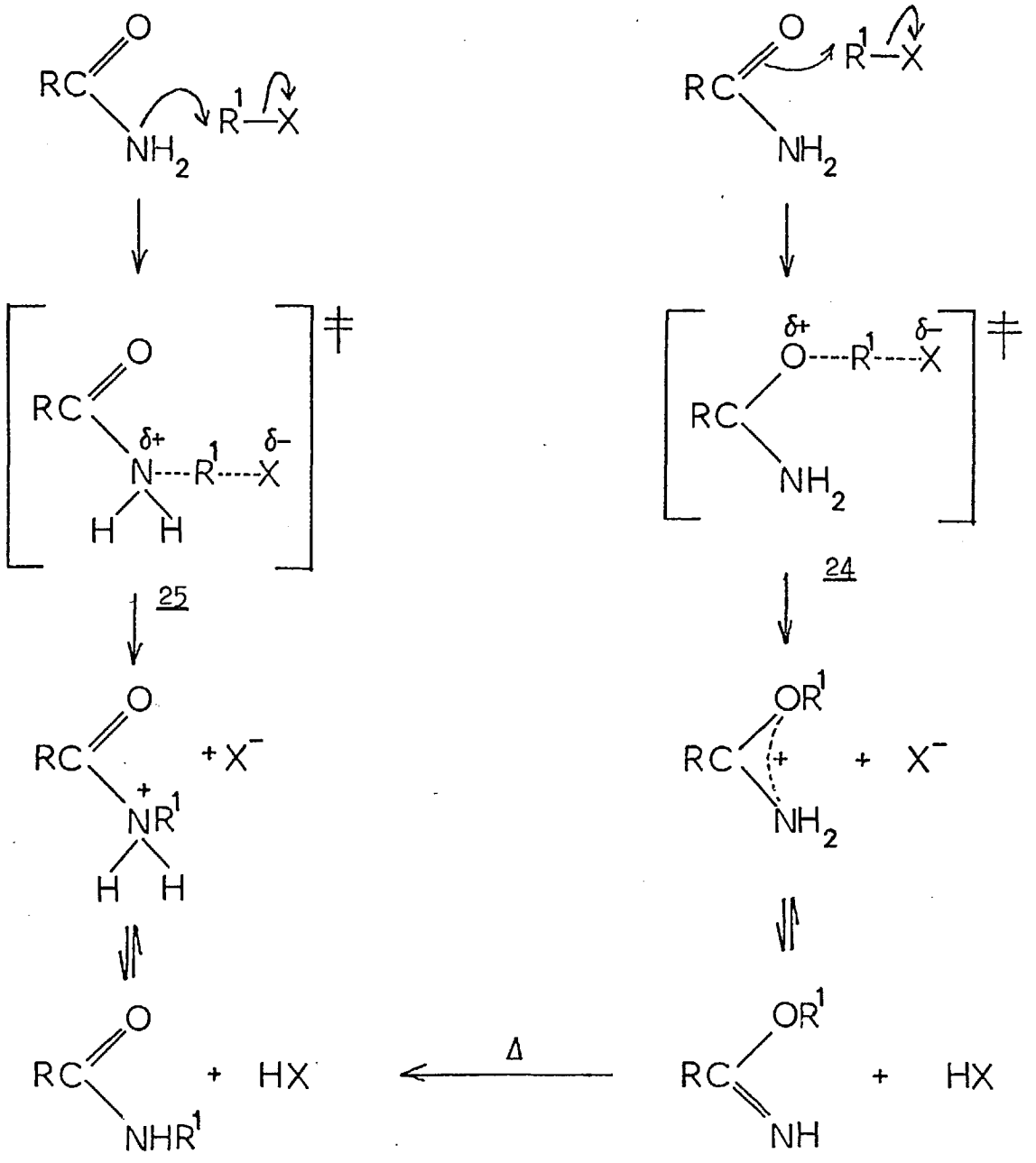
R-X	(Salt)	N-R(%)	O-R(%)
MeI	Na	95	5
MeI	K	92	8
MeI	Ag	74	12
i-PrBr	Na	29	68
i-PrBr	K	27	71
i-PrBr	Ag	No alkylation	
$PhCH_2Cl$	Na	94	6
$PhCH_2Br$	Na	97	3
$PhCH_2Br$	Ag	54	46

Table 1.6

R-X	Solvent	N-R (%)	O-R (%)
MeI	DMF	74	12
MeI	Ether	37	42
MeI	Benzene	3	97
MeI	Hexane	3	97
$PhCH_2Br$	DMF	54	46
$PhCH_2Br$	Benzene		100
$PhCH_2Br$	Pentane		100

An overall appraisal of the experimental findings for amide alkylation under neutral conditions suggests that O-alkylation arises from reactions carried out under kinetic control, but these may transform to the thermodynamically stable N-alkylamides at higher temperatures. Additional evidence [73] for this interpretation comes from examination of the transition states for O- and N-alkylation (Scheme 1.9). Delocalisation of the nitrogen lone pair electrons

Scheme 1.9



should dissipate charge and lower the energy of the transition state (24) for O-substitution. No comparable effect is possible in the corresponding transition state for direct N-substitution (25); the induced positive charge is therefore localised on the nitrogen atom and the transition-state energy is accordingly higher.

It can be seen that the interpretation suggested by Challis and Challis [73] implies that neutral amides are not ambident nucleophiles. As noted earlier, Gompper and Christmann [81] have attempted to account for the tendency towards O- and N- alkylation by various reagents in terms of Kornblum's theory of ambident reactivity [1]. The result is unsatisfactory, however, for it requires that the most S_N1-like transition state will be associated with substitution at the nitrogen atom, which is the atom of lower electronegativity. This is, of course, contrary to Kornblum's predictions.

Amide anions are found to react predominantly on the nitrogen atom to give N-alkylamides. This preference for N-alkylation, however, is drastically altered by the addition of silver salts [80] to the reaction mixture, and appreciable amounts of O-alkylated products are then obtained. The reason for preferential O-substitution in the presence of silver salts has not been investigated thoroughly and no entirely satisfactory explanation is available. Since the reactions are performed at ambient temperatures, it seems unlikely that O- to N-rearrangements, encountered in neutral solutions, are important. Kornblum [1] has suggested that in common with the alkylation of other ambident anions, silver salts may enhance the unimolecular character of the reaction with alkyl halides, thereby promoting alkylation at the more electronegative atom. The studies by Hopkins et al [6] suggest that the heterogeneous nature of the silver salt reactions appears to favour O-alkylation, and

the increased importance of this pathway in non-polar solvents may arise from the lower solubility of the silver amide salt in such media, rather than from mechanistic reasons. The observation that O-substitution occurs in the homogeneous alkylation of sodium 2-pyridone [6] would suggest however that there is some 1,3 ambident character in the amide anion.

1.3.4 ACYLATION OF AMIDES

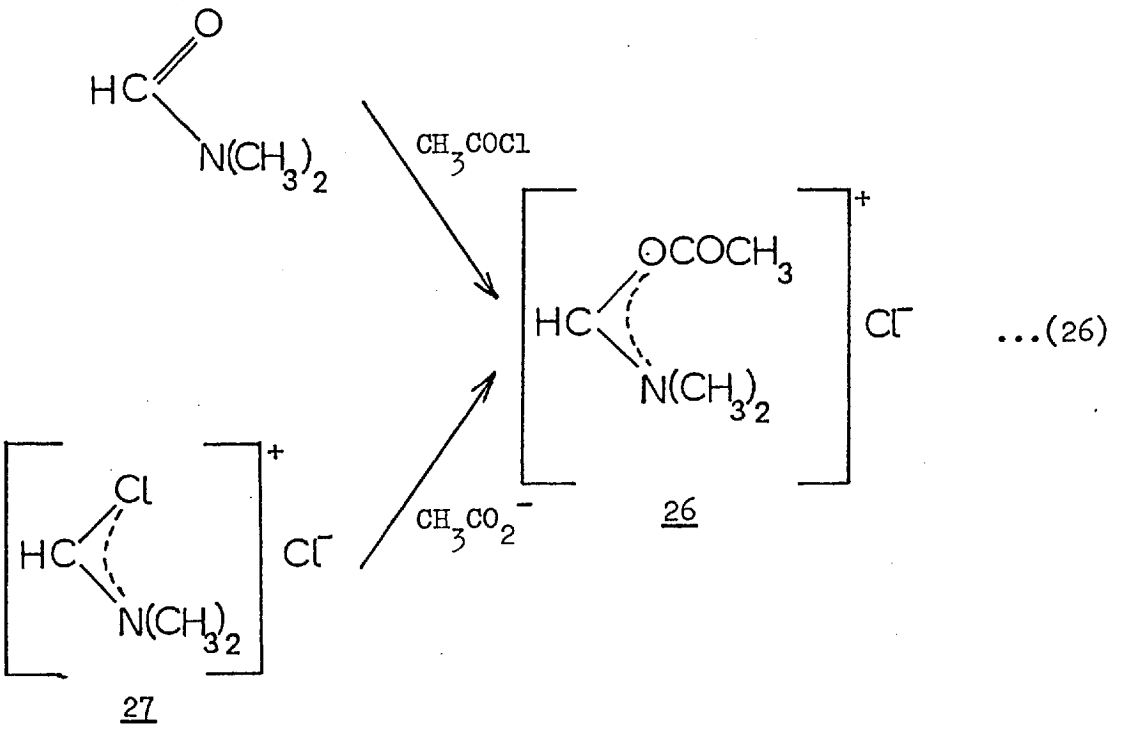
Primary and secondary amides usually undergo N-substitution with reagents such as acyl chlorides and anhydrides. With primary amides the substitution reaction is in competition with the dehydration reaction, which leads to the formation of a nitrile [93] (Equation (24)). Tertiary amides form only salt-like addition complexes [94] (Equation (25)), which

$$RCONH_2 + R_2COX \longrightarrow RC{\equiv}N + R_2COOH \qquad \ldots\ldots\ldots(24)$$

can be isolated at low temperatures [94]. It has been shown that the

$$RCONR^1R^2 + R^3COX \rightleftharpoons \left[RC\begin{matrix} OCOR^3 \\ \\ NR^1R^2 \end{matrix} \right]^+ X^- \qquad \ldots(25)$$

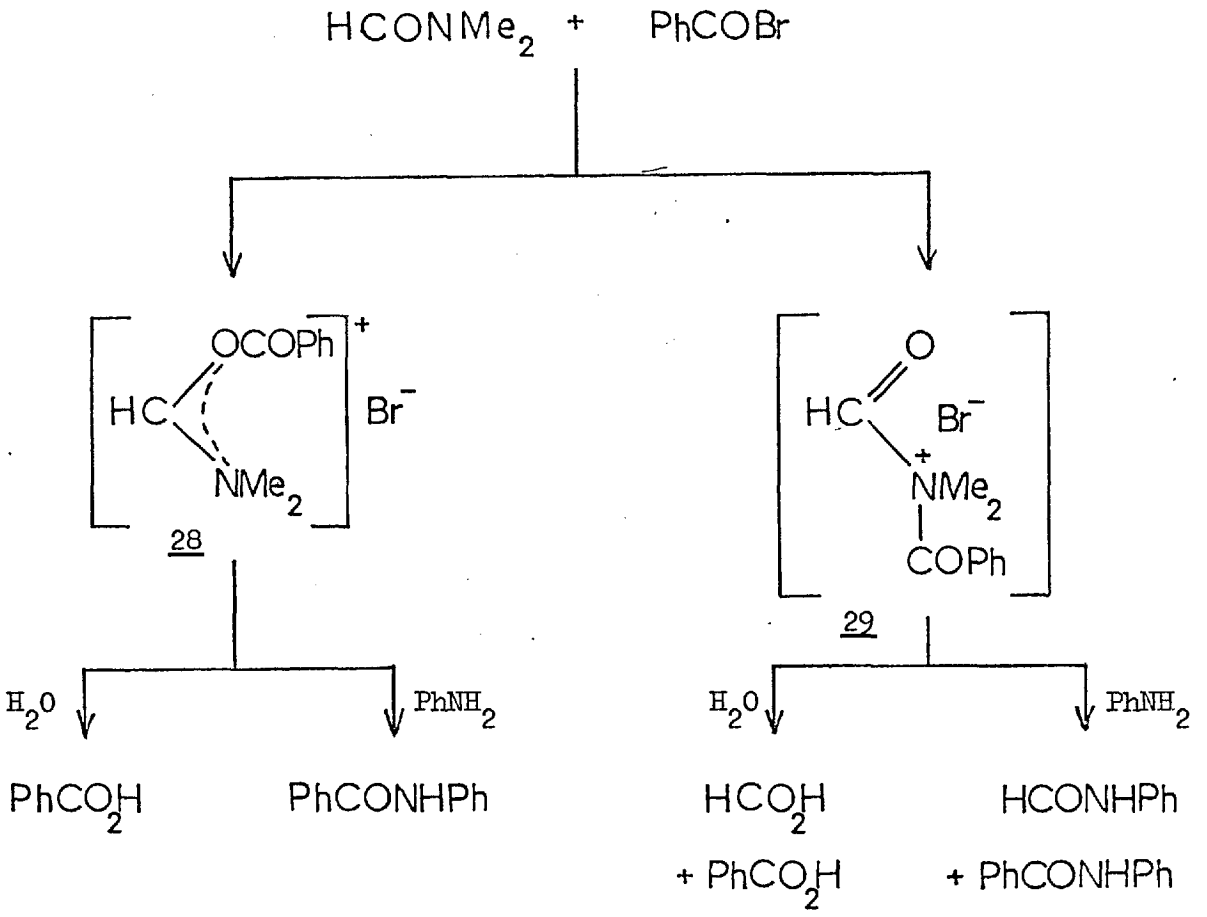
complexes (26) obtained by condensation of the imidoyl chloride (27) with acetate ion, and of dimethylformamide with acetyl chloride, are identical (Equation (26))[95]. The formation of a common intermediate implies that 26 must be an O-acyl-complex.



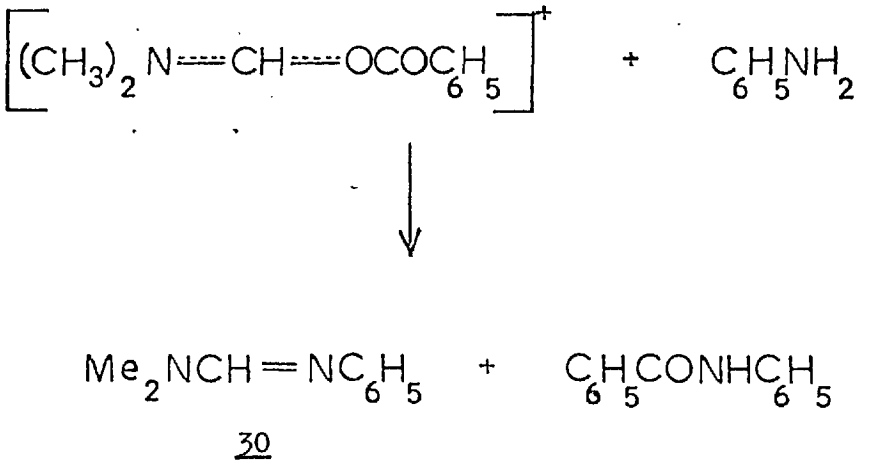
Additional evidence for an O-acylated intermediate comes from the decomposition of the ionic complex, derived from dimethylformamide and benzoyl bromide, with water which results in the production of benzoic but not formic acid [94]. Similarly, decomposition with aniline results in the formation of benzanilide but not formanilide [94]. These results also are only consistent with an O-acyl structure for the intermediate (28) and not the N-acyl structure (29)(Scheme 1.10).

Bredereck [96] has pointed out, however, that these reactions should be interpreted as proceeding *via* the free acid bromide, since, under the above conditions, dissociation of the complex into its components would be expected. Using aniline as a nucleophile, and the benzoyl bromide derived complex, Bredereck [96] showed that both acyl and formyl C-attack occurred (Scheme 1.11). The relative amount of N,N-dimethyl-N-phenylformamidine (30), was found to increase with increasing dimethylformamide concentration. It can be seen nevertheless that the formation of the amidine product is consistent with an O-acyl type of intermediate.

Scheme 1.10



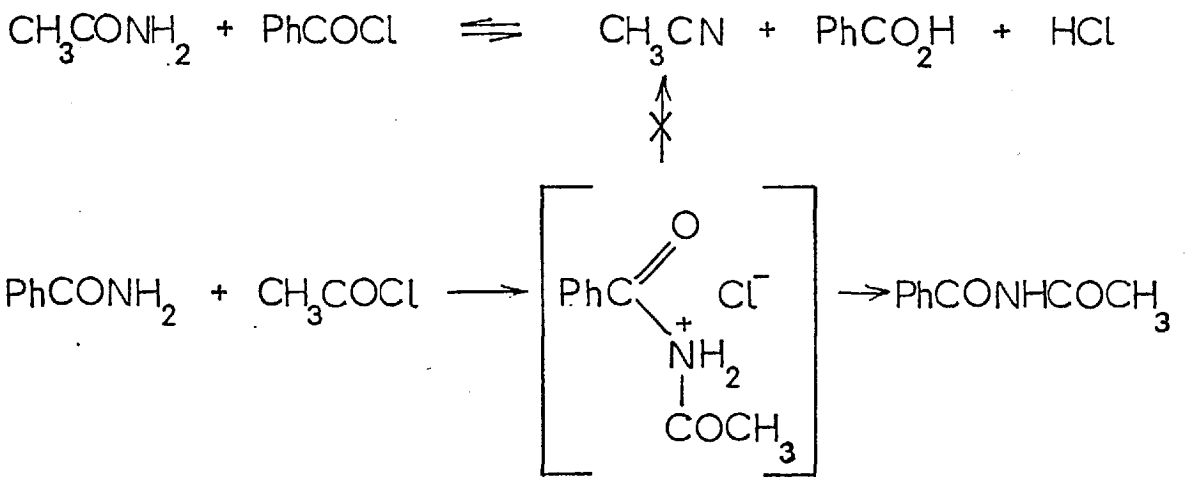
Scheme 1.11



A recent n.m.r. study by Martin and Naulet [97], has confirmed Hall's [94] earlier findings, and an O-acyl structure was postulated for the complexes obtained with dimethylformamide and acyl chlorides and bromides. A similar O-acyl intermediate was proposed by several workers [98,99] for the complex between dimethylformamide and chloroformates.

Other indirect evidence pointing to the intermediacy of an O-acyl structure is obtained from the acylation reaction of primary amides. As stated earlier, these reactions are complicated by the formation of three products, namely di-and tri-acylamines, and the nitrile. The failure to observe any acetonitrile in the reaction of acetyl chloride and benzamide [100], whereas acetamide and benzoyl chloride yield only nitrile [100], rules out the N-acylamide as a possible intermediate in dehydration (Scheme 1.12). This result is consistent, however, with an O-acylisoimide intermediate.

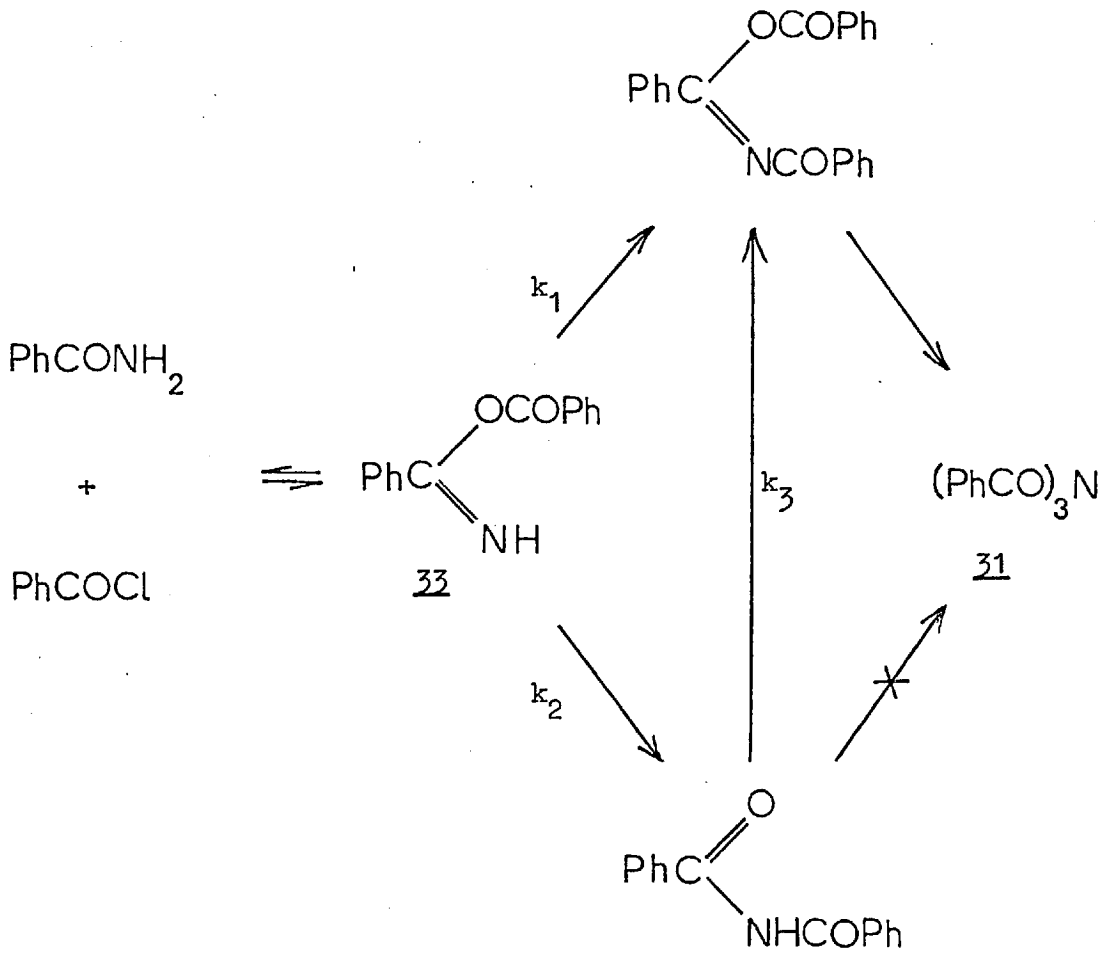
Scheme 1.12



The intermediacy of an O-acyl structure is also indicated by the work of Thompson [101], who studied the benzoylation of benzamides.

Under identical reaction conditions, it was found that tribenzamide (31) was formed more slowly from dibenzamide (32) than from benzamide itself. These results tend to eliminate 32 as an intermediate, but favour a mechanism involving a rapid second substitution of the O-acylisoimide (33), followed by a 1,3 O-N aroyl migration. If the mechanism involving 33 as an intermediate is valid, then $k_1 > k_2 > k_3$ (Scheme 1.13).

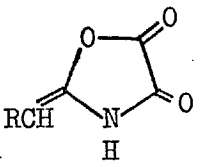
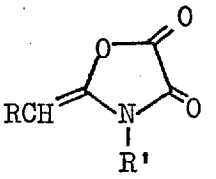
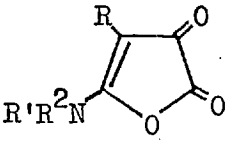
Scheme 1.13



With oxalyl chloride, the most powerful evidence for the formation of O-acylisoimides is obtained. The reaction products of the oxalyl chloride acylation of an amide depend to a large extent upon

the amide structure, and clearly reflect the bifunctional character of oxalyl chloride [102, 103, 104] (Table 1.7).

Table 1.7

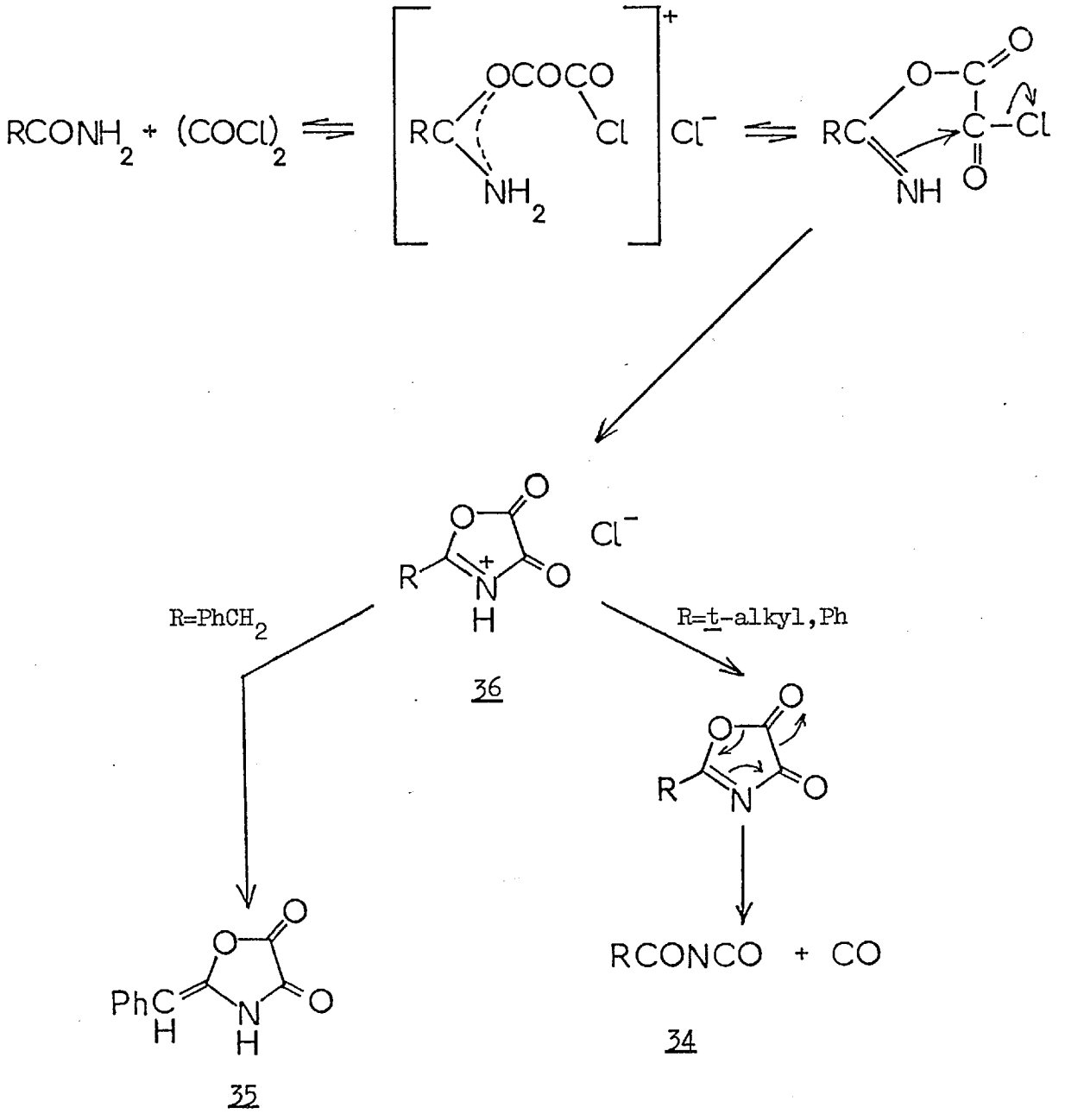
Amide Type	Products
$RCONH_2$	RCONCO + CO
RCH_2CONH_2	
RCONHR'	RCONR'COCOCl
RCH_2CONHR'	 or RCONR'COCOCl
$RCH_2CONR'R^{2*}$	

(* Two equivalents of oxalyl chloride required)

With primary and secondary amides it is found that the nature of the R group is important. When R has no α-hydrogen atoms

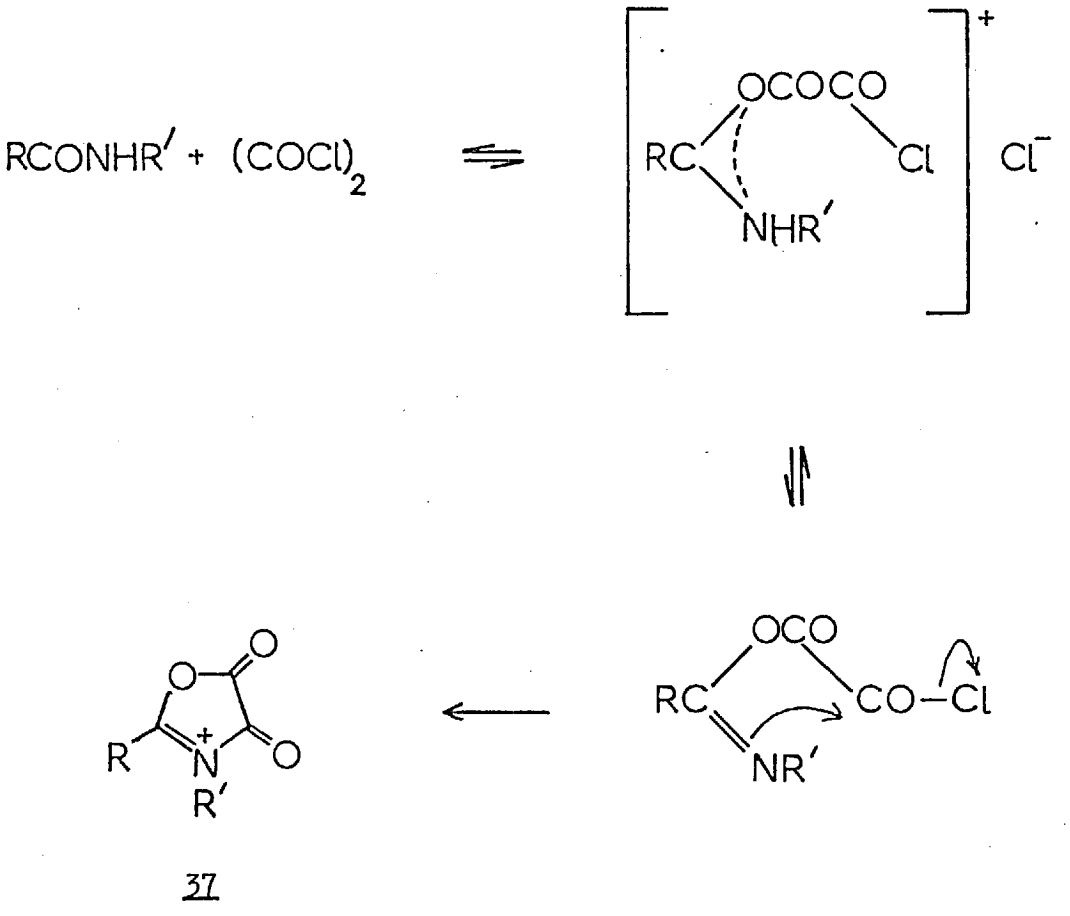
(e.g. Ph,t-Bu etc), the O-acyl intermediate decomposes on heating to give an isocyanate (34)[104,105]. When the R group is benzyl, for example, cyclisation and elimination to an enamine (35) occurs [103]. Speziale [103] postulated the reaction mechanism as shown below (Scheme 1.14) to explain the products. After an initial O-attack, leading to the O-oxaloylisoimide which then cyclises to give an intermediate (36). The intermediate then either eliminates ($R=PhCH_2$) or decomposes to the isocyanate (R=Ph etc).

Scheme 1.14



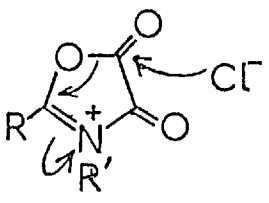
Secondary amides (RCONHR'R=Ph) produce an N-acylamide derivative [103] via a cyclic intermediate 37 analogous to that postulated for primary amides (Scheme 1.15)

Scheme 1.15



37

The cyclic intermediate (37) in this case cannot achieve stability by proton loss and thus ring opening occurs instead, presumed to be initiated by nucleophilic attack of chloride ion on the acyl carbonyl atom (Equation (26)).



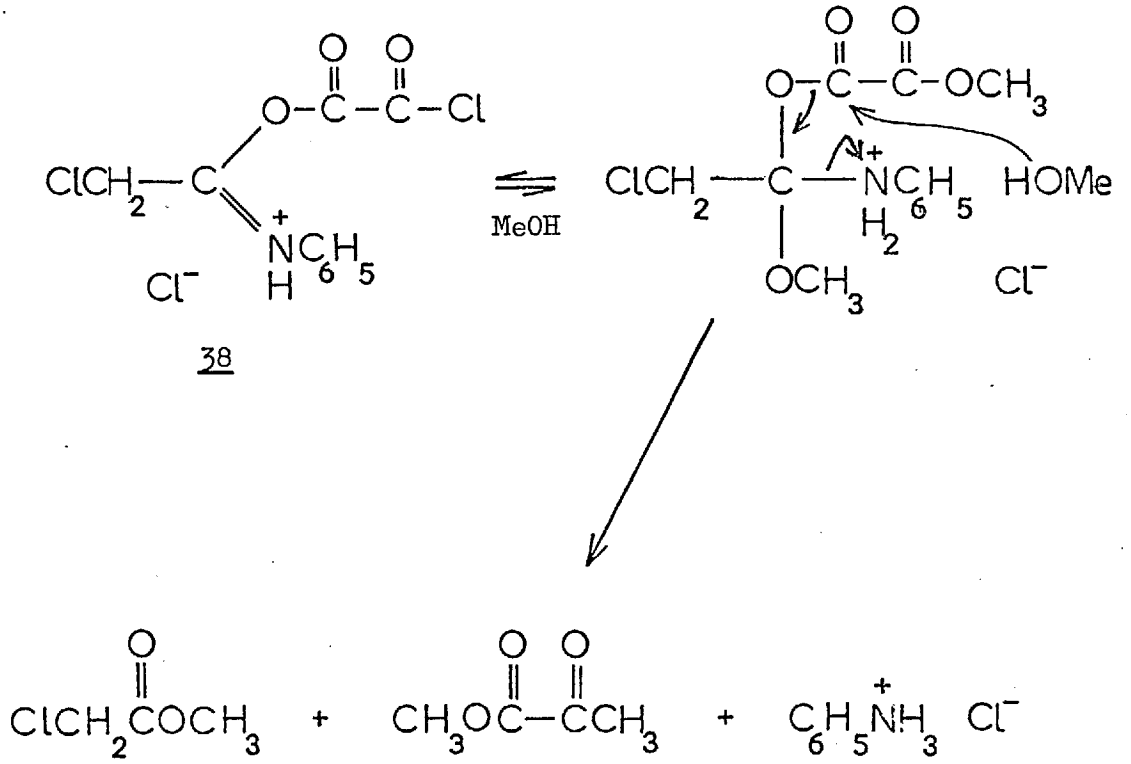
$$\longrightarrow \quad RCONR'COCOCl \qquad \ldots.(26)$$

37

.....(26)

Direct evidence for a mechanism involving initial O-acylation, comes from trapping experiments [103] using methanol. During the early stages (< 20%) of the reaction of ∝-chloroacetanilide with oxalyl chloride, the methanol-trapped products were a mixture of methyl chloroacetate, methyl oxalate and aniline hydrochloride all of which can be explained by interaction of 38 with methanol (Scheme 1.16)

Scheme 1.16

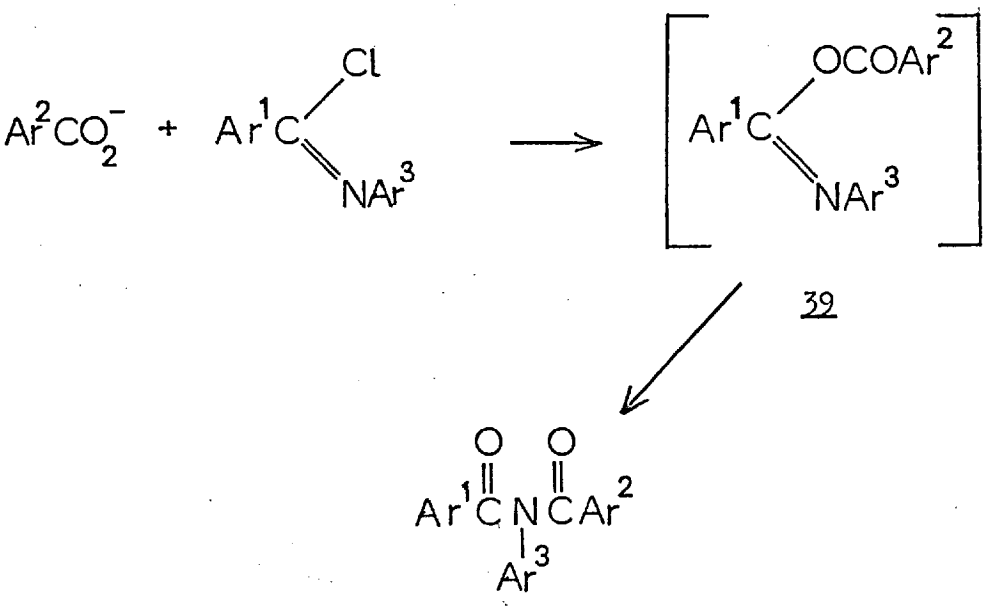


38

Addition of methanol after 100% reaction, however, produced only the ester, methyl-N-chloroacetyloxanilate ($ClCH_2CON(Ph)COCO_2Me$), the expected solvolysis product of the N-acylamide derivative, $ClCH_2CON(Ph)COCOCl$. These findings clearly demonstrate that N-substitution by oxalyl chloride did not occur in the early part of the reaction.

From all the evidence available, whether indirect or otherwise, an amide acylation mechanism involving an O-acylisoimide intermediate is very plausible and explains satisfactorily the observed products for all three classes (primary, secondary and tertiary) of amide in their acylation reactions.

The final proof, however, lies in the isolation of the proposed O-acyl isoimide intermediate. Many workers have tried, but failed in their attempts to prepare the O-acyl compound [106,107]. Indeed, it was the failure to obtain the expected O-acyl product from the treatment of imidoyl halides with benzoate salts (Equation (27)) that led Mumm to discover the O-aryl imidate rearrangement [108].



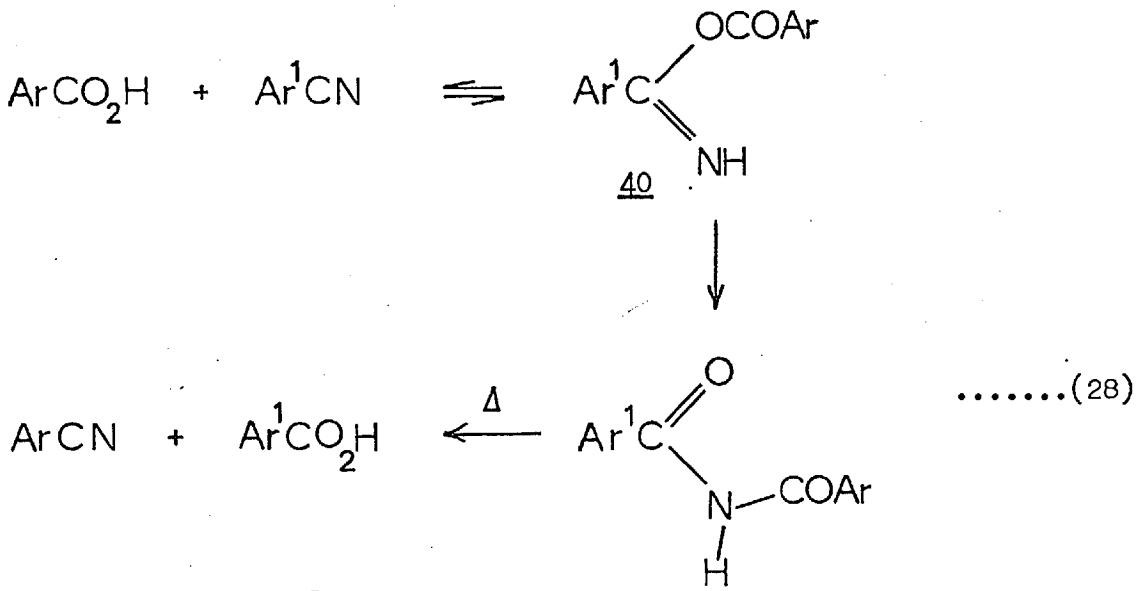
39

.....(27)

Since the initial report of the isolation of an O-acyl intermediate in 1893 [107], there have been numerous proposals of these compounds existing as labile intermediates in a variety of reactions, other than amide acylation.

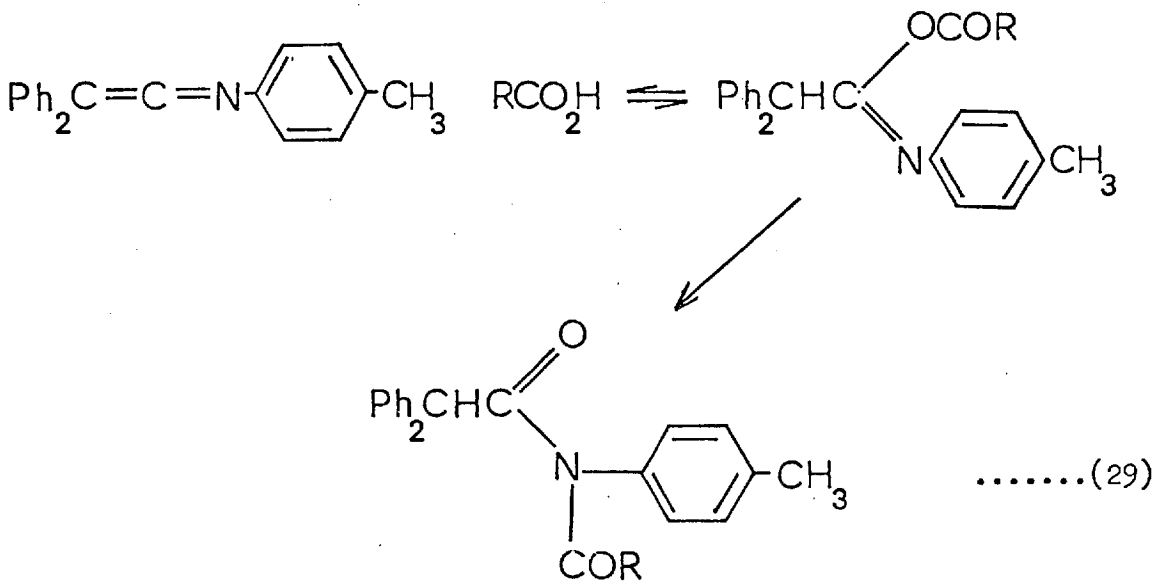
Toland and Ferstandig [109] invoked a mechanism (Equation (28)) involving an O-acylisoimide (40) in the reaction of aromatic nitriles and

aromatic acids. By suitable choice of nitrile and acid nearly quantitative yields of the exchange products were observed.



.....(28)

Stevens and Munk [110] proposed a similar mechanism for the action of ketenimines on carboxylic acids (Equation (29)).

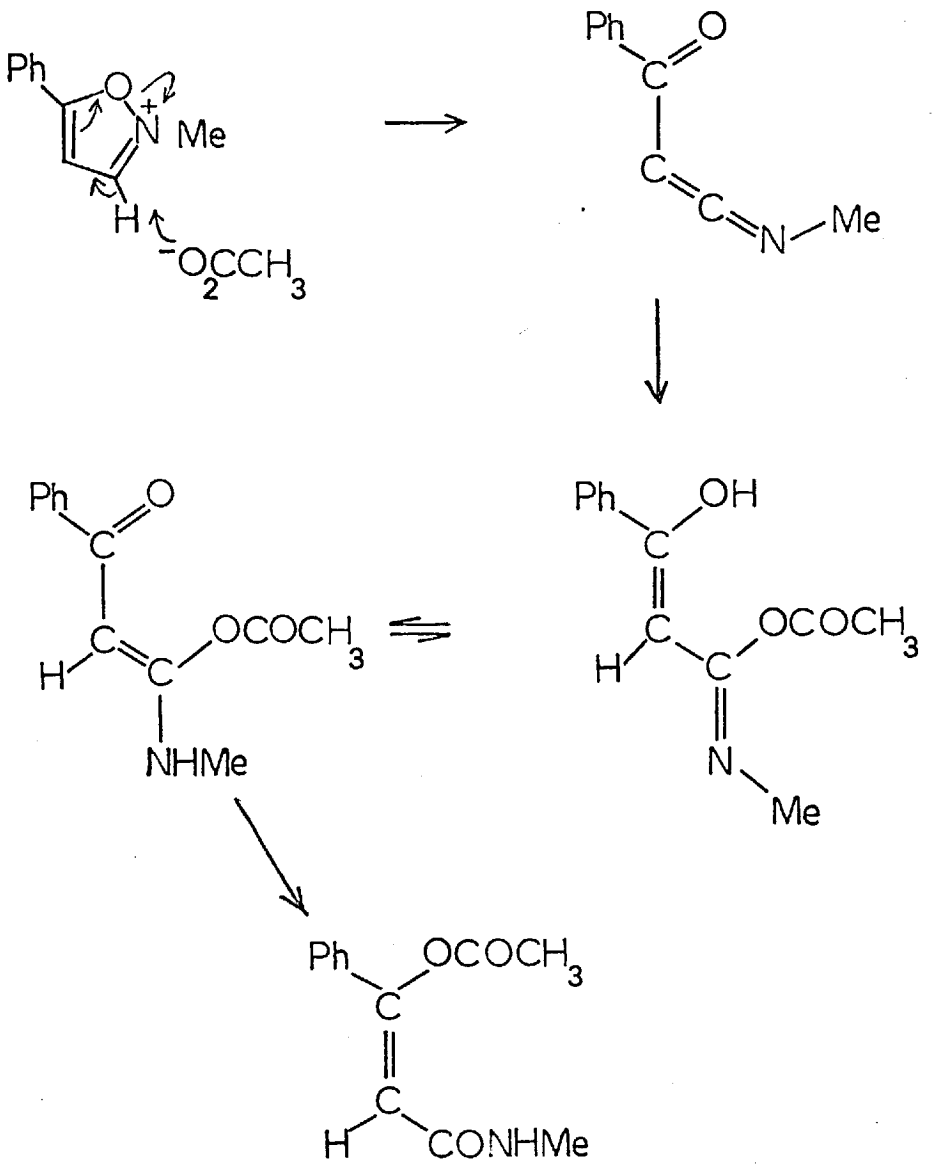


.....(29)

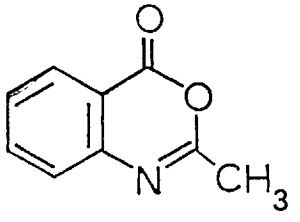
Woodward and Olofson [111] examined the reaction of N-methyl-5-phenylisoxazolium cation with acetate ion. The proposed pathway to products is shown in Scheme 1.17.

In none of the above studies, however, has the postulated intermediate been isolated. Cyclic materials such as 2-methyl-3,1-benzoxazin-4-one (41) [112] or N-methyl phthalisoimide (42) [113] have been prepared in which

Scheme 1.17



the normally rapid 1,3 acyl group migration from oxygen to nitrogen is absent due to the unfavourable steric factors.



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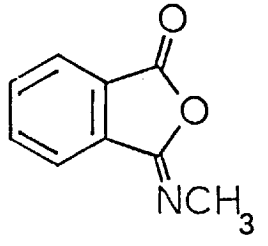
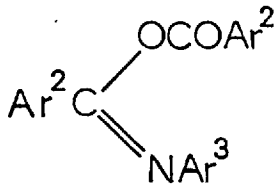


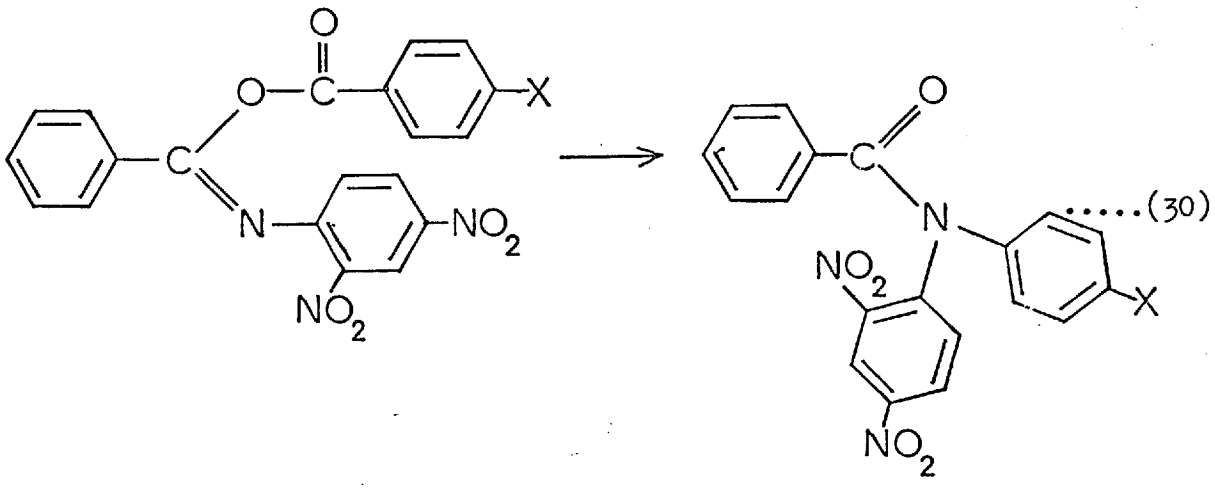
42

Curtin and Miller [114,115] were successful in preparing, isolating and studying the properties of the first acyclic O-acylisoimide 43, containing a 2,4-dinitrophenyl substituent on nitrogen.



43

They stated that the electron withdrawing groups in Ar^3 are necessary to depress the nucleophilicity of the imide nitrogen atom, and thus reduce the tendency for the rearrangement to the N-benzoyl product. They prepared a series of N-(2,4-dinitrophenyl)benzimidoyl benzoates containing para-substituents in Ar^2, and studied the kinetics and mechanism of their rearrangement to 45, the N-benzoylamide (Equation (30)).



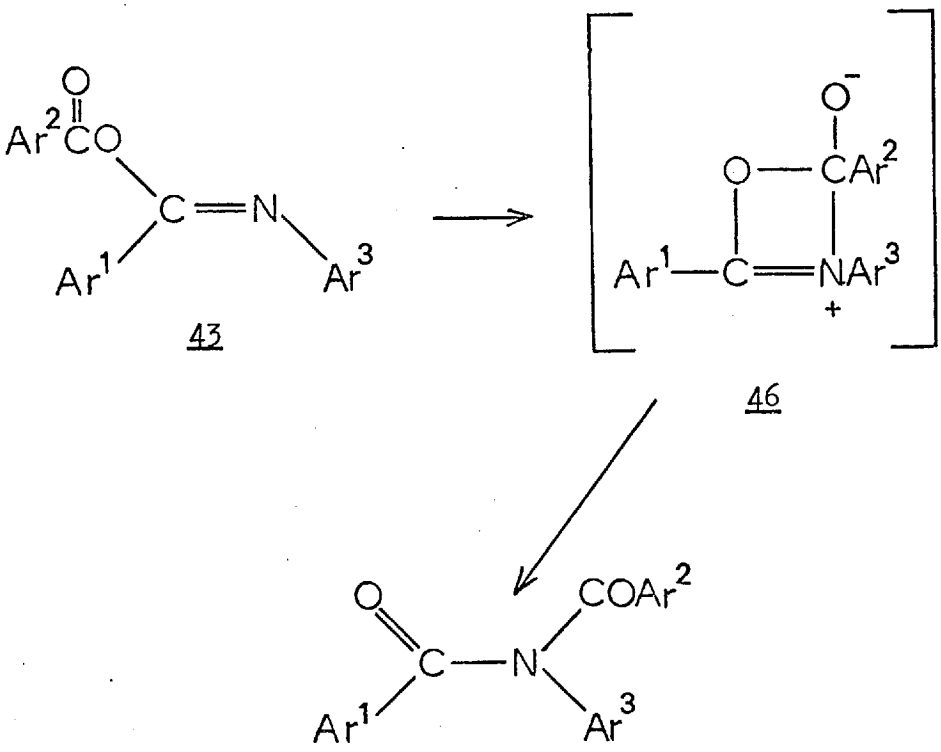
44 45

(X = H, CH_3O, Br, NO_2)

The O-acylisoimides were found to rearrange to 45 in benzene or acetonitrile solution at temperatures of 40-65°C, and kinetic measurements

showed that the reactions were first-order and that the rates were not affected by the addition of small amounts of acetic acid or calcium hydride. The rates were somewhat faster in acetonitrile for any given compound, and, in either solvent, the presence of an electron withdrawing substituent in the migrating ring accelerated the rearrangement. A normal carbonyl addition mechanism, proceeding through a dipolar transition state (46) was proposed [115] (Scheme 1.18).

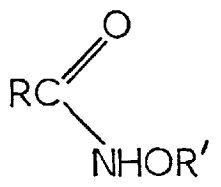
Scheme 1.18



Schwarz [116] prepared further O-acyl compounds (43) with $Ar^2=C_6H_5$ and various para-substituents in Ar^1 and Ar^3. In no case did Ar^3 have two nitro substituents, so the compounds were too labile for easy isolation. The rearrangements to imides were monitored at 0^oC by an infra-red method and half-lives were calculated. The results of Schwarz [116] lent support to the mechanism of Curtin and Miller [115].

1.3.5 ALKYLATION OF N-HYDROXYAMIDES

N-hydroxyamides bear three potential sites for alkylation, the hydroxylamine oxygen, the nitrogen and the carbonyl oxygen to form an N-alkoxyamide (47), an N-alkyl-N-hydroxyamide (48) and an alkyl N-hydroxyimidate (49) respectively.



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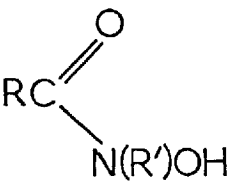

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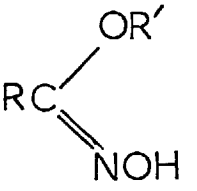
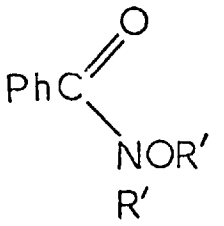
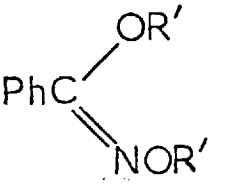


49

Extensive study has shown that the monoalkylation of the potassium salt of N-hydroxybenzamide results in the exclusive or preferential formation of an N-alkoxybenzamide [117,118]. This is in contrast with an unsubstituted amide (Section 1.1.3) which under similar conditions gives preferentially the N-alkylamide. Further dialkylation of N-hydroxyamides or monoalkylation of N-alkoxyamides as their alkali metal or silver salts appears to give an alkyl N-alkoxyimidate 50 rather than the N-alkyl-N-alkoxyamide 51 [117,119,120].



51



50

It therefore seems that the anions of N-hydroxyamides and N-alkoxyamides behave very differently towards alkylation that the corresponding unsubstituted amides, where only the silver salt reaction

gives rise to any O-alkyl product. A recent investigation by Johnson *et al* [121], however, suggests this deduction requires modification. They found [121] that the potassium salts of N-alkoxyamides on reaction with primary alkyl bromides gave primarily the N-alkylated product (51) and not the O-substituted product (50), as previously reported. These findings were confirmed by Chehata *et al* [122].

Johnson *et al* [121], also found that the product distributions for the potassium salt reactions were sensitive to the structure of the alkylating agent. A small increase in the amount of oxygen alkylation was observed with increase in the length of the straight chain of the primary alkyl bromide, but more dramatically, isopropyl halides gave more alkylation on oxygen than on nitrogen (Table 1.7)[121]. It was shown that the conversion of the O-alkyl compound into the N-alkyl isomer did not occur under the above reaction conditions.

Table 1.7

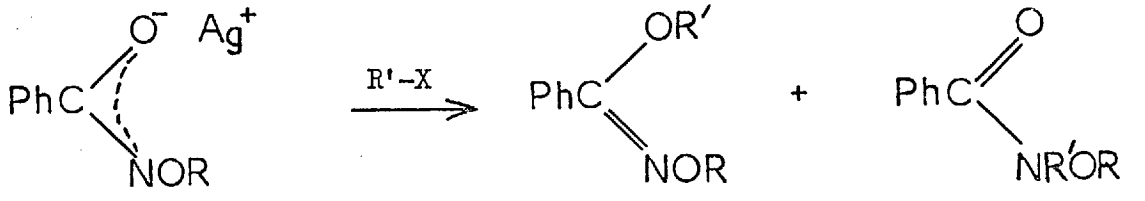
EFFECT OF ALKYLATING AGENT ON THE ALKYLATION PRODUCTS OF THE POTASSIUM SALTS OF N-ALKOXYAMIDES

Alkylating Agent (R'-X)	R	Yield (%) 52 $C_6H_5C(OR'):NOR$	53 $C_6H_5CON(R')OR$
Ethyl bromide	n-C_3H_7	25	75
Ethyl iodide	n-C_3H_7	20	80
n-Propyl bromide	n-C_3H_7	26	74
n-Propyl iodide	n-C_3H_7	20	80
Isopropyl bromide	n-C_3H_7	78	22
Isopropyl iodide	n-C_3H_7	63	37

The observed results are consistent with Kornblum's theory of ambident reactivity since the observed increase in O-alkylation parallels the increase in S_N1 character of the transition state. The "hard" and "soft" acid and base theory also explains the observed results in respect of the dependency of the product distribution on the structure of the alkyl halide.

In addition the observed dependency of the product ratio upon the leaving group is also consistent with the "hard" and "soft" acid and base theory, since iodide is a softer base than bromide and thus greater alkylation at the "soft" nitrogen site of the N-alkoxyamide would be predicted.

Silver ion clearly plays an important part in the direction of alkylation of N-alkoxyamides as with amides themselves. Thus alkylation of the silver salts of N-alkoxyamides gives rise to an alkyl N-alkoxyimidate 52 [121] and this probably explains the earlier discrepancy (Equation (31)).



52 53 .....(31)

Johnson [121] also reported the effect of the alkylating agent upon the product distribution of the silver salt reactions, but interpretation of these results is difficult because all the reactions were performed in heterogeneous conditions. In general, however, similar dependencies upon the alkylating agent can be observed (Table 1.8). The decrease in the yield of O-alkylated product using benzyl bromide in dimethylformamide

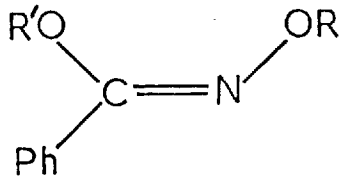
is probably due to two pathways operating, one homogeneous and the other heterogeneous.

Table 1.8

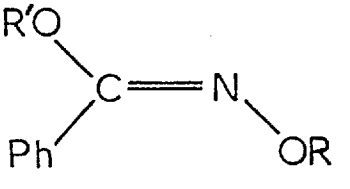
EFFECT OF ALKYLATING AGENT UPON THE ALKYLATION PRODUCTS OF N-ALKOXYAMIDE SILVER SALTS

Alkyl Halide	R	Solvent	Yield % 52 $C_6H_5C(OR'):NOR$	53 $C_6H_5CON(R')OR$
MeI	n-C_3H_7	Ether	62	38
EtI	n-C_3H_7	Ether	92	8
n-PrBr	n-C_3H_7	Ether	92	8
i-PrBr	n-C_3H_7	Ether	98	2
i-PrI	n-C_3H_7	Ether	98	2
$PhCH_2Br$	n-C_3H_7	Ether	91	9
$PhCH_2I$	n-C_3H_7	Ether	55	45
$PhCH_2Br$	n-C_3H_7	DMF	75	25
$PhCH_2I$	n-C_3H_7	DMF	68	32

Further, it is interesting to note that Johnson [121] was also able to prepare and separate the geometrical isomers of the O-alkylated product, 52a and 52b, from these silver salt reactions.

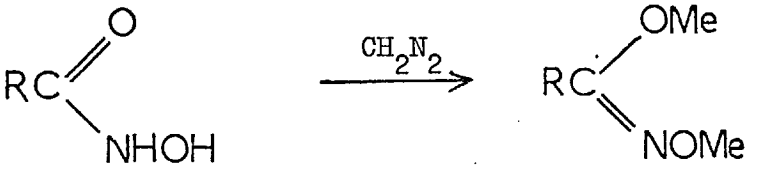


52a



52b

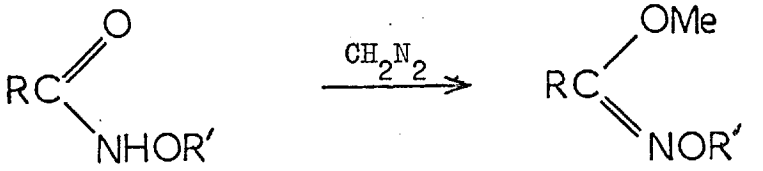
The alkylation of N-hydroxy-and N-alkoxyamides under neutral conditions has rarely been studied. It has been shown, however, that the di-alkylation of N-hydroxyamides with diazomethane, in the absence of base, produces methyl N-methoxyimidates 54 [123] (Equation (32)).



.....(32)

54

Unfortunately there is no evidence as to which site is alkylated first but recently Blaser et al [124] showed that reaction of N-alkoxyamides with diazomethane gave methyl N-alkoxyimidate products (Equation (33)).



.....(33)

Thus alkylation of N-alkoxyamides proceeds on the carbonyl oxygen, as in unsubstituted amides [125,126].

1.3.6 ACYLATION OF N-HYDROXYAMIDES

Acylation of N-hydroxyamides invariably takes place on the hydroxyl function, to form N-acyloxyamides [117] (Equation (34)). These products (55) undergo a thermal rearrangement reaction, to give isocyanates (Equation (35)), known as the Lossen rearrangement [127].

$$RCONHOH \xrightarrow{R'COCl} RCONHOCOR' \quad \text{55} \qquad \ldots\ldots(34)$$

$$RCONHOCOR' \xrightarrow{\Delta} R{-}N{=}C{=}O \qquad \ldots\ldots(35)$$

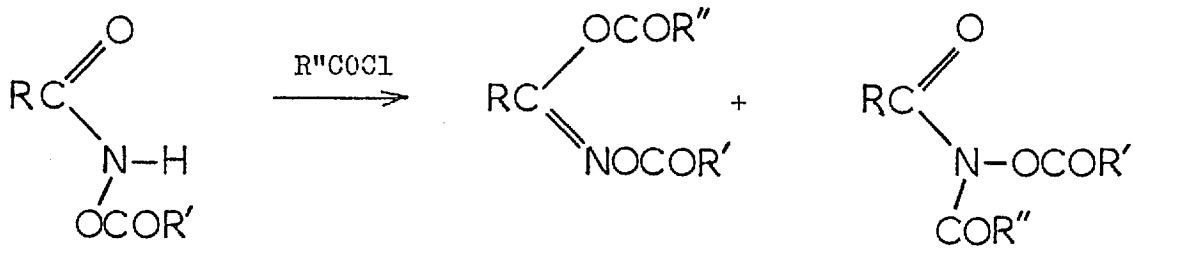
Not only acid chlorides and anydrides, but also isocyanates, ketene and diketene can be used as acylating agents [128,129] to effect the Lossen rearrangement. More reactive acid halides, such as sulphonyl halides [130,131], induce an almost spontaneous Lossen rearrangement, presumably via species 56 (Equation (36)).

$$RCONHOH + PhSO_2Cl \longrightarrow \left[R\overset{\overset{O}{\|}}{C}NHOSO_2Ph \right] \quad \text{56} \qquad \ldots\ldots(36)$$

$$\swarrow$$

$$R{-}N{=}C{=}O$$

Where the Lossen rearrangement is not rapid, it has been shown [132] that further acylation of N-acyloxyamides takes place on both oxygen and nitrogen atoms, to give products 57 and 58 (Equation (37)). Only rarely have these products been separated and identified [133,134], due to

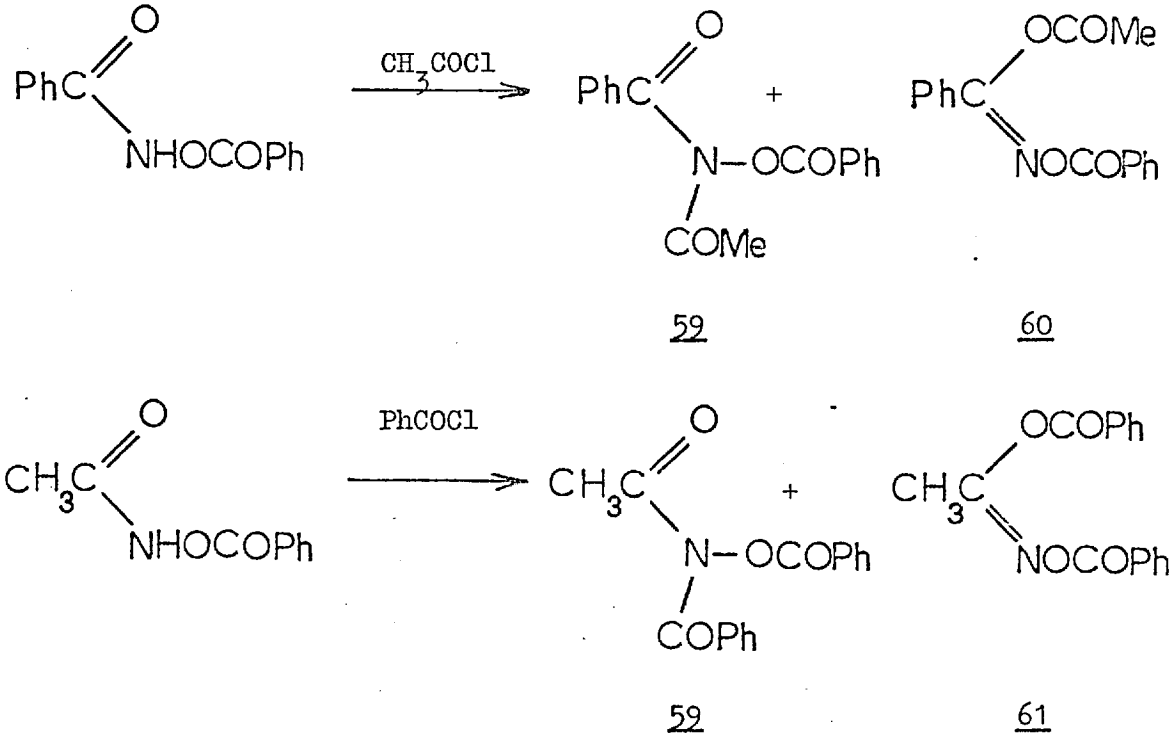


.....(37)

57 58

their tendency to exist in polymorphic form and to their sensitivity to acids, bases and heat. The nature of the reaction has been demonstrated by Jones [132], who compared the products of the acetylation of N-benzoyloxybenzamide with those obtained in the benzoylation of N-benzoyloxyacetamide. Each was found to produce a pair of isomers, one of which was common to both reactions, and must therefore result from N-acylation (Scheme 1.19).

Scheme 1.19

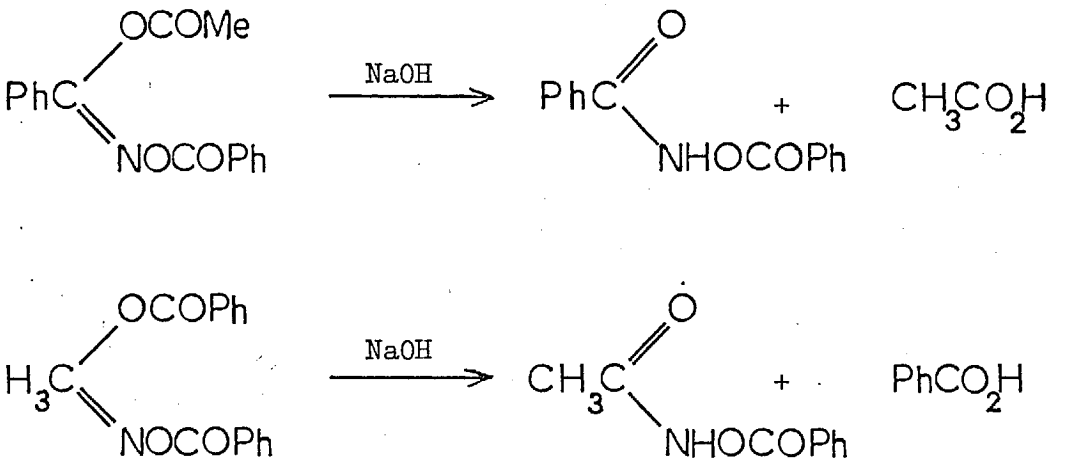


59 60

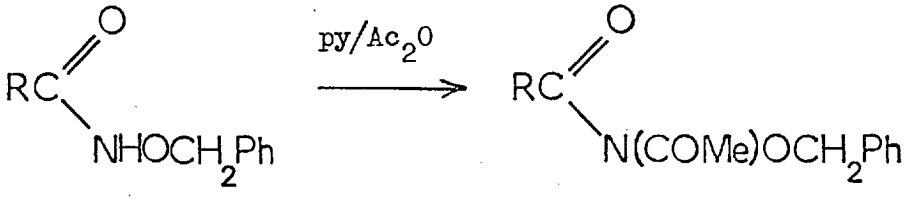
59 61

After separation of the common product (59), Jones [132] was able to distinguish between 60 and 61 by the difference in their behaviour on basic hydrolysis (Scheme 1.20).

Scheme 1.20



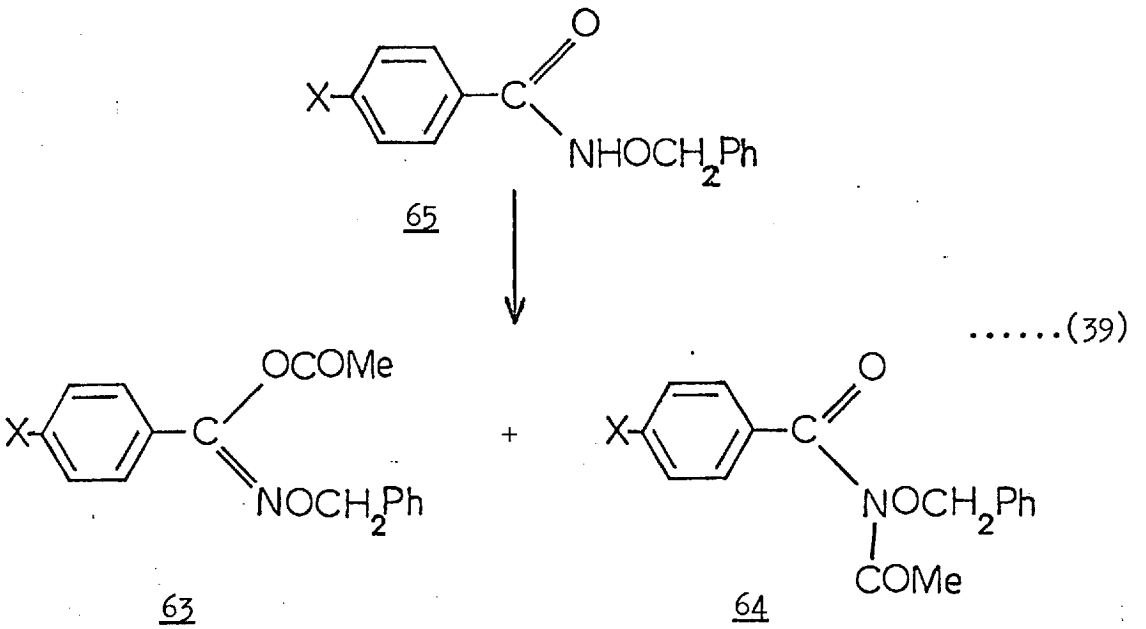
The acylation of N-alkoxyamides is simpler in that the Lossen rearrangement only occurs in exceptional cases but it was generally considered [119,127] to require vigorous conditions or very reactive reagents. Hearn and Ward [135], however, have shown that N-benzyloxyamides are readily acetylated in high yield at room temperature. The N-benzyloxy derivatives of aliphatic amides were found to yield only one product, which was shown by spectroscopic methods to be the N-acetyl-N-benzyloxyamide, 62 (Equation (38))[135].



.....(38)

62

N-benzyloxyarylamides formed both the O- and N-acetyl isomers, 63 and 64 respectively (Equation (39)). By varying the para group (X), Hearn and Ward concluded that the ratio of isomers, 63 and 64, depended upon the electronic effects induced by the para-substituent. Thus the 4-methoxy compound (65, X=MeO) gave a 93% yield of the O-acetyl derivative (63, X=MeO), but only a 50% yield of the



.....(39)

corresponding O-acetyl compound was obtained when the 4-nitro derivative was acetylated under the same conditions [135].

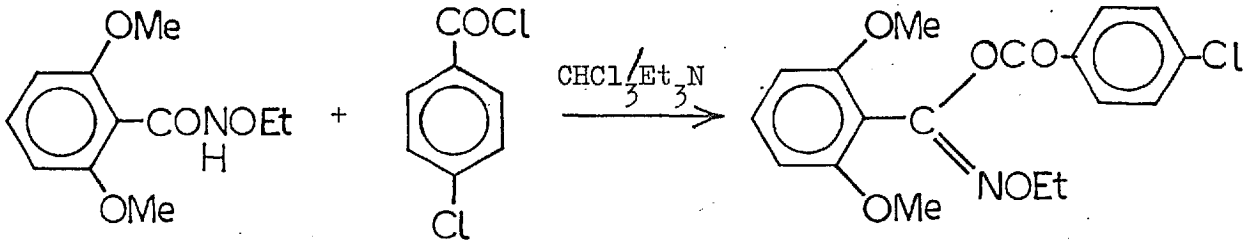
Hearn and Ward also studied the acetylation of the metal salts of N-alkoxyamides (Table 1.9)[135].

Table 1.9

Amide	M^+	Product
$CH_3CONHOCH_2Ph$	K	$CH_3CON(COMe)OCH_2Ph$
$CH_3CONHOCH_2Ph$	Ag	$CH_3C(OCOMe):NOCH_2Ph$
$PhCONHOCH_2Ph$	K	$PhC(OCOMe):NOCH_2Ph$
$PhCONHOCH_2Ph$	Ag	$PhC(OCOMe):NOCH_2Ph$

All the above reactions were heterogeneous, and thus a direct comparison with the unsubstituted amide salt acylations is impossible.

Several other workers [136,137] have reported the preparation of stable O-acylisoimides in the acylation of N-alkoxyamides (Equations (40), (41)).



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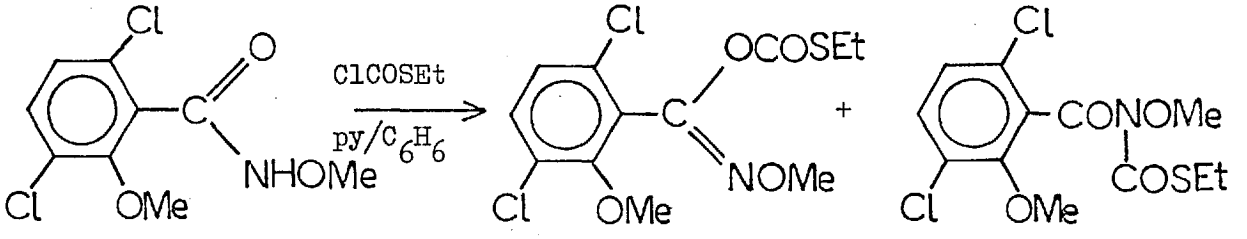


.....(41)

It can be seen that the reactions of N-hydroxyamides are not directly comparable with the reactions of unsubstituted amides, since electrophilic substitution generally occurs on the hydroxyl function and not the amide nitrogen atom. From the results observed with N-alkoxyamides, however, it seems that there is a great deal of similarity with unsubstituted amides and many of the conclusions drawn about amides are applicable in this case. Thus alkylation of N-alkoxyamide anions proceeds predominantly at the nitrogen atom but at the oxygen atom when the neutral molecule is employed. The acylation of N-alkoxyamides in neutral solution is found to give mixed O- and N-acylation, which differs from unsubstituted amides where only N-acylation is observed. This result may be explained, however, by assuming that the kinetic O-acyl product is much more stable in the case

of N-alkoxyamides than unsubstituted amides. In order to verify this assumption, the acylation of N-alkoxyamides was studied in detail.

P A R T T W O

DISCUSSION OF THE EXPERIMENTAL RESULTS

CHAPTER II

THE ALKYLATION OF PHENOLS

2.1 INTRODUCTION

In order to obtain convenient rates of alkylation, it was thought necessary to study a phenolic system in which the reactivity of the neutral molecule approached that of the conjugate base. The reported data of Kornblum for the alkylation of phenoxide [34] and 2-naphthoxide ions [35] seemed to suggest that in these particular systems the above criterion was met. For this reason, therefore, the alkylation reactions of the phenol/phenoxide ion and 2-naphthol/2-naphthoxide ion were studied. It can be seen that 2-naphthol behaves as a 1,3 ambident system, but phenol can react in a 1,3 or 1,5 manner leading to ortho- and para-alkylphenols. This additional complication of two C-alkylated products in the phenol system led to the 2-naphthol system being studied.

The choice of alkylating agent was governed by similar considerations concerning the alkylation rate. Hart [39] has shown that tertiary alkyl halides are particularly effective alkylating agents for phenol but suffer the disadvantage of solvolysis of the intermediate carbonium ion in hydroxylic solvents [34], and hence the choice of solvent is limited by this factor. Further, the cleavage of t-alkylphenyl ethers under acidic conditions has been shown [38] to be a facile process. In order to avoid the above problems as far as possible and still retain moderate reactivity of the alkylating system, the secondary alkyl halide, benzyl bromide, was chosen.

Although the absolute rates of reaction were not required in the present study, it was thought desirable to have a method of monitoring the alkylation products which avoided a large amount of handling and sampling. Preliminary investigation showed that with a suitable column,

gas-liquid chromatography (g.l.c.) assay would be satisfactory and the majority of studies involved this technique. Some results were confirmed by an alternative nuclear magnetic resonance (n.m.r.) assay (Section 2.2.2).

2.2 ANALYTICAL METHODS

2.2.1 GAS-LIQUID CHROMATOGRAPHY

Kornblum [34,35] used rather extreme conditions (230°C) for his g.l.c. analyses using a column of Silicone oil/Chromosorb W. A more suitable column for phenols used tris-(2,4-xylenyl)-phosphates as the liquid phase, but its volatility makes it unsuitable for the higher boiling phenols [138]. For example the high boiling points of naphthols together with their polar nature cause problems of peak-tailing and long retention times. This problem can be overcome by methylation or trimethylsilylation of the phenolic mixture, with subsequent analysis of the more volatile and less polar methyl [138,139] or trimethylsilyl [140] ethers. This method is slower than direct analysis and requires that the conversion procedures do not result in the preferential loss of any one isomer.

An alternative approach by which retention times can be lowered is to reduce the concentration of the liquid phase provided the solid support is not itself strongly adsorbing. For example, supports such as Celite possess surface hydroxyl groups which may interact strongly with polar compounds, although again these can be transformed by treatment of the support with hexamethyldisilazane into trimethylsilyl ether groups [141]. Alternatively, non-polar glass beads [142] or 'Teflon' [143] may be used as the support. It has been found that polar and less volatile compounds may be eluted at relatively low

temperatures by using a solid support of glass beads with low concentrations of the liquid phase [144]. For example. Hishta et al [145] were able to separate 2- and 4-hydroxydiphenylmethanes using a column of glass beads lightly loaded with a liquid phase of diethylene glycol succinate polyster (DEGS). By using a high carrier-gas flow-rate, short retention times were obtained at relatively low temperatures (140-175°C)[145].

Originally, the substrate examined was 2-naphthol, which is advantageous because C-alkylation leads to only one product, whereas with phenol both ortho- and para-substituted products are obtained. It was anticipated that by replacing the DEGS liquid phase with the less polar diethylene glycol adipate polyester (DEGA)[146], g.l.c. analysis of both phenol, 2-naphthol and their benzylated products would be feasible. The results obtained with the prepared column are shown in Table 2.1, and for comparison those obtained using general purpose columns are given in Tables 2.2 and 2.3.

It can be seen that both phenol and the alkylated phenols are eluted satisfactorily from the DEGA polyester column under very mild conditions. 2-Naphthol, however and 1-benzyl-2-naphthol, although eluted, were found to give a certain amount of peak tailing, which, in the case of 1-benzyl-2-naphthol was quite considerable.

On the basis of these results, the present study was confined to the phenol/phenoxide ion system. In some cases the g.l.c. analysis of the reaction solutions was carried out using a linear temperature programme (100-170°C, 10°C $min.^{-1}$), in order to obtain the concentrations of all species in solution, but generally a fixed temperature was employed (Section 5.2.2) to give traces such as Fig.2.1.

Fig.2.1 g.l.c. spectrum of phenol/benzyl bromide alkylation reaction in 50% EtOH/CCl_4 ($\frac{v}{v}$) at 40°C.

(i) 2-Hydroxydiphenylmethane.

(ii) 4-Hydroxydiphenylmethane.

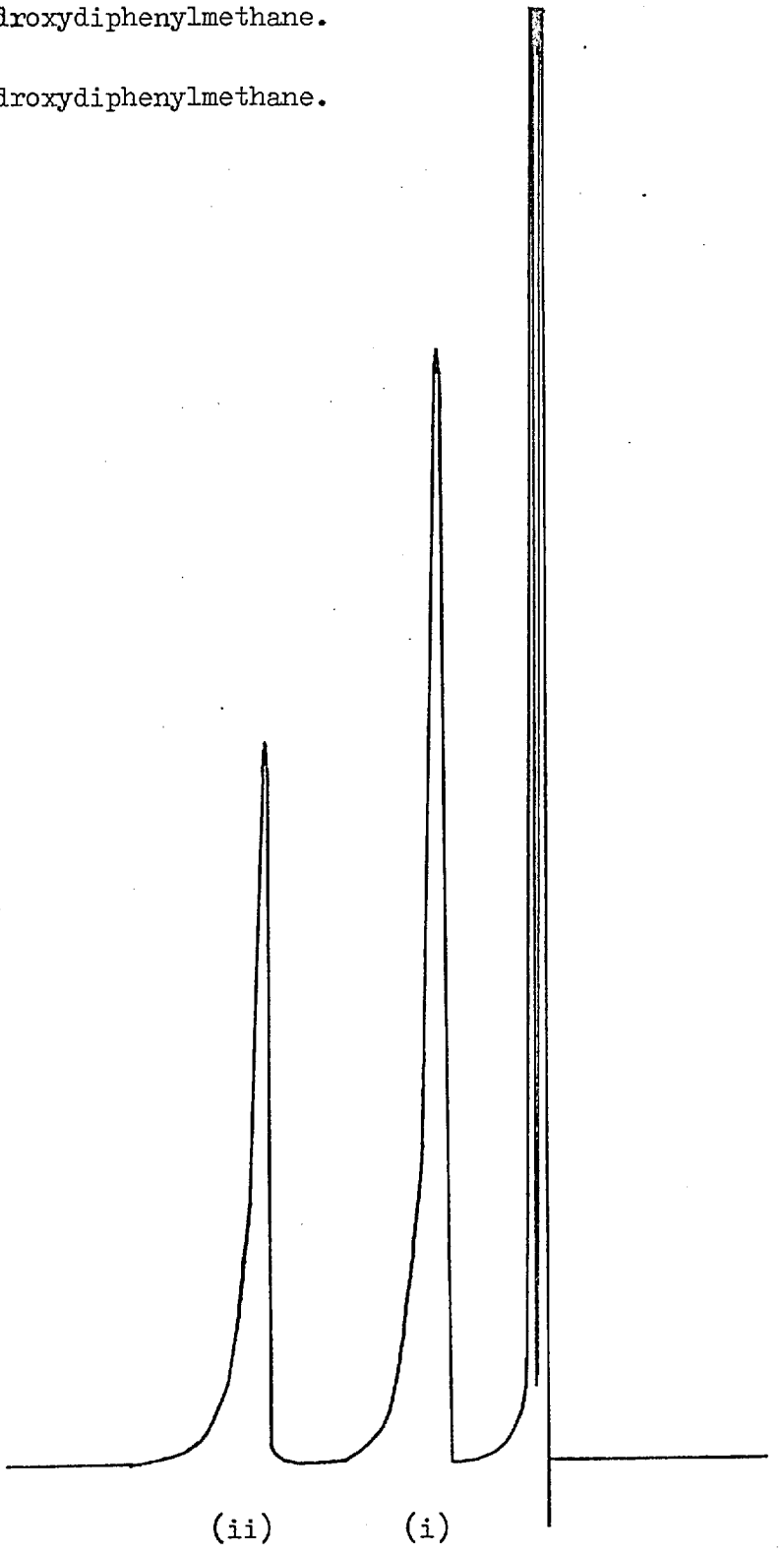


Table 2.1

COLUMN : 1 metre, stainless steel, 0.3% DEGA on glass beads

(i) CONDITIONS : Column temperature = 190°C;
Injection Temperature = 250°C;
Nitrogen = 38 p.s.i.; Air = 24 p.s.i.;
Hydrogen = 17 p.s.i.

Compound	Retention Time (mns)
2-Naphthol	1.75
1-Benzyl-2-Naphthol	14.50 (Peak Tailing)
Benzyl-2-Naphthyl Ether	1.25

(ii) CONDITIONS : Column temperature = 170°C;
Injection Temperature = 225°C;
Nitrogen = 30 p.s.i.; Air = 24 p.s.i.;
Hydrogen = 17 p.s.i.

Compound	Retention Time (mns)
Phenol	0.25
Benzylphenyl Ether	0.375
2-Hydroxydiphenylmethane	1.92
4-Hydroxydiphenylmethane	4.25

Table 2.2

COLUMN : 2 metre, $\frac{1}{8}$" stainless-steel, Carbowax 20M/Chromosorb W

CONDITIONS : Column Temperature = 200°C;
Injection Temperature = 275°C
Nitrogen = 50 p.s.i.; Hydrogen = 18 p.s.i.;
Air = 24 p.s.i.

COMPOUND	RETENTION TIME (mns.)
Phenol	6.7
Benzylphenyl Ether	28.75 (tailing)
2 - and 4-Hydroxydiphenylmethane	Not eluted
2-Naphthol	Not eluted
1-Benzyl-2-Naphthol	Not eluted

Table 2.3

COLUMN : 2 metre, $\frac{1}{8}$" stainless-steel, Silicone grease/Chromosorb P.

CONDITIONS : Column Temperature = 200°C;
Injection Temperature = 275°C;
Nitrogen = 58 p.s.i.; Hydrogen = 18 p.s.i.;
Air = 24 p.s.i.

COMPOUND	RETENTION TIME(mns.)
Phenol	2.0
Benzylphenyl Ether	12.5
2-Hydroxydiphenylmethane	23.0 (Tailing)
4-Hydroxydiphenylmethane	Not eluted
2-Naphthol	Not eluted
Benzyl-2-Naphthyl Ether	Not eluted

A series of standard solutions of benzylphenyl ether, 2- and 4-hydroxydiphenylmethane were prepared and it was shown that there was a linear relationship between peak height and concentration for all the above compounds (Figs. 2.2, 2.3 and 2.4).

Fig. 2.2 CALIBRATION CURVE FOR BENZYLPHENYL ETHER.

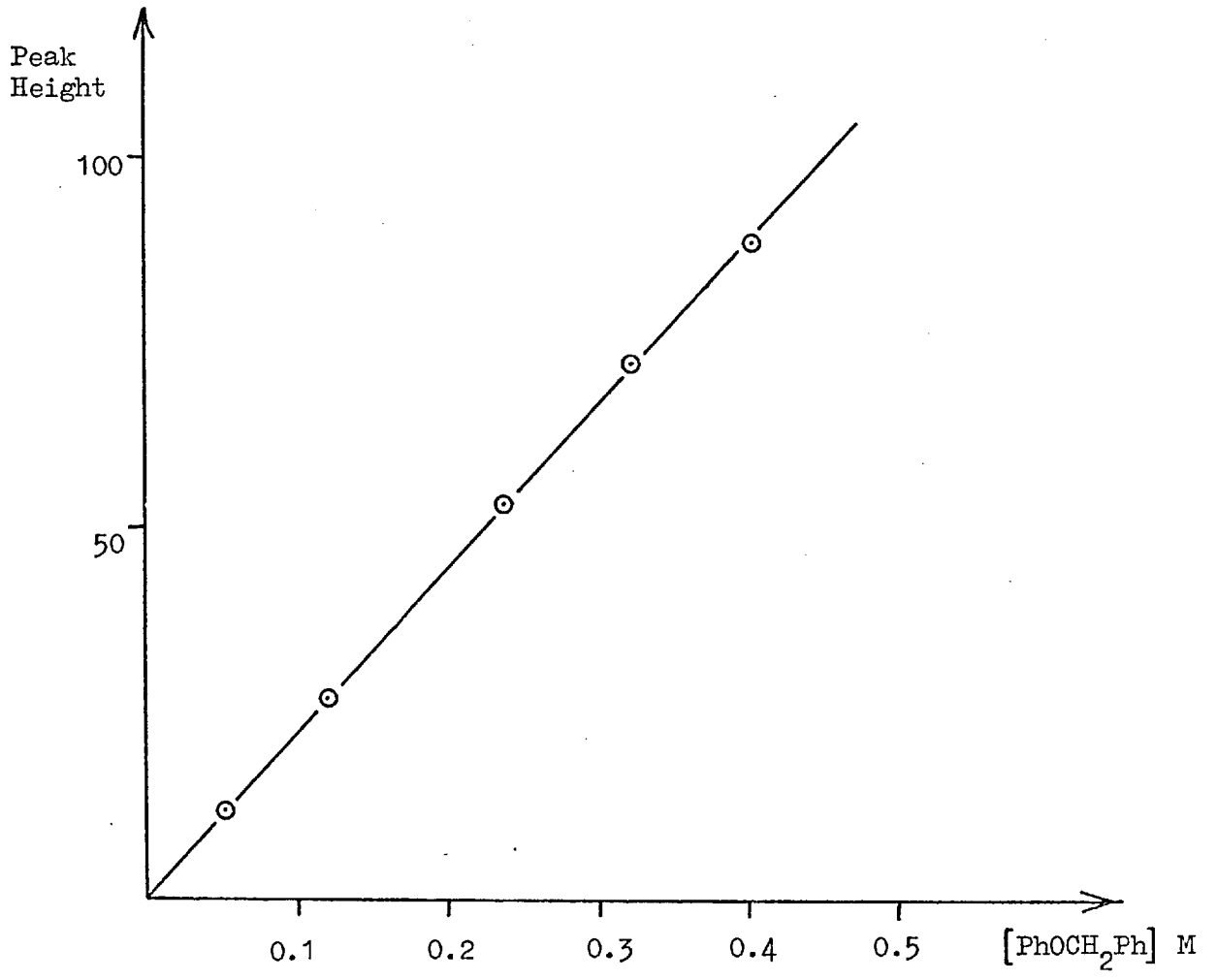


Fig. 2.3 CALIBRATION CURVE FOR 2-HYDROXYDIPHENYLMETHANE

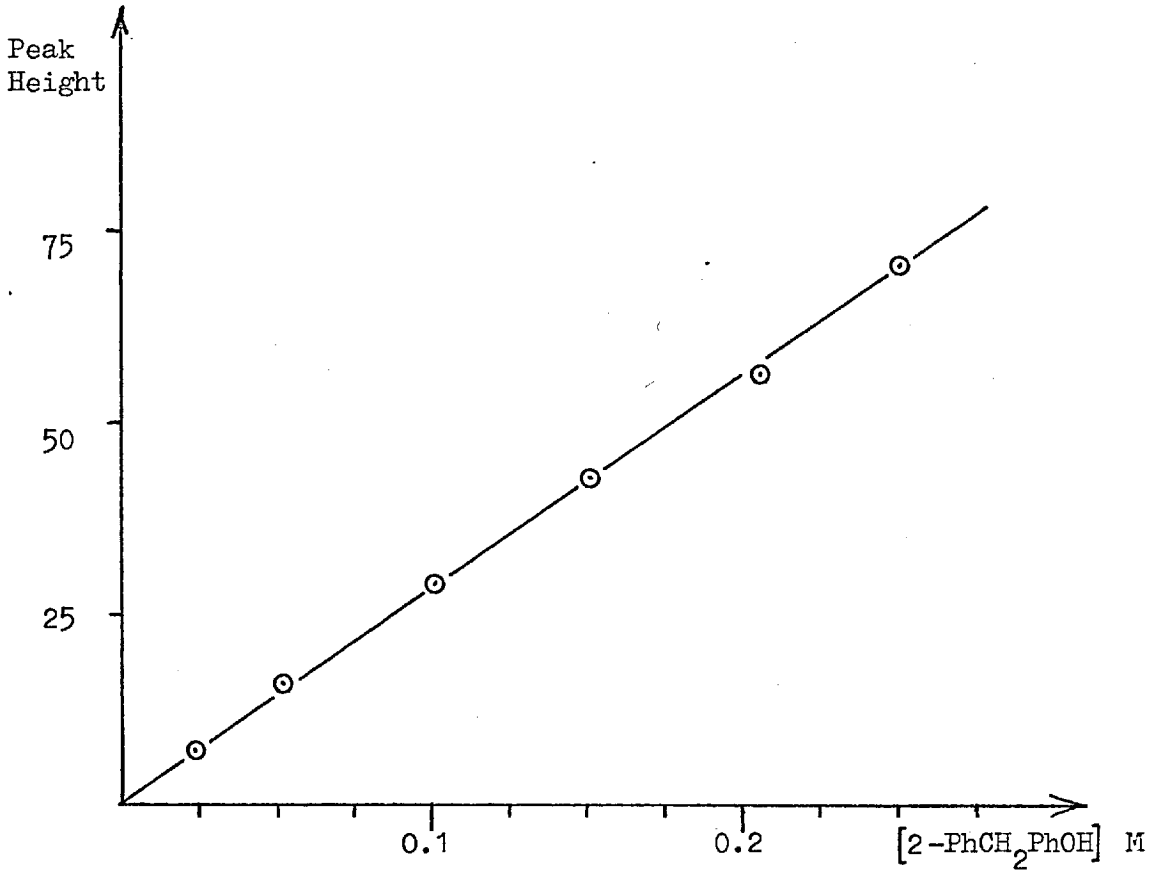
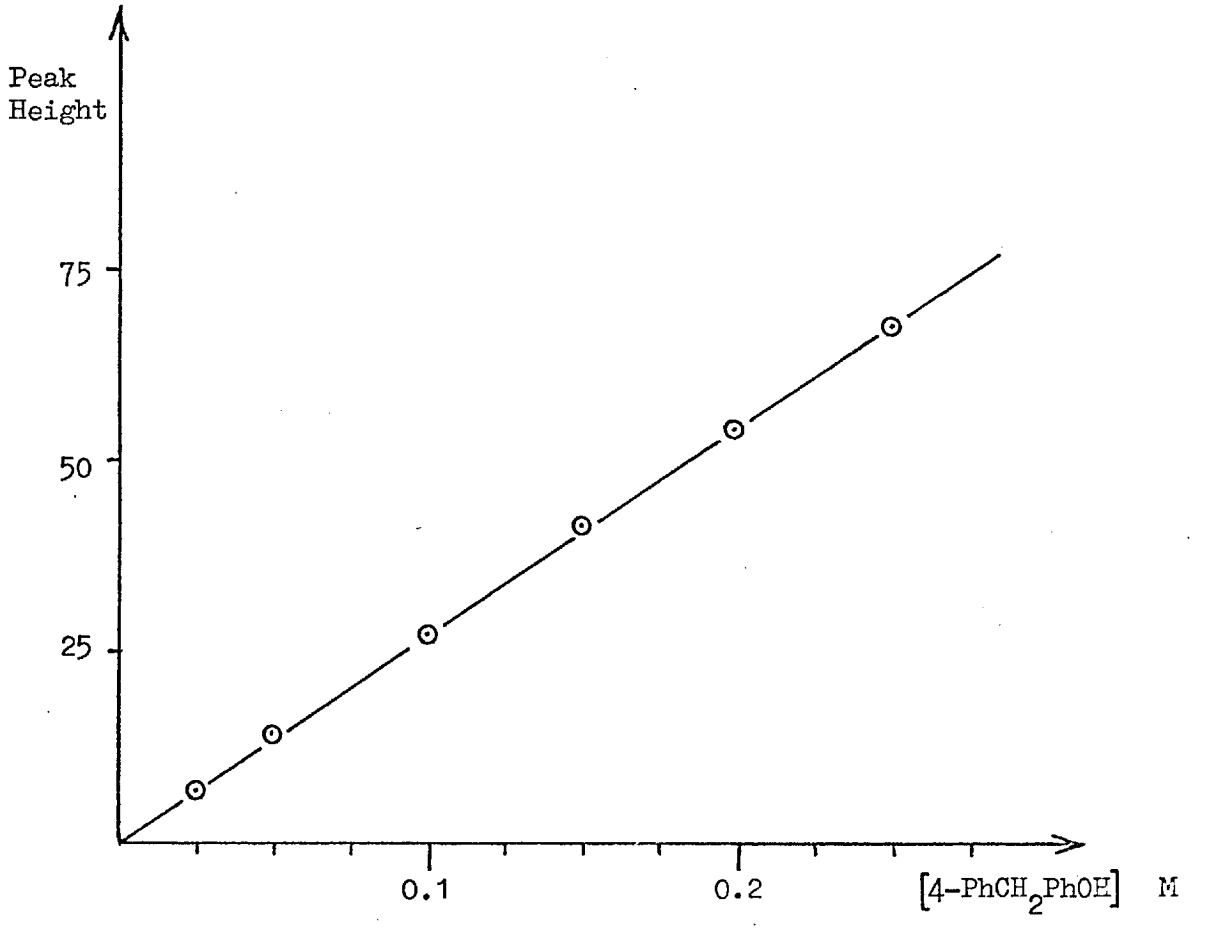


Fig. 2.4 CALIBRATION CURVE FOR 4-HYDROXYDIPHENYLMETHANE



2.2.2 NUCLEAR MAGNETIC RESONANCE PROCEDURE

One of the major problems encountered with the g.l.c. technique described in Section 2.2.1 was adequate control of the reaction conditions to prevent any adventitious water entering the reactions during sampling. This was particularly important in the studies of neutral phenol alkylations in which long reaction times were involved. The problem was minimised, however by placing Suba-seals on the reaction vessels and sampling *via* the seal with a microlitre syringe. In some cases, the g.l.c. results of the neutral phenol alkylation reactions were confirmed by the n.m.r. technique. It was found that the percentage reaction and the actual site of alkylation could be determined by n.m.r., making use of the benzylic methylene chemical shift of the products (Table 2.4).

2.3 SOLVENT SYSTEM

Since the heterogeneity [28,29,30] of the reaction medium appears to be an important factor determining the site of phenol alkylation, it was considered necessary to use a solvent in which both phenol and phenoxide ion were soluble to effect reaction of both under homogeneous conditions. Dimethylsulphoxide satisfied the criterion of solubility but severely interfered with the g.l.c. assay of the reaction solutions. In addition, the slow reaction between phenol and benzyl bromide was found to be complicated by a competing reaction between the solvent and the alkyl halide. This reaction between dimethylsulphoxide and alkyl halides has been reported [147,148] to proceed at measurable rates at room temperature

Table 2.4

CHEMICAL SHIFTS OF THE BENZYLIC METHYLENE SIGNAL OF BENZYL BROMIDE AND BENZYLATED PHENOL PRODUCTS IN CARBON TETRACHLORIDE

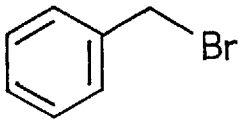
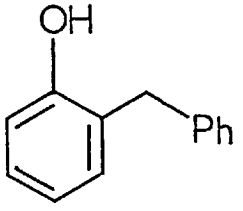
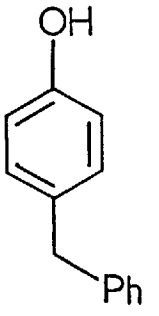
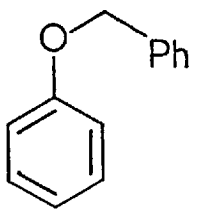
Compound	$-CH_2-$ (δ)
	4.50
	3.85
	3.92
	5.05

Table 2.5

SOLVENT	T(°C)	[PhOH] M.	[PhONa] M.	[$PhCH_2Br$] M.	Yield % (g.l.c.)		Yield % (isolated)	
					O-	C-	O-	C-
DMSO	25		0.04	0.004	100%		100%	
DMSO	25	0.04		0.004	SOLVOLYSIS			
EtOH	25		0.04	0.004	90%		88%	
EtOH	40	0.04		0.004		100%		100%
CCl_4*	40		0.04	0.004	65%	35%		
CCl_4	40	0.04		0.004		100%		100%

* heterogeneous reaction

and thus this particular solvent was not considered further. In ethanol, the alkylation of sodium phenoxide was found to be complicated by a competing solvolysis reaction, but the yields of the benzylethyl ether side-product were only small (ca. 10%). Phenol itself gave only C-substituted products, but the rate of this reaction was very slow ($t_{\frac{1}{2}} \approx 22$ days), and therefore all subsequent phenol alkylations in ethanol were performed at temperatures of 40°C and 60°C ($t_{\frac{1}{2}} \approx 18$ days, 13 days, respectively). In pure carbon tetrachloride, sodium phenoxide was insoluble but homogeneous conditions could be effected by the addition of ethanol (50%, $\frac{v}{v}$). Further, the rate of the neutral molecule reaction leading to C-substitution was slightly faster in carbon tetrachloride (40°C approx. $t_{\frac{1}{2}} = 16$ days). These considerations led to a mixed solvent system of ethanol/carbon tetrachloride (50%, $\frac{v}{v}$) being adopted for the present study.

2.4 ALKYLATION OF PHENOL/PHENOXIDE ION IN EtOH/Cl_4

The preliminary investigation into the alkylation reaction was concerned with establishing the order of the reaction with respect to the substrate concentration. In Table 2.6 the effect of the substrate concentration and the alkyl halide concentration upon the alkylation rate (i.e. $t_{\frac{1}{2}}$) are given.

It can be seen from Table 2.6 that the reaction is approximately first-order with respect to phenol and the alkyl halide. Reactions with both phenol and phenoxide ion were homogeneous. The observed products from the phenol and phenoxide ion alkylations are given in Table 2.7.

Table 2.6

ALKYLATION OF PHENOL AND SODIUM PHENOXIDE IN EtOH/CCl_4

[PhOH] M.	[PhONa] M.	[$PhCH_2Br$] M.	T(°C.)	$t_{\frac{1}{2}}$ (hours)
0.04		0.004	40	384
0.02		0.004	40	720
0.004		0.004	40	*
0.02		0.008	40	370
	0.04	0.004	25	0.25

* Too slow to be measured

Table 2.7

PRODUCT RATIOS IN THE ALKYLATION OF PHENOL AND PHENOXIDE ION WITH BENZYL BROMIDE IN EtOH/CCl_4

[PhOH] M.	[PhONa] M.	[$PhCH_2Br$] M.	T(°C.)	Total Yield	Yield (%) C	O
	0.04	0.004	25	95		100
0.04		0.004	40	98	100	

The high product yields suggest that there are no competing solvolytic pathways. Control experiments with only the solvent and alkylating agent were found to be unchanged (g.l.c. assay) after similar reaction times (ca. 1000 hours), and confirm this deduction.

When phenol was used as the substrate, 100% C-alkylation was observed, in contrast to exclusive O-alkylation with phenoxide ion. This suggests clearly that pH of the reaction medium has a profound effect on the products. From the results (Table 2.6) it can also be seen that the phenol/phenoxide ion reactivity is not as similar as had been anticipated from the work of Kornblum. A comparison of the half-lives for the phenol and phenoxide ion alkylations in Table 2.6 reveals a factor of ca. 1400 for the difference in reactivity. When Kornblum performed the alkylation of sodium phenoxide in phenol solvent, the rates were of approximately similar magnitudes, but the phenol concentration was in thirty-fold excess over the sodium phenoxide (value computed from Kornblum's data). In this particular reaction, therefore, the phenol/phenoxide ion reactivity ratio is approximately 1:30 in favour of phenoxide.

The ortho:para ratio for the C-alkylated products obtained with phenol in the present study was determined by g.l.c. as 1.5:1 at 40°C. This contrasts with the results of Kornblum [34] for sodium phenoxide alkylations in water (27°C) and phenol (43°C), for which ortho:para ratios of 1:1.6 and 1:1 respectively were observed. The effect of temperature upon the observed ortho:para ratio was found to be very significant (Table 2.8)

A possible explanation to account for the predominance of ortho-alkylated product at low temperatures and the para-isomer at higher temperatures is that there is a difference in activation energies

Table 2.8

EFFECT OF TEMPERATURE UPON THE ORTHO:PARA RATIO IN THE REACTION OF PHENOL WITH BENZYL BROMIDE IN EtOH/CCl_4

T(°C.)	[PhOH] M.	[$PhCH_2Br$] M.	ortho:para
25	0.04	0.004	3.62:1
25	0.02	0.004	3.57:1
40	0.04	0.004	1.50:1
60	0.04	0.004	1.0 :1.1
75	0.04	0.004	1.0 :1.5
75	0.02	0.004	1.0 :1.47

for the two processes which manifests itself in the observed temperature dependent ortho:para ratio. Another possible explanation is that at lower temperatures, the directing capability of the hydroxyl function is important. It is known that phenol hydrogen-bonds with alkyl halides [149], and this type of interaction would lead to preferential attack at the ortho position in phenol at lower temperatures. A third possible explanation to account for the observed results is that at lower temperatures benzylphenyl ether is first formed in the reaction, which subsequently undergoes an intramolecular rearrangement, catalysed by hydrogen bromide (Scheme 2.1).

In order to investigate this hypothesis, several reactions were carried out to determine the stability of benzylphenyl ether in a typical phenol alkylation reaction, in which the hydrogen bromide would be provided by the reaction of phenol and benzyl bromide.

Scheme 2.1

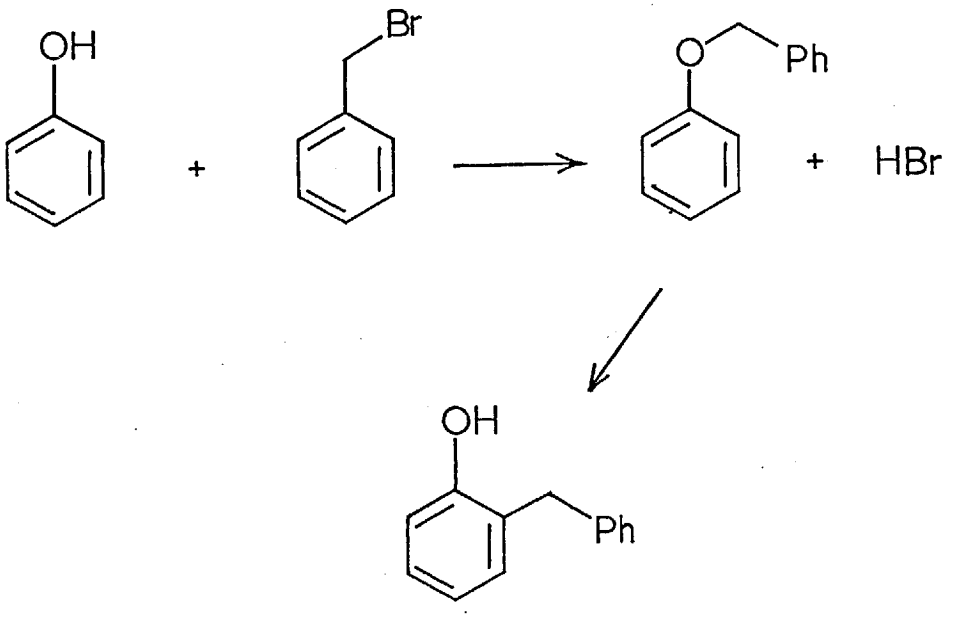


Table 2.9

EFFECT OF BENZYLPHENYL ETHER UPON THE ORTHO:PARA RATIOS IN THE ALKYLATION OF PHENOL WITH BENZYL BROMIDE IN EtOH/CCl_4

T(°C.)	$[PhOCH_2Ph]$ M.	[PhOH] M.	$[PhCH_2Br]$ M.	Yield ortho:para
25	0.004	0.04	0.004	3.6 :1
25		0.04	0.004	3.62:1
40	0.004	0.04	0.004	1.5 :1
40		0.04	0.004	1.5 :1
75	0.004	0.04	0.004	1.0 :1.5
75		0.04	0.004	1.0 :1.5

Examination by g.l.c. showed that the added benzyl phenyl ether disappeared very rapidly after an initial induction period, presumably due to low hydrogen bromide concentrations. The products from the cleavage of benzyl phenyl ether were shown to be phenol and benzyl bromide by comparison of the concentrations of ortho- and para-alkylated phenols in those reactions with added benzyl phenyl ether and those containing only phenol and benzyl bromide.

It was thought possible that during the g.l.c. sampling procedure adventitious water may have entered the above reactions and thus the results were confirmed using the n.m.r. technique (Section 2.2.2) with carbon tetrachloride as the solvent. This allowed greater control upon the reaction conditions since the solution was sealed in an n.m.r. tube, and thus the possibility of erroneous results arising from the g.l.c. sampling procedure were avoided. The results for the alkylation of phenol with benzyl bromide in carbon tetrachloride are given in Table 2.10, along with the results of alkylations carried out in the presence of added benzylphenyl ether.

From the results in Table 2.10, it can be seen that a thermal rearrangement of benzylphenyl ether in the absence of the reactants is ruled out. In addition, reaction between the benzyl bromide and the ether to give the benzyl ethers of ortho- and para-benzyl phenol may also be ruled out on the evidence of the n.m.r. spectra (no signals at $\delta 4.0$). This was confirmed by g.l.c. analysis of the reaction solution. The cleavage of benzylphenyl ether appears therefore to be catalysed by the hydrogen bromide released in the reaction of phenol and benzyl bromide. This deduction was confirmed by adding hydrogen bromide to a solution of benzylphenyl ether in 50% ethanol-carbon tetrachloride ($\frac{v}{v}$), thermostatted at 40°C. The reaction was monitored by g.l.c., and the only products

Table 2.10

ALKYLATION OF PHENOL WITH BENZYL BROMIDE IN 50% ($\frac{v}{v}$) ETHANOL-CARBON TETRACHLORIDE

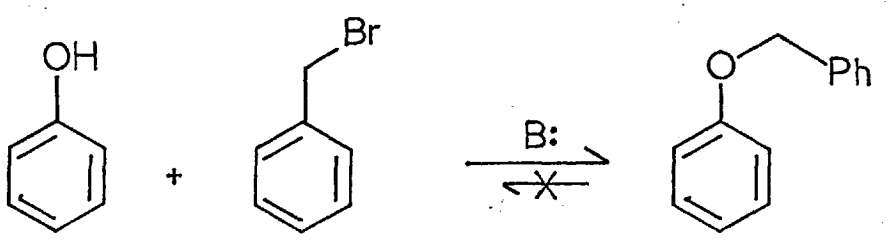
T(^{o}C.)	[$PhOCH_2Ph$] M.	[PhOH] M.	[$PhCH_2Br$] M.	[4-$PhCH_2PhOH$]	Stability of $PhOCH_2Ph$	C-alkylated pr. ortho:para
75	0.005				No rearrangement	
75	0.005	0.05	0.005		Rearrangement	1:1.4
75	0.005		0.005		No reaction	
40	0.005	0.05	0.005		Rearrangement	1:1
40		0.05	0.005			1:1
75		0.05	0.005			1:1.4
75		0.05	0.005			1:1.38
75		0.05	0.005	0.005		1:3.8

observed from the cleavage of benzylphenyl ether under the above conditions were phenol and benzyl bromide.

The ortho:para ratio of the C-alkylated products can be seen from Tables 2.9 and 2.10 to be unaffected by added benzylphenyl ether.

The above results show that the C-alkylated products observed in the reaction of phenol and benzyl bromide, are derived from direct C-alkylation of the phenol ring, and not through the rearrangement of an intermediate benzylphenyl ether. It can be seen that the above results do not conclusively prove whether O-attack occurs in typical neutral phenol alkylation reactions, since it has only been shown that the O-attack under the above conditions would be reversible.

In order to establish whether O-substituted products could form from neutral phenol itself, attempts were made to remove the hydrogen bromide from the reaction solution, thus making the ether formation irreversible (Equation (42)). Several different methods were investigated



.....(42)

to remove the hydrogen bromide. Passage of nitrogen gas through the reaction solution met with limited success as authentic benzylphenyl ether added to the reaction solutions was found to be slowly cleaved into phenol and benzyl bromide. The difficulties experienced with this method, e.g. evaporation of solvent and adquate control of conditions, led to further systems being considered. Addition of pyridine to a reaction solution containing phenol and benzyl bromide in carbon tetrachloride led to the formation of benzylphenyl ether in 100% yield. The pyridine here

certainly fulfils a dual role, in that it complexes with the phenol, and also removes any hydrogen bromide produced (Table 2.11).

Table 2.11

ALKYLATION OF PHENOL WITH BENZYL BROMIDE IN CARBON TETRACHLORIDE

T(°C.)	[PhOH] M.	[$PhCH_2Br$] M.	HBr (B:) Scavenger	Product (%) O-	C-
60	0.04	0.004	N_2 gas		100
60	0.04	0.004	Pyridine, 0.004M	100	
60	0.04	0.004	EPP,	95	5

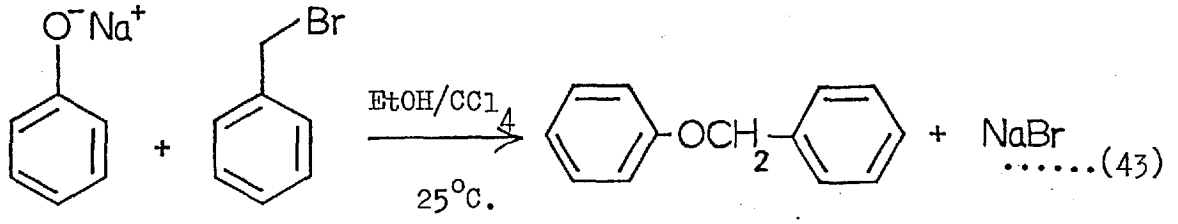
The removal of hydrogen bromide from the reaction solution was also accomplished using 1,2-epoxy-3-phenoxypropane (EPP) which has been shown [150] to be a non-alkaline hydrogen bromide scavenger. The addition of EPP to the reaction solution of phenol and benzyl bromide in carbon tetrachloride led to the formation of benzylphenyl ether (95%) and only traces of C-alkylated products. This suggests that in reactions of neutral phenol, attack at the O-site is reversible under the acidic conditions (i.e. benzylphenyl ether is the kinetic product) but C-alkylated products are stable and are the thermodynamic products.

2.5 DISCUSSION

It is clear from earlier work that several factors, principally those of homogeneity [28,29,30] steric [32] and cation effects [35], exert an influence over the products obtained from the alkylation of phenols.

The recognition of acidity as an important factor however, seems to have escaped the attention of many investigators. From the present results it can clearly be seen that the acidity of the medium does play a significant role in the determination of the site of alkylation of phenol.

The alkylation of sodium phenoxide with benzyl bromide in 50% EtOH-CCl_4($\frac{v}{v}$) proceeds *via* an S_N2 mechanism, leading to the formation of benzylphenyl ether and sodium bromide (Equation (43)).



.....(43)

The by-product in this reaction is an organic salt and therefore the basicity of the medium should decrease as the reaction proceeds until at completion, a "neutral" solution is present. Here the possibility of acid-catalysed rearrangement is reduced except in hydroxylic solvents. For the reaction of phenyl with benzyl bromide, the mechanism for the C-alkylation is almost certainly an S_N2-type process. The high yields of C-alkylated phenols and the apparent lack of any competing solvolysis of the benzyl halide argue against an S_N1 mechanism, involving a benzyl carbonium ion. The intermediate for C-alkylation, however, cannot be ascertained, and may be a dienone-type intermediate, similar to that proposed by Challis [151,152] and de la Mare [18,19] for the nitrosation and halogenation of phenol, respectively or a normal Wheland σ-complex.

In the neutral molecule reaction the by-product, whether reaction occurs at the oxygen or carbon sites, is hydrogen bromide. As the reaction proceeds, therefore, there will be a gradual increase in the acidity of the medium until saturation levels are reached. Under these conditions, the attack at phenolic oxygen is certainly reversible, but C-alkylation remains

an irreversible process (Table 2.10). By removing the hydrogen halide as it is liberated from the reaction between phenol and benzyl bromide, it has been shown that the formation of the benzylphenyl ether becomes the predominant pathway i.e. under normal phenol alkylation conditions, the ether formation is reversible.

From the above results it may be concluded that:-

(i) in basic conditions, the formation of benzylphenyl ether is irreversible;

(ii) in neutral (acidic) conditions, benzylphenyl ether is formed reversibly and is therefore under kinetic control, but the formation of ortho- and para-alkylphenols is irreversible and hence C-alkylation is a thermodynamically-controlled reaction.

Kornblum [1] in his original report of the factors which control the site of substitution of an ambident ion concluded that the nature of the transition state was important. In S_N1-type transition states Kornblum would predict attack at the most electronegative site, the ortho- and para-carbon atoms of the phenol ring. From the present results, it can be seen that both O- and C-alkylation are derived from S_N2 processes, which is in disagreement with the predictions of Kornblum's theory. In addition, it has been proven that attack at the most electronegative atom (i.e. oxygen) occurs preferentially both in neutral molecule and conjugate base reactions, but depending upon the acidity of reaction conditions, this attack may or may not be reversible.

The above results would suggest that the neutral phenol molecule is not an ambident nucleophile, but the observed behaviour in the alkylation may be explained in terms of kinetically-controlled O-substitution and thermodynamically-controlled C-substitution. From Kornblum's reported results for the alkylation of phenoxide anion with benzyl chloride [34], a PhO^-:PhOH reactivity ratio of 30:1 was computed.

From the observed rates for the alkylation of phenol and phenoxide anion in 50% ethanol/carbon tetrachloride, the PhO^-:PhOH reactivity ratio of 1400:1 was calculated. It would seem, therefore, that in the alkylation of phenoxide anion in phenol solvent, the observed O- and C-alkylation is due solely to the reaction of phenoxide anion and the alkyl halide, and not the phenol and the alkyl halide. This result tends to suggest that phenoxide anion is an ambident nucleophile. It is possible, however, that the O-alkylated product is rapidly formed in these reactions, but its formation is reversible and thus an equilibrium is set up between the benzylphenyl ether and the reagents, which allows the neutral phenol alkylation to compete. Unfortunately, Kornblum [34] did not monitor the alkylation of phenoxide ion in phenol at timed intervals, but only reported the percentage reaction after ca. 20 hours.

Hart [38] in his studies on the uncatalysed alkylation of phenol using tertiary alkyl halides showed that the reaction was first-order with respect to the phenol concentration and this was interpreted as a rate determining attack by the phenol molecule on the t-alkyl carbonium ion. The product from these reactions was the para-t-alkylphenol. The effect of pyridine upon this reaction was reported by Swain [153], who found that the alkylation of phenol with triphenylmethyl chloride in the presence of pyridine gave the phenyl ether in 100% yield. It appears, therefore, that under the reaction conditions used by Hart [38], the formation of the O-alkyl product is possible, but under the acidic conditions this reaction is reversible. A similar conclusion was reached by Hart [38] who showed that although a t-alkylphenyl ether was rapidly cleaved under acidic conditions, its formation (and subsequent cleavage) could not be ruled out as a concurrent process in the alkylation of phenol with t-alkyl halides to give para-t-alkylphenols. It can be seen that if this situation holds, and

O-attack does occur in the above conditions, the oxygen atom of neutral phenol is the most reactive site in both S_N1 and S_N2 alkylation pathways, but the reversibility of this step is dependent upon the acidity of the medium.

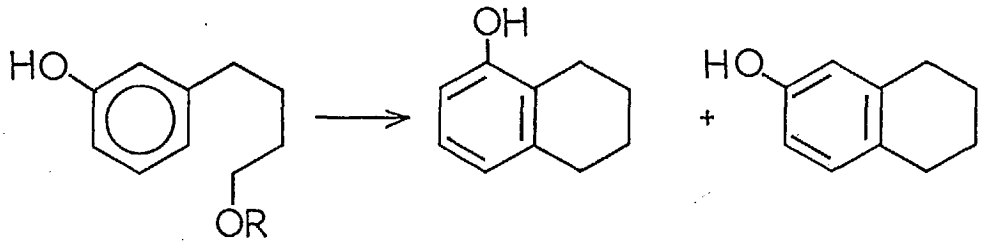
A reversible ether-formation step would also explain the results of Hart [154] using optically-active phenylethyl chloride. It was found that the alkylation of sodium phenoxide using optically active phenylethyl chloride, an S_N2 process for which inversion of configuration would be expected, gave an optically active ether, which retained 76% of its optical activity although inversion had occurred [154]. The alkylation of phenol was also shown [155] to be an S_N2 process, but here a mixture of 55% ortho- and 45% para-phenylethyl phenols, with only a small amount of optical activity, were obtained. Further work to determine the kinetics of the racemisation of optically active phenylethyl chloride in phenol, showed [156] that the expression for the racemisation rate (Equation(44)), contained first-order terms in phenol

$$\text{Rate} = k_1(\text{RCl})(\text{PhOH}) + (k_2+k_3)(\text{RPhOH})(\text{RCl}) \qquad .....(44)$$

hydrogen chloride, and the alkylation products (RPhOH). Hart was unable to give a mechanism to account for the observed kinetic behaviour, but it can be seen that a rapid, reversible formation of an O-alkylated intermediate would fit all the experimental evidence. It was found [156] that the racemisation rate was almost as fast as the C-alkylation rate in phenol and, in addition, hydrogen chloride in the absence of phenol did not racemise optically active phenylethyl chloride. These results are consistent with the rapid, reversible O-alkylation step given above.

From the data in Table 2.8 it is clear that the dependence of the ortho:para ratio upon temperature in reactions between phenol and

benzyl bromide is not the result of an intramolecular rearrangement of an intermediate O-alkyl product. Duggan and Murphy [159] reported a similar temperature-dependent ortho:para ratio as that observed in the present work (Table 2.12) using compound 66 as an intramolecular



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66 67 68

C-alkylation model. Intermolecular O-alkylation was restricted by using dilute solutions of 66.

Table 2.12

SOLVENT	T°(C)	ortho:para (67:68)
MeOH	65	1.0:1.43
	35	1.0:1.00
H_2O	100	1.0:1.63
	35	1.0:0.86
DMF	153	1.0:0.89
	35	1.0:0.37

Alkylation of neutral phenol with suitable alkylating agents should lead to ether formation if by-products do not make this reaction reversible. Accordingly reaction of triethyloxonium tetrafluoroborate with phenol in dichloromethane (to ensure homogeneous conditions) was

found to proceed at room temperature to give phenetole (69) as the only observed product (Equation (46)).

$$(C_2H_5)_3O^+BF_4^- + PhOH \longrightarrow PhOEt + Et_2O \quad .....(46)$$

69

2.6 SUMMARY

From the data which have been collected, it is clear that the acidity of the reaction medium plays an important part in determining the site of alkylation of a phenoxide ambident nucleophile in homogeneous conditions. The tendency for electrophilic reagents to react preferentially at carbon of neutral phenolic compounds is interpretable in terms of kinetically-controlled O-alkylation but thermodynamically-controlled C-alkylation. This interpretation also explains the proposed ambident reactivity of neutral phenol. Attempts to interpret the tendency towards O- and C-alkylation using Kornblum's [1] theory of ambident reactivity clearly fail for they require that the most S_N1-like transition state will be associated with substitution on carbon. This is, of course, contrary to Kornblum's predictions.

It is apparent, therefore, that Kornblum's [1] theory cannot adequately explain the observed behaviour in the neutral molecule reaction, and even in the case of phenoxide anion can only agree in part with the observed results. The formation of ethers in such high yield from the alkylation of phenoxide anion with benzyl chloride and phenylethyl chloride (reactions which have been shown to have strong S_N2 character) is itself contrary to the predictions of Kornblum. The PhO^-:PhOH reactivity ratio, calculated from the alkylation of phenol and its conjugate base with benzyl bromide in 50% ethanol-carbon tetrachloride, has been shown to be ca 1400:1. This ratio would suggest that in the alkylation of sodium phenoxide in

phenol solvent, the observed products are derived entirely from the phenoxide anion reaction and not from any interaction between the neutral phenol and the alkyl halide. The half-life for sodium phenoxide alkylation in phenol, however, is much higher than that observed in the present study, and two explanations to account for this observation are possible:-

(a) The phenoxide anion is strongly hydrogen-bonded to the neutral phenol and thus reacts as a neutral phenol molecule, favouring C-alkylation.

(b) The phenoxide anion reacts rapidly with the alkyl halide to give an O-alkylated product, which is, however, unstable and is slowly cleaved to regenerate reagents.

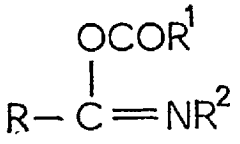
Kornblum [34] did not study the alkylation of sodium phenoxide in phenol further in order to justify his hypothesis that hydrogen-bonding was the reason for the observed results. It can be seen that differentiation between (a) and (b) is possible by carrying out dilution experiments with an inert solvent and by monitoring the reaction at timed intervals. From the available data, however, no conclusive evidence is available to determine whether or not phenoxide anion is an ambident nucleophile.

CHAPTER III

THE ACYLATION OF AMIDES

3.1 INTRODUCTION

O-acylisoimides (70) have been invoked as intermediates in the



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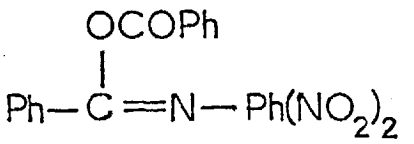
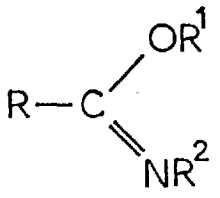


44

acylation of amides and in a number of other reactions(Section 1.3), but they have rarely been isolated presumably because of their low stability. The thermal rearrangement of O-acylisoimides was first studied by Curtin and Miller [115], who were able to isolate the O-acylisoimide (44) with a 2,4-dinitrophenyl N-substituent. The rate of thermal rearrangement observed for 44 by Curtin and Miller [115] demonstrated both the instability of the compound and confirmed the supposition that at the temperature at which amide acylations are performed, the O-acylisoimide intermediate would exist only as a transient species.

The rearrangement of O-alkyl imidates (71) is known [87,88,89]

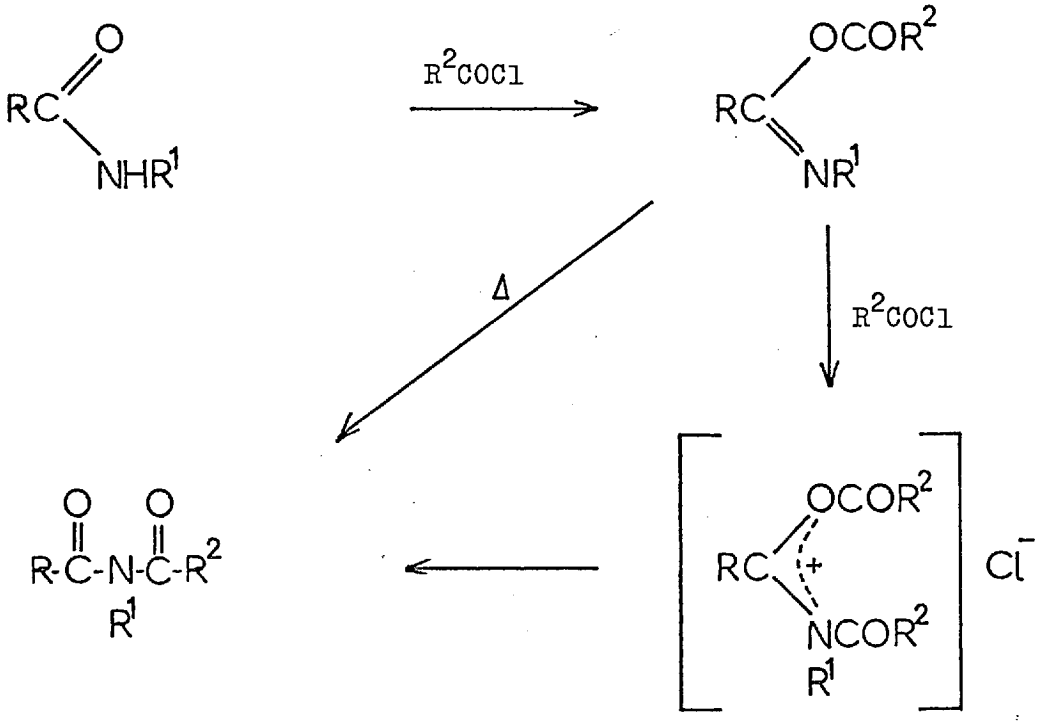


71

to be catalysed by a variety of electrophilic reagents. It was of

interest, therefore, to determine whether or not a similar situation holds with O-acylisoimides, i.e. in addition to an intramolecular, thermal process, a catalysed intermolecular pathway is operative in the rearrangement reaction (Scheme 3.1).

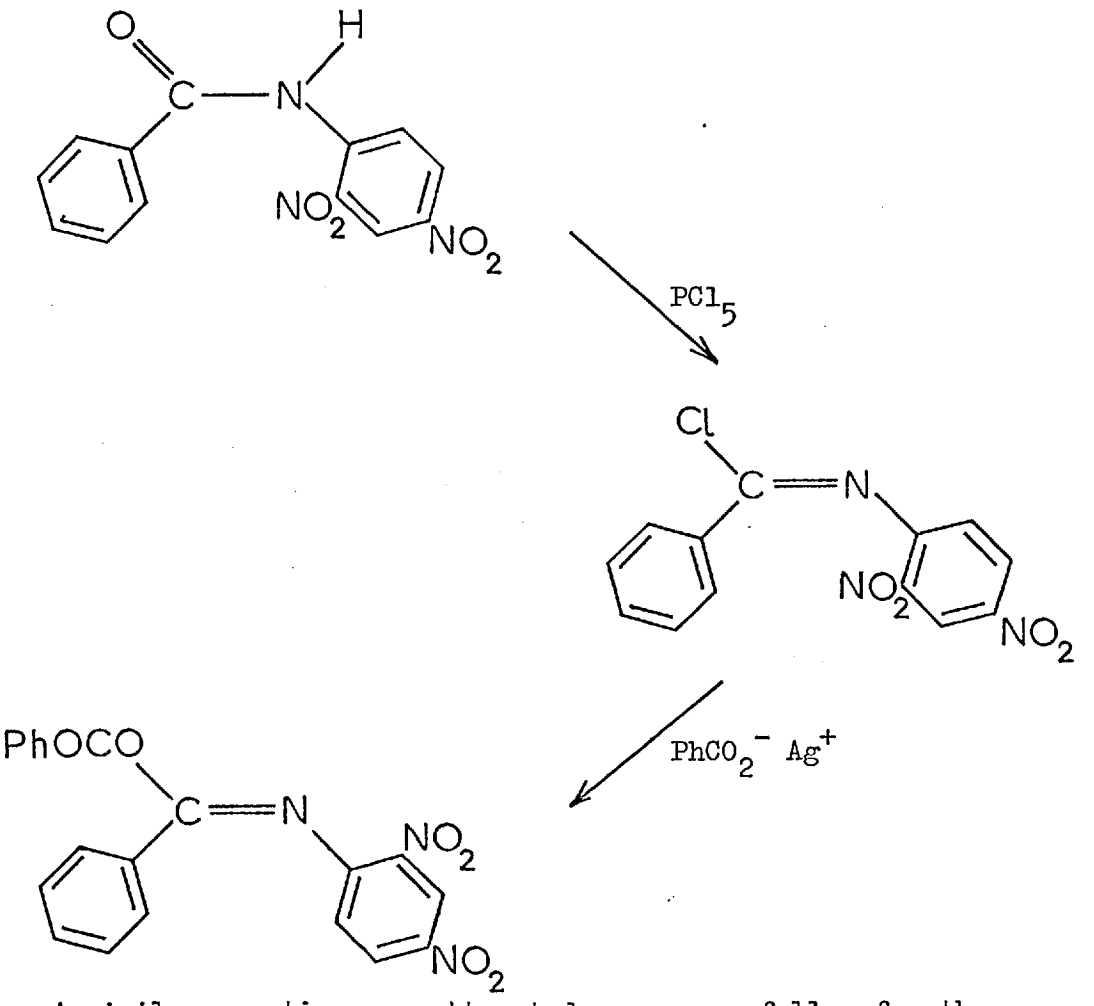
Scheme 3.1



3.1.1 SYNTHESIS OF SUBSTRATES

The procedure of Curtin and Miller [115] was used to prepare the O-acylisoimide (44) by reaction of N-(2,4-dinitrophenyl)benzimidoyl chloride with silver benzoate at 0°C (Scheme 3.2). Studies by Schwarz [116] showed that a 2,4-dinitrophenyl substituent on nitrogen has a profound effect upon the rate of this reaction and therefore much longer reaction times than those reported were used. The yields of the N-(2,4-dinitrophenyl)benzimidoyl benzoate were much higher than those obtained by Curtin and Miller [115].

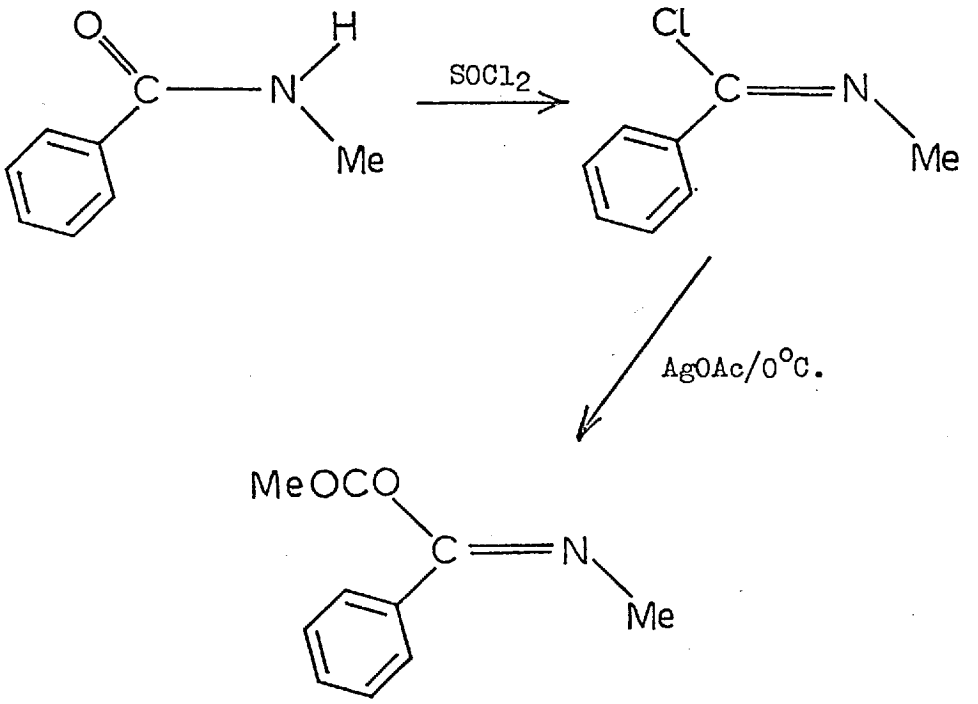
Scheme 3.2



A similar reaction was attempted, unsuccessfully, for the preparation of N-methylbenzimidoyl acetate 72 (Scheme 3.3)

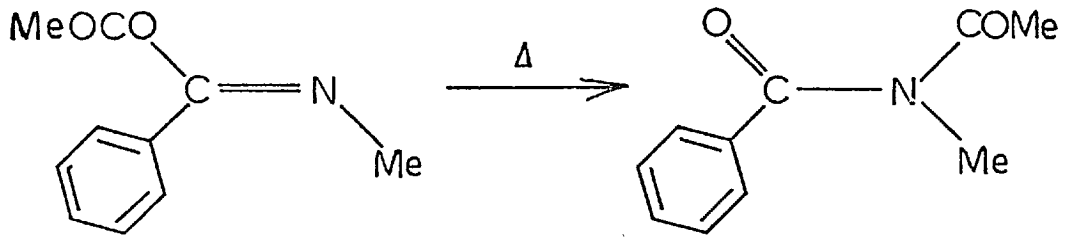
The product obtained from the reaction was an oil which gave peaks at 1760cm^{-1}(O-$\overset{O}{\overset{\|}{C}}$-) and 1680cm^{-1}(C=N) in its i.r. spectrum. The n.m.r. spectrum ($CDCl_3$) gave signals at 2.18(3H,s) and 3.23(3H,s) in addition to the aromatic signals. On standing at room temperature, the above spectra were found to change rapidly to give spectra which were superimposable with those of authentic N-acetyl-N-methylbenzamide. Spectroscopic evidence suggested therefore that the O-acylisoimide 72

Scheme 3.3



72

was formed but rearrangement proceeded rapidly at room temperature to N-acetyl-N-methylbenzamide 73 (Equation (47)).



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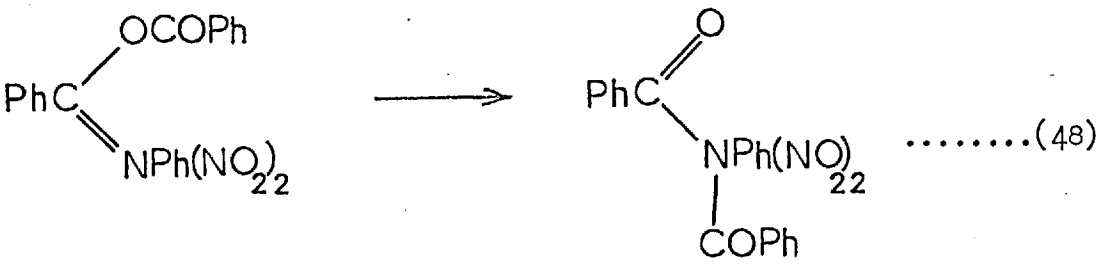
72 73

Greater control of the temperature was used in subsequent attempts to prepare 72 , which, under these circumstances was obtained as a solid crystalline product when stored at -10°C.

The rate of thermal rearrangement of 72 was such that N-(2,4-dinitrophenyl) benzimidoyl benzoate was chosen to study the effect of electrophilic reagents upon the rearrangement.

3.1.2 MEASUREMENT OF REARRANGEMENT RATES

The infra-red method reported by Curtin and Miller [115] was used to monitor the rearrangement of N-(2,4-dinitrophenyl)benzimidoyl benzoate to N-2,4-dinitrophenyl-N-benzoylbenzamide (Equation (48)).



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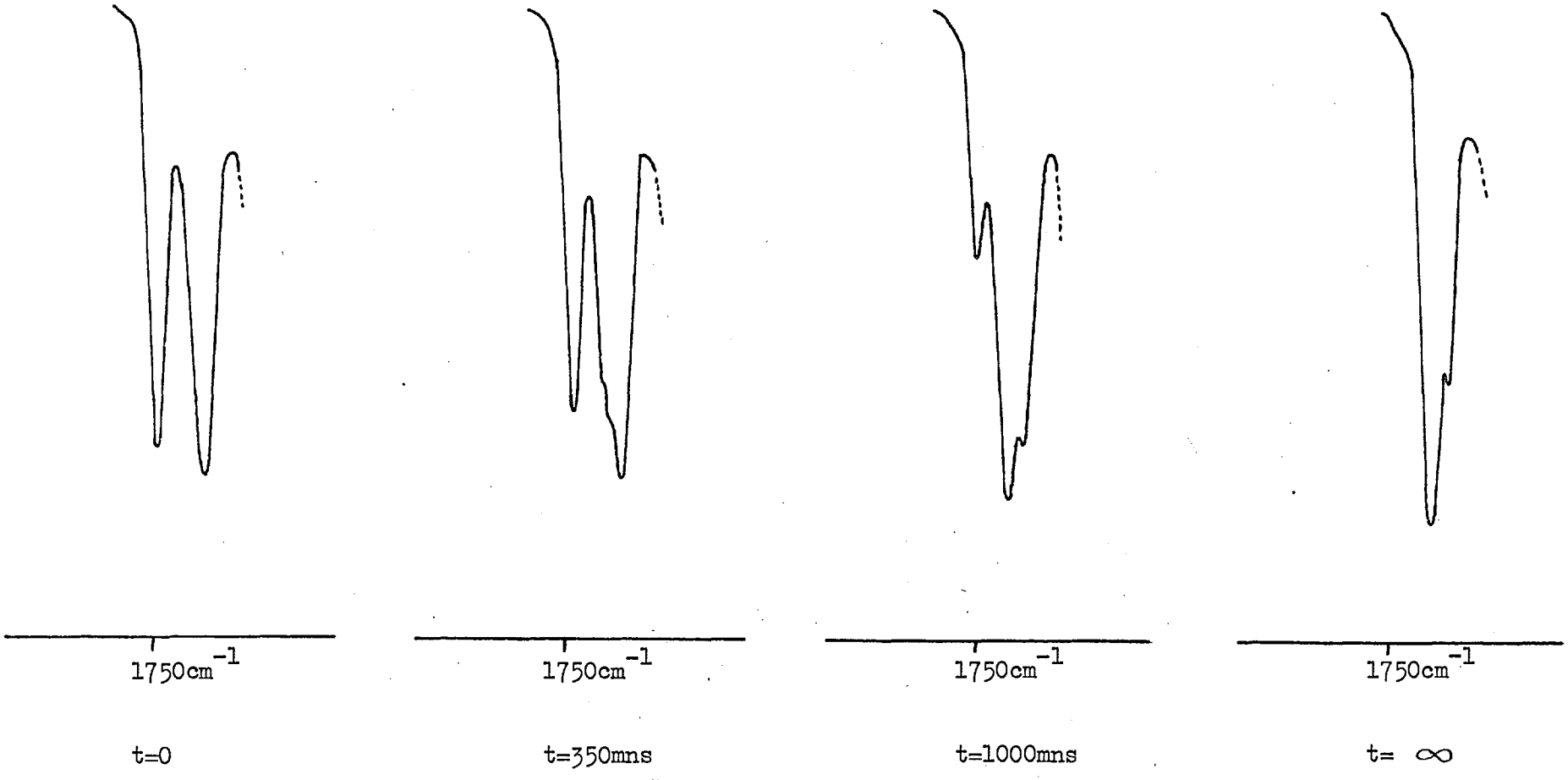
The carbonyl stretching frequency of the substrate occurs at ca.1760cm^{-1} in acetonitrile, but in the rearranged product, an imide, the carbonyl frequencies occur at ca.1710,1685cm^{-1}. The rearrangement reaction was monitored by following the disappearance of the substrate carbonyl peak. First-order rate constants were calculated from a plot of log Y versus time, where

$$Y = \frac{A - A_\infty}{A_o - A_\infty}$$

and A_∞ is the absorbance at time '∞' and A_t and A_o are the absorbances at times t=t and t=0 respectively. Spectra obtained in a typical kinetic run are shown in Fig. 3.1 .

Fig.3.1 Time dependence of the carbonyl stretching region of the i.r. spectrum of N-(2,4-dinitrophenyl)benzimidoyl benzoate in acetonitrile at 25°C.



3.2 RESULTS

In order to determine a suitable temperature at which to follow the catalysed rearrangement, the variation of the thermal rate with temperature was studied (Table 3.1). It was found that at temperatures above 40°C, the thermal rate was too fast to obtain highly reliable kinetic data.

Table 3.1

THERMAL REARRANGEMENT OF N-(2,4-DINITROPHENYL)BENZIMIDOYL BENZOATE

[Sub] = 0.1M Solvent = CH_3CN

T(°C)	$k_1(s^{-1})$
25	1.4×10^{-5} **
43	1.18×10^{-4} *
60	6.08×10^{-4}

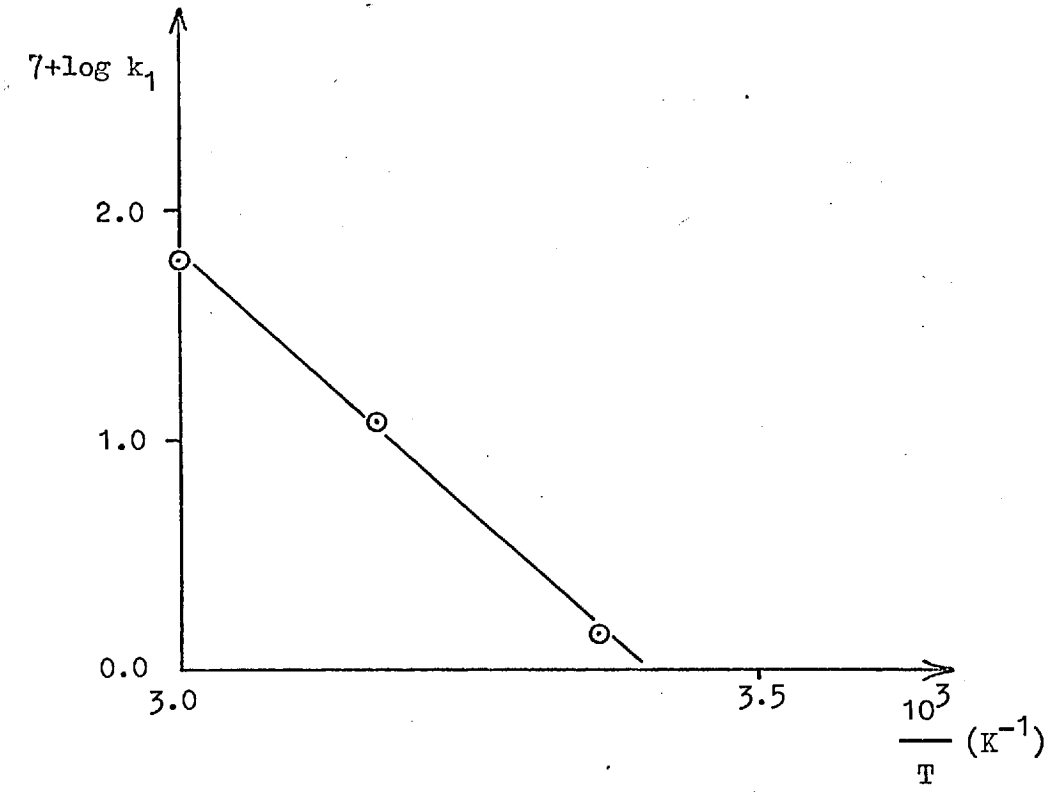
* Result obtained by Curtin and Miller.[115]

** Mean value of three kinetic runs.

The Arrhenius plot (Fig 3.2) demonstrates that the value obtained by Curtin and Miller [115] is in agreement with those obtained in the present study. The activation energy for the rearrangement in acetonitrile was calculated to be 85.3 $kJ.M^{-1}$, and the entropy of activation -12.4J/M.deg. from the Arrhenius plot

(values at 25°C). Curtin and Miller [115] obtained values of 99.6kJ.M.$^{-1}$ and -10.0J./Mdeg. for ΔH and ΔS respectively for the

Figure 3.2



thermal rearrangement reaction in benzene at 54.45°C, and these results agree favourably with those obtained in the present study.

A temperature of 25°C was chosen to study the effects of electrophilic reagents upon the rearrangement rate of O-acylisoimide 44. At this temperature, the rate of the thermal rearrangement was thought to be sufficiently low ($t_{\frac{1}{2}} \approx 800$mns.) to permit reliable measurement of the catalytic rate. The rearrangement rates observed in reactions containing benzoyl chloride and methyl iodide are given in Table 3.2, where it is clear that neither benzoyl chloride nor methyl iodide significantly catalyse the rearrangement reaction. It was thought that by using highly reactive acylating and alkylating

Table 3.2

CATALYSED REARRANGEMENT OF N-(2,4-DINITROPHENYL)BENZIMIDOYL BENZOATE

$[Sub]_o$ = 0.1M Solvent = CH_3CN T = 25°C

[Cat]	$10^5 k_1 (s^{-1})$
0.005 PhCOCl	1.4
0.05 PhCOCl	1.4
0.005 MeI	1.3
0.05 MeI	1.4

agents, a catalytic intermolecular reaction would be observed. The results obtained with some highly reactive electrophiles are given in Table 3.3.

The failure to observe a catalysed intermolecular pathway at 25°C suggested that at even lower temperatures (0°C), where the thermal intramolecular reaction would be slower, a catalysed rearrangement reaction would be possible. The difficulties involved, however, in monitoring the reaction at 0°C, particularly the requirement for thermostatted infra-red cells, were thought to be so large that further amide systems were studied.

Table 3.3

CATALYSED REARRANGEMENT OF N-(2,4-DINITROPHENYL)BENZIMIDOYL BENZOATE

$[Sub]_o$ = 0.1M Solvent = CH_3CN T = 25°C

[Cat]M	$10^5 k_1 (s^{-1})$
0.126 Me_2SO_4	1.4
0.05 Me_2SO_4	1.3
0.006 CH_3COCl	1.4
0.1 CH_3COCl	1.4
0.033 $(CH_3)_3CCOCl$	1.5
0.04 $ZnCl_2$	1.4

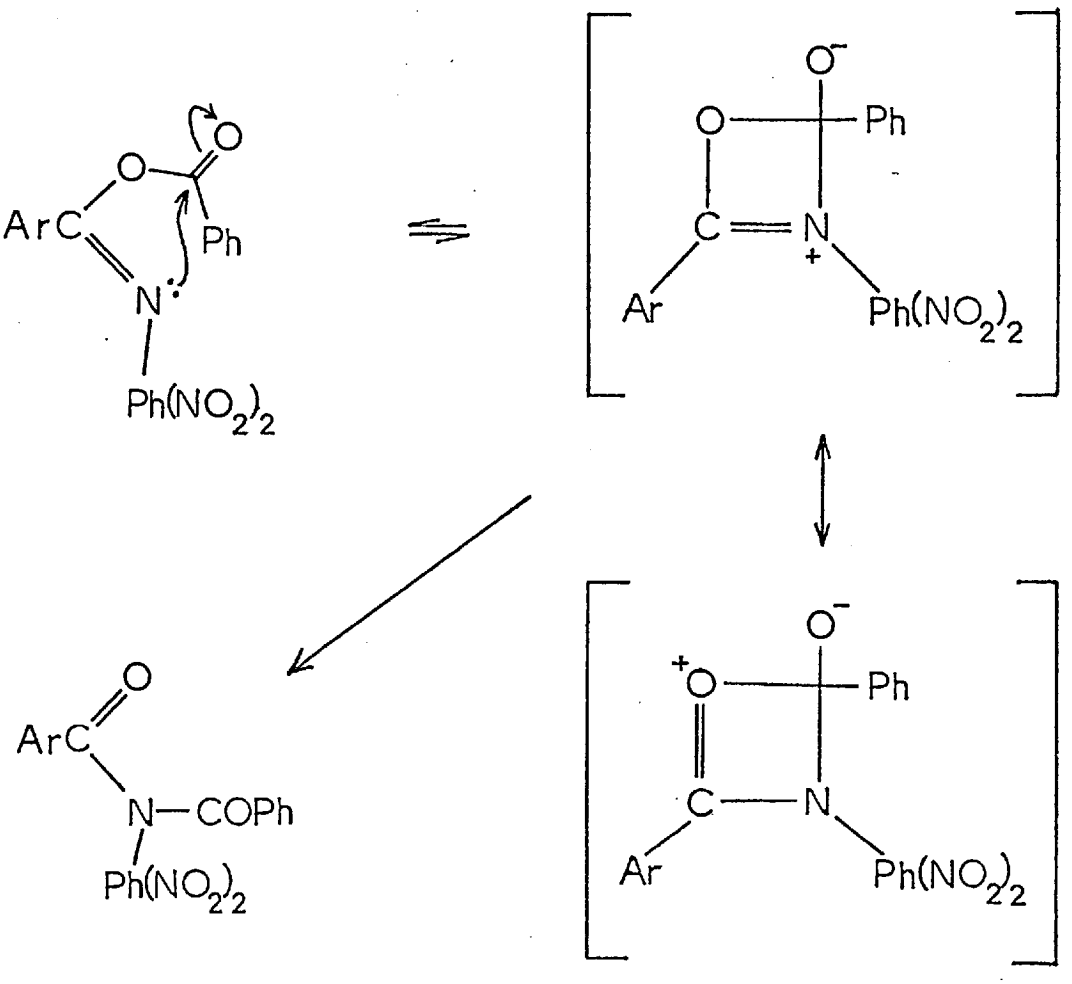
3.3 DISCUSSION

The intramolecularity of the thermal rearrangement was demonstrated by Curtin and Miller [115], who found that the thermal reaction was insensitive to added acetic acid and calcium hydride. In addition, the observed solvent dependency of the rearrangement reaction is also indicative of the intramolecular nature of the thermal rearrangement. The variation of a reaction rate with the solvent is used as an important criterion of mechanism [160,161]. In the present example, the rate of rearrangement of the O-acylisoimide 44, was found to show a low sensitivity to the solvents used. Thus on changing the solvent from benzene (ε_{25}=2.27)[162] to acetonitrile (ε=37.5)[162], a two-fold increase in the rate of rearrangement occurred [115]. This

small solvent sensitivity is similar to that encountered in dipolar cycloaddition reactions[163]. When the sensitivity of the rate of the rearrangement to the dielectric constant of the solvent is compared with that shown by the reaction of tertiary amines with alkyl halides[164] (a reaction which involves 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.

Curtin and Miller[115] proposed a mechanism involving initial nucleophilic attack by the lone-pair of electrons on the imino-nitrogen at the carbonyl carbon to give a zwitterionic four-membered transition state (Scheme 3.4).

Scheme 3.4



A second description involves considering the 1,3-acyl migration as a sigmatropic rearrangement and describing the mechanism in terms of the principle of conservation of orbital symmetry [165]. In this mechanism the orbital containing the lone pair of electrons on the nitrogen and the π-orbitals of the carbonyl group do not take part in the reaction, the only orbitals involved are the sigma-bonding orbitals of the C-O bond, and the π-bonding orbitals of the C=N bond. The suprafacial process (Fig.3.3) is thermally forbidden, while the antarafacial process (Fig.3.4) in which the acetyl group migrates across the face of the π-system is thermally allowed, is unlikely for steric reasons, particularly since it is not observed in 1,3-hydrogen migrations [165] where steric requirements are much less.

It can be seen therefore that an interpretation of the results in terms of the stepwise mechanism proposed by Curtin and Miller [115] is favoured. For the stepwise mechanism either step can be rate determining. Rate limiting nucleophilic attack at the carbonyl group of the O-acylisoimide would be expected to show reasonably large sensitivity to substituents in the benzoate ring by comparison with the reaction of a series of benzoyl chlorides with aniline (ρ=1.18). The slow breakdown of the tetrahedral intermediate would show a lower sensitivity. Thus Menger has observed ρ-values of 1.02 to 1.4 for the uncatalysed addition of pyrrolidine to acyl-substituted phenylbenzoates [166] in acetonitrile under conditions where collapse of the tetrahedral intermediate is rate determining. The ρ-value observed by Curtin and Miller (ρ +0.6)[115] for the 1,3-benzoyl migration, would suggest that the relative magnitudes of the formation and breakdown of the tetrahedral intermediate are much closer than in the intermolecular process. Breakdown of the tetrahedral intermediate

Fig.3.3 SUPRAFACIAL 1,3 SIGMATROPIC REARRANGEMENT

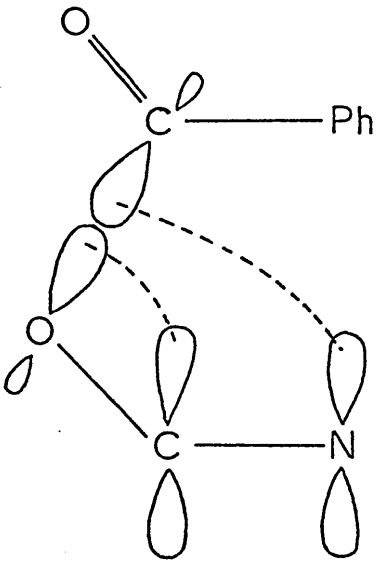
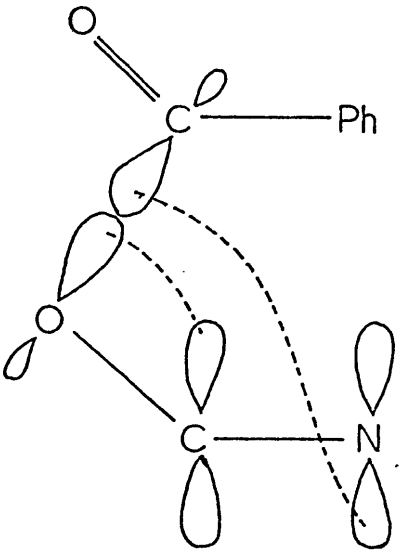
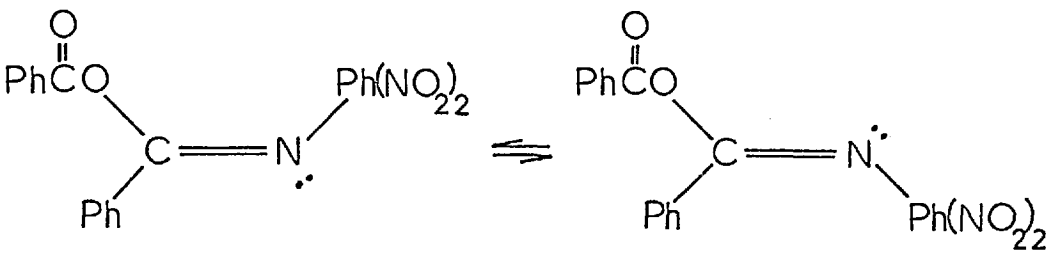


Fig.3.4 ANTARAFACIAL 1,3 SIGMATROPIC REARRANGEMENT



is unlikely to be rate determining for the 1,3 acyl migration as a very good leaving group is present. Furthermore a considerable driving force would be present for the breakdown of the four-membered ring. Rate determining formation of the tetrahedral intermediate would seem more likely. The ρ-value observed for the migrating ring indicates that if this is the case a very early transition state is necessary. This supposition would also agree with the observed solvent effect.

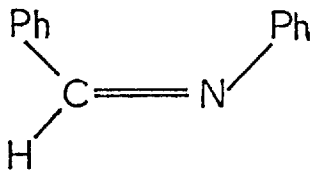
The possibility of cis-trans isomerism in N-(2,4-dinitrophenyl) benzimidoyl benzoate was discussed by Curtin and Miller [115] who assumed that the isolated compound was the trans-form by comparison with related compounds such as cis-azobenzene and cis-stilbene, in which the destabilizing steric interation of the two cis-phenyl groups is so great as to suggest that the trans-isomer is the more stable. Additional evidence was provided by the n.m.r. spectrum of the O-acylisoimide. Thus Curtin and Miller presumed that a trans structure was the predominant isomer of the O-acylisoimide and that cis-trans interconversion (Equation (49)) would be fast compared



.....(49)

to the subsequent rearrangement which might be expected to take place via the cis-isomer [115].

In order to demonstrate that this assumption was valid, the thermal rearrangement rates of the O-acylisoimides were compared with the rates observed for the cis-trans isomerisation of N-benzylideneaniline (74) and triarylimines (75), which have been shown [167,168] to be ca. 1-10 s^{-1} at similar temperatures to those used for the rearrangement reaction.



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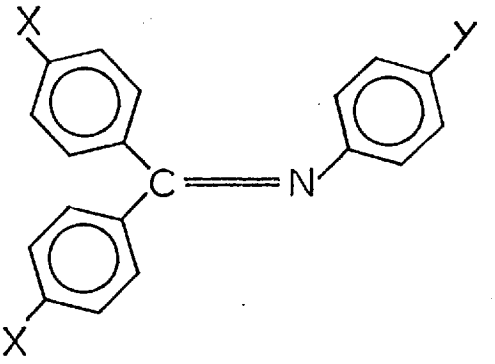


75

The failure to observe a catalytic rate for the rearrangement reaction is explicable in terms of a predominant cis structure for the N-(2,4-dinitrophenyl)benzimidoyl benzoate. The available evidence, however, favours a rapidly equilibrating mixture of cis and trans isomers. Additional evidence for this conclusion comes from the studies of Wettermark [169] on a series of N-benzylidene-4-substituted-anilines. Electron-withdrawing substituents were found [169] to accelerate the cis-trans conversion rate, which is consistent with decreasing double bond character in the C=N bond. Kessler [170] has recently published results which agree with Wettermark's earlier findings.

It is widely recognised that intramolecular processes are favoured over intermolecular processes owing to the "proximity" and "orientation" effects [171] which reflect the artificially enhanced collision numbers and the improved steric positioning of

intramolecular processes, respectively. Rate enhancements of between 10^3 and 10^6 are often observed for the intramolecular route [172]. The effective molarity (E.M.) (defined in terms of the k intra/k inter ratio) may therefore be between 10^3M. and 10^6M.. It is considered that much larger rate enhancements are possible in appropriate systems [171].

In the O-acylisoimide rearrangement, the low ΔS value observed by Curtin and Miller [115], and in the present study for the thermal rearrangement in benzene (ΔS=-10.0J./Mdeg.) and acetonitrile (ΔS=-12.4J./Mdeg.) reflects the "proximity" and "orientation" effects expected for the intramolecular reaction. The entropy advantage of intramolecular reactions over intermolecular reactions follows from the considerable loss of translational entropy in intermolecular reactions which must accompany the bringing together of reactants to form the transition state. An additional entropy advantage is gained by the "orientation" effect.

The rapid cis-trans isomerisation about the C=N bond also favours the intramolecular pathway by constant equilibration of the unreactive trans-form. An explanation to account for the observed results is that the effective molarity of the benzoate function in N-(2,4-dinitrophenyl) benzimidoyl benzoate is so large, as a result of the above factors, that added electrophilic species cannot effectively compete with the intramolecular pathway. Further, the above results suggest that although the nucleophilicity of the nitrogen atom is important for O-acylisoimide stability, the actual rate of cis-trans isomerisation about the C=N bond is also important. It can be seen that a 2,4-dinitrophenyl substituent on nitrogen has two opposing effects upon the stability of the O-acylisoimide. The first, reduced

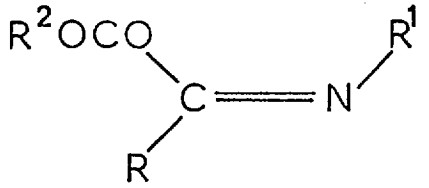
nucleophilicity of the nitrogen atom, leads to stabilisation and the second, increased rate of cis-trans isomerisation, facilitates the intramolecular rearrangement. When these effects are balanced out, the reduced nucleophilicity of the nitrogen atom is dominant, and the O-acylisoimide is relatively stable. Curtin and Miller [115] showed that a 2- or 4-nitrophenyl substituent on nitrogen leads to an unstable O-acylisoimide. This result can be interpreted in the above terms since the decrease in the rate of cis-trans isomerisation in these systems would be outweighed by the increase in nucleophilicity of the nitrogen atom. A similar explanation would account for the observed behaviour of N-methylbenzimidoyl acetate. The relative importance however of the nitrogen nucleophilicity versus the rate of cis-trans isomerisation cannot be deduced from the available data.

CHAPTER IV

THE ACYLATION OF N-ALKOXYAMIDES

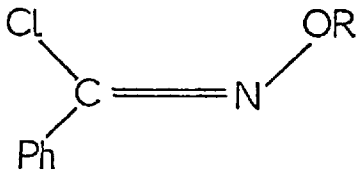
4.1 INTRODUCTION

The results of Chapter III suggest that for structures where the acyl function and the nitrogen lone pair electrons are rigidly held trans to each other (i.e. rotation about the C=N bond is absent), the O-acylisoimide would be extremely stable, and, in principle, examination of a catalysed intermolecular O-N rearrangement pathway would be possible. Specifically, for compounds such as 70, intramolecular rearrangement should be unimportant because of the configuration of the groups about the C=N bond.

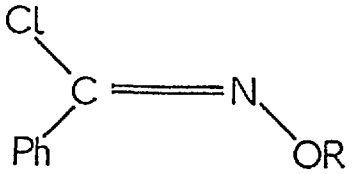


70

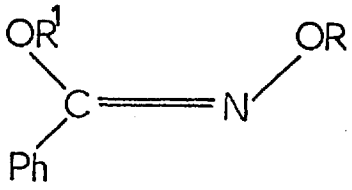
Geometrical isomerism due to restricted rotation about the C=N bond is commonly observed in systems where an electronegative atom such as oxygen [173,174], nitrogen [175,176,177] or halogen [178] is bonded to the imino nitrogen atom. For example, Johnson has been able to prepare the geometric isomers of the benzimidoyl halides [179,180] (76a, 76b) and the alkyl imidate derivatives [121] (52a, 52b) of amides bearing an N-alkoxy substituent. Attempts to prepare these isomers without the above nitrogen substituents have failed, presumably because of rapid isomerisation [181,182,183,184].



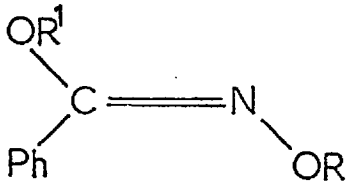
76a



76b

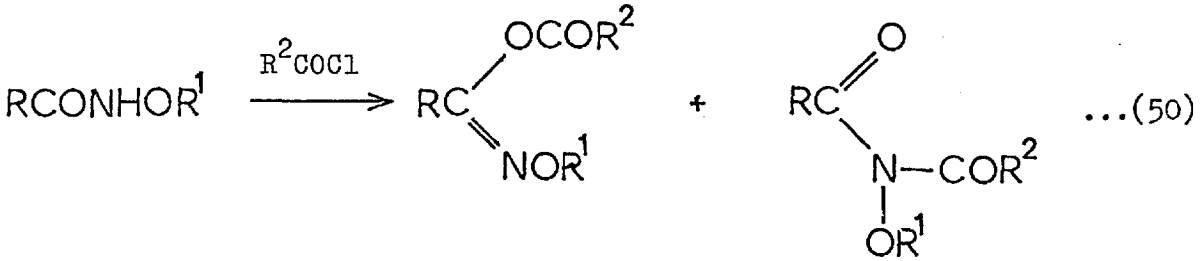


52a



52b

The acylation of N-benzyloxyamides has been found to result in both O- and N-substitution [135] (Equation (50)). No evidence was



...(50)

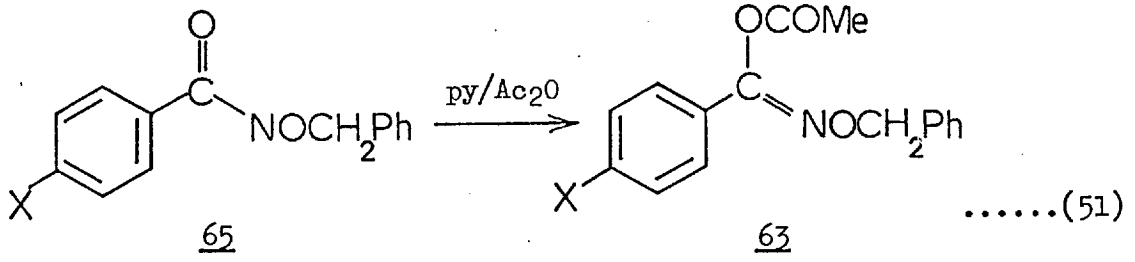
offered by Hearn and Ward [135] to account for the unusual observation that O-acylisoimides can actually be isolated in this particular case. It can be seen, however, that the previous interpretation, involving restricted rotation about the C=N bond would explain the stability of the O-acylisoimide. N-alkoxyamides therefore appeared to be much better substrates to examine the mechanism of amide acylation because the O-acylisoimide was apparently stable.

4.1.1 SYNTHESIS OF SUBSTRATES

N-alkoxyamides are generally prepared by the hydroxaminolysis of the corresponding ester followed by alkylation [118], or by acylation of an O-substituted hydroxylamine [135]. The first method is often time consuming and is susceptible to further reaction of the N-alkoxyamide to yield mixtures of dialkyl products [118]. A recent method for the preparation of N-alkyl-N-hydroxyamides involves diacylation of an N-substituted hydroxylamine followed by alkaline hydrolysis of one of the acyl groups[63,185], and a similar approach is applicable to the synthesis of N-alkoxyamides.

The low yields obtained for the alkylation of N-hydroxyamides [180] (29-75%), led to the synthetic route shown below being adopted (Scheme 4.1). The alkoxyamine was prepared from N-hydroxyphthalimide [186] and then acylated with the appropriate acyl chloride.

The N-benzyloxybenzimidoyl acetates (63) were then prepared from the N-benzyloxyamides (65) by reaction with acetic anhydride/ pyridine at room temperature (Equation (51)).

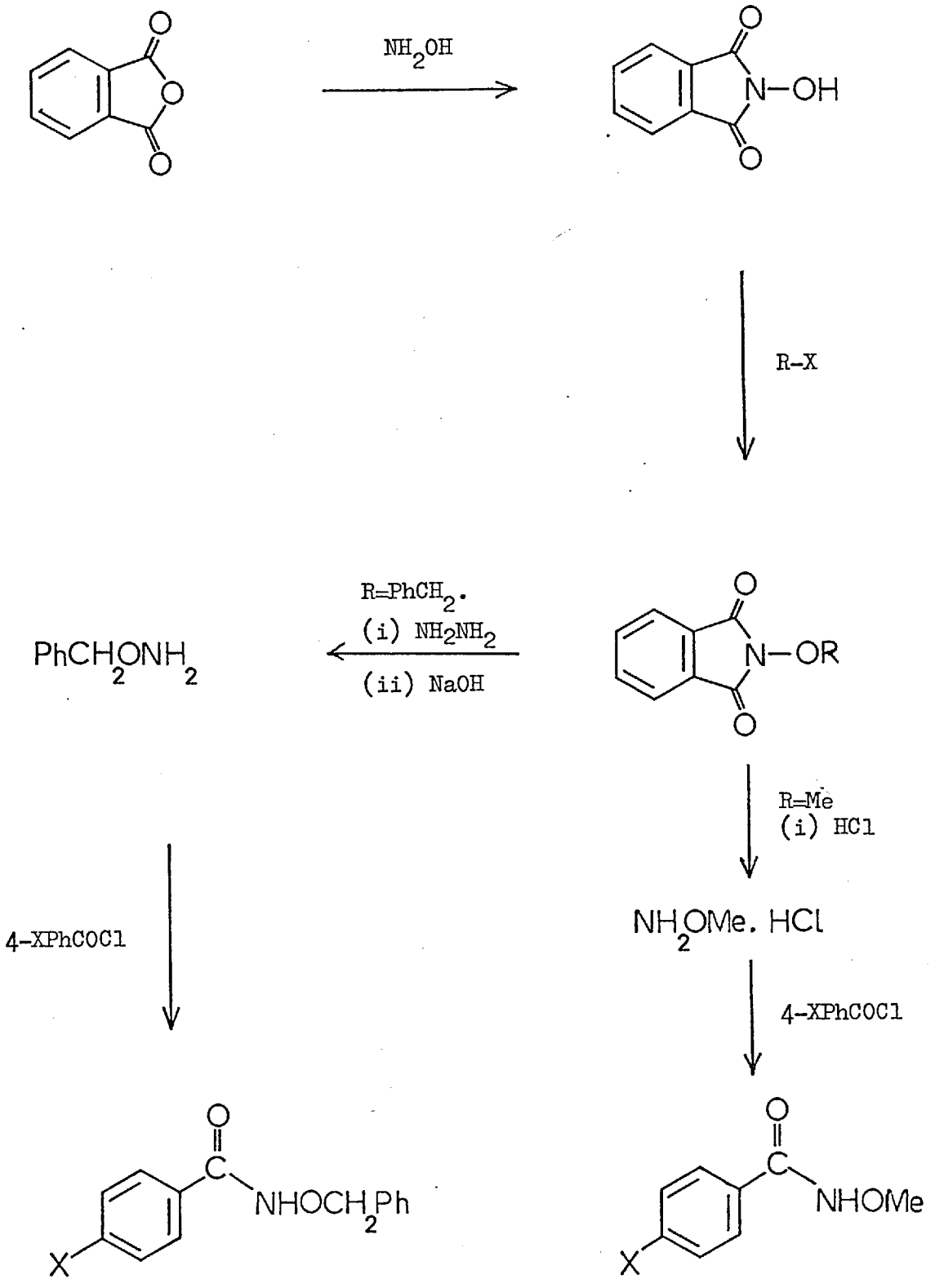


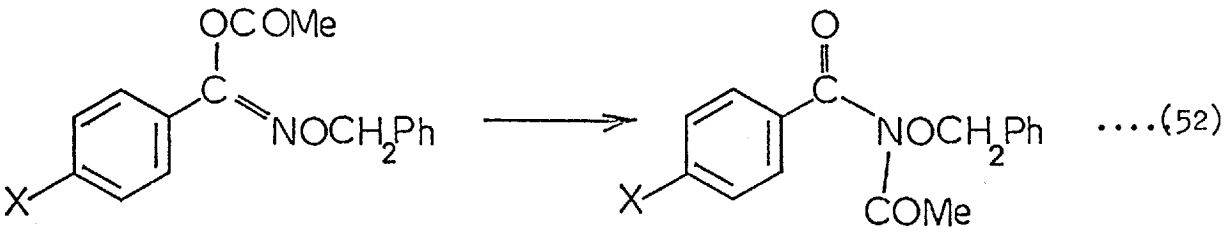
65 63 .....(51)

4.1.2 MEASUREMENT OF REARRANGEMENT RATES

The rearrangement of 63 to 64 (Equation (52)) can be followed by several methods. The change in ultra-violet absorption is feasible but absorptions by catalysts (e.g. acyl halides) are a complicating factor. Infra-red absorption, following the disappearance

Scheme 4.1


NH2OH
N–OH
R–X
R=PhCH2.
(i) NH2NH2
(ii) NaOH
PhCH2ONH2
N–OR
R=Me
(i) HCl
NH2OMe. HCl
4-XPhCOCl
4-XPhCOCl
NHOCH2Ph
NHOMe
X
X



....(52)

63 64

of the carbonyl stretching frequency of 63 at ca.1780cm^{-1} avoids this complication (c.f. Section 3.1.2) as does examination of the n.m.r. chemical shift of both benzylic methylene and acetyl hydrogen in the conversion of 63 to 64.

The i.r. method is in principle more accurate than the n.m.r. procedure, but suffers the disadvantage of requiring sampling each time a reading is taken. This requirement is particularly troublesome when highly reactive hygroscopic catalysts are employed. The n.m.r. method can be carried out with a single solution (0.5ml.) sealed in an n.m.r. tube. It was decided to use the n.m.r. technique to monitor the rearrangement reaction in view of the control of the reaction conditions which can be obtained. The n.m.r. spectra of N-benzyloxy-4-nitrobenzimidoyl acetate and its rearrangement product, N-acetyl-N-benzyloxy-4-nitrobenzamide, are shown in Fig. 4.1 and 4.2, respectively.

Fig.4.1 N.m.r. spectrum of N-Benzyloxy-4-nitrobenzimidoyl acetate in $CDCl_3$/TMS.

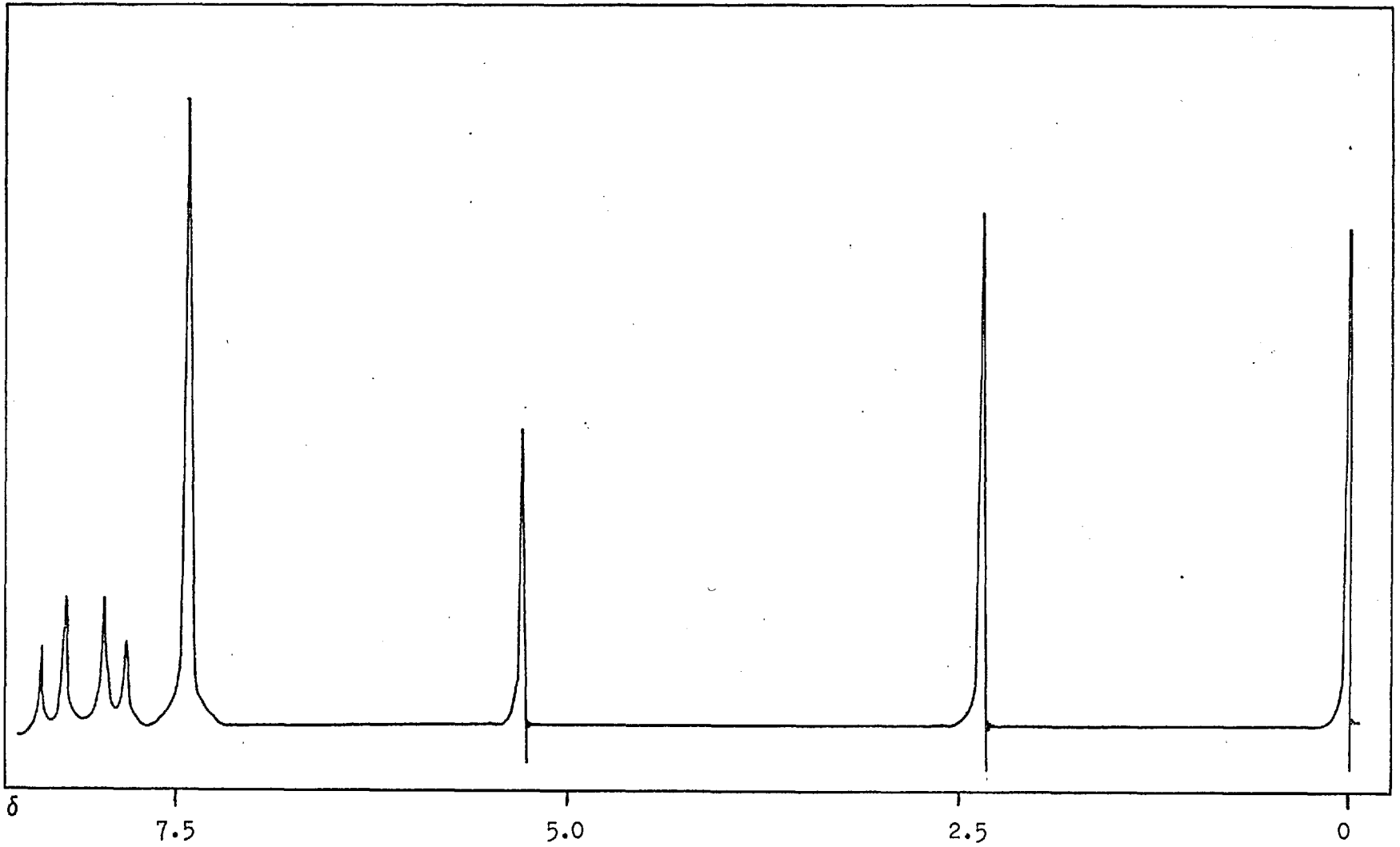
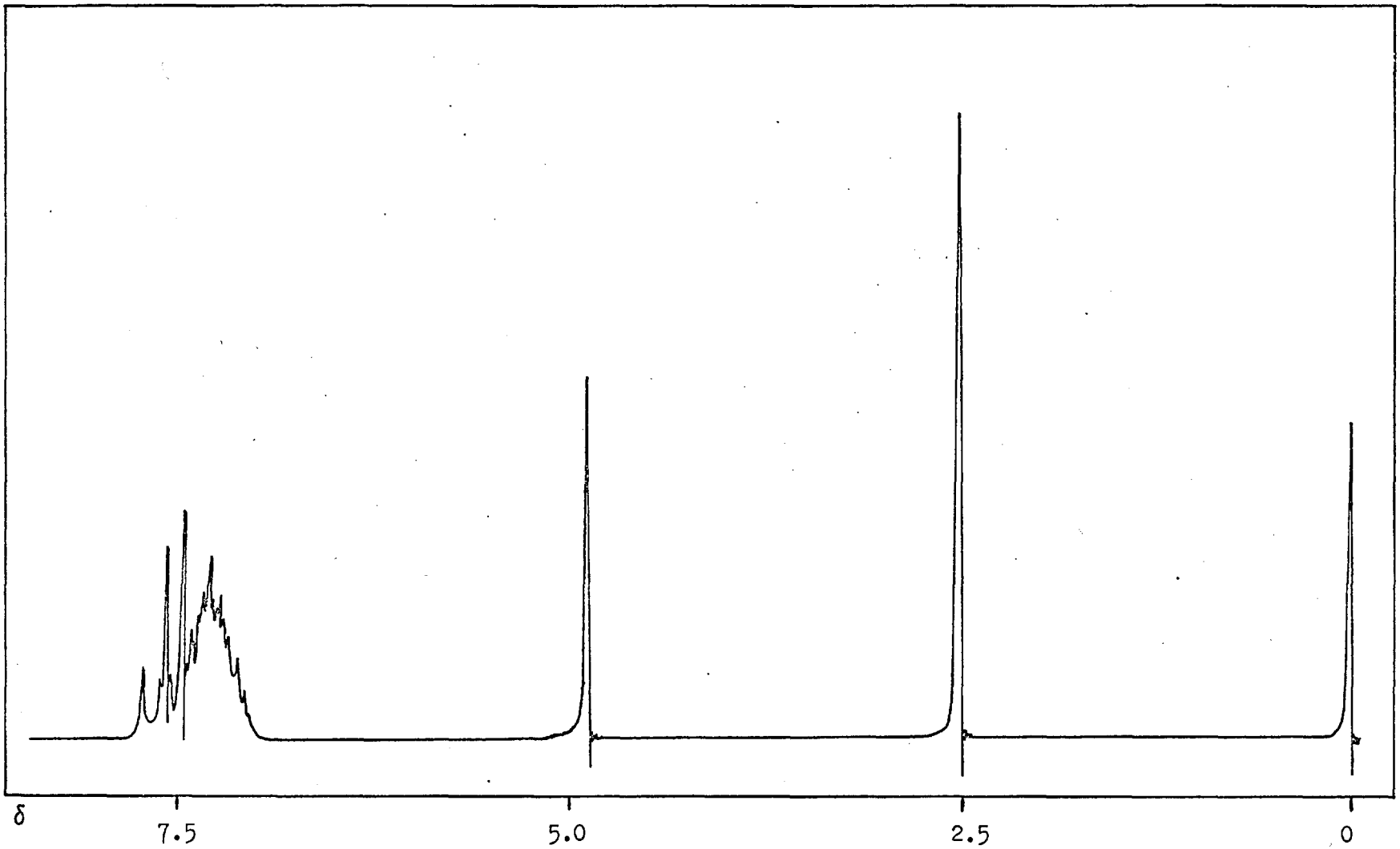


Fig.4.2 N.m.r. spectrum of N-acetyl-N-benzyloxy-4-nitrobenzamide in $CDCl_3$/TMS.



RESULTS

4.2 RATES OF ACETYLATION OF N-ALKOXYAMIDES

The formation of O-acylisoimides from N-benzyloxybenzamides was found to be very rapid at room temperature. Although there was a change in the chemical shift of the methylene signal during the formation of the O-acylisoimide, the reaction was so rapid in deuterochloroform that it was not found possible to take n.m.r. measurements with any reasonable degree of accuracy. Attempts to reduce the pyridine and acetic anhydride concentrations to decrease the rate, met with limited success because the N-alkoxyamides were found to be only moderately soluble in chloroform when the pyridine concentration was decreased. In order to obtain reasonable accuracy with the n.m.r. method fairly concentrated solutions (ca.0.2M) are usually required.

It was possible, however, to monitor the formation of N-benzyloxy-4-nitrobenzimidoyl acetate by an U.V. method in carbon tetrachloride because the λ max of the O-acylisoimide occurred at 300nm. in this case and thus was removed from the absorptions of the pyridine and acetic anhydride (200-285nm). In all other cases, however, the λ max of the O-acylisoimides fell within this region. The results obtained with this method are shown in Table 4.1.

The pseudo first-order plots were found to be linear

$$\text{Rate} = k_1 [\text{Sub}] \qquad \ldots\ldots\ldots(53)$$

to at least 90% reaction, and the rate equation derived from these results is shown in Equation (54)).

$$\text{Rate} = k_2[\text{py}]\ [\text{Ac}_2\text{O}]\ [\text{Sub}] \qquad \ldots\ldots(54)$$

Table 4.1

ACETYLATION OF N-BENZYLOXY-4-NITROBENZAMIDE USING PYRIDINE/ACETIC ANHYDRIDE IN CARBON TETRACHLORIDE

INITIAL $[4\text{-}NO_2C_6H_4CONHOCH_2Ph] = 1 \times 10^{-3}$M T = 30°C

$[py]^*$ M.	$[Ac_2O]$ M.	$10^4 x k_1 (s^{-1})$	$10^3 k_2$ $(l^2M^{-2}s^{-1})$
1.0	1.0	37.69	3.77
0.8	1.0	29.46	3.68
0.6	1.0	21.84	3.64
0.4	1.0	14.87	3.71
0.2	1.0	6.94	3.47
1.0	0.8	28.70	3.59
1.0	0.6	20.89	3.48
1.0	0.4	14.87	3.71
1.0	0.2	7.24	3.62

* The abbreviation 'py' refers to pyridine

The rate calculated for N-benzyloxy-4-nitrobenzimidoyl acetate is probably slower than, for example, the rate of acetylation of N-benzyloxy-4-methoxybenzamide, where the presence of the electron-donating 4-methoxy group should increase the electron-density on the carbonyl oxygen. The rapid rates observed for the acetylation of N-benzyloxy-4-nitrobenzamide confirm the qualitative results obtained synthetically using the n.m.r. method to monitor the reaction.

4.3 THERMAL REARRANGEMENT

The O-acylisoimides prepared by the acetylation of N-benzyloxyamides were found to be stable for long periods ($>$ 4 weeks) when heated alone in chloroform, nitrobenzene or carbon tetrachloride solutions at 60°C. By analogy with O-alkyl benzimidates it was anticipated that rearrangement could be effected by electrophilic catalysts such as acylating agents. This observation was confirmed early on, but it was also apparent that various bases also catalysed the rearrangement reaction. It is convenient to deal with the base-catalysed rearrangement first.

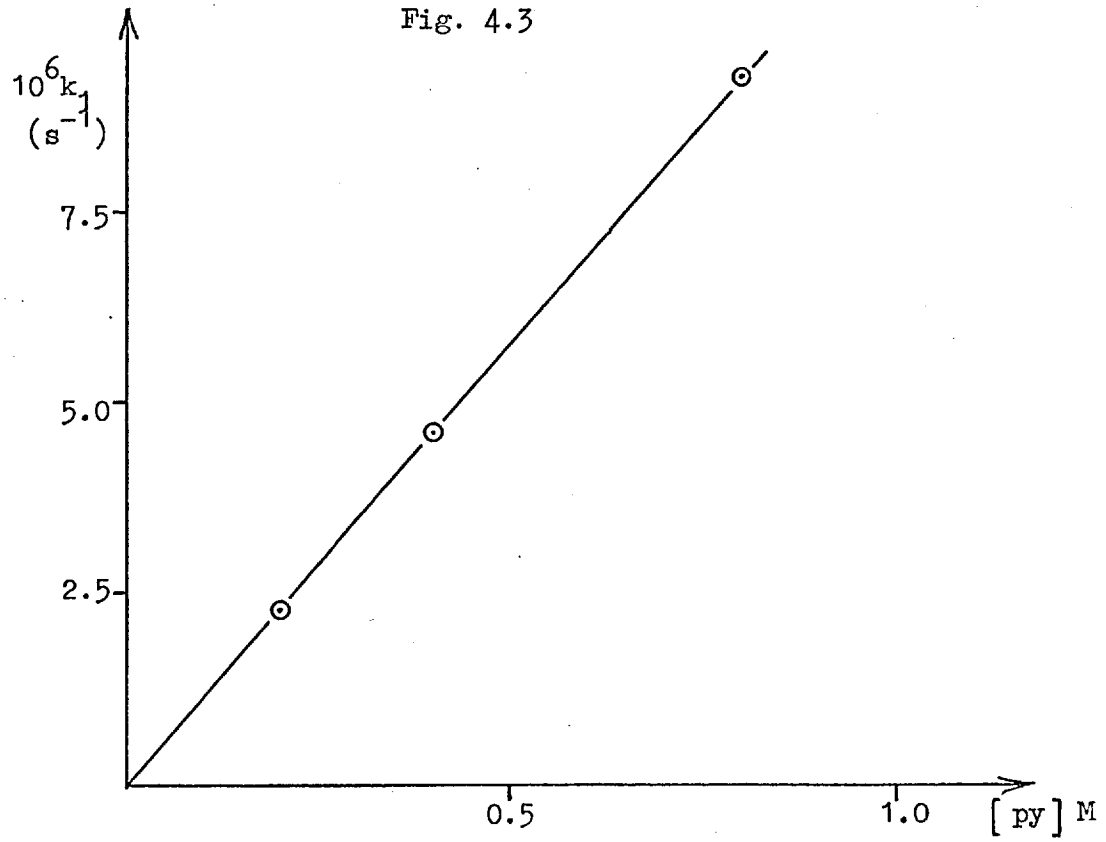
4.4 PYRIDINE/ACETIC ANHYDRIDE CATALYSIS

The yields obtained in the preparation of the O-acylisoimides depend significantly upon the reaction time. Monitoring the reaction by n.m.r. and by U.V. (Section 4.2) showed that the formation of O-acylisoimide was extremely rapid at room temperature (approx. $t_{\frac{1}{2}}$=2mns.), and isolation after ca.30 minutes gave greater than 90% yield of the required product. Hearn and Ward [135], however, allowed reaction to

continue overnight at room temperature and their yields of O-acylisoimide varied from 93% for the 4-methoxy system to 50% in the case of the 4-nitro compound. These observations suggested that the pyridine/acetic anhydride reagent also catalysed the O-N rearrangement reaction.

This possibility was examined for N-benzyloxy-4-nitrobenzimidoyl acetate in nitrobenzene, using equimolar concentrations of pyridine and acetic anhydride, and pseudo first-order rate coefficients (Equation (55)) are given in Table 4.2. It can also be seen that the reaction is first-order with respect to [substrate], as implied by Equation (55). The kinetic orders with respect to catalyst components are not immediately obvious because the plot of k_1 versus [py] $[Ac_2O]$ is not linear but plots of either [py] or $[Ac_2O]$ versus k_1 are (Fig. 4.3). This result rules out a simple third order rate

Fig. 4.3



equation (Equation (55)) and suggests that both pyridine and acetic

Table 4.2

CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-NITROBENZIMIDOYL ACETATE USING PYRIDINE/ACETIC ANHYDRIDE IN NITROBENZENE AT 60°C

[SUB] M.	$[Ac_2O]$ M.	[py] M.	$10^6 k_1 (s^{-1})$
0.4	0.2	0.2	2.3
0.4	0.4	0.4	4.6
0.8	0.8	0.8	9.17
0.2	0.4	0.4	4.88
0.2	0.8	0.8	8.95
0.4	0.8	0.8	9.20
0.8	0.8	0.8	9.35
0.4	0.2	0.2	2.38

Table 4.3

PYRIDINE/ACETIC ANHYDRIDE CATALYSED REARRANGEMENT OF $4\text{-}XC_6H_4C(OCOMe):NOCH_2Ph$ IN NITROBENZENE

INITIAL [Sub] = 0.4M T = 60°C.

X	$[Ac_2O]$ M.	[py] M.	$10^7k_1(s^{-1})$
NMe_2	0.8	0.8	3.60
MeO	0.8	0.8	7.60
MeO	0.8	0.8	7.30
MeO	0.4	0.4	3.40
MeO	0.2	0.2	1.60
Me	0.8	0.8	6.50
Me	0.4	0.4	3.30
H	0.8	0.8	9.42
H	0.4	0.4	4.51
H	0.2	0.2	2.30
Cl	0.8	0.8	30.0
Cl	0.4	0.4	13.0
Cl	0.2	0.2	6.7

anhydride exert independent catalyses. Similar results were

$$\text{Rate} = k_1[\text{py}][\text{Ac}_2\text{O}][\text{Sub}] \qquad \ldots\ldots\ldots(55)$$

obtained for all the 4-substituted O-acylisoimides examined (Table 4.3).

To investigate the catalysis further, the [pyridine] was varied holding the [acetic anhydride] constant to give the results shown in Table 4.4. The plot of k_1 versus [pyridine] shown in Fig. 4.4, is clearly curved at low pyridine concentrations but the intercept is zero.

Table 4.4

EFFECT OF [PYRIDINE] UPON THE PYRIDINE /ACETIC ANHYDRIDE CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-NITROBENZIMIDOYL ACETATE IN NITROBENZENE AT 60°C

INITIAL [SUB] = 0.4M. $[\text{Ac}_2\text{O}] = 0.8\text{M}.$

[PYRIDINE] M.	$10^6 k_1 (s^{-1})$
0.05	1.06
0.10	1.84
0.20	3.70
0.40	5.42
0.80	9.17

Fig. 4.4

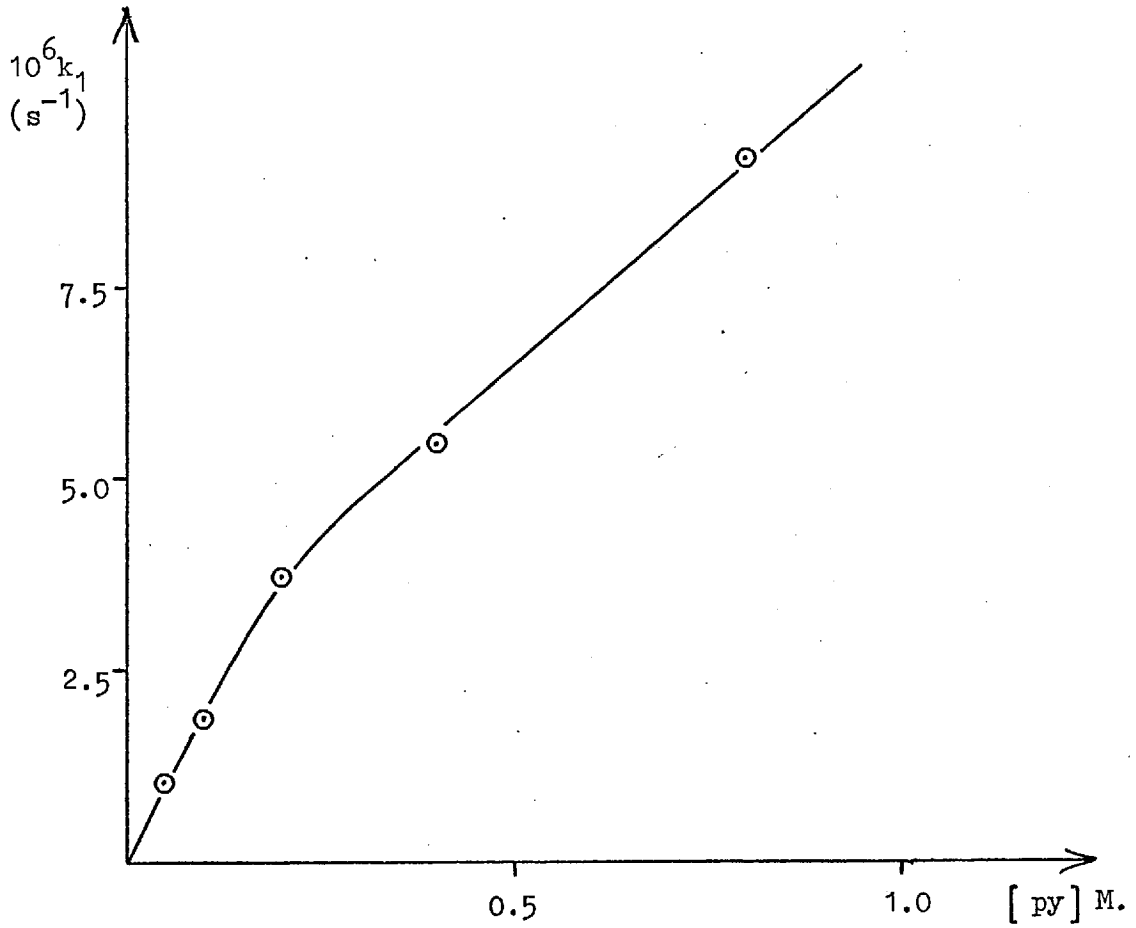
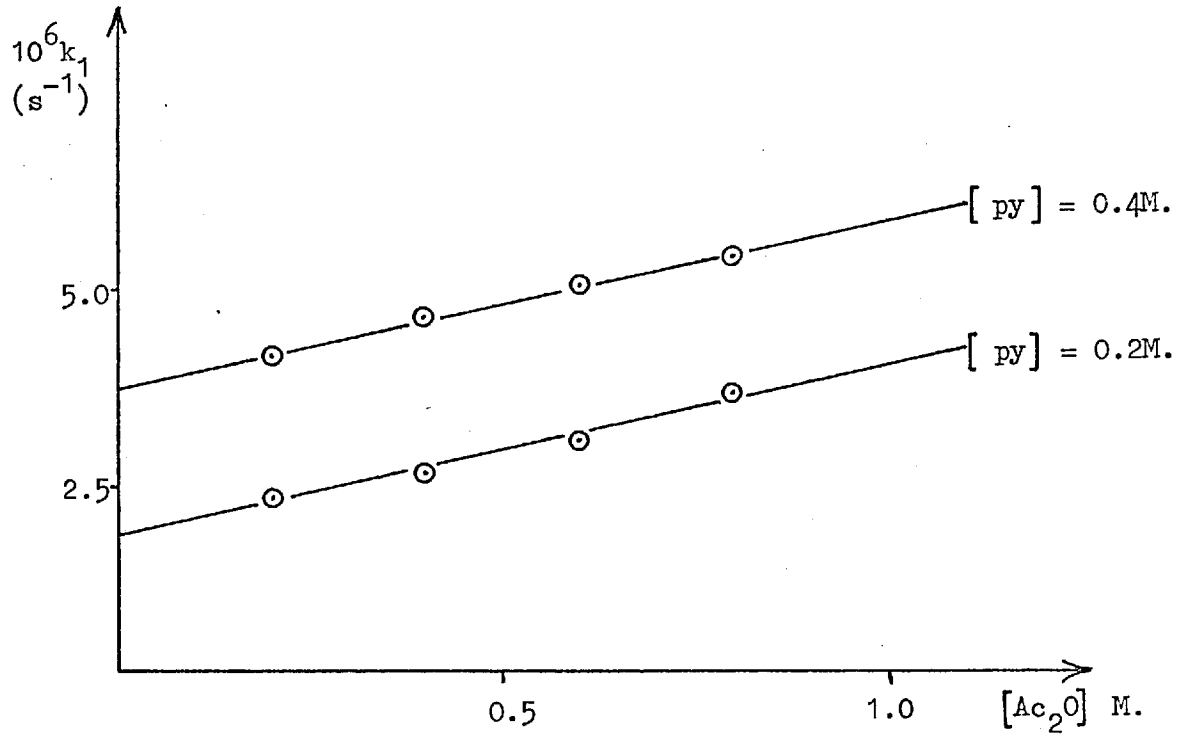

$10^6 k_1$ (s^{-1})
7.5
5.0
2.5
0.5
1.0
[py] M.

Fig. 4.5


$10^6 k_1$ (s^{-1})
[py] = 0.4M.
[py] = 0.2M.
5.0
2.5
0.5
1.0
[Ac_2O] M.

Rates of rearrangement observed when the [acetic anhydride] was varied at constant [pyridine] are given in Table 4.5, and graphically in Fig. 4.5. Here positive intercepts are obtained

Table 4.5

EFFECT OF [ACETIC ANHYDRIDE] UPON THE PYRIDINE/ACETIC ANHYDRIDE CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-NITROBENZIMIDOYL ACETATE IN NITROBENZENE AT 60°C

INITIAL [SUB] = 0.4M

[py] M.	$[Ac_2O]$ M.	$10^6 k_1 (s^{-1})$
0.4	0.2	4.09
0.4	0.4	4.60
0.4	0.6	5.00
0.4	0.8	5.42
0.2	0.2	2.25
0.2	0.4	2.60
0.2	0.6	3.02
0.2	0.8	3.60
0.2		2.07
0.4		4.17

whose value depends on the [pyridine] . This also implies that the pyridine-catalysis is independent of the acetic anhydride concentration. The latter deduction was confirmed by observation (see Table 4.5) of substantial rearrangement rates for pyridine in the absence of acetic

anhydride-corresponding to the intercepts of Fig. 4.5. Comparison of the intercepts in Fig. 4.5 suggests that the reaction has a first-order dependence on [pyridine] , but in the presence of acetic anhydride (cf. curvature of Fig. 4.4) this simple dependence breaks down. Further, the kinetic order with respect to the [acetic anhydride] , (calculated from a plot of log k_1 versus log $[Ac_2O]$) is very small (0.2). Both aberrant results stem (as is discussed further below) from catalysis by acetate ion, but here it can be seen that pyridine catalysis is the major contributor to rearrangement in the presence of acetic anhydride/pyridine. This implies that this combination does not catalyse the rearrangement reaction by acting as an acetylating agent alone, but acts mainly as a base catalyst.

4.4.1 PYRIDINE-CATALYSED REARRANGEMENT - SUBSTITUENT EFFECTS

The effect of 4-phenyl substituents was examined for the pyridine-catalysed rearrangement and found to be significant with electron-withdrawal facilitating the base catalysed pathway (Table 4.6). A Hammett plot of log k_2 versus σo gave a ρ-value of +1.49 (Fig. 4.6). The correlation coefficient for the plot of log k_2 versus σ_o was found to be 0.996 , compared to a value of 0.989 obtained in the corresponding plot of log k_2 versus σ . Thus it can be seen that the substituent effects are more accurately fitted to σ_o, the normal substituent constant than σ. This result will be discussed more fully in a later section. From the results with the 4-nitro O-acylisoimide (Table 4.6) it can be seen that the reaction is first-order both in substrate and in pyridine and the k_2 values calculated for other substrates assumes this rate equation is also applicable.

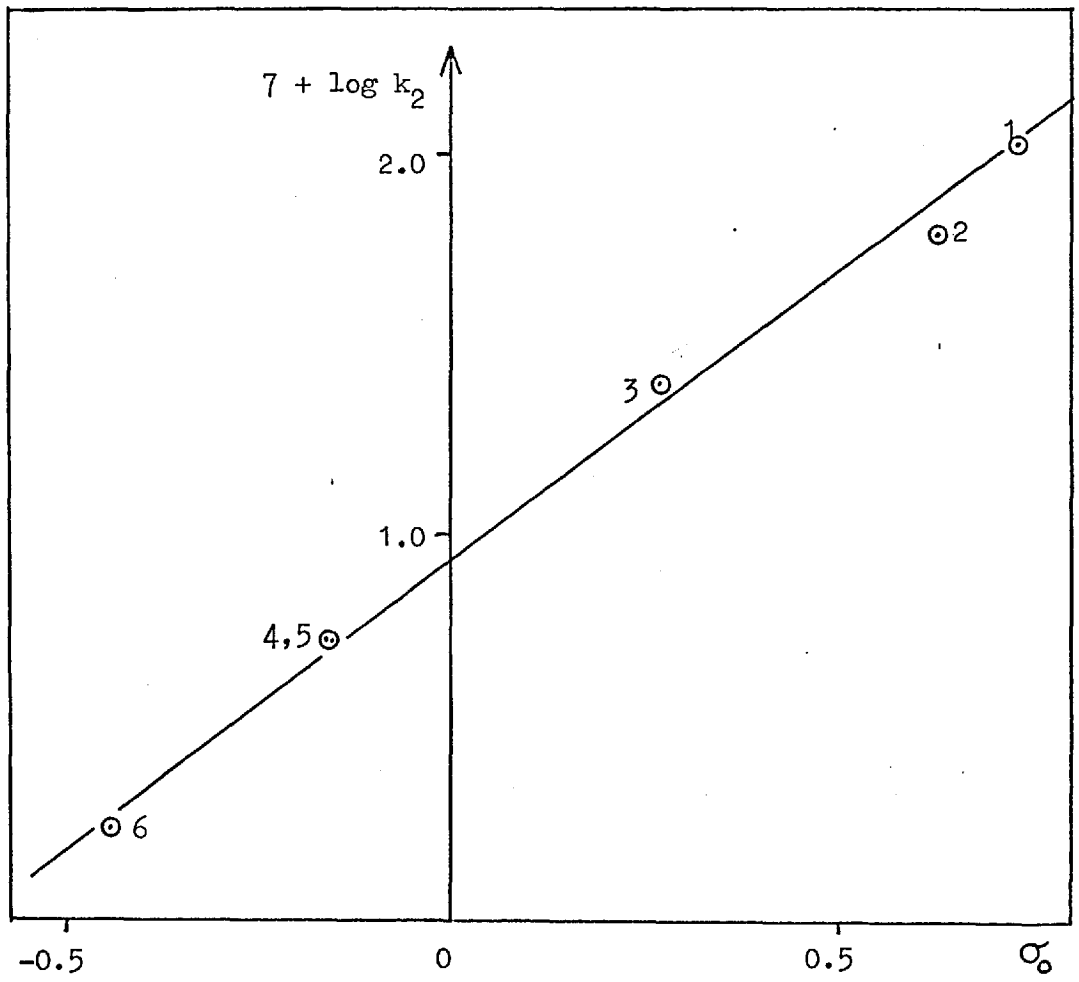
Table 4.6

PYRIDINE-CATALYSED REARRANGEMENT OF
4-X-$C_6H_4C(OCOMe):NOCH_2Ph$ IN NITROBENZENE AT 60°C

X	[Sub] M.	[py] M.	$10^6k_1(s^{-1})$	$10^6k_2 1M^{-1}s^{-1}$
NO_2	0.2	0.4	4.21	10.53
NO_2	0.4	0.4	4.17	10.43
NO_2	0.8	0.4	4.76	11.90
NO_2	0.4	0.8	8.75	10.94
NO_2	0.8	0.8	8.92	11.15
MeO	0.4	0.8	0.43*	0.54
Me	0.4	0.8	0.43*	0.54
Cl	0.4	0.8	2.03*	2.54
CN	0.4	0.8	4.88*	6.10
NMe_2	0.4	0.8	0.13*	0.16

* The k_1 given is the average of three kinetic runs

Fig. 4.6



1. N-benzyloxy-4-nitrobenzimidoyl acetate.

2. N-benzyloxy-4-cyanobenzimidoyl acetate.

3. N-benzyloxy-4-chlorobenzimidoyl acetate.

4. N-benzyloxy-4-methylbenzimidoyl acetate.

5. N-benzyloxy-4-methoxybenzimidoyl acetate.

6. N-benzyloxy-4-dimethylaminobenzimidoyl acetate.

4.4.2 PYRIDINE-CATALYSED REARRANGEMENT OF RADIO-LABELLED SUBSTRATES

To gain further mechanistic insight into the pyridine-catalysed rearrangement, cross-product experiments were conducted with radio-labelled N-benzyloxy-4-cyanobenzimidoyl 1-C^{14} -acetate. The radio-labelled substrate was rearranged in the presence of the 4-nitro O-acylisoimide using pyridine as the catalyst. After rearrangement, the N-acetyl products of the 4-cyano and 4-nitro compounds were isolated and assayed for C^{14} using liquid scintillation. The results for this particular experiment are given in Table 4.7. It can be seen

Table 4.7

PYRIDINE-CATALYSED REARRANGEMENT OF 4-CNPhC($OC^{14}OMe$):$NOCH_2Ph$ IN THE PRESENCE OF 4-NO_2PhC(OCOMe):$NOCH_2Ph$ IN DEUTEROCHLOROFORM AT 60°C

COMPOUND	SPECIFIC ACTIVITY (COUNTS/ mg.)
4-CN-$C_6H_4C(OC^{14}OMe):NOCH_2Ph$	91,000
4-CN-C_6H_4-CON(COMe)OCH_2Ph	54,212
4-NO_2-C_6H_5-CON(COMe)OCH_2Ph	29,487

that the crossover or 'scrambling' of the C^{14}-labelled acetyl group is high under the above conditions, but complete equilibration of the C^{14}-label is not observed. This suggests that rearrangement involves the formation of acetylpyridinium ion which may then attack either substrate.

4.4.3 CATALYSIS BY OTHER NITROGEN BASES

Catalysis by nitrogen bases other than pyridine was examined briefly and these results are given in Table 4.8. The reaction between imidazole and N-benzyloxy-4-nitrobenzimidoyl acetate was very rapid

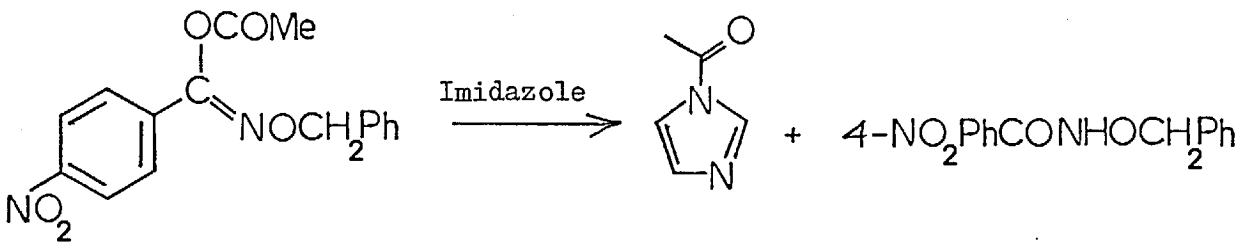
Table 4.8

BASE-CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-NITROBENZIMIDOYL ACETATE IN NITROBENZENE AT 60°C

Initial [Sub] = 0.4M.

Amine	[Catalyst] M.	$10^4 k_1 (s^{-1})$	$10^4 k_2 (1M^{-1}s^{-1})$
1-Acetylimidazole	0.4	0.0155	0.039
Pyridine	0.4	0.042	0.105
2,6-Lutidine	0.4	No Reaction	
1-Methylimidazole	0.28	6.74	24.07
Triethylamine	0.4	0.1	0.25

(approx. $t_{\frac{1}{2}}$ = 6mns at 38°C) and was found (by n.m.r. and product isolation) to give 1-acetylimidazole and N-benzyloxy-4-nitrobenzamide as the only observed products (Equation (56)). 2,6-Lutidine was found



.....(56)

to be a very poor catalyst for this system and no significant rearrangement occurred after five weeks at 60°C.

The above evidence favours the intermolecular mechanism involving the formation of N-acetyl intermediates from the catalyst.

4.5 ACETATE CATALYSIS

The observation of catalysed rearrangement of O-acylisoimides with tertiary nitrogen bases led to the study of acetate ion as a catalyst system. The acetate ion was provided by tetramethylammonium acetate for these studies, which were performed in deuterochloroform solvent. It was found that the rearrangement rates observed for acetate ion catalysis were much higher than those observed for the tertiary nitrogen bases (Table 4.9).

All reactions were found to give good first-order plots (Fig. 4.7) and the constancy of the k_2 values demonstrate that the reaction is also first-order in acetate. In order to demonstrate the inter- or intramolecular nature of this reaction, a similar approach to the pyridine rearrangement was adopted using a labelled substrate.

4.5.1 ACETATE CATALYSED REARRANGEMENT OF LABELLED SUBSTRATE

The rearrangement of the labelled substrate was performed in deuterochloroform solvent. When the reaction was complete, the N-acetyl-N-benzyloxy-4-cyanobenzamide product was purified by thin-layer chromatography and the product assayed for C^{14} using a liquid scintillation counter. The results are given in Table 4.10.

Table 4.9

ACETATE CATALYSED REARRANGEMENT OF 4-X-$C_6H_4C(OCOMe):NOCH_2Ph$ IN DEUTEROCHLOROFORM AT 60°C

X	[Sub] M.	$[Me_4\overset{+-}{N}OAc]$ M.	$10^4k_1(s^{-1})$	$10^3k_2(1M^{-1}s^{-1})$
NO_2	0.4	0.150	6.40	4.27
NO_2	0.4	0.205	8.36	4.08
NO_2	0.4	0.335	13.55	4.04
CN	0.4	0.15	5.60	3.73
CN	0.4	0.185	6.75	3.65
CN	0.4	0.360	13.24	3.68
Cl	0.4	0.277	3.57	1.29
Cl	0.4	0.400	5.40	1.35
Cl	0.4	0.575	7.67	1.33
MeO	0.4	0.150	0.60	0.40
MeO	0.4	0.265	1.10	0.42
MeO	0.4	0.400	1.64	0.41
NMe_2	0.4	0.180	0.24	0.13
NMe_2	0.4	0.252	0.35	0.14
NMe_2	0.4	0.480	0.66	0.14

Fig. 4.7. Acetate-catalysed rearrangement of N-benzyloxy-4-cyanobenzimidoyl acetate.

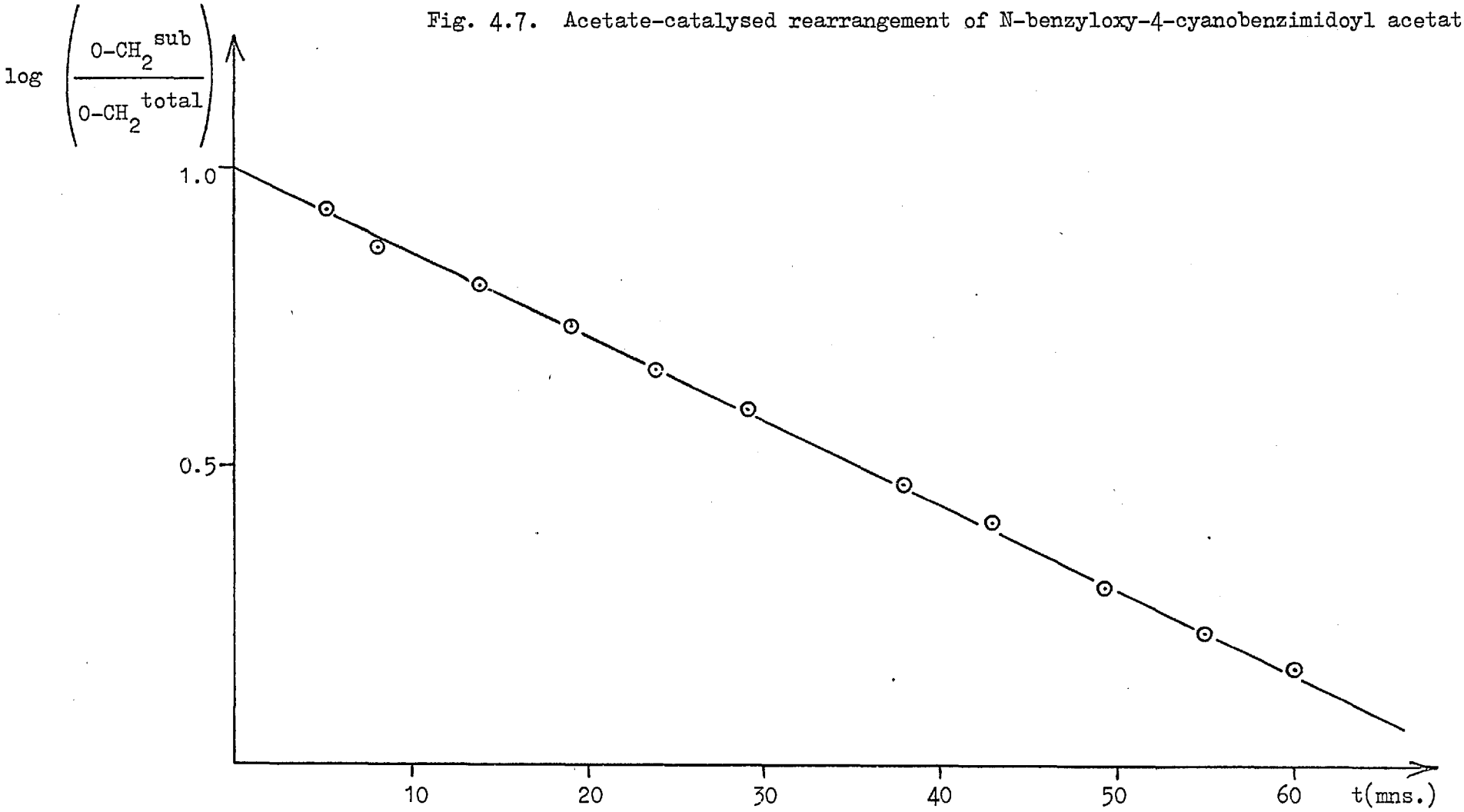


Table 4.10

ACETATE-CATALYSED REARRANGEMENT OF 4-CN-$C_6H_4C(OC^{14}OMe):NOCH_2Ph$ IN DEUTEROCHLOROFORM AT 60°C

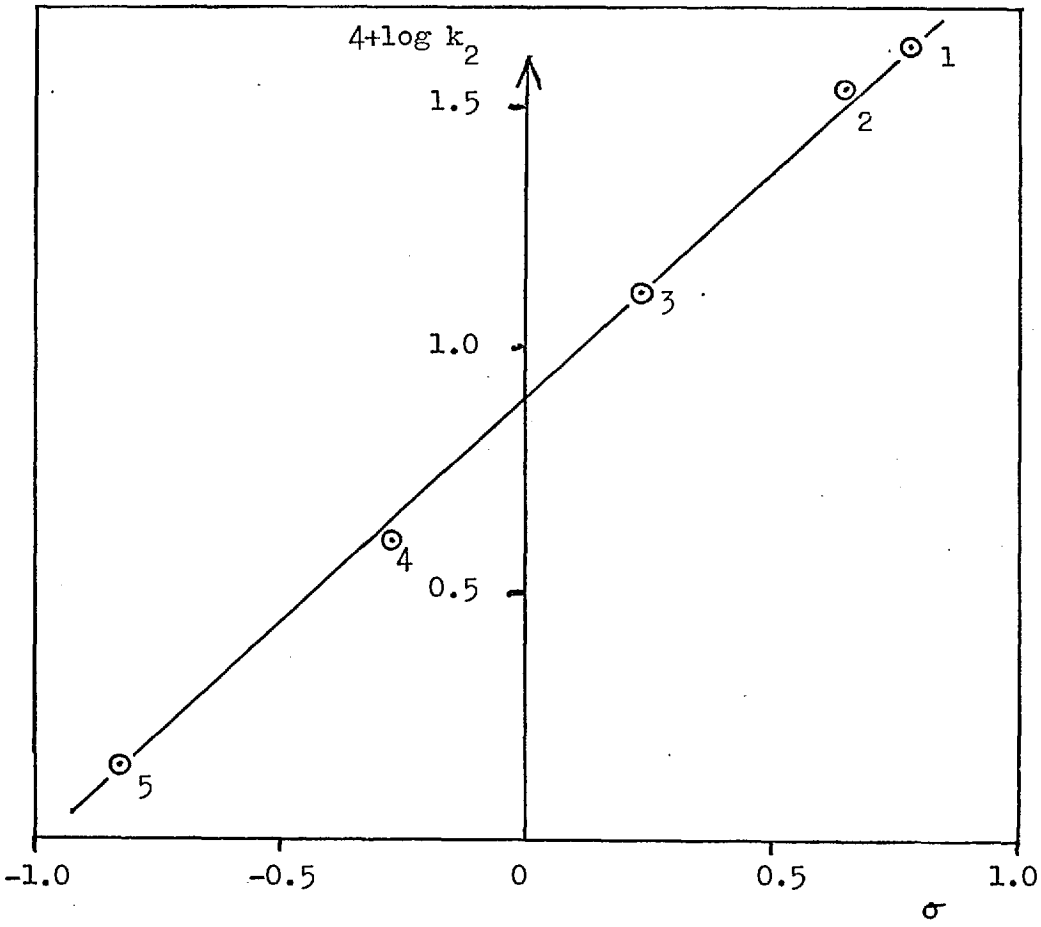
COMPOUND	SPECIFIC ACTIVITY (COUNTS / mg)
4-CN-$C_6H_4C(OC^{14}OMe):NOCH_2Ph$	58,357
4-CN-$C_6H_4CON(COMe)OCH_2Ph$	52,751

From Table 4.10 it is clear that there is high retention of C^{14} label using acetate ion to rearrange the O-acylisoimide system. This suggests that acetate catalysis involves an intramolecular pathway in contrast to the pyridine catalysis. A Hammett plot of log k_2 versus σ gives a ρ-value of +0.94 (Fig. 4.8) with a correlation coefficient of 0.996 . The corresponding plot of log k_2 versus σ_o , was found to be curved, in contrast to the pyridine catalysis, with a lower correlation coefficient of 0.923 .

4.6 CATALYSIS BY ACYLATING AGENTS

The results of Section 4.4 suggest that pyridine/acetic anhydride is an insufficiently reactive reagent to catalyse the O-N rearrangement of the O-acylisoimide. One complicating factor here is the presence of pyridine which clearly acts as a base catalyst. The question of whether catalysis by acylating agents occurs in the absence of base catalysts remains.

Fig.4.8



1. N-benzyloxy-4-nitrobenzimidoyl acetate.

2. N-benzyloxy-4-cyanobenzimidoyl acetate.

3. N-benzyloxy-4-chlorobenzimidoyl acetate.

4. N-benzyloxy-4-methoxybenzimidoyl acetate.

5. N-benzyloxy-4-dimethylaminobenzimidoyl acetate.

Several acylating reagents were examined but the results were found to be complex. However, relatively simple kinetics were obtained with trichloroacetyl chloride and it is this particular acylating system which will be described first.

4.6.1 HALOACYL HALIDES

Studies upon the acylation of 2-nitroaniline [187] have shown that mono- and tri-chloroacetyl chlorides are much more reactive than acetyl chloride. This result led to the examination of chloroacetyl chlorides as catalyst systems. The reaction was monitored by the appearance of the acetyl chloride signal (ca. δ 2.7), and the observed first-order rate constants given in Table 4.11 were calculated using a Swinburne plot, since the reaction is not pseudo first-order in this case. Typical n.m.r. spectra are shown in Fig 4.9.

The above results suggest that the reaction follows Equation (57) and the constancy of k_2 confirmsthis deduction.

$$\text{Rate} = k_2[\text{Sub}]\,[\text{RCOCl}] \qquad \ldots\ldots(57)$$

4.6.2 AROYL HALIDES

Aroyl halides were found to be poor catalysts for the rearrangement reaction and the kinetic studies were complicated by the release of the more reactive acetyl halides (Equation (58),Fig.4.10)

After a small amount of reaction between the O-acylisoimide and the aroyl halide to give a low concentration of acetyl halide, a competitive reaction was set up between the aroyl and acetyl halides. The reactivity of acetyl halides is much greater than that of aroyl

Table 4.11

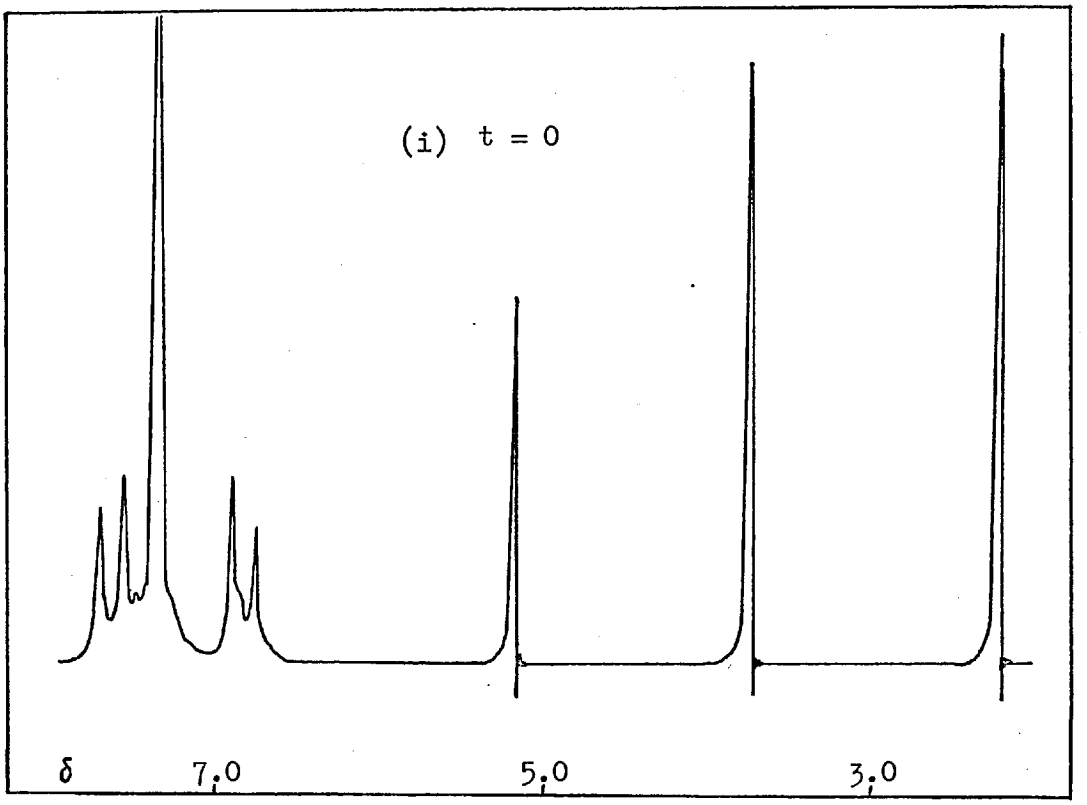
CATALYSED REARRANGEMENT BY CHLOROACETYL CHLORIDES AT 60°C

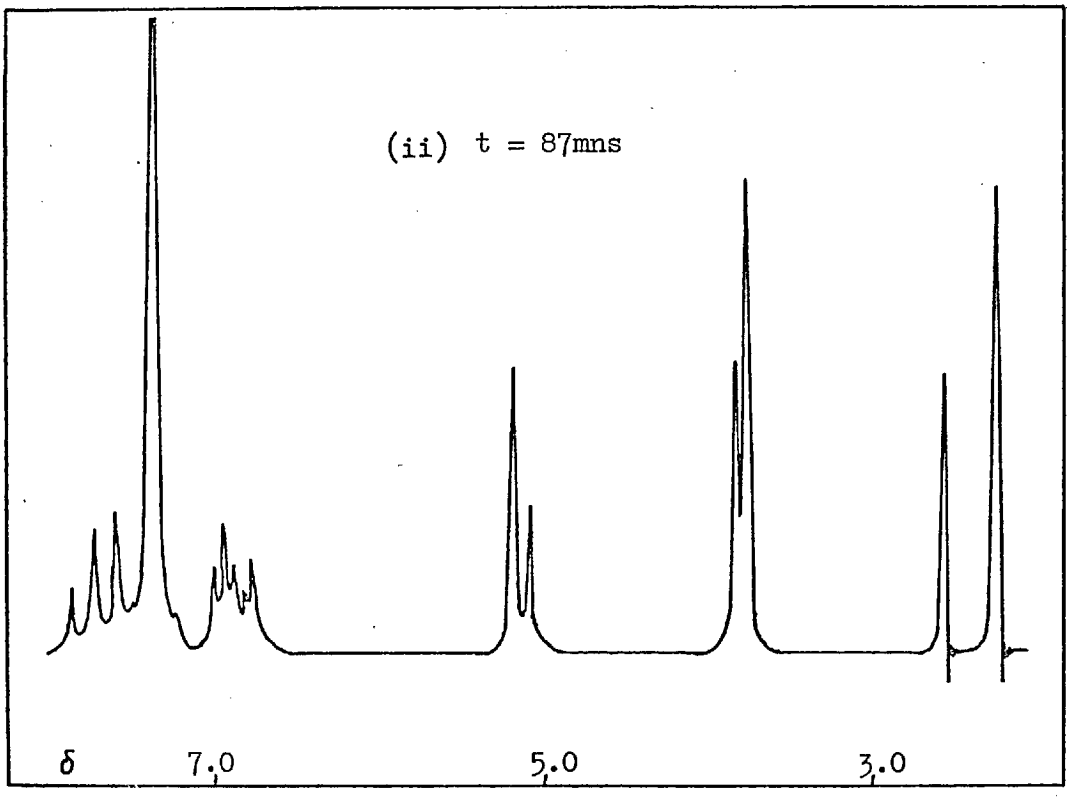
Substrate = 4-MeO-PhC(OCOMe):$NOCH_2Ph$ Solvent = CCl_4

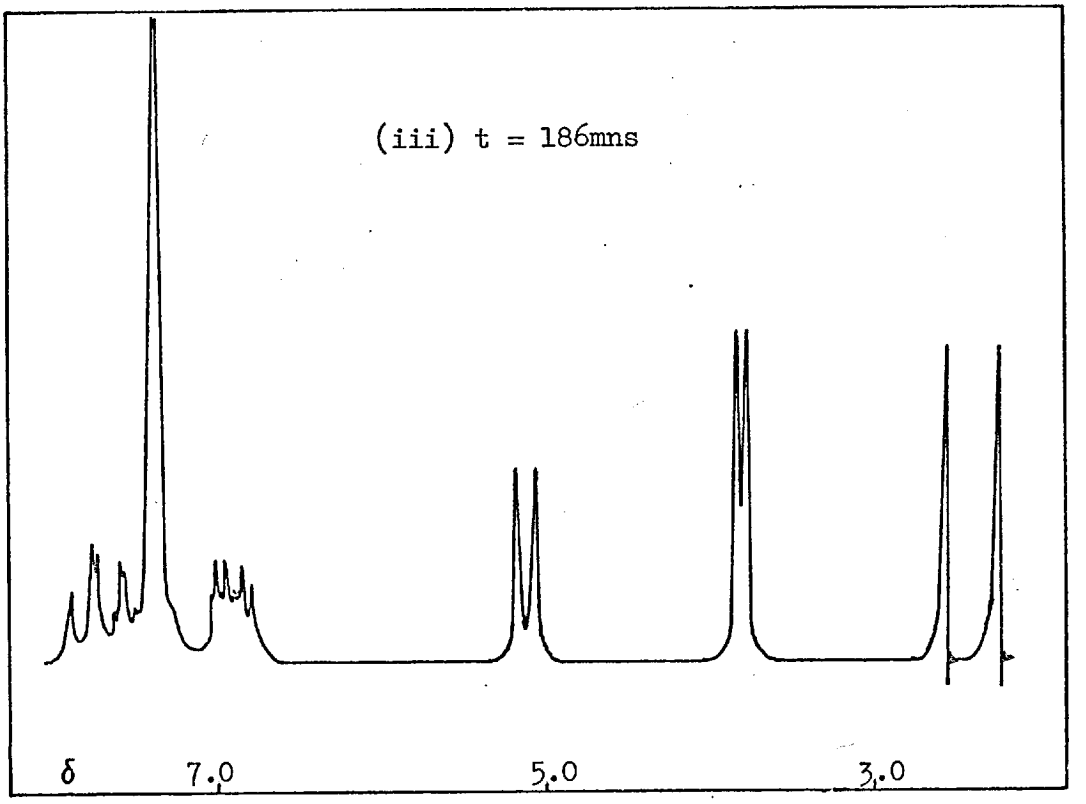
[Cat] M.	[Sub] M.	10^4k_1 ($s.^{-1}$)	10^4k_2 ($l.M.^{-1}s.^{-1}$)
0.2CCl_3COCl	0.2	0.4*	2.00
0.4CCl_3COCl	0.2	0.79	1.98
0.4CCl_3COCl	0.4	0.84	2.10
0.8CCl_3COCl	0.8	1.65	2.06
0.8CCl_3COCl	0.4	1.69	2.11
0.8CCl_3COCl	0.2	1.61	2.01
0.2$ClCH_2COCl$	0.4	0.21*	1.05
0.4$ClCH_2COCl$	0.4	0.39	0.98
0.8$ClCH_2COCl$	0.4	0.84	1.05

(* Calculated from the first 50% reaction)

Fig.4.9 Trichloroacetyl chloride catalysed rearrangement of N-benzyloxy-4-methoxybenzimidoyl acetate in CCl_4 at 60°C.






(iii) t = 186mns
δ
7.0
5.0
3.0

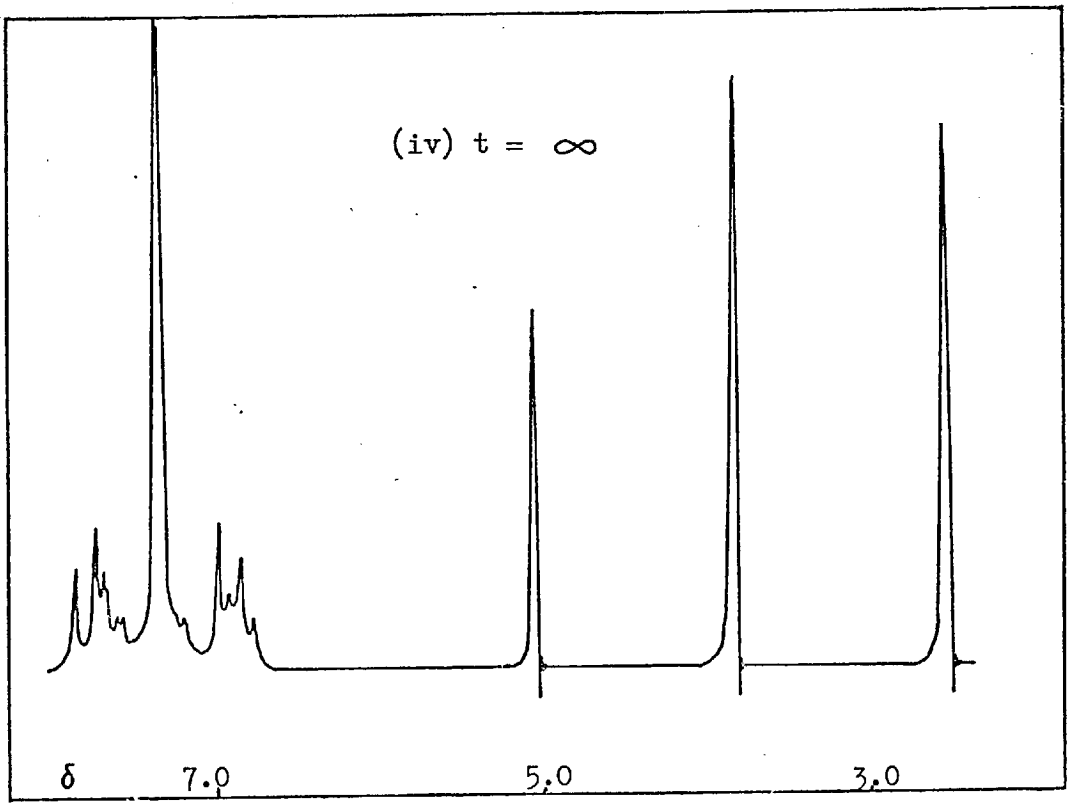
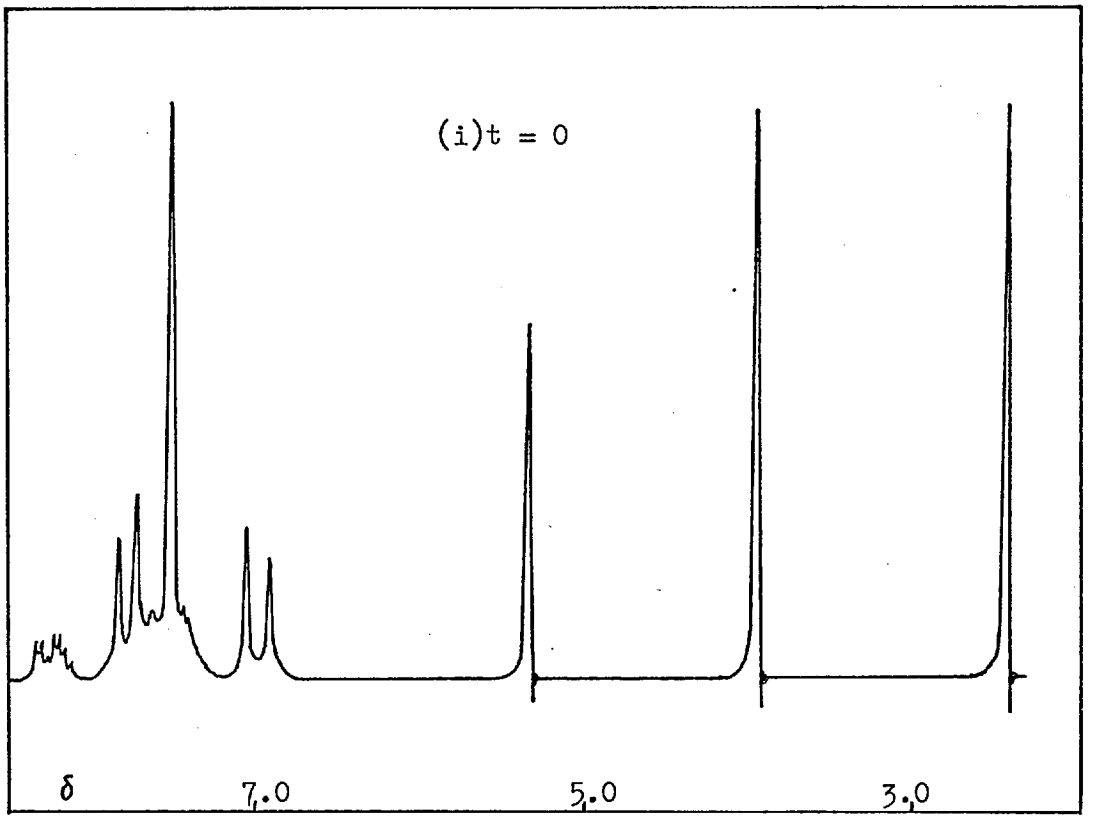
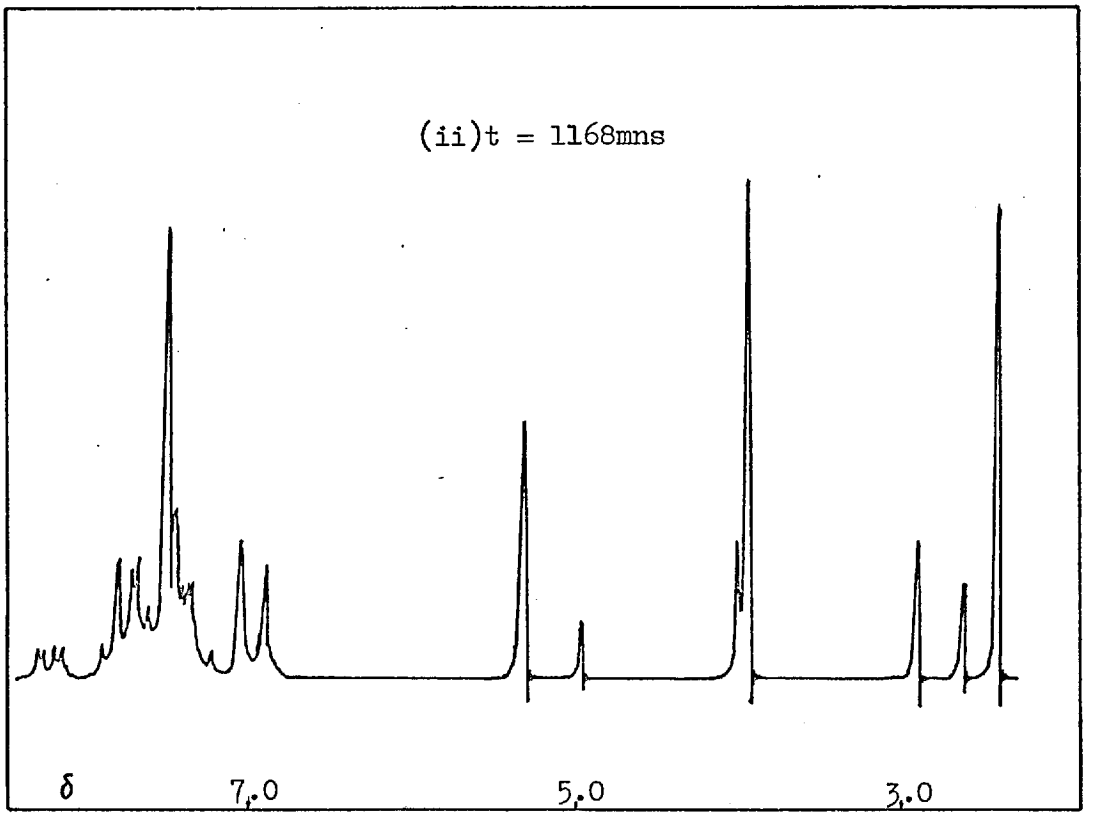
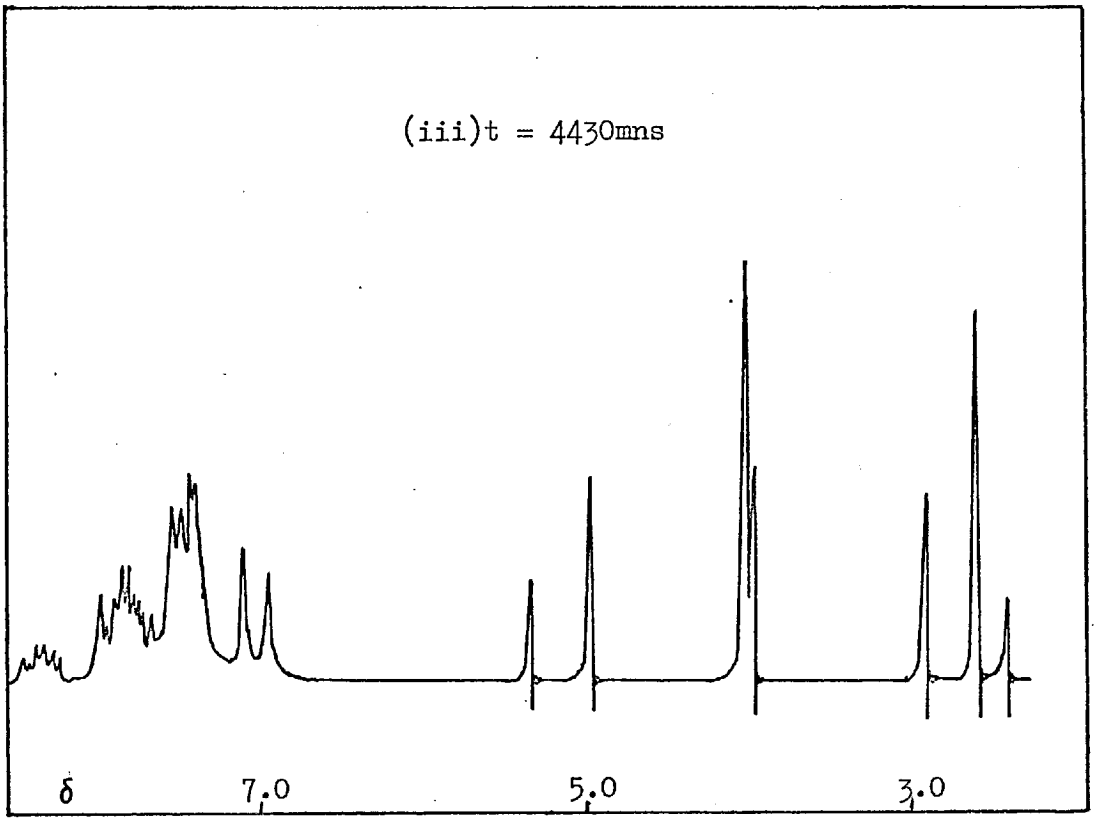
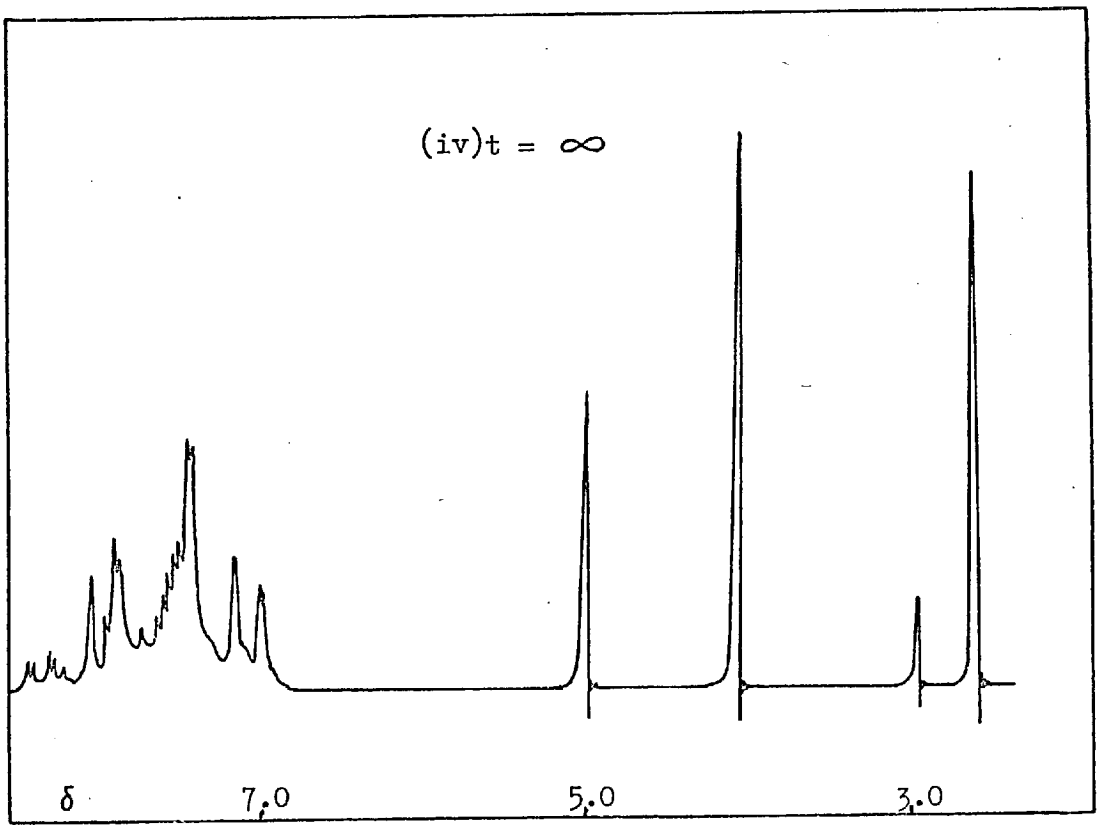

(iv) t = ∞
δ
7.0
5.0
3.0

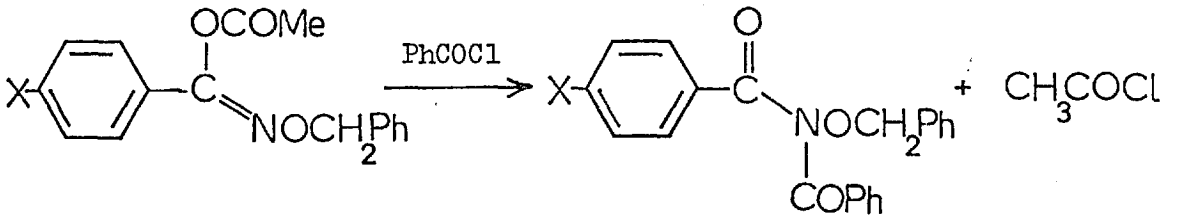
Fig.4.10 Benzoyl bromide catalysed rearrangement of N-benzyloxy-4-methoxybenzimidoyl acetate at 60°C.






(iii)t = 4430mns
δ
7.0
5.0
3.0


(iv)t = ∞
δ
7.0
5.0
3.0

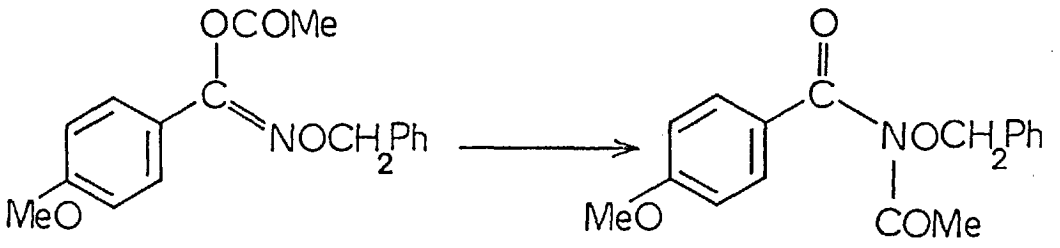


.....(58)

halides, and thus only a small percentage (ca.10-20%) of the final product was attributable to catalysis by aroyl halides. A further complication with these particular catalysts is the tendency for N-acylamides to undergo acyl exchange.

4.6.3 ACYL HALIDES

Rearrangement by these catalysts were examined in detail, but the results are difficult to interpret. The rearrangement rates of N-benzyloxy-4-methoxybenzimidoyl acetate in carbon tetrachloride (Equation (59)) to N-acetyl-N-benzyloxy-4-methoxybenzamide in the presence of acetyl chloride and acetyl bromide are reported in Table 4.12.



.....(59)

Individual kinetic runs were found to give good, linear first-order plots to ca. 90% reaction (see Experimental). This was confirmed by variation of the [substrate] at constant [catalyst]

Table 4.12

CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-METHOXYBENZIMIDOYL ACETATE IN CARBON TETRACHLORIDE AT 60°C

Initial [Sub] = 0.4M.

[Cat] M.	$10^6 k_1 (s^{-1})$
$0.04CH_3COCl$	1.6
$0.20CH_3COCl$	3.0
$0.40CH_3COCl$	4.4
$0.02CH_3COBr$	2.5
$0.04CH_3COBr$	3.8
$0.20CH_3COBr$	11.1
$0.40CH_3COBr$	18.0
$0.80CH_3COBr$	20.1 (21.0)*

(* This value of k_1 was determined from the initial slope of the first-order plot, which was found to show curvature after ca. 40% reaction)

(Table 4.13). The order with respect to the catalyst was anticipated as first-order but a plot of k_1 versus [catalyst] gave a curve (Fig. 4.11)

Table 4.13

EFFECT OF [SUBSTRATE] UPON THE REARRANGEMENT RATE IN CARBON TETRACHLORIDE AT 60°C

Catalyst = CH_3COBr = 0.2M.

[4-MeOPhC(OCOMe):$NOCH_2Ph$] M.	$10^5 k_1 (s^{-1})$
0.2	1.25
0.4	1.11
0.8	1.11

with little or no increase in the rearrangement rate at catalyst concentrations in excess of 0.4M. Further, at high catalyst concentrations, the disappearance of substrate does not follow first-order kinetics and thus the values of k_1 given in Table 4.12 are those calculated from the initial slope of the first-order plot. The effect of the [substrate] upon the reaction rate was also studied at high catalyst concentrations. First-order plots of the data were again curved and the k_o values given in Table 4.14 represent the initial rates calculated from the percentage reaction versus time plot.

Fig.4.11

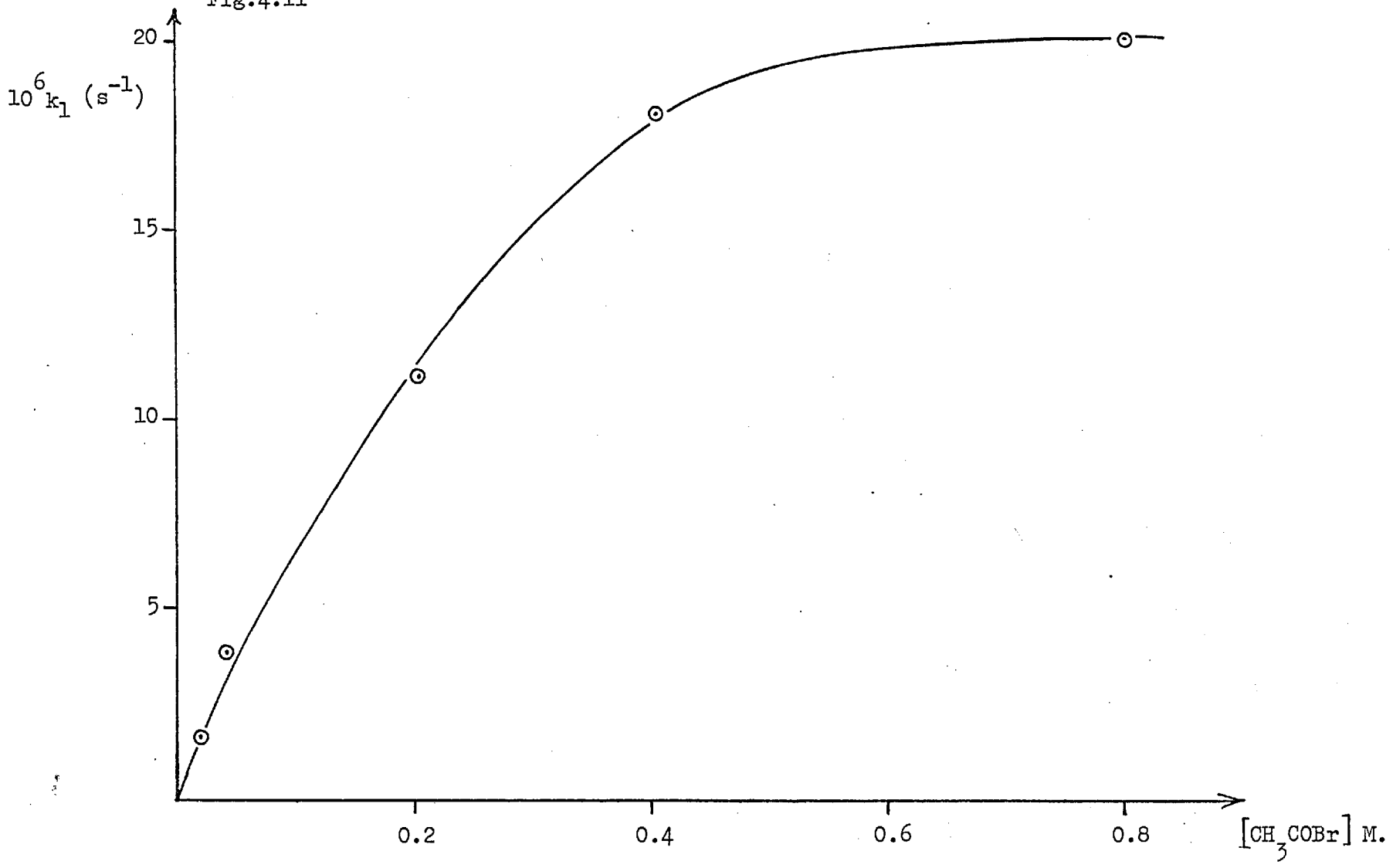


Table 4.14

EFFECT OF [SUBSTRATE] UPON THE REARRANGEMENT RATE AT HIGH CATALYST CONCENTRATIONS

$T = 60^{o}C$ Initial [Catalyst] = 0.8M.CH_3COBr Solvent = CCl_4

[4-MeOPhC(OCOMe):$NOCH_2Ph$] M.	$10^5 k_o (Ms^{-1})$
0.2	0.54
0.4	0.84
0.8	1.43

It was thought that at high catalyst concentrations the observed effect may have been due to a change in polarity of the medium since the dielectric constant of carbon tetrachloride is very low and the acetyl bromide has a relatively high dielectric constant. In order to examine this possibility further, work was conducted using nitrobenzene as solvent.

In nitrobenzene, two distinct behaviours were again observed for the acetyl bromide catalysed rearrangement. At low concentrations of catalyst, the rearrangement was found to follow kinetics which were apparently mixed first- and zero-order, since the first-order plot was linear only for ca.60% reaction (see Fig.4.12). At high acetyl bromide concentrations (>0.4M.) good zero-order kinetics with respect to substrate were observed. The k_1 values given in Table 4.15 are

Fig.4.12

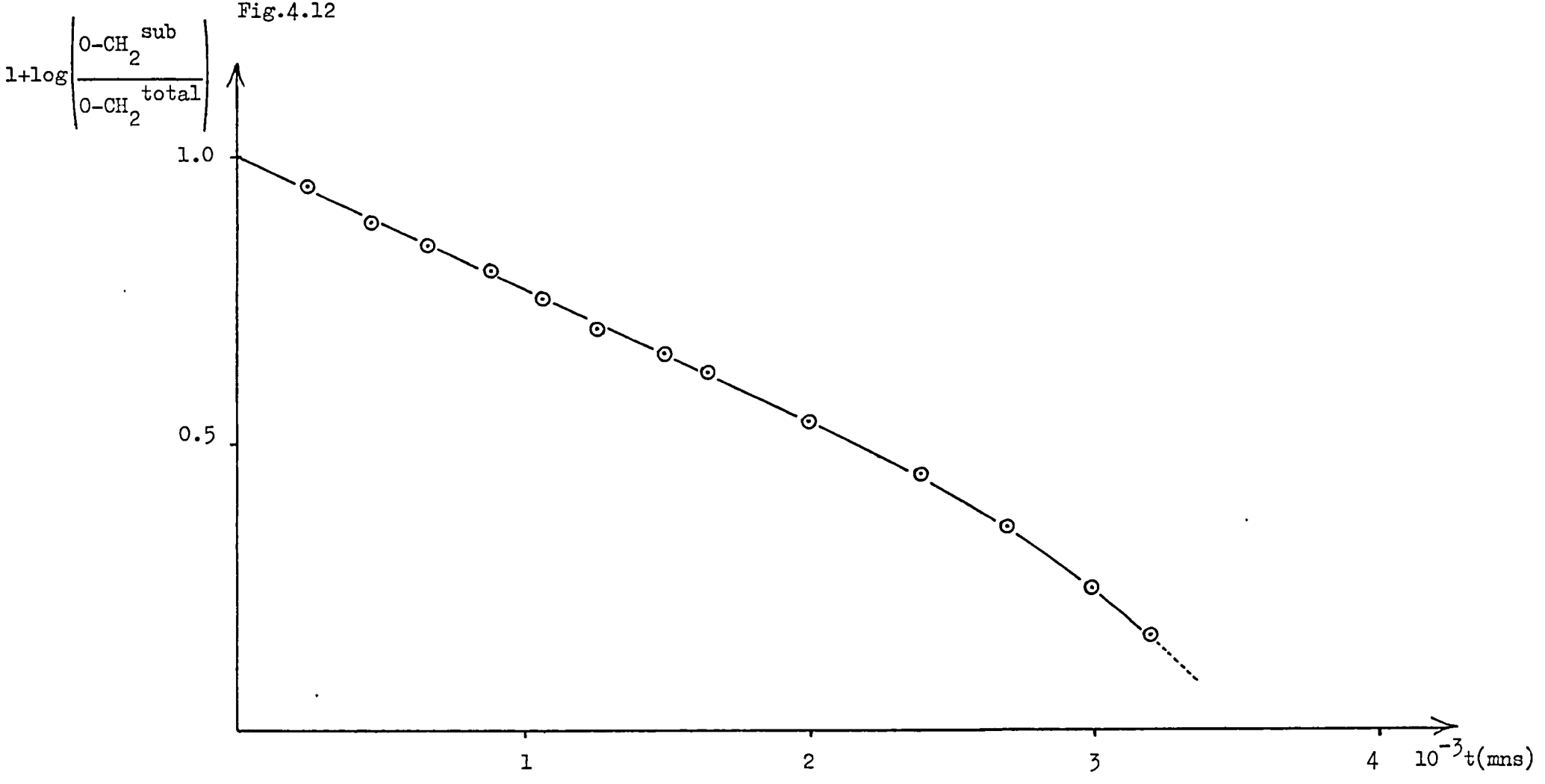


Table 4.15

CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-NITROBENZIMIDOYL ACETATE

$T = 60^{o}C$ Initial [Sub] = 0.4M. Solvent = $PhNO_2$

[Cat] M.	$10^6 k_1 (s^{-1})$
0.082CH_3COBr	2.20
0.136CH_3COBr	4.82
0.272CH_3COBr	8.97
0.408CH_3COBr	13.30

Table 4.16

CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-NITROBENZIMIDOYL ACETATE

$T = 60^{o}C$ Initial [Sub] = 0.4M. Solvent = $PhNO_2$

[Cat] M.	$10^5 k_o (Ms^{-1})$
0.68CH_3COBr	2.86 (3.04)
1.36CH_3COBr	5.80
2.72CH_3COBr	11.50

those calculated from the first-order plots, and the k_o values given in Table 4.16 are calculated from the percentage reaction versus time plots. Spectra from a typical kinetic run are shown in Fig.4.13.

At catalyst concentrations intermediate to these two extremes, the reaction appeared to be of fractional order with respect to the [substrate] , since neither first- nor zero-order plots were linear. This apparent changeover may be the result of either a change in mechanism or a change in the rate determining step.

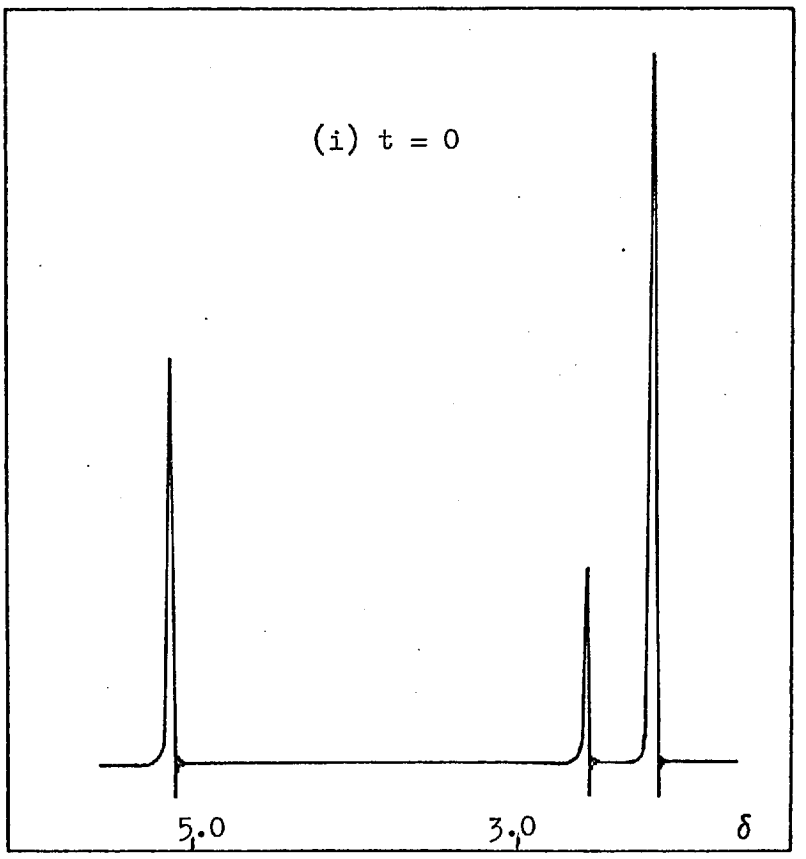
In order to examine the zero-order region further the effect of added bromide ion upon the reaction rate was studied. Due to solubility problems, the solvent was changed to deuterochloroform, in which the rearrangement reaction had been shown to be zero-order at high catalyst concentrations. The observed results with added bromide ion are shown in Table 4.17.

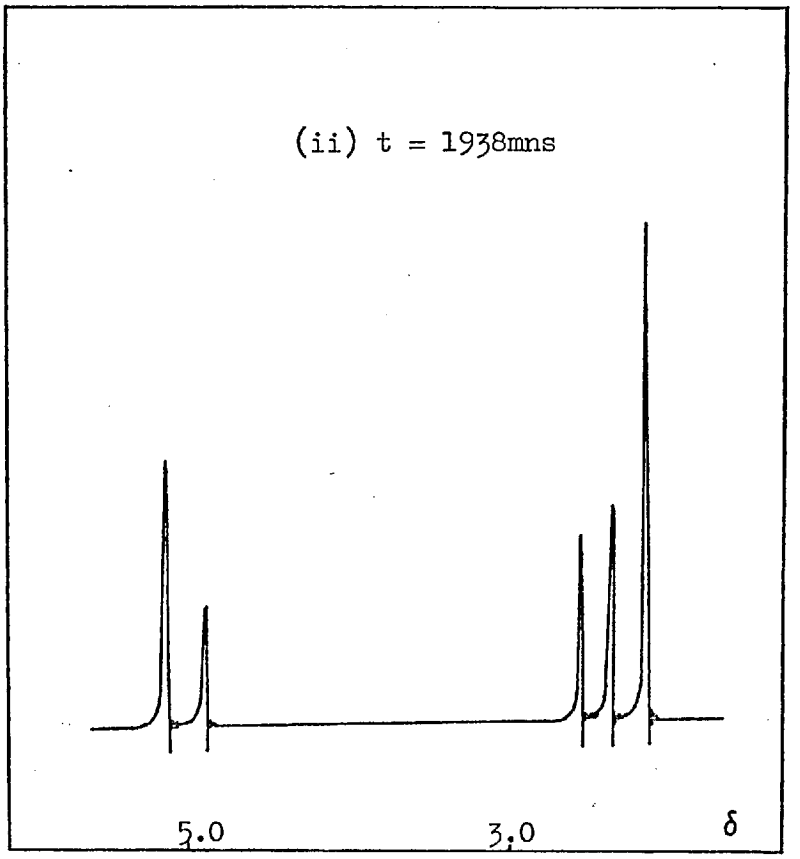
At low acetyl bromide concentrations, the reaction was found to be first-order in [substrate] in deuterochloroform, and the effect of added bromide ion upon the rearrangement rate is shown in Table 4.18.

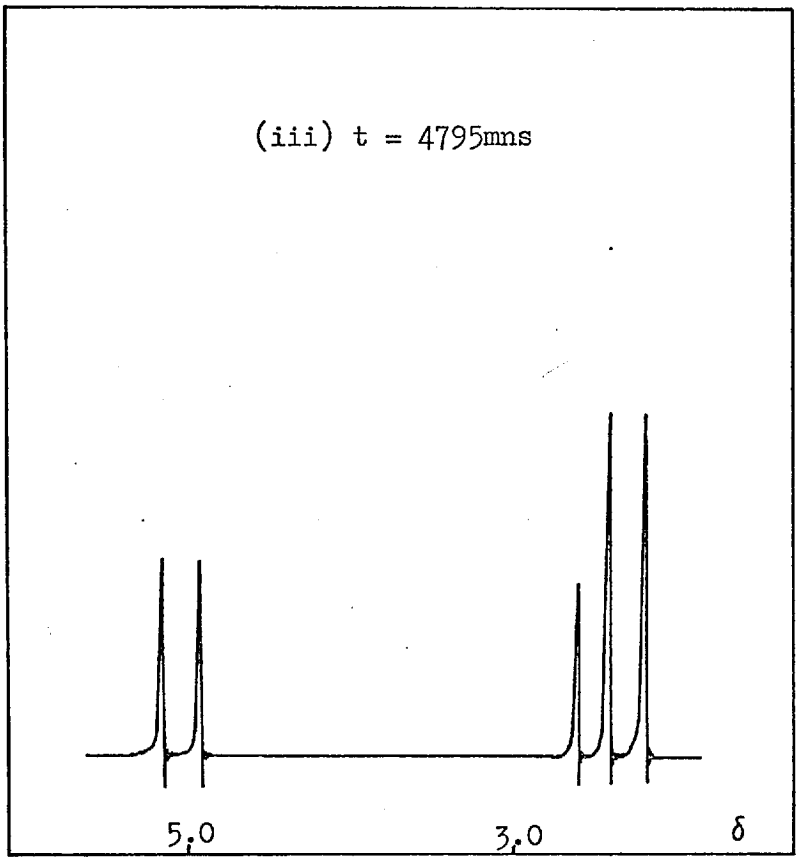
Bromide ion itself was found to catalyse the rearrangement of the O-acylisoimides and the rate constants given in Table 4.19 were calculated from the first-order plot.

The non-stoichiometric behaviour observed in the rearrangement reaction using acetyl bromide catalyst was thought to be due to a free-radical component in the rearrangement pathway. This interpretation followed from the kinetic studies in carbon tetrachloride in which the expression for the rearrangement rate appeared to show a half-power dependence upon the acetyl bromide concentration, which is

Fig.4.13 Acetyl bromide catalysed rearrangement of N-benzyloxy-4-nitrobenzimidoyl acetate in nitrobenzene at 60°C






(iii) t = 4795mns
5.0
3.0
δ

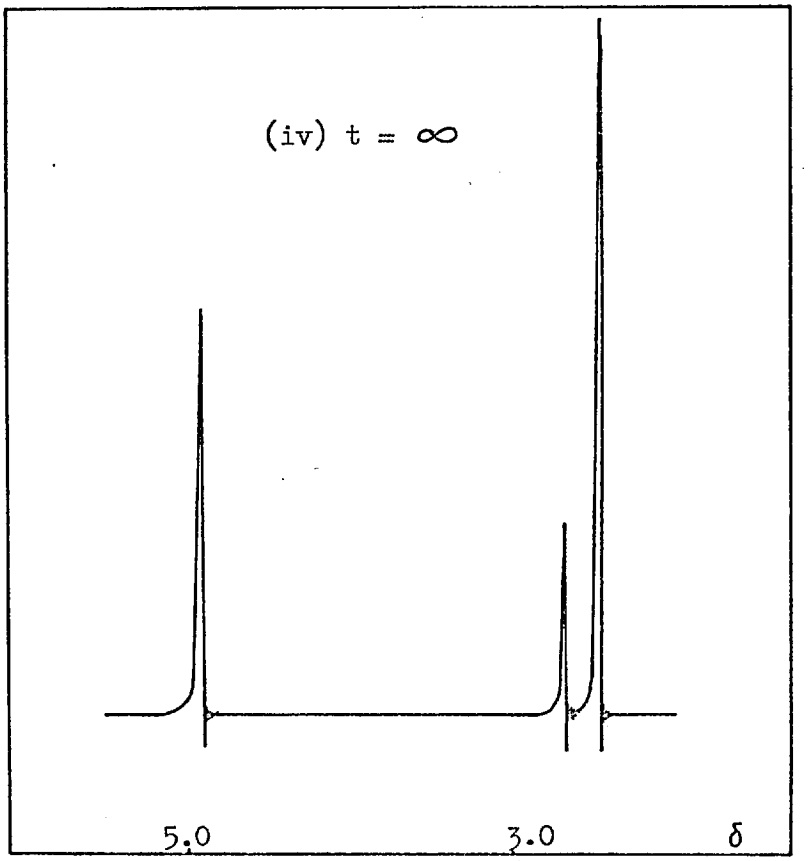

(iv) t = ∞
5.0
3.0
δ

Table 4.17

EFFECT OF BROMIDE ION UPON THE REARRANGEMENT RATE AT HIGH ACETYL BROMIDE CONCENTRATIONS

$T = 60^{\circ}C$ Solvent = $CDCl_3$ Initial $[CH_3COBr] = 0.68M.$

Initial $[4\text{-}NO_2\text{-}PhC(OCOMe):NOCH_2Ph] = 0.4M.$

$[Et_4N^+Br^-]M.$	$10^7k_o(Ms^{-1})$
	8.4
0.214	7.5
0.485	10.6
0.860	15.0

Table 4.18

EFFECT OF ADDED BROMIDE ION AT LOW ACETYL BROMIDE CONCENTRATIONS

$T = 60^{\circ}C$ Substrate = $4\text{-}MeO\text{-}PhC(OCOMe):NOCH_2Ph$ Solvent = $CDCl_3$

[Sub] M.	[Cat] M.	$[Et_4NBr]M.$	$10^5k_1(s^{-1})$
0.4	0.2		4.15
0.4	0.2	0.1	1.99
0.4	0.2	0.2	2.88
0.4	0.2	0.4	3.36

commonly observed in free radical reactions [187]. Further, acetyl bromide has been used as a free-radical initiator for the oxidation of cumene [188].

Table 4.19

BROMIDE ION CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-NITROBENZIMIDOYL ACETATE IN DEUTEROCHLOROFORM AT 60°C

Initial[Sub] = 0.4M.

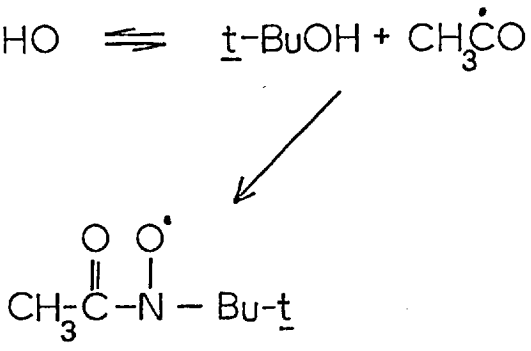
$[Et_4N^+Br^-]$ M.	$10^7 k_1 (s^{-1})$	$10^7 k_2 (1M^{-1}s^{-1})$
0.48	3.26	6.79
0.68	4.45	6.54
1.08	7.19	6.66

The acetyl radical which would be derived from the homolysis of the C-Br in acetyl bromide (Equation (60)) could not be detected by

$$CH_3-\overset{\overset{O}{\|}}{C}-Br \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}\cdot + Br\cdot \qquad .....(60)$$

e.s.r. using a solution of the acyl halide in benzene. This result may have been due to the low concentrations of the radical and thus further attempts were involved with increasing the concentration of the radical by spin-trapping the unstable acetyl radical. Mackor et al [189] have used nitroso-tert-butane to trap acetyl radicals derived from the

oxidation of acetaldehyde with tert-butoxy radicals [190] and analysed the stable acetyl-tert-butane nitroxide radical (77) by e.s.r. (Equation (61)). This experiment was repeated using benzene as the solvent and the experimental g- value obtained for the trapped



.....(61)

77

species (77) of 2.0068 (a_N = 8 gauss) was in agreement with that obtained earlier by Mackor et al [189]. The addition of acetyl bromide to a solution of nitroso-tert-butane in benzene gave only a pale red solution in contrast to the vivid blue colour observed for 77, and the e.s.r. spectrum showed no signals attributable to the trapped radical These results appear to rule out the possibility of a free-radical pathway for the rearrangement reaction.

4.7 DISCUSSION

In amide acylation the relatively high reagent reactivity permits reaction under mild conditions, (cf. amide alkylation using alkyl halides), where kinetically controlled O-acylation might be expected. Isolation of the anticipated O-acylisoimide product has rarely been possible in the case of unsubstituted amides. The exceptions are cyclic materials such

as 2-methyl-3,1-benzoxazin-4-one [112] or N-methylphthalisoimide [113] in which the carbonyl group is sterically inaccessible to the nucleophilic nitrogen and one report in which the stability of the isoimide form was attributed to the reduced nucleophilicity of the nitrogen due to the presence of a 2,4-dinitrophenyl group [115]. The present results show, in agreement with earlier work [135], that O-acylisoimides derived from N-alkoxyamides are sufficiently stable to be isolated. Thus the O-acylisoimide obtained from N-methylbenzamide was found to be very unstable (Section 3.1.1) but that derived from N-methoxybenzamide has been prepared and shown to be relatively stable (Section 5.3.2.5).

Previous work [135] indicated that the proportion of O- and N-acylated products obtained in the acylation of neutral N-alkoxyamides depended upon a number of factors, including the structure of the N-alkoxyamide and the acylating agent. From the present work it is also clear that the reaction conditions and in particular the temperature play a vital part. Before discussing these results it seems pertinent to establish the function of structure on the rearrangement process.

From Chapter III, it was deduced that structural factors exert their influence on O-acylisoimide stability by the configuration of the groups around the C=N bond. In addition, the nucleophilicity of the nitrogen atom was deduced to be a second factor determining O-acylisoimide stability. N-hydroxy-and N-alkoxyamides are much more basic than the corresponding unsubstituted amides as is shown by their pK_a values in Table 4.20. In addition N-hydroxy-and N-alkoxyamides and other nucleophiles such as hydroxylamine and hydrazine are often found to be more reactive than predicted [195] by the appropriate Brönsted

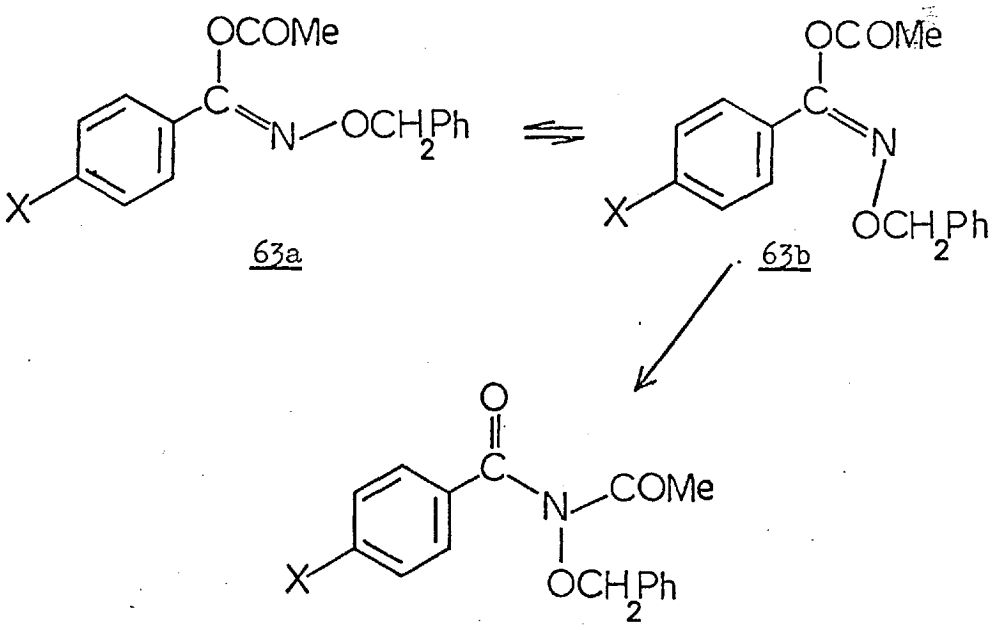
Table 4.20

Amide	pK_a	Reference
$4\text{-}NO_2PhCONHOMe$	9.09	191
$4\text{-}NO_2PhCONHOCH_2Ph$	9.20	191
$4\text{-}NO_2PhCON(Me)OH$	10.29	191
$4\text{-}NO_2PhCONHOH$	8.99	191
$4\text{-}NO_2PhCONHOH$	8.12(8.01)	192,193
$4\text{-}NO_2PhCONH_2$	-1.86	194

relation. This appears to be due to the lone pair of electrons adjacent to the nucleophilic nitrogen atom [196], which led Edwards and Pearson[195] to refer to this enhanced nucleophilicity as the α- effect. It can be seen therefore that an explanation to account for the observed stability in terms of low nitrogen nucleophilicity may be ruled out as a result of the above factors.

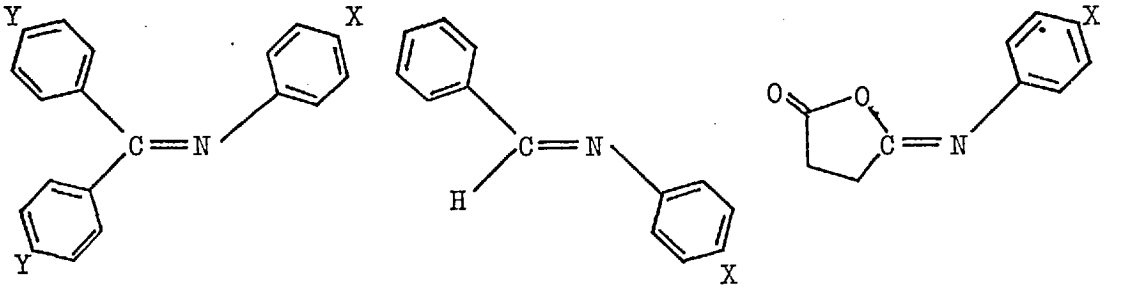
The second factor which was considered to be important in determining the stability of the O-acylisoimide was the configuration of the functional groups about the C=N bond. The intramolecular, thermal rearrangement of O-acylisoimides to the N-acylisomers, requires that the lone pair electrons of the nitrogen atom be cis (63b) to the acetate group (Scheme 4.2). Since there is considerable evidence to indicate that oxime ether derivatives do not undergo thermally induced cis-trans isomerisation in the absence of catalysts [178,197],

Scheme 4.2



63a 63b

the absence of thermal rearrangement with the O-acylisoimide suggests that the acetate group is trans to the lone pair on the nitrogen atom (63a). The cis-trans isomerism, 63a to 63b, proceeds via a nitrogen inversion mechanism. It has been found that the barriers to nitrogen inversion in imines, 78, 79 and 80 are effectively decreased by electron withdrawal by X [169,178,198,199], and the accepted mechanism of isomerisation involves

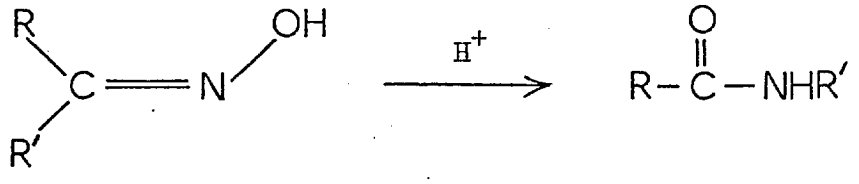


78 79 80

a 'lateral shift' [200]. In the case of compounds containing an oxygen atom bonded to the nitrogen atom of the C=N bond, the barrier to nitrogen inversion is increased [200]. Although the precise reasons for this effect are not entirely clear, comparison with acylic hydroxylamines [201] (which exhibit similar barriers) suggests that both the electronegativity

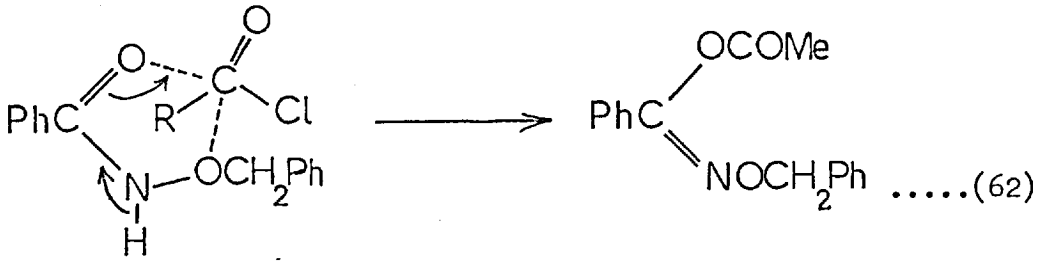
of the oxygen atom and the repulsions of the lone pairs on nitrogen and oxygen contribute to the observed increase in the barrier to nitrogen inversion. This high barrier to inversion in compounds possessing the C=N-O- linkage is clearly reflected in the observed behaviour of oximes in the Beckmann rearrangement, in which a stereospecific migration is observed [202] (Scheme 4.3). If the barrier to nitrogen

Scheme 4.3



inversion is not high in oximes i.e. if cis-trans isomerisation is possible, it can be seen that mixed products would be observed.

Thus O-acylisoimides derived from N-alkoxyamides are formed stereospecifically in the trans-form, and their stability is due to the low cis-trans isomerisation rate. The stereospecific formation of the trans-isomer of the O-acylisoimide may be rationalised in terms of participation of the oxygen atom attached to the nitrogen atom, which either loosely combines or reacts with the acylating agent followed by



.....(62)

acylation at or intramolecular rearrangement to the carbonyl oxygen (Equation (62)). It can be seen that either one of these factors

would account for the observed trans configuration of the final product. Participation by the alkoxy function has also been invoked to explain the high ortho:para ratios observed in the acylation of anisole with acyl nitrates [203,204]. It has been suggested that at least part of the reaction proceeds via an initial attack on the oxygen atom of the alkoxy group, followed by an intramolecular rearrangement which would favour ortho-substitution.

Reactivity of O and N atoms

The present results support the interpretation suggested by Challis and Challis [73] for reactions of neutral amides in which the site of acylation is considered in terms of kinetically- and thermodynamically-controlled reactions. At low temperatures, O-acylation has been found to be dominant (Section 5.3.2.4), but at high temperatures acylation occurred at the nitrogen atom (Section 5.3.3.1) This kind of temperature dependent specificity clearly demonstrates that the above interpretation is valid for the acylation of neutral amides.

The acylation of N-alkoxyamides using pyridine/acetic anhydride was found to be rapid at 25°C in carbon tetrachloride solvent. Studies using N-benzyloxy-4-nitrobenzamide as the substrate have shown that the second-order rate constant is $3.77 \times 10^{-3} l^2 M^{-2} s^{-1}$. Unfortunately, the U.V. method employed to monitor this reaction was only suitable for the 4-nitro compound and rates could not be determined for N-benzyloxybenzamides with other 4-substituents. It can be seen, however, that the k_2 calculated for the 4-nitro compound would be expected to be the lowest value for all the N-benzyloxy-4-substituted benzamides studied, since in this case the 4-nitro substituent decreases the basicity of the carbonyl oxygen by electron withdrawal.

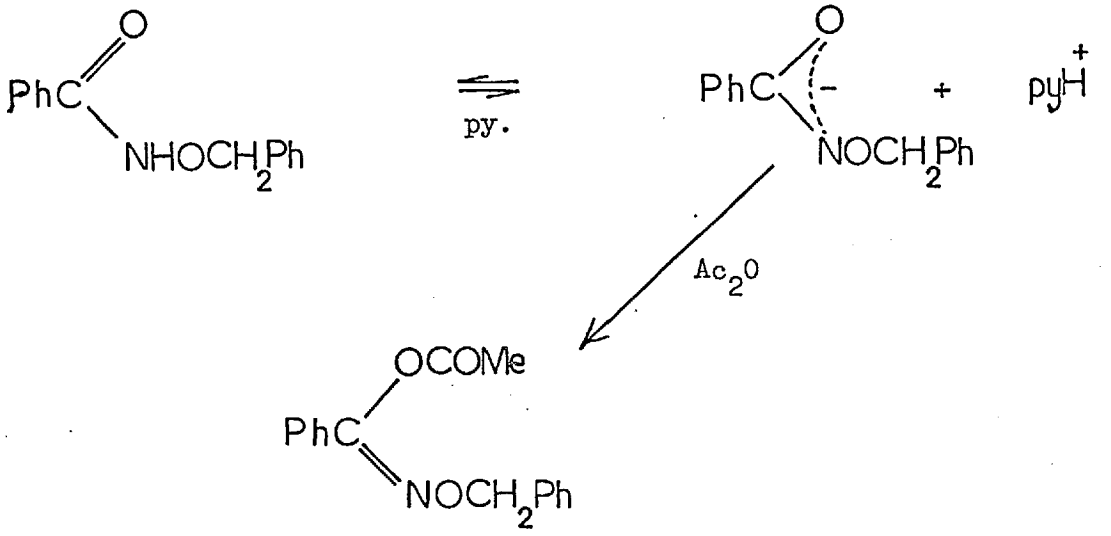
The rate expression for O-acylation (Equation (63)) is similar to that observed elsewhere for acetylation by acetic anhydride in

$$\text{Rate} = k_2(\text{Py})(\text{Ac}_2\text{O})(\text{Sub}) \qquad \ldots\ldots(63)$$

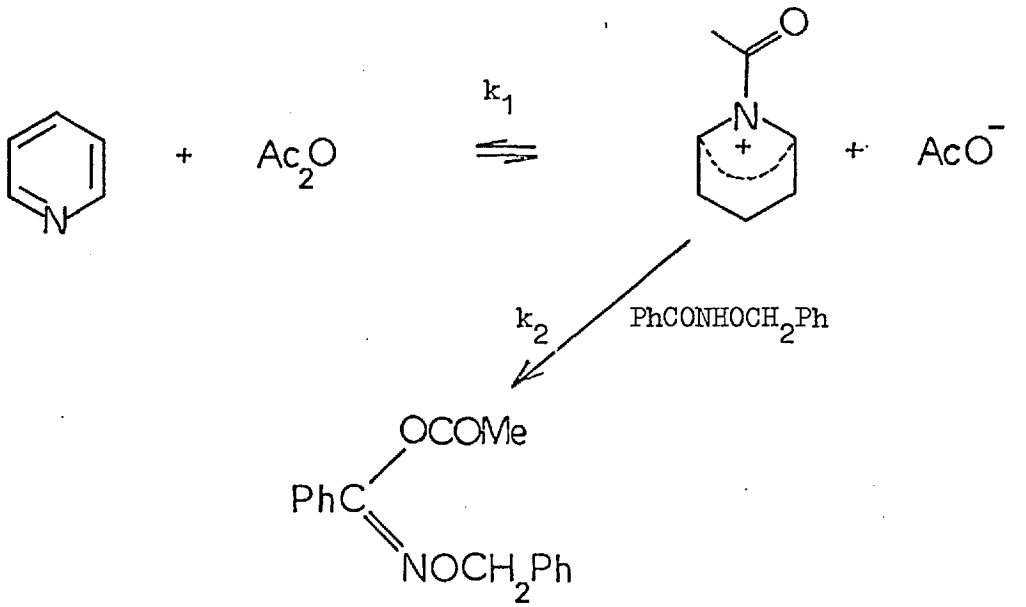
pyridine [205]. It is consistent with either a rate limiting step involving attack of a pyridine/amide complex (presumably amide anion) upon acetic anhydride (Scheme 4.4) or a rapid pre-equilibrium formation of acetylpyridinium ion which subsequently slowly acetylates the neutral N-benzyloxybenzamide (Scheme 4.5). In Scheme 4.5, it can be seen that in order to obtain a first-order term in substrate, step k_2, would have to be rate limiting.

Bonner and Hillier [205] have shown that in the acetylation of phenol using pyridine/acetic anhydride in carbon tetrachloride, the rate determining step is the acylation of the pyridine/phenol complex and no evidence was found for the formation of the acetylpyridinium ion this system. However, phenol is much more acidic than the amide system used in the present case, and it seems probable that reaction in this particular case occurs <u>via</u> a phenoxide anion. By analogy with amide alkylation in which the homogeneous alkylation of the amide anion takes place solely on the nitrogen atom, it seems doubtful that the mechanism shown in Scheme 4.4 would lead to the observed O-acylation. The mechanism shown in Scheme 4.5, involving acetylation of the <u>neutral</u> amide molecule with acetylpyridinium ion would seem to fit the general behaviour observed in neutral amide/amide anion reactions and lead to O-acetylation. Further evidence for this interpretation comes from the pyridine catalysed rearrangement of O-acylisoimideswhich is discussed below.

Scheme 4.4



Scheme 4.5



Pyridine-Catalysed O-N Rearrangement

Previous work had shown that the yields of N-benzyloxybenzimidoyl acetates were dependent upon the 4-substituent of the aryl ring when N-benzyloxybenzamides were acetylated using pyridine/acetic anhydride at room temperature [135]. The present study has shown that the initial acylation in all cases is at the carbonyl oxygen and, in addition, the thermal O-N rearrangement pathway is not substantial at room temperature. It follows that the low yields of certain O-acylisoimides obtained by Hearn and Ward [135] arise from catalysed rearrangement of the O-acylisoimide by the pyridine/acetic anhydride reagent.

Further studies have confirmed the above deduction and the O-acylisoimides rearranged to the N-acyl isomers in the presence of pyridine/acetic anhydride. Pseudo first-order kinetics with respect to the substrate concentration were observed for all the O-acylisoimides studied. Further work to investigate the dependency of the rearrangement rate upon the pyridine and acetic anhydride concentrations showed that a pyridine-catalysed pathway, independent of the acetic anhydride concentration was operative. This pyridine catalysed pathway was found to be dominant for O-acylisoimides with electron-withdrawing substituents, but in those with electron donating substituents it appears to be less dominant (Table 4.21).

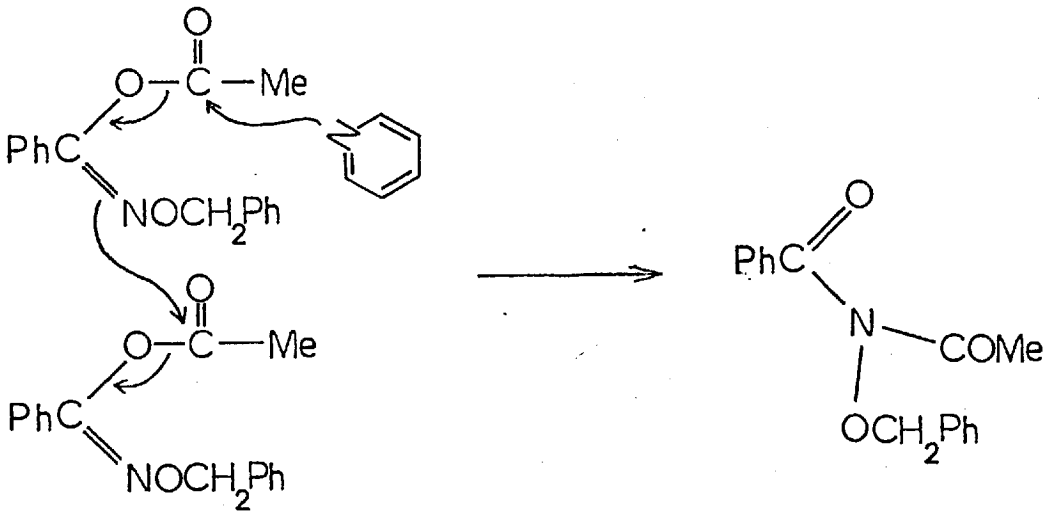
The kinetics observed for the pyridine-catalysed rearrangement were overall second-order i.e. first order in [substrate] and in [pyridine]. This observation immediately rules out one of the three mechanisms possible for the pyridine-catalysed rearrangement reaction (Scheme 4.6) in which second-order kinetics with respect to substrate would be expected. The two potential mechanisms remaining are an

Table 4.21

PYRIDINE AND PYRIDINE/ACETIC ANHYDRIDE CATALYSED REARRANGEMENT OF 4-X-PhC(OCOMe):$NOCH_2Ph$ IN NITROBENZENE AT 60°C

X	$[Ac_2O]$ M.	[py] M.	$10^6k_1(s^{-1})$
NMe_2	0.8	0.8	0.36
NMe_2		0.8	0.13
MeO	0.8	0.8	0.76
MeO		0.8	0.43
Me	0.8	0.8	0.65
Me		0.8	0.43
Cl	0.8	0.8	3.00
Cl		0.8	2.03
NO_2	0.8	0.8	9.20
NO_2		0.8	8.92

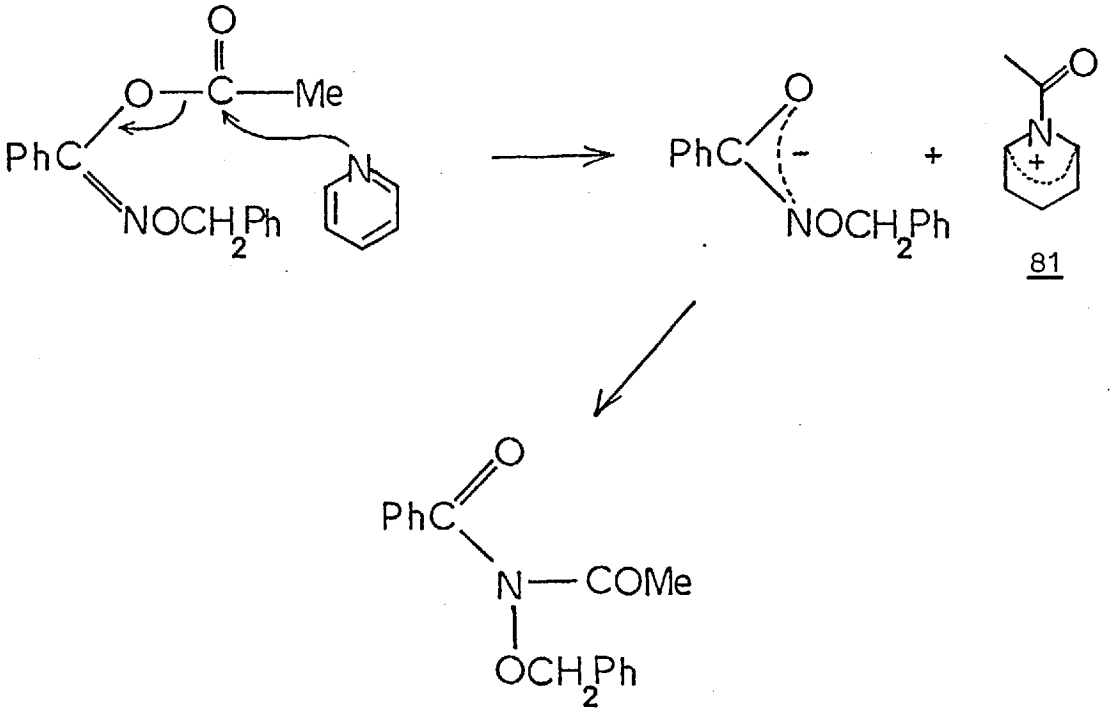
Scheme 4.6



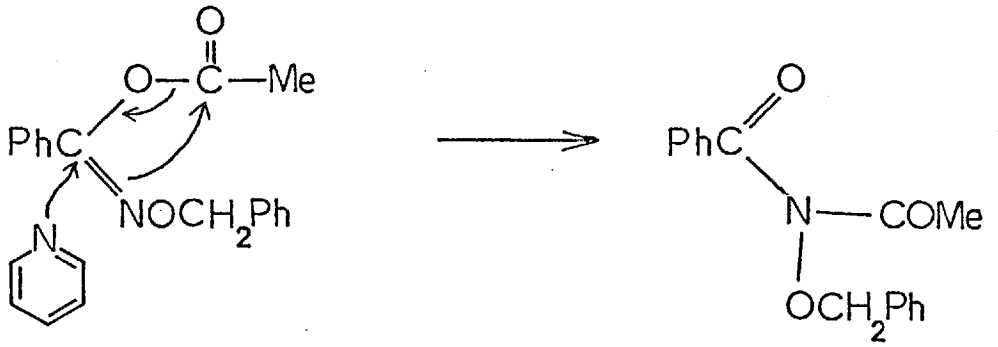
intermolecular route involving an initial nucleophilic attack by pyridine upon the acyl carbonyl (Scheme 4.7) and an intramolecular pathway featuring pyridine attack upon the imido-carbon (Scheme 4.8). It can be seen that in Scheme 4.7 in order to obtain first-order kinetics with respect to substrate, the acetyl pyridinium ion (81) once formed must react with the amide anion and not the substrate.

The available evidence favours the intermolecular pathway (Scheme 4.7). Thus a Hammett plot of log k_2 versus σ gave poor correlation but a plot of log k_2 versus σ_o, the normal substituent constant was found to give a good straight line ($r = 0.996$) of slope $\rho = +1.49$. The observation that a linear plot is obtained for the σ_o plot suggests that the site of pyridine attack is removed from the 4-substituted phenyl ring. The values of σ_o[206,207] are derived from reactions in which the reaction site is insulated from the ring to such an extent that there is only a minimal and constant amount of resonance involving the ring and its substituents. In addition the cross-products experiment, using radio-labelled substrate, demonstrates

Scheme 4.7

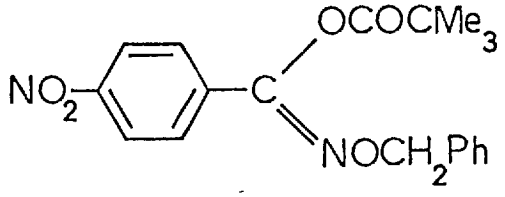


Scheme 4.8



the intermolecular nature of the reaction. Although the C^{14}-label is not fully equilibrated under these conditions, it can be seen from a comparison of their pyridine-catalysed rates ($4\text{-}NO_2, k_2=1.1\times10^{-5}\,lM^{-1}s^{-1}$, $4\text{-}CN, k_2=0.6\times10^{-5}\,lM^{-1}s^{-1}$) that complete equilibration would not be expected under these conditions. The results with other tertiary nitrogen bases lead to a similar conclusion concerning the reaction mechanism. 2,6-Lutidine was found to be a poor base catalyst for the rearrangement reaction which is consistent with the earlier findings of Butler and Gold [208] who showed that pyridine catalyses the hydrolysis of acetic anhydride but 2,6-lutidine does not. Imidazole was found to attack at the acyl carbonyl to give 1-acetylimidazole and other imidazole derivatives in which the secondary nitrogen atom of the imidazole was blocked, e.g. 1-methylimidazole and 1-acetylimidazole, were found to rearrange the O-acylisoimide.

The available evidence therefore, favours an intermolecular mechanism involving attack at the acyl carbonyl atom, followed presumably by rapid recombination of the amide anion and the acetylpyridinium ion to give the observed product. The failure of pyridine to rearrange N-benzyloxy-4-nitrobenzimidoyl pivalate 82 is consistent with this interpretation. This result allows further



82

interpretation of the earlier studies on the formation of the O-acyl isoimide, where it was shown that reaction may occur via the amide anion (Scheme 4.4) or the neutral molecule (Scheme 4.5). The

present results suggest that, as observed in many amide anion reactions, acylation takes place at the nitrogen site in homogeneous solution (Scheme 4.7). It appears that the observed mechanism in the pyridine-catalysed rearrangement reinforces earlier deductions and the formation of O-acylisoimides occurs *via* the neutral molecule and not the amide anion.

Acetate Catalysed Rearrangement

The rates observed in the acetate-catalysed rearrangement of O-acylisoimides were much higher than those for the pyridine catalysed rearrangement (Table 4.22). Although the pK_a values of pyridine and acetate ion are similar in magnitude in water [209,210], it is possible that in deuterochloroform acetate ion becomes a stronger base than pyridine. Unfortunately, the pK_a values for these bases have not been measured in the required solvent. Similar considerations

Table 4.22

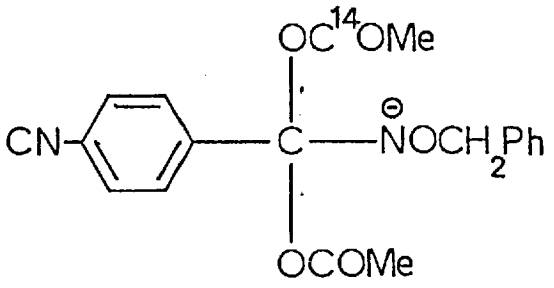
BASE-CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-NITROBENZIMIDOYL ACETATE IN DEUTEROCHLOROFORM AT 60°C

Base	$10^6 k_2 (1M^{-1}s^{-1})$
Pyridine	3.22
Acetate	4130.00

regarding the rearrangement mechanism are present in the acetate-catalysed rearrangement as in the pyridine-catalysed pathway.

Thus an intermolecular (Scheme 4.9) or intramolecular pathway (Scheme 4.10) may be operative. It was found that the Hammett plot of log k_2 *versus* σ for the acetate reactions gave a good correlation (r = 0.996) for the observed substituent effects. The corresponding plot of log k_2 versus σ_o was poorly fitted (r = 0.923) unlike the observed behaviour for pyridine catalysis. In order to determine the inter- or intramolecularity of the acetate catalysed rearrangement mechanism, a radio-labelled substrate was employed. Thus it can be seen that in the intermolecular mechanism (Scheme 4.9) the final N-acyl product should contain in theory 50% of the original C^{14}-label, but in the intramolecular rearrangement, the C^{14}-label should be retained. The results of this particular experiment showed that 90% of the C^{14}-label was retained in the final N-acyl product.

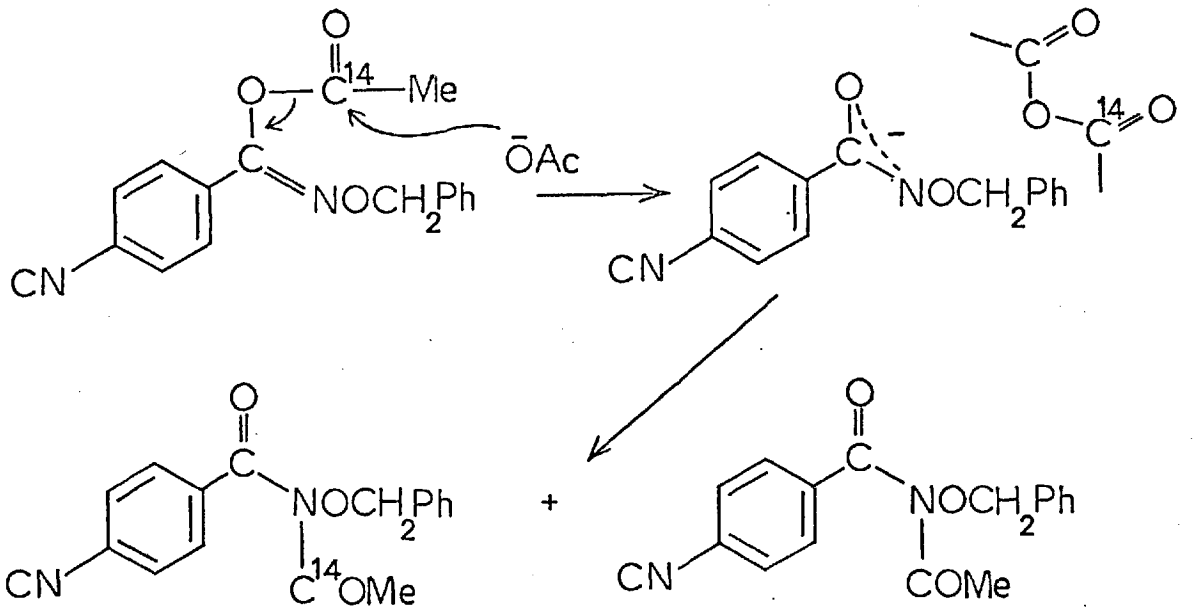
The available evidence, therefore favours the intramolecular pathway (Scheme 4.10). In order to account for the low ρ-value observed and the high retention of C^{14}-label, it can be seen that an 'early' transition state must be invoked. If the transition state were 'late', and the tetrahedral intermediate (83) was formed, equilibration of the label from the symmetrical transition state would



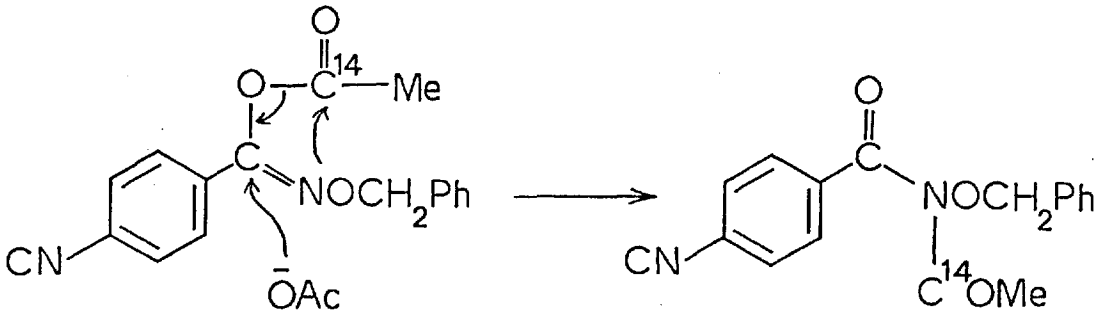
83

be expected. The results would lead to the conclusion, therefore, that either an 'early' transition state or a synchronous process is operative. Further evidence for an intramolecular process comes from the rearrangement of N-benzyloxy-4-nitrobenzimidoyl pivalate with acetate ion to give N-benzyloxy-N-pivaloyl-4-nitrobenzamide.

Scheme 4.9

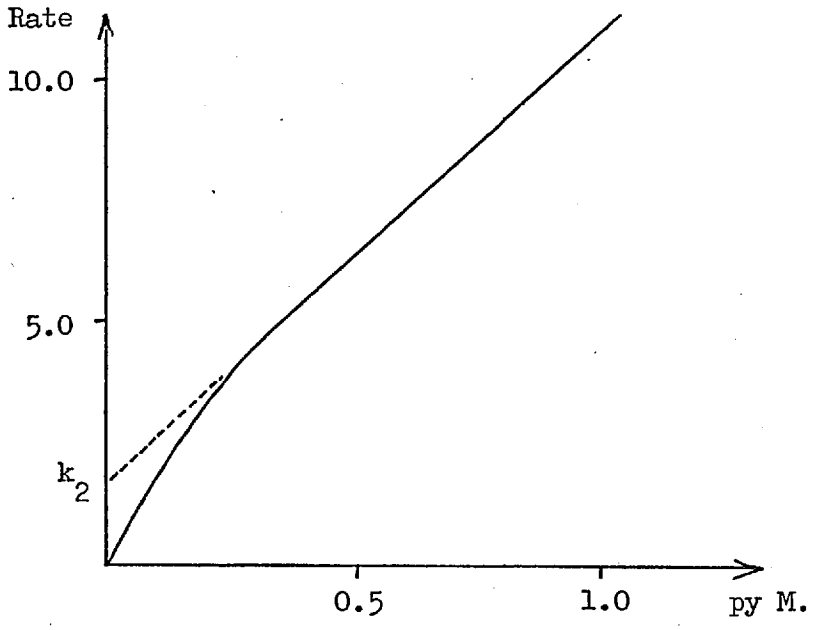


Scheme 4.10



The catalysed rearrangement observed in the presence of acetate ion suggests that the observed behaviour in the pyridine/acetic anhydride catalysed rearrangement at low pyridine concentrations is due to the presence of acetic acid as an impurity in the acetic anhydride. Thus at low concentrations of pyridine the observed rate is due to a combination of pyridine and acetate rates. The acetate rate is dependent upon the pyridine concentration until all the acetic acid impurity is converted to acetate ion at which time the acetate rate becomes constant. In this region therefore, the observed changes in rate should be linearly related with pyridine concentration, which is observed (Fig. 4.14).

Fig. 4.14



Extrapolation of this linear region therefore gives an intercept which is attributable to the acetate rate (k_2). This interpretation would also account for the low dependency upon the acetic anhydride concentration. The intercept and the slope of the rate plots for pyridine/acetic anhydride catalysis allow an approximate value to be

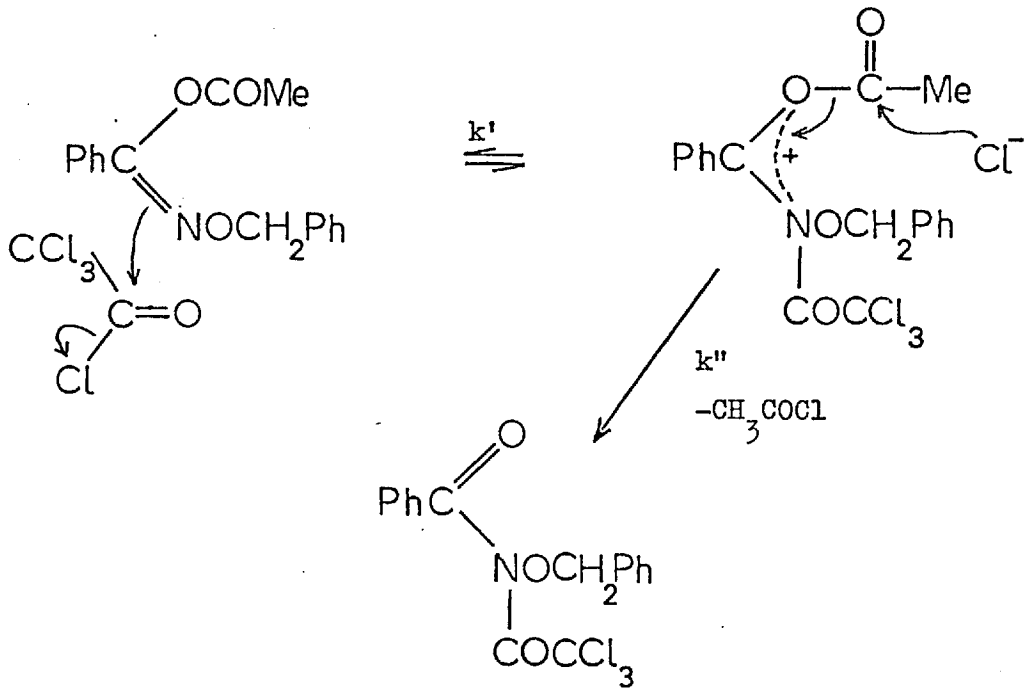
calculated for the acetic acid impurity in acetic anhydride as 0.01%. In the case of the more basic O-acylisoimides (e.g. 4-NMe_2, 4MeO) it is possible that a third catalyst, acetylpyridinium ion is involved in the rearrangement mechanism. It has been shown, however, that acetylpyridinium ion does not react with O-acylisoimides bearing an electron-withdrawing 4-substituent.

In contrast to the base-catalysed rearrangement pathway which follows relatively simple kinetics, the observed behaviour with acyl halides was found to be rather complex. Chloroacetyl chlorides, however, were found to follow simple kinetics, first-order in [substrate] and in [catalyst] (Equation (64)), which is consistent with a

$$\text{Rate} = k_2[\text{Sub}]\,[CCl_3COCl] \qquad .....(64)$$

mechanism shown in Scheme 4.11.

Scheme 4.11



The rate limiting step in Scheme 4.11 may be either k' or k". In the case of acetyl chloride and acetyl bromide, the observed kinetics i.e. zero-order in [substrate] at high [catalyst], and mixed-order in [substrate] at low [catalyst], suggest that there is a rate limiting step containing terms only in the [catalyst]. Attempts to detect or spin-trap the acetyl radical derived from homolysis of the C-Br bond failed, and thus interpretation of the results in terms of a free-radical mechanism were ruled out. Heterolysis of the C-Br bond to give the acylium ion (Equation (65)), is known to occur in dipolar aprotic solvents [211,212,213], but generally a hydrogen halide

$$CH_3COBr \rightleftharpoons CH_3C{\equiv}O^{+} + Br^{-} \qquad .....(65)$$

is required to function as a Brönsted acid and promote the ionisation [213] (Equation (66)). Satchell [211], however, has stated

$$CH_3COBr \rightleftharpoons CH_3C{\equiv}O^{+} + HBr_2^{-} \qquad .....(66)$$

that even in 'dry' solvents, some hydrolysis of the acetyl bromide occurs giving the hydrogen bromide which may then catalyse the ionisation. Thus it is possible that even in the 'dry' solvents used in the present study, ionisation of the acetyl bromide may occur to give the reactive acylium ion. The observed effect of bromide ion at low and high catalyst concentrations is not in agreement with this ionisation mechanism, however, since the rearrangement rate at high catalyst concentrations would be expected to decrease upon the addition of bromide ion and not increase as observed experimentally. It has also been shown that the observed behaviour is not due to nucleophilic attack by bromide ion upon the O-acylisoimide system (c.f. pyridine, acetate catalysis), since the rearranged rates by bromide ion are much

lower than those observed for the acetyl bromide catalysed rearrangement.

The behaviour of acetyl bromide in the rearrangement reaction appears to be intermediate to that of bases (nucleophilic catalysis) and trichloroacetyl chloride (electrophilic catalysis). Further, the observed zero-order region suggests that a rate limiting step involving heterolysis of the C-Br bond of acetyl bromide is present.

4.8 SUMMARY

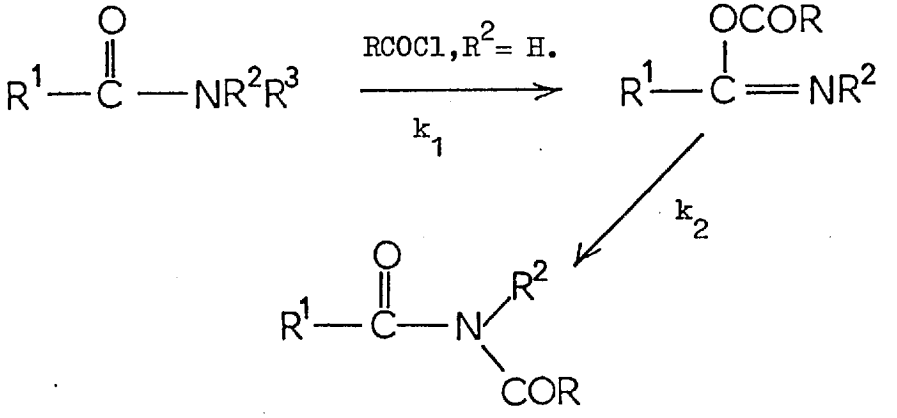
From the data which has been collected, it is clear that the temperature of the reaction plays a vital part in determining the site of acylation of neutral amides. At low temperatures O-acylation is dominant, but at high temperatures N-acylation becomes the preferred process. It appears therefore that predictions based upon the kinetic-thermodynamic relationship proposed by Challis and Challis[73] are in agreement with the experimental findings. The observed results cannot be interpreted in terms of Kornblum's theory of ambident reactivity[1], which would predict acylation at the nitrogen site in all cases for the neutral molecule. Predictions based upon "hard" and "soft" acid and base theory [9,10] are confirmed by the observed results since it has been found that the "hard" centre of the amide moiety, the oxygen atom, reacts with the "hard" carbonyl carbon atom of acetylating agents. These results also follow from the perturbation theory [16], which would predict reaction at the oxygen atom in a charge-controlled reaction.

It appears therefore that the overall mechanism for amide acylation is as shown in Scheme 4.12.

In the case of amides which have no electronegative substituents attached to nitrogen, k_1 is the rate determining step, followed by a

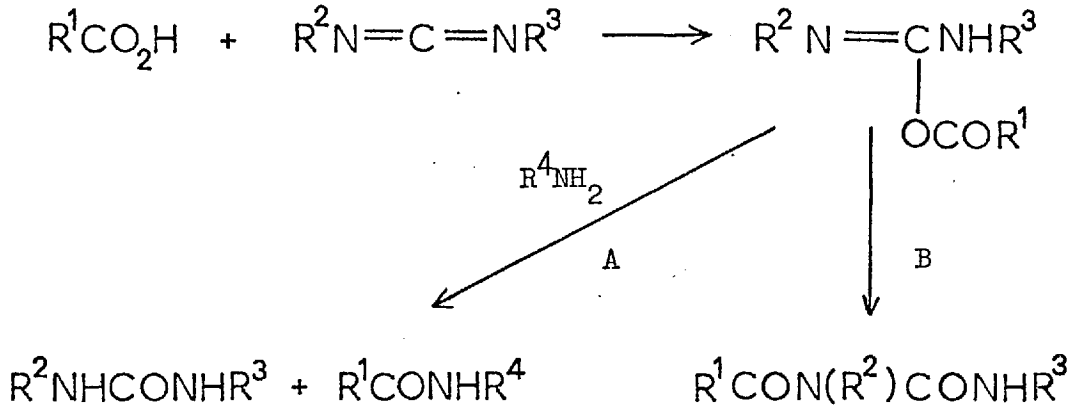
rapid thermal, intramolecular rearrangement to the N-acyl product. Amides which have oxygen or nitrogen atoms bonded to the nitrogen atom, show a reversal of this pattern and k_2 is rate-determining. Under these circumstances it has been shown that the observed effect is due to the stereospecific formation of the trans isomer of the O-acylisoimide and also to the absence of cis-trans isomerisation. In cases where $k_1 > k_2$, the rearrangement of the O-acylisoimide intermediate has been shown to be catalysed by a variety of electrophilic species and in addition, nucleophilic catalysis may also be observed.

Scheme 4.12



The catalysis of the rearrangement by tertiary amine bases has some important implications in the field of peptide chemistry particularly in carbodiimide-mediated condensations [214,215,216] which have been postulated to proceed via an O-acylisoimide intermediate (Scheme 4.13).

Scheme 4.13

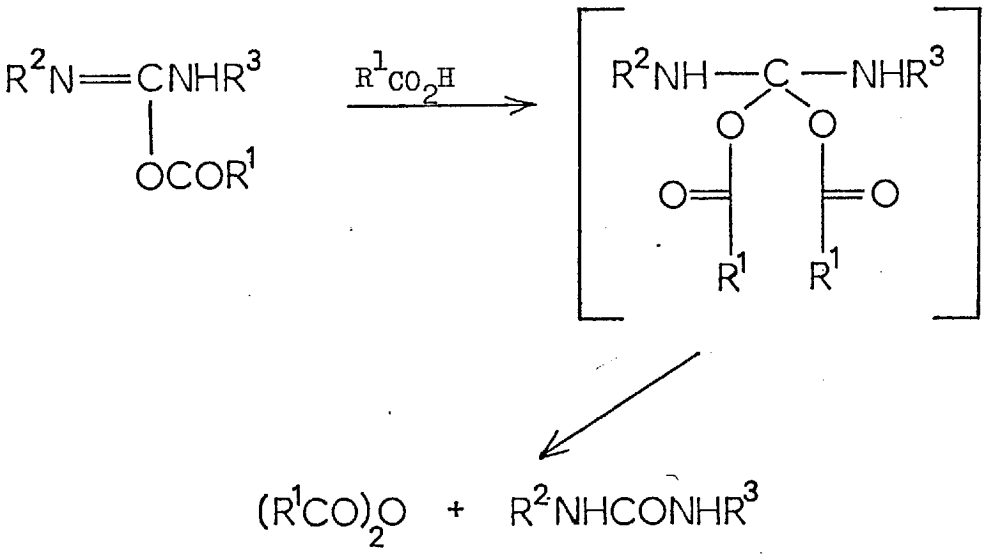


The intramolecular rearrangement (B) to the N-acylurea is prominent at ordinary temperatures, but it has been found that this wasteful side reaction can be minimised by the appropriate choice of solvent and by working at temperatures below 0°C.

Other acylatable species may replace R^4NH_2. Hence the use of excess acid leads to the symmetrical anhydride (Scheme 4.14). Excess of R^1CO_2H is often used in aminolysis (Scheme 4.13) in order to repress route B, and it is possible that under such conditions the acylation of the amine is, in fact, due to the anhydride.

A recent kinetic study [217] shows that in carbon tetrachloride or acetonitrile the reaction with acids is first-order in carbodiimide but greater than first-order in acid. It is thought, therefore that dimeric R^1CO_2H maybe involved, so facilitating both the formation of the O-acylisoimide and its decomposition to the anhydride and urea. This notion is supported by the reduced proportion of acylurea obtained when the solvent is changed from acetonitrile to carbon tetrachloride, for in the latter solvent more of the acid will be dimeric. This

Scheme 4.14



result and others, also eliminates the possibility that the acylurea is produced by acylation of the urea by the anhydride or by O-acylisoimide.

When an amine, R^4NH_2 is also present the rate of loss of diimide is reduced, owing to deactivation of the acid on forming various ion-paired, salt-like species e.g. $R^1CO_2^-N^+H_3R_4$. Alone the amine does not attack the imide and its acylation will not occur in the absence of acid. Whether or not the amine is acylated by the O-acylisoimide or by the anhydride (Scheme 4.14) is not clearly settled by this kinetic study. The balance between paths A and B depends upon the amine but here also the observed phenomena have still to be rationalised.

From the present study it has been shown that secondary amines are acetylated with O-acylisoimide but tertiary amines catalyse the O ⟶ N rearrangement. The observation that lower temperatures reduce the wasteful O ⟶ N rearrangement reaction in carbodiimide reactions also follows from the present work.

P A R T T H R E E

THE EXPERIMENTAL DETAILS

CHAPTER V

Melting points were determined on a Kofler hot-stage apparatus. Infra-red spectra were recorded as mulls (Nujol), unless otherwise specified, on a Perkin-Elmer 157G spectrophotometer. N.m.r. spectra were measured with a Varian T60 spectrometer for solutions in $^{2}H_{1}$-chloroform (except where stated otherwise) with tetramethylsilane as an internal reference. Radioactive assay was made on a Beckman LS200 scintillation counter. G.l.c. measurements were obtained using a Perkin-Elmer F11 Gas Chromatograph. U.V. measurements were obtained using a Pye-Unicam SP1800 spectrometer and were performed in methanol solution unless stated otherwise.

In the sections on preparation of substrates, the term 'evaporation' refers to the removal of solvent under reduced pressure.

5.1 ALKYLATION OF PHENOL

5.1.1 PREPARATION AND PURIFICATION OF SUBSTRATES, REAGENTS AND SOLVENTS

Solvents [218]

Whenever possible, the solvents used in the course of this work were 'AnalaR' grade, and, in all cases, further purification to remove residual water was carried out. Carbon tetrachloride (AnalaR) was distilled (b.p. 77-78°C/760mm.Hg.) from phosphorus pentoxide. Diethyl ether, and toluene (AnalaR) were dried over sodium wire and distilled. Dimethylsulphoxide was dried over calcium hydride, and distilled (b.p. 75-76°C/12mm.Hg.). Ethanol (AnalaR) was dried with calcium sulphate and distilled (b.p. 77-78°C/760mm.Hg.). Tetrahydrofuran was heated under reflux with lithium aluminium hydride and distilled (b.p. 65-66°C/760mm.Hg.).

Phenol

AnalaR-grade phenol was used throughout the course of this study. The phenol was dried by azeotropic distillation of water with benzene and distilled (b.p. 85-86°C/20mm.Hg.).

2-Naphthol

2-Naphthol was purified and dried by vacuum sublimation (100°C/3mm.Hg.), m.p. 122-123°C (Lit.[218] 122.5-123.5°C).

Benzyl bromide

Benzyl bromide was dried over calcium hydride and distilled (b.p. 114-115°C/15mm.Hg.) to give a colourless liquid, n_D^{20} 1.5759 (Lit.[218] n_D^{20} 1.5752).

Triethyloxonium tetrafluoroborate [219]

Epichlorhydrin (17.6g.) was slowly added to a stirred solution of boron trifluoride etherate (31.5ml.) in ether (65ml.), the rate of addition being controlled to maintain a temperature of 40°C. The mixture was heated under reflux for one hour after complete addition and stored overnight at room temperature. The supernatant liquid was then withdrawn from the crystalline mass under an atmosphere of dry nitrogen. The crystalline solid was washed with ether (3 x 100ml.) and stored under ether 33g.(87%), m.p. 88-91°C (Lit.[219] 91-92°C).

Sodium phenoxide [34]

To a cooled suspension of sodium hydride (24.0g.) in tetrahydrofuran (50ml.) was added a solution of phenol (33.0g.) in tetrahydrofuran (100ml.). When addition was complete, the reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting mixture was filtered in a dry, nitrogen atomosphere and the filtrate added to a n-hexane (2l.). The resultant white precipitate was filtered, washed with hexane (5 x 100 ml.), and dried overnight in a desiccator (34.0g., 83%).

Sodium-2-naphthoxide [35]

To a solution of 2-naphthol (25.0g.) in methanol (85ml.) was added sodium hydroxide (AnalaR, 6.7g.) in water (40ml.). The methanol and most of the water were removed under reduced pressure at 100°C, residual water being removed by heating for three hours at 100°C/1mm.Hg.

After cooling, the salt was dissolved in tetrahydrofuran (40ml.) and filtered. The filtrate was treated with benzene (100ml.), and the precipitated sodium-2-naphthoxide (17.0g., 60%) was removed by filtration and dried (100°C/1mm.Hg.).

5.1.2 PREPARATION AND PURIFICATION OF PRODUCTS

1-Benzyl-2-naphthol [35]

2-Naphthol (6.9g.) was added to a solution of sodium hydroxide (1.9g.) in water (50ml.). When the stirred mixture had become homogeneous, benzyl bromide (8.2g.) was added dropwise. After stirring for 24 hours at room temperature the reaction solution was poured into water and acidified (18% HCl). After addition of benzene (100ml.), the solution was extracted with Claisen potash [220] (3 x 50ml.). The Claisen potash extract was acidified at 0°C with 18% hydrochloric acid, extracted with benzene and dried (Na_2SO_4). Evaporation of solvent gave a light brown solid (8.65g.), which was crystallised from 80% formic acid [33], and then from hexane to give needle crystals of 1-benzyl-2-naphthol (8.3g., 74%), m.p. 112-113°C (Lit.[220] 111-112°C).

δ	4.5 (2H,s), 5.0 (1H,br.s), 7.28-8.1 (12H,m)
ν_{max}	3475,1630,1585,1275,837,790,770,735cm.$^{-1}$

Benzyl-2-naphthyl ether [35]

To a stirred solution of sodium-2-naphthoxide (8.0g.) in dimethylformamide (35ml.) was added a solution of benzyl bromide

(8.2g.) in dimethylformamide (15ml.). The rate of addition was controlled such that the temperature never exceeded ca.35°C. When the addition was complete the mixture was poured into water acidified with 18% hydrochloric acid, and extracted with benzene. The benzene extract was washed with Claisen potash [220], water and dried (Na_2SO_4). Evaporation of solvent gave a yellow solid (9.95g.), m.p. 90-98°C. Recrystallisation gave benzyl-2-naphthyl ether (8.8g., 83%), m.p. 99-100°C (Lit.[221] 99°C).

δ	5.25 (2H,s), 7.23-7.96 (12H,m)
ν_{max}	1625,1600,1265,1227,1187,1030,850,830,760,740,705cm.$^{-1}$

Benzylphenyl ether

The method given below is a modification of the original procedure of Gomberg et al [222].

A solution of phenol (14.0g.) and benzyl chloride (12.6g.) in 10% ($\frac{W}{V}$) sodium hydroxide (60ml.) was heated under reflux for one hour. After extraction with ether, the excess phenol was removed from the ethereal solution by extraction with dilute alkali (3 x 50ml.). After drying ($MgSO_4$) evaporation of solvent gave a pale yellow oil, which on recrystallisation (ethanol) gave white crystals of benzyl-phenyl ether (71%), m.p. 39°C (Lit.[222] 39°C).

δ (CCl_4)	5.05 (2H,s), 6.83-7.36 (10H,m)
ν_{max}	1600,1495,1455,1250,775,700cm.$^{-1}$

2-Hydroxydiphenylmethane [223]

A solution of phenol (23.5g.) in toluene (50 ml.) was added to a stirred suspension of finely powdered sodium hydride (6.0g.) in toluene (100ml.) at ca 40°C. After one hour the reaction mixture was heated under reflux for a further hour.

Benzyl chloride (31.6g.) in toluene (20ml.) was added to the suspension of sodium phenoxide and, after heating under reflux for a further two hours, the reaction was left overnight at room temperature.

The mixture was then washed with water to remove the precipitated sodium chloride, dried (Na_2SO_4) and the solvent evaporated to give an oil. The oil was dissolved in Claisen potash [220] (250ml.) and freed from neutral matter by extraction with petroleum ether (5 x 50ml.). The alkaline solution was then concentrated to remove the alcohol, acidified and extracted with ether. After drying (Na_2SO_4) and removal of solvent, a light yellow oil was obtained, which on distillation (b.p. 171°C/13mm.Hg.) gave the required product as a colourless oil (85%).

2-Hydroxydiphenylmethane exists in two forms, a stable form (m.p.[224] 51.5°C) and a metastable form (m.p.[220] 21.5°C). The oil obtained was shown to be the desired product by comparison of its i.r., n.m.r. spectra with those of authentic material [225]. The phenylurethane derivative had m.p. 116-117°C, (Lit.[220] 117°C).

δ (CCl_4)	3.85 (2H,s), 4.86 (1H,s), 6.38-7.2 (5H,m), 7.13 (5H,s)
ν_{max}(film)	3450,1590,1490,1450,760,735,705cm.$^{-1}$

4-Hydroxydiphenylmethane

4-Hydroxydiphenylmethane (ex.Koch-Light) was recrystallised several times from ethanol, to give white needles and vacuum dried m.p. 84°C (Lit.[226] 84°C).

δ (CCl_4)	3.92 (2H,s), 4.78 (1H,br.s), 6.63-7.12 (4H,q), 7.23 (5H,s)
ν_{max}	3200,1600,1515,1495,1250,860,800,740,710cm.$^{-1}$

5.1.3 ANALYTICAL METHODS

As discussed in Section 2.2.1, analysis of reaction solutions was effected by quantitative g.l.c. assay using a DEGA column. In some cases, confirmation of the g.l.c. results was obtained by an n.m.r. method (Section 2.2.2).

5.1.3.1 Preparation of DEGA Column

A solution of DEGA (ex.Perkin-Elmer, 3g.), and 85% phosphoric acid (0.5g.) in acetone (100ml.) was prepared. One millilitre of the above solution was added to a mixture of Corning glass beads (80-100 mesh, 9.965g.) in acetone (10ml.). The acetone was then allowed to evaporate to give the required column packing.

The g.l.c. column (1 metre, stainless-steel, $\frac{1}{8}$" internal diameter) was then packed with the coated stationary phase and conditioned for twenty-four hours at 150°C.

5.1.3.2 Procedure for g.l.c. assay of reactions

In order to obtain the concentrations of both reactants and products in the alkylation reactions a temperature programme was

required ($10^{\circ}C$ $min.^{-1}$, 100-$170^{\circ}C$), but it was found that peak tailing of the ring-alkylated phenols became a problem. In order to prevent this problem, all g.l.c. analyses were conducted at a constant column temperature of $170^{\circ}C$ using a high carrier-gas flow rate. The reactions were monitored by sampling the reaction solutions and injecting the sample (1 μl) directly onto the g.l.c. column.

5.1.3.3 Preparation of g.l.c. Reaction Solutions

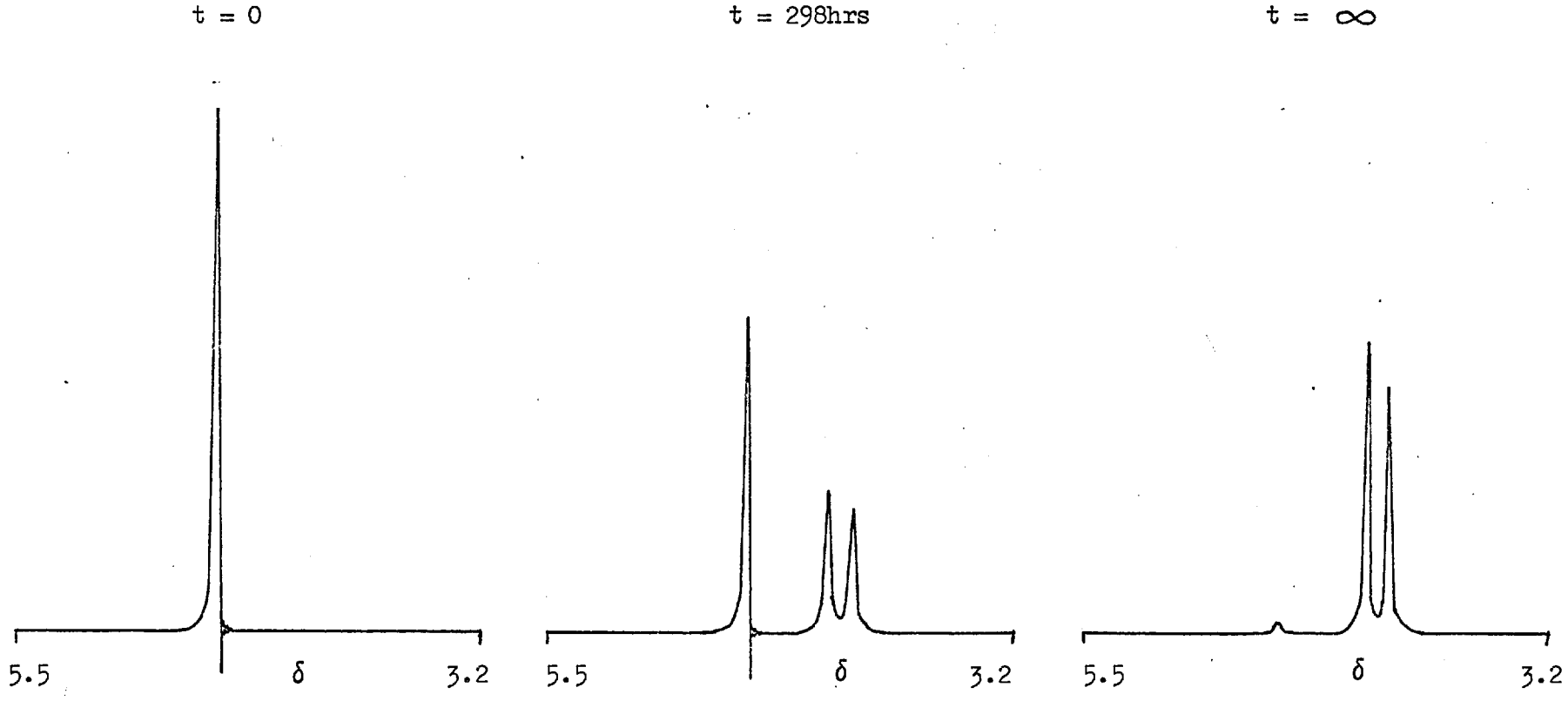
All the reactions were carried out with an excess of phenol, usually five- or ten-fold, over benzyl bromide. For example, phenol (4.7g.) and benzyl bromide (0.855g.) were dissolved in 10ml. of 50% ethanol-carbon tetrachloride ($\frac{v}{v}$) at room temperature. A one microlitre aliquot of the solution was immediately analysed by g.l.c. under the standard conditions. The flask, equipped with a Suba-Seal, was then suspended in a constant temperature bath at the required temperature and aliquots withdrawn at timed intervals were assayed. The g.l.c. instrument was calibrated at least once per day with standard solutions.

Generally the reactions were followed to completion and, in most cases, products were isolated and authenticated by melting-point and spectral comparison with authentic material.

5.1.3.4 Procedure for n.m.r. Assay of Reactions

In this procedure, a solution of phenol (4.7g.), benzyl bromide (0.85g.) in carbon tetrachloride (25ml.) was prepared and a small aliquot (0.5ml.) was placed in an n.m.r. tube, which was then sealed and placed in a thermostatted bath at the required temperature. A series of n.m.r. spectra at timed intervals were then recorded. Sample n.m.r. spectra are shown in Fig. 5.1.

Fig.5.1 N.m.r. spectra in CCl_4 of a reaction solution of phenol (0.04M.) and benzyl bromide (0.004M.) at 60°C



5.1.3.5 Accuracy of g.l.c. and n.m.r. Assaying Procedures

The g.l.c. method was found to be extremely sensitive for the detection of the alkylated products of phenol. Standard solutions of alkylated phenols (0.015g.), phenol (4.985g.) in ethanol (10ml.) were prepared and it was shown that concentrations as low as 0.5% could be detected in all cases for benzylphenyl ether, and 2- and 4-hydroxydiphenylmethane. The accuracy of the g.l.c. assay is therefore very high, and the main errors associated with the g.l.c. technique are likely to arise from the entry of water into the reaction flask and also evaporation of solvent. In order to minimise the solvent loss and prevent entry of adventitious water into the reaction flask, Suba-Seals were used to stopper the reaction flasks and the reaction solutions were sampled through the septum.

The problems associated with ingress of water and solvent loss were not encountered in the n.m.r. technique because the reaction solutions were sealed in the n.m.r. tubes. However the detection limit was much higher than the g.l.c. analysis (ca.3%) and, in addition, the actual determination of the concentrations of the C-alkylated products, by an integration method, was much less accurate. The main problem with the n.m.r. technique, however, was that it was limited in its use to the neutral phenol reaction because of the insolubility of sodium phenoxide in organic solvents which are amenable to the n.m.r. method.

In those neutral phenol alkylation reactions which were performed in carbon tetrachloride, it was found that the results of n.m.r. and g.l.c. techniques complemented each other and no significant variation in the results was observed.

Table 5.1

T(°C)	[PhOH] M.	[$PhCH_2Br$] M.	g.l.c.Technique ortho:para	n.m.r.Technique ortho:para
75	0.05	0.005	1 :1.47	1:1.4
40	0.05	0.005	1.08:1	1:1

5.2 ACYLATION OF AMIDES

5.2.1 PREPARATION AND PURIFICATION OF SOLVENTS, SUBSTRATES AND REAGENTS

Solvents [218]

Benzene was dried over sodium wire and distilled (b.p. 80°C/760mm.Hg). Acetonitrile was dried over calcium hydride and distilled (b.p. 81-82°C/760mm.Hg) from phosphorus pentoxide. Toluene was dried over sodium wire and distilled (b.p. 110-111°C/760mm.Hg.). Acetyl chloride was heated under reflux with phosphorus pentachloride, then distilled. The distillate was then redistilled (b.p. 52°C/760mm.Hg) from one-tenth volume dimethylaniline.

Methyl iodide

Methyl iodide was purified by shaking with dilute aqueous sodium bisulphite until colourless, then washed with water, dilute aqueous sodium carbonate, water and finally dried with calcium chloride. After distilling (b.p. 42-43°C/760mm.Hg.) the reagent was stored over copper.

Benzoyl chloride

A solution of benzoyl chloride (100ml.) in benzene (70ml.) was washed with 5% sodium bicarbonate solution (2 x 30ml.), separated, dried with calcium chloride and distilled (b.p. 56°C/4mm.Hg.).

The synthetic route leading to the O-acylisoimide, N-(2,4-dinitrophenyl)benzimidoyl benzoate, was described in Section 3.1.1. The imidoyl chloride was prepared from N-2,4-dinitrophenylbenzamide, and then reacted with silver benzoate.

N-(2,4-dinitrophenyl)benzamide

The most convenient method for this preparation was that reported by Muttelet[227]. A mixture of 2,4-dinitroaniline (18.3g.) and benzoyl chloride (14.1g.) was heated to 180°C. As soon as reaction began the heating was discontinued and the contents of the flask solidified. After recrystallisation ($PhCH_2OH$) and washing with petroleum ether (40-60°C), the golden yellow needles of N-(2,4-dinitrophenyl)benzamide (27.2g., 95%) were vacuum-dried at 150°C for 24 hours m.p. 201-202°C (Lit.[115] 200-202°C, Lit.[227] 220°C).

δ (d_6-DMSO)	7.63-8.63 (7H,m), 8.9 (1H,d)
ν_{max}	3340,3100,1685,1610,1595,1245,1145,750,720,700cm.$^{-1}$

N-(2,4-dinitrophenyl)benzimidoyl chloride

A mixture of N-(2,4-dinitrophenyl)benzamide (28.7g.) and phosphorus pentachloride (21.4g.) in benzene (50ml.) was heated under reflux for two hours. After evaporation of the solvent and washing with hexane (3 x 50ml.) the product was recrystallised

(benzene) to give yellow needles of N-(2,4-dinitrophenyl)benzimidoyl chloride (26.3g., 86%), m.p. 122-124°C (Lit.[115] 117-120°C, Lit.[228] 122-124°C).

δ 7.22 (1H,d,J=8Hz), 7.46-8.26 (5H,m), 8.50 (1H,q,J=8Hz,J'=3Hz), 9.0 (1H,d,J'=3Hz)

ν_{max} 1650,1600,1535,1510,1360,920,780,760,735,710cm.$^{-1}$

N-(2,4-dinitrophenyl)benzimidoyl benzoate[115]

N-(2,4-dinitrophenyl)benzimidoyl chloride (4.75g.) was stirred for 72 hours at room temperature with dry silver benzoate (3.75g.) in ether (35ml.). The resulting suspension was filtered to remove precipitated silver chloride and, after washing with ether (3 x 50ml.) and evaporation of solvent at room temperature, the required product was obtained as a pale-yellow solid (3.6g.). Two recrystallisations (toluene/petroleum ether (40-60°C)) gave the product as colourless plates (2.0g., 20%) m.p. 87-90°C (Lit.[115] 90°C).

δ 7.2 (1H,d), 7.6-8.1 (10H,m), 8.32 (1H,q), 8.85 (1H,d)

ν_{max} 1740,1670,1600,1525,1350,1260,1245,1215,1060,1035,780, 755,730,710cm.$^{-1}$

The n.m.r. spectrum of the final product showed toluene (δ 2.46) present in the purified sample. The product was therefore recrystallised from ether/petroleum ether (60-80°C) to give the pure product, m.p. 90°C (Lit.[115] 90°C).

Found: C, 61.08; H, 3.44; N, 10.76; Calculated for $C_{20}H_{13}N_3O_6$: C, 61.38; H, 3.35; N, 10.74%

N-Methylbenzamide

The Schotten-Baumann procedure [229] was used as follows. To methylamine (25% $\frac{w}{v}$ aqueous solution, 28ml.) in 10% ($\frac{w}{v}$) sodium hydroxide (180ml.) was added benzoyl chloride (28ml.). After shaking for a few minutes, the precipitated N-methylbenzamide was filtered off and recrystallised (ethanol/water) to give the pure product as colourless needles (88%) m.p. 81-82°C (Lit.[230] 81.5-82.5°C).

δ 2.9, 2.98 (3H,d), 7.33-7.97 (5H,m), 9.02 (1H,br.s)

ν_{max} 3320,1630,1605,1580,1550,1410,1165,720,715,700cm.$^{-1}$

N-Methylbenzimidoyl chloride [231]

N-Methylbenzamide (4.6g.) and thionyl chloride (13.1g.) were heated together ca 60°C for sixteen hours. The excess thionyl chloride was then removed by distillation at reduced pressure (2cm.Hg.). Distillation of the residue gave N-methylbenzimidoyl chloride (b.p. 81°C/8mm.Hg.) as a colourless oil (3.65g., 70%).

δ 3.42 (3H,s), 7.33(3H,m), 8.00 (2H,m)

ν_{max}(liquid film) 1665,1445,1235,1000,880,775,700cm.$^{-1}$

N-Methylbenzimidoyl acetate

A solution of N-methylbenzimidoyl chloride (3.85g.) in ether (10ml.) was cooled to 0°C and slowly added to a stirred suspension of

silver acetate (4.15g.) in ether (25ml.) held at 0°C. The reaction was exothermic and the addition of imidoyl chloride was at such a rate that little temperature rise occurred. After addition was complete the mixture was filtered and the solvent evaporated at room temperature to give a colourless oil, which was very unstable and rearrangement to the N-acyl compound occurred in the process of recording i.r. and n.m.r. spectra.

δ	2.18 (3H,s), 3.23 (3H,s), 7.6 (5H,m)
ν_{max}(film)	1760,1680,1200,1030,770,730,700cm.$^{-1}$

On standing at room temperature for a few minutes, the above spectra were found to have changed, giving the results below

δ	2.33 (3H,s), 3.21 (3H,s), 7.60 (5H,m)
ν_{max}(liquid film)	1700,1660,1315,1300,1140,1055,1035,815,740, 720cm.$^{-1}$

5.2.2 PREPARATION OF PRODUCTS

N-(2,4-dinitrophenyl)-N-benzoylbenzamide

Benzoyl chloride (56.0g.) was added to a suspension of 2,4-dinitroaniline (20g.) in pyridine (50ml.) and the mixture was heated for five hours under reflux. After cooling and addition of 10% hydrochloric acid (400ml.), a precipitate was obtained, which was dried in vacuo. The unreacted 2,4-dinitroaniline was removed by sublimation to give the title compound as the residue, m.p. 173-175°C. Recrystallisation (ethanol) gave N-(2,4-dinitrophenyl)-N-benzoylbenzamide as colourless plates (65%) m.p. 174-175°C (Lit.[115] 173.5-174.5°C)

δ 7.37 (4H,m), 7.75 (7H,m), 8.31 (1H,q,J=4Hz,J'=9Hz), 8.93 (1H,d,J=4Hz)

ν_{max} 1710,1670,1600,1520,1450,1358,1338,1240,1148,908,837, 720,700cm.$^{-1}$

N-Acetyl-N-methylbenzamide

To a solution of N-methylbenzamide (4.6g.) in benzene (50ml.), acetic anhydride (3g.) and acetyl chloride (0.5g.) were added. The solution was heated under reflux for two hours. After cooling the solution was washed with 10% hydrochloric acid (2 x 100ml.), saturated sodium bicarbonate (2 x 100ml.), water (2 x 100ml.), and dried ($MgSO_4$). Evaporation of solvent gave a colourless crystalline product (5.7g., 94%), which was recrystallised (chloroform/petroleum ether (40-60°C)) to give N-acetyl-N-methylbenzamide as colourless needle crystals, m.p. 39-39.5°C.

δ 2.33 (3H,s), 3.20 (3H,s), 7.6 (5H,m)

ν_{max} 1680(br),1320,1270,1135,1040,1020,795,730,708,650cm.$^{-1}$

Found : C, 67.89; H, 6.48; N, 7.79. $C_{10}H_{12}NO_2$

requires: C, 67.78; H, 6.26; N, 7.90%.

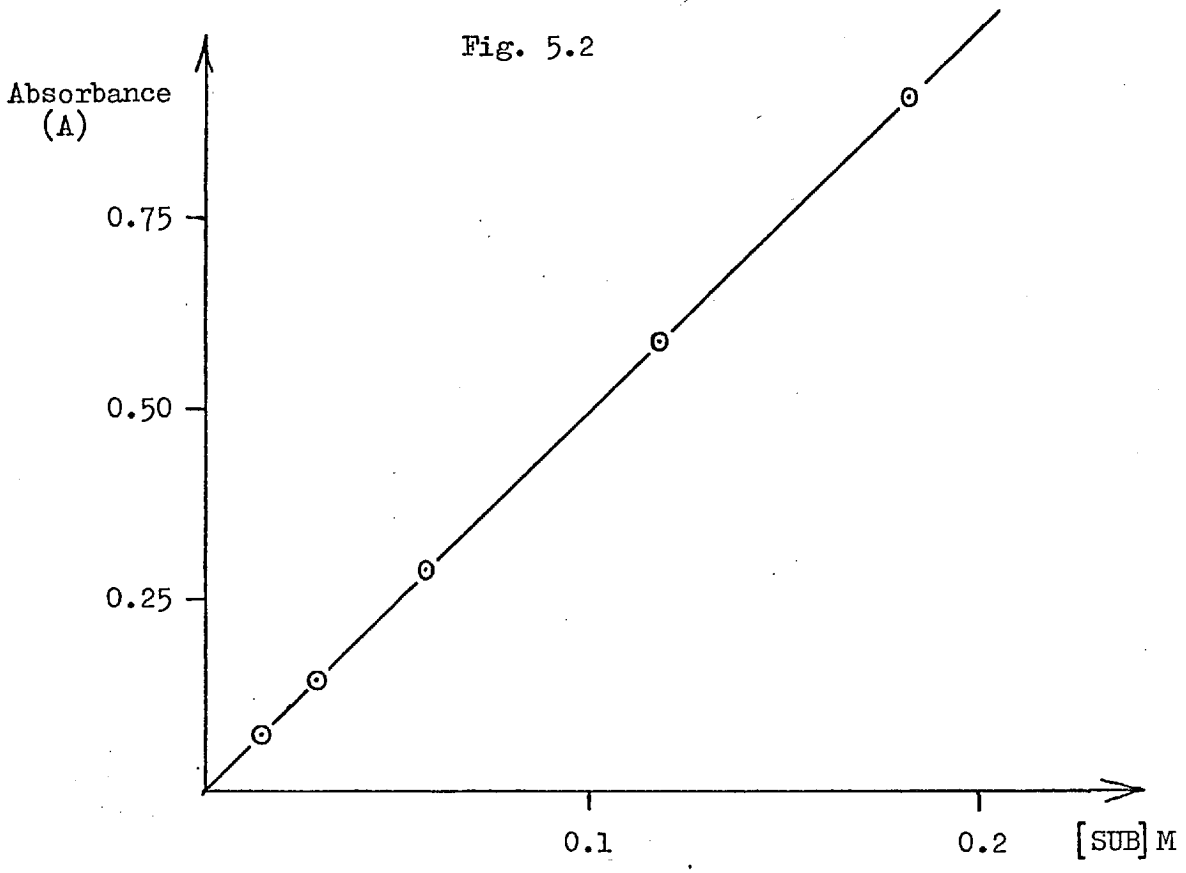
5.2.3 MEASUREMENT OF REARRANGEMENT RATES OF N-(2,4-DINITROPHENYL)BENZIMIDOYL BENZOATE

As mentioned in Section 3.1.2 the rearrangement of the O-acyliosoimide was followed using an infra-red technique by monitoring the disappearance of the carbonyl absorbance at ca.1750cm.$^{-1}$ of the substrate. The solvent used in this reaction was acetonitrile, which was chosen because of the high solubility of the isoimide and also

because it does not absorb appreciably at the frequency of interest (1800-1700cm.$^{-1}$).

Matched sodium chloride cells (0.1mm. path length) were used to monitor the raction solutions. Several standard solutions of the O-acylisoimide in acetonitrile were prepared and the compound was shown to follow the Beer-Lambert law over the concentration range used (Figure 5.2).

Fig. 5.2



The reaction solutions were prepared by dissolving the N-(2,4-dinitrophenyl)benzimidoyl benzoate (0.38g.) in acetonitrile in a 10ml. graduated flask. After an initial reading of the absorbance, the flask was equipped with a Suba-Seal and thermostatted in a bath at 25 $\pm$ 0.2°C. A series of aliquots (0.5ml.) were removed *via* the Suba-Seal at timed intervals for assay.

The thermal rearrangement rate was calculated as an average from three kinetic runs. Rearrangement rates in the presence of catalysts were measured by a similar procedure. In most cases the products from the kinetic runs were isolated and were shown by i.r. and mixed m.p. analysis to be the rearranged product, N-(2,4-dinitrophenyl)-N-benzoylbenzamide.

5.2.4 ANALYSIS OF KINETIC DATA

Normally infinity absorbances in kinetic runs were within 5% of the value calculated from the original concentration of the substrate. The first-order rate constants were calculated from a graphical method and, in some cases, a weighted least-squares computer programme. Both these methods calculated the slope of the plot of log Y versus time, where Y is given by the expression in Equation (67) and A is the absorbance.

$$Y = \frac{A - A_\infty}{A_o - A_\infty} \qquad \ldots\ldots(67)$$

Table 5.2 illustrates the data obtained in the thermal rearrangement reaction.

Table 5.2

THERMAL REARRANGEMENT OF N-(2,4-DINITROPHENYL)BENZIMIDOYL BENZOATE IN ACETONITRILE AT 25 ± 0.2°C

$[PhC(OCOPh):NPh(NO_2)_2]$ = 0.16M. A_∞ = 0.065

t (mns)	A	$A-A_\infty$	% Reaction	$10^5 k_{obs}(s^{-1})$
0.0	0.835	0.77		
75.0	0.785	0.72	6.5	1.49
150.0	0.760	0.695	9.7	1.14
275.0	0.690	0.625	18.8	1.26
350.0	0.645	0.580	24.7	1.34
600.0	0.538	0.473	38.6	1.35
1000.0	0.403	0.338	56.1	1.37
1365.0	0.315	0.250	67.5	1.37
1530.0	0.288	0.223	71.0	1.35
1600.0	0.279	0.214	72.2	1.33
1675.0	0.265	0.200	74.0	1.34
1725.0	0.258	0.193	75.0	1.34

k_{obs}(mean) = $1.33 \times 10^{-5} s^{-1}$

k_{obs}(graphical) = $1.34 \times 10^{-5} s^{-1}$

5.3 ACYLATION OF N-ALKOXYAMIDES

5.3.1 PREPARATION AND PURIFICATION OF REAGENTS AND SOLVENTS

Solvents [218]

Carbon tetrachloride (AnalaR) was dried over phosphorus pentoxide and distilled (b.p. 77-78°C/760mm.Hg.). Deuterochloroform was dried by standing over activated Lindetype 4A molecular sieve. Nitrobenzene (AnalaR) was dried over calcium hydride and distilled (85-86°C/8mm.Hg.). Dimethylsulphoxide was dried over calcium hydride and distilled (b.p. 75-76°C/12 mm.Hg.). Benzene and diethyl ether were dried by standing over sodium wire. Petroleum ether (40-60°C) and n-hexane were dried by standing over calcium chloride.

Acyl halides

Acetyl chloride was refluxed with phosphorus pentachloride for several hours to remove traces of acetic acid and distilled (b.p. 50-52°C/760mm.Hg.). The distillate (100ml.) was then redistilled (b.p. 52°C/760mm.Hg.) from quinoline (10ml.) to remove any remaining hydrochloric acid [218].

Acetyl bromide was fractionally distilled (b.p. 73-76°C/760mm.Hg.). The distillate was treated with 1%($\frac{w}{w}$) dimethylaniline and refractionated (b.p. 74-76°C/760mm.Hg.). The pure acetyl bromide was then treated with sodium and distilled (b.p. 76°C/760mm.Hg.)[232].

Trichloroacetyl chloride was prepared from trichloroacetic acid (41g.) by treatment with thionyl chloride (40g.), using dimethylformamide (0.5ml.) as a catalyst [233]. The trichloracetyl chloride was purified by fractional distillation (b.p. 118°C/760mm.Hg.).

Chloroacetyl chloride was prepared by heating under reflux a solution of chloroacetic acid and benzoyl chloride and distilling the more volatile chloroacetyl chloride as it formed [234]. The crude product was fractionally distilled (b.p. 106°C/760mm.Hg.).

The majority of the aroyl halides were prepared by reaction of the appropriate 4-substituted benzoic acid with thionyl chloride in benzene [7]. Aroyl halides prepared in the above way were 4-methoxybenzoyl chloride (b.p. 91°C/1mm.Hg.), 4-methylbenzoyl chloride (b.p. 119°C/24mm.Hg.), 4-chlorobenzoyl chloride (b.p. 111°C/18mm.Hg.), 4-dimethylaminobenzoyl chloride, m.p. 148-149°C (toluene) 4-nitrobenzoyl chloride, m.p. 75°C (petroleum ether (60-80°C)), 4-cyanobenzoyl chloride, m.p. 78-80°C (ether/petroleum ether (40-60°C)).

Pyridine [218]

Pyridine (AnalaR) was dried by heating under reflux with potassium hydroxide, followed by fractional distillation (b.p. 115-116°C/760mm.Hg.). The distillate was stored over Linde type 4A molecular sieve.

Triethylamine

Triethylamine was distilled (b.p. 89°C/760mm.Hg.) from calcium hydride and stored over Linde type 4A molecular sieve.

Imidazole

After crystallisation from benzene, imidazole was vacuum-dried at 40°C, m.p. 89-90°C (Lit.[218] 89.5-90°C).

2,6-Lutidine

2,6-Lutidine was dried (KOH), distilled and after the addition of 4%($\frac{v}{v}$) Boron trifluoride was redistilled (b.p. 144°C/760mm.Hg.).

Tetramethylammonium acetate

Tetramethylammonium acetate was prepared by neutralising a solution of tetramethylammonium hydroxide with acetic acid [235]. Evaporation of solvent gave tetramethylammonium acetate as a hygroscopic, white solid which was stored in a desiccator over phosphorus pentoxide. This preparation ensured that the ammonium salt did not contain silver or chloride ion impurities.

Tetraethylammonium bromide

Tetraethylammonium hydroxide was neutralised with hydrobromic acid and removal of solvent gave tetraethylammonium bromide as a white solid. The salt was recrystallised (ethanol/ether) and vacuum-dried (110°C).

Acetic anhydride

Acetic anhydride (500g.) was stored over phosphorus pentoxide (50g.) for three hours. The anhydride was then distilled and the fraction (b.p. 137-138°C/760mm.Hg.) was further dried with phosphorus pentoxide for twelve hours. A final fractional distillation gave acetic anhydride (b.p. 137-138°C/760mm.Hg.) as a colourless liquid.

5.3.2 PREPARATION OF SUBSTRATES

The synthetic route chosen for the O-acylisoimides was outlined in Section 4.1.2. It was thought necessary to introduce the alkoxy

function as early as possible in the synthesis of N-alkoxyamides owing to the poor yields obtained in the conversion of N-hydroxyamides into N-alkoxyamides [180] and thus benzyloxyamine was first prepared. The benzyloxyamine was subsequently acylated with the required para-substituted aroyl halide to give the N-alkoxyamide, which was then further acetylated to give the O-acylisoimide substrate.

5.3.2.1 Preparation of Benzyloxyamine and Methyloxyamine N-Hydroxyphthalimide [236]

Hydroxylamine hydrochloride (40g.) was added to an aqueous solution of phthalic anhydride (70g.) and sodium carbonate (53g.) and the resulting solution was held at 60°C for 30 minutes. The solution was cooled to ca.10°C and fine, white needles of N-hydroxyphthalimide precipitated. The product was recrystallised (ethanol) and vacuum-dried to give N-hydroxyphthalimide (90%) m.p. 237-240°C (Lit.[237] 220-226°C).

δ (d_6-DMSO) 7.81 (4H,s), 10.77 (1H,s)

ν_{max} 3140,1780,1735,1708,1195,1145,985,890,710cm.$^{-1}$

N-Benzyloxyphthalimide [186]

A mixture of N-hydroxyphthalimide (30g.) and anhydrous potassium carbonate (19.3g.) in dimethylsulphoxide (200ml.) was prepared. Benzyl chloride (45.6g.) was slowly added, the addition being controlled so that the temperature did not rise above 30°C. The mixture was then left overnight.

The resultant mixture was poured into ice-water (600ml.), and the colourless crystals which separated were filtered, washed with water (3 x 20ml.) and recrystallised (ethanol) to give colourless

prisms of N-benzyloxyphthalimide (43g., 93%) m.p. 145-147°C (Lit.[186] 145-147°C).

δ 5.15 (2H,s), 7.39 (5H,m), 7.79 (4H,s)

ν_{max} 1780,1720,1385,1140,995,890,780,710cm.$^{-1}$

Benzyloxyamine [186]

A mixture of N-benzyloxyphthalimide (30.4g.) and hydrazine hydrate (80% aqueous solution, 8.28g.) in ethanol (900ml.) was heated under reflux for two hours. The mixture was then cooled and concentrated hydrochloric acid (14.5ml.) slowly added. The precipitated phthalhydrazide was filtered and washed with ethanol (3 x 50ml.) and water (3 x 100ml.). Evaporation of the combined filtrate and washings gave colourless crystals of benzyloxyamine hydrochloride.

The hydrochloride was dissolved in water (600ml.) and sodium hydroxide (pellets) was added until an oily layer separated. After extraction into ether (5 x 50ml.) and drying (KOH), the crude product was obtained as an oily residue on evaporation of the solvent. The crude product was distilled to give pure benzyloxyamine, (b.p. 57-58°C/2mm.Hg., Lit.[186] 118-119°C/30mm.Hg.) 13.4g., 90.5%.

δ (d_6-DMSO) 4.48 (2H,s), 5.96 (2H,br.s), 7.29 (5H,s)

ν_{max}(liquid film) 3300,3030,1580,1455,1210,1190,1000,755,710cm.$^{-1}$

N-Methoxyphthalimide [186]

A mixture of N-hydroxyphthalimide (38.8g.) and anhydrous potassium carbonate (21.0g.) in dimethylsulphoxide was prepared.

Methyl iodide (57.5g.) was added dropwise at such a rate that the temperature of the mixture did not exceed 30°C. When the addition was complete the mixture was stirred at room temperature for 24 hours.

The mixture was then poured into ice-water (1000ml.) and the colourless crystals which separated were filtered and washed with water (3 x 100ml.). Extraction of the aqueous washings with benzene afforded a second crop of crystals on evaporation of the organic solvent.

The crystals of the first- and second-crops were combined and recrystallised (ethanol) to give N-methoxyphthalimide (76.0g., 90%) as colourless crystals m.p. 132-133°C (Lit.[186] 133°C).

δ (d_6-DMSO)	4.00 (3H,s), 7.8 (4H,s)
ν_{max}	1790,1735,1480,1190,1140,1000,895,710cm.$^{-1}$

Methyloxyamine hydrochloride[186]

N-Methoxyphthalimide (54.0g.) and hydrochloric acid (550ml., 6M) were heated under reflux with stirring. After heating for thirty minutes, the mixture was stored overnight at 5°C. The phthalic acid precipitate was filtered and washed with cold water (2 x 50ml.). Evaporation of the filtrate and washings gave a white solid, which was dissolved in ethanol (200ml.) and benzene (100ml.) added. After evaporation of the solvent and recrystallisation of the residue (EtOH/Et_2O), colourless plates (24.5g., 95%) of methyloxyamine hydrochloride were obtained, m.p. 150-151°C (Lit.[186] 150-151°C).

δ (d_6-DMSO)	3.84 (3H,s), 10.5 (3H,br.s)
ν_{max}	2700(br),1200,1148,1040,885cm.$^{-1}$

5.3.2.2 Preparation of N-Benzyloxy-4-substituted benzamides

The general method for the preparation of the title compounds is given below. It was found that the use of the amine hydrochloride instead of the free amine led to a decrease in the yield of ca.15-20%, and thus the free amine was used in all cases.

The aroyl chloride (0.01M.) in benzene (50ml.) was slowly added to a stirred solution of benzyloxyamine (0.011M.) and triethylamine (0.011M.) in benzene (150ml.) at 5-10°C. When the addition was complete, the solution was stirred for one-hour at 10°C and allowed to warm to room temperature. Chloroform was added at this point to those reactions which gave a product insoluble in benzene.

The organic solution was washed with 10% hydrochloric acid (2 x 100ml.), saturated sodium bicarbonate solution (2 x 100ml.) and water. After drying ($MgSO_4$), evaporation of solvent gave a crystalline product, which was purified by recrystallisation.

Using the above procedure, the following compounds were prepared:

N-Benzyloxy-4-nitrobenzamide (94% from chloroform/hexane)

m.p. 165.5-166°C (Lit.[135] 166°C)

δ 5.13 (2H,s), 7.47 (5H,s), 7.93 (2H,d,J=9Hz)
8.35 (2H,d,J=9Hz), 9.10 (1H,br.s)

ν_{max} 3200,1640,1520,1355,880,860,760,740,710cm.$^{-1}$

λ_{max},nm (log ε) 263 (4.06)

N-Benzyloxy-4-cyanobenzamide (89% from ether/hexane)

m.p. 148-149°C (Lit.[135] 148-149°C)

δ 5.03 (2H,s), 7.43 (5H,s), 7.78 (4H,s), 9.30 (1H,br.s)

ν_{max} 3160,2230,1640,1520,1480,1040,915,900,855,754,747,700cm.$^{-1}$

λ_{max},nm (log ε) 235 (4.24)

N-Benzyloxy-4-chlorobenzamide (90% from chloroform/hexane)

m.p. 161-162°C (Lit.[135] 161-162°C)

δ 5.07 (2H,s), 7.33-7.78 (4H,m), 7.47 (5H,s),
9.28 (1H,br.s)

ν_{max} 3200,1620,1500,1480,900,855,775,755,740,710cm.$^{-1}$

λ_{max},nm (log ε) 237 (4.15)

N-Benzyloxybenzamide (85% from chloroform/petroleum ether (60-80°C))

m.p. 108-109°C (Lit.[135] 108-109°C)

δ 5.00 (2H,s), 7.20-7.77 (5H,m), 7.33 (5H,s),
9.21 (1H,br.s)

ν_{max} 3235,1643,1505,925,900,805,760,740,705cm.$^{-1}$

λ_{max},nm (log ε) 217 (4.12), 224 (4.09)

N-Benzyloxy-4-methylbenzamide (95% from chloroform/hexane)

m.p. 133-134°C (Lit.[135] 133-133.5°C)

δ 2.35 (3H,s), 5.00 (2H,s), 7.16 (2H,d,J=9Hz), 7.40 (5H,s), 7.63 (2H,d,J=9Hz), 9.26 (1H,br.s)

ν_{max} 3190,1640,1490,1313,1034,895,834,743,700cm.$^{-1}$

λ_{max}, nm (log ε) 234 (4.20)

N-Benzyloxy-4-methoxybenzamide (88% from chloroform/hexane)

m.p. 113-113.5°C (Lit.[135] 113.113.5°C)

δ 3.78 (3H,s), 5.00 (2H,s), 6.86 (2H,d,J=9Hz), 7.41 (5H,s), 7.73 (2H,d,J=9Hz), 9.31 (1H,br.s)

ν_{max} 3240,1640,1600,1490,1320,1260,860,760,710cm.$^{-1}$

λ_{max}, nm (log ε) 254 (4.23)

N-Benzyloxy-4-dimethylaminobenzamide (91% from chloroform/hexane)

m.p. 153-154°C

δ 3.00 (6H,s), 5.03 (2H,s), 6.63 (2H,d,J=9Hz), 7.42 (5H,s), 7.63 (2H,d,J= 9 Hz), 9.34 (1H,br.s)

ν_{max} 3230,1630,1610,1480,1305,830,738,700cm.$^{-1}$

λ_{max}, nm (log ε) 306 (4.25)

N-Benzyloxy-2,4,6-trimethylbenzamide (90% from chloroform/hexane)

m.p. 106-107°C (Lit.[135] 106-107°C)

δ 2.18 (6H,s), 2.23 (3H,s), 5.03 (2H,s), 6.8 (2H,s), 7.42 (5H,s), 8.77 (1H,br.s)

ν_{max} 3140,1640,1045,880,735,698cm.$^{-1}$

λ_{max},nm (log ε) 261 (2.73)

5.3.2.3 Preparation of N-Methoxy-4-nitrobenzamide

A solution of 4-nitrobenzoyl chloride (3.7g.) in chloroform (20ml.) was added slowly to a cooled suspension of methyloxyamine hydrochloride (1.67g.) in chloroform (30ml.) and pyridine (5ml.). When the addition was complete, the reaction solution was allowed to warm to room temperature and poured into ice-water. After extraction into chloroform, the organic layer was washed with 10% hydrochloric acid (3 x 50ml.), saturated sodium bicarbonate (3 x 50ml.), water and dried ($MgSO_4$). Evaporation of solvent gave a crystalline product which was recrystallised from ethyl acetate to give yellow needles (3.06g., 78%) m.p. 182-183°C (Lit.[63] 180°C).

δ (d_6-DMSO) 3.83 (3H,s), 8.05 (2H,d,J=8Hz), 8.32 (2H,d,J=8Hz), 9.18 (1H,br.s)

ν_{max} 3170,1655,1600,1515,1350,1048,938,870,850,725,720cm.$^{-1}$

5.3.2.4 Preparation of N-(Benzyloxy)benzimidoyl acetates

A general method was used to acetylate the N-benzyloxybenzamides and the procedure is given below.

The N-benzyloxybenzamide (0.5g.) was dissolved in pyridine (3ml.) and acetic anhydride (3ml.), and a sample of the reaction solution (0.5ml.) was placed in an n.m.r. tube. The reaction was monitored by following the appearance of the benzylic methylene signal of the product, which occurred downfield (ca.6-10Hz) from that of the starting material. Using this method, it was shown that the formation of the product was extremely rapid (approx. $t_{\frac{1}{2}}$ at ca.38°C = 2 minutes).

When the reaction had reached completion as shown by n.m.r., the solution was poured into ice-water and extracted with chloroform (3 x 30ml.). The organic layer was then washed with saturated sodium bicarbonate solution (2 x 50ml.), 10% hydrochloric acid (2 x 50ml.), water (2 x 50ml.) and dried ($MgSO_4$). Evaporation of solvent at ca 30°C gave a viscous oil which usually crystallised on standing. Further purification of the product was effected by recrystallisation.

Compounds prepared using the above procedure were:

N-Benzyloxy-4-nitrobenzimidoyl acetate (90. from ether/hexane)

m.p. 88-88.5°C (Lit.[135] 88-88.5°C)

δ 2.34 (3H,s), 5.28 (2H,s), 7.43 (5H,s), 7.91 (2H,d,J=9.0Hz), 8.29 (2H,d,J=9.0Hz)

ν_{max} 1770,1620(sh),1595,1530,1350,1320,1195,1075,1020,865,765,720, 710cm.$^{-1}$

λ_{max},nm (log ε) 300 (4.20)

Found: C,61.35; H,4.49; N,8.89. Calculated for $C_{16}H_{14}N_2O_5$; C,61.15; H,4.49; N,8.92%

N-Benzyloxy-4-cyanobenzimidoyl acetate (94% from ether/hexane)

m.p. 82.5 - 83°C (Lit.[135] 70%, 82-83°C)

δ 2.33 (3H,s), 5.26 (2H,s), 7.43 (5H,s), 7.76 (4H,d)

ν_{max} 2230,1768,1195,1070,1017,970,839,828,745,700cm.$^{-1}$

λ_{max},nm (log ε) 276 (4.37)

Found: C,69.28; H,4.99; N,9.45. Calculated for $C_{17}H_{14}N_2O_3$: C,69.37; H,4.79; N,9.52%

N-Benzyloxy-4-chlorobenzimidoyl acetate (91% ether/hexane)

m.p. 66-67°C (Lit.[135] 83%, 66-67°C)

δ 2.30 (3H,s), 5.23 (2H,s), 7.38 (2H,d,J=9.0Hz), 7.43 (5H,s), 7.69 (2H,d,J=9.0Hz)

ν_{max} 1765,1630,1480,1318,1195,1175,1095,1065,1023,1010,965,840, 825,758,720,705cm.$^{-1}$

λ_{max},nm (log ε) 262 (4.31)

Found: C,63.20; H,4.67; N,4.5; Cl,11.91.

Calculated for $C_{16}H_{14}NClO_3$: C,63.27; H,4.65; N,4.61; Cl,11.70%

N-(Benzyloxy)benzimidoyl acetate (90% from ether/hexane)

m.p. 44-45°C (Lit.[135] 90%, 44-45°C)

δ 2.30 (3H,s), 5.23 (2H,s), 7.27-7.83 (5H,m), 7.4 (5H,s)

ν_{max} 1760,1618,1450,1210,1075,1020,775,760,705cm.$^{-1}$

λ_{max},nm (log ε) 256 (3.96)

Found: C,71.24; H,5.46; N,5.31. Calculated for $C_{16}H_{15}NO_3$: C,71.35; H,5.61; N,5.21%

N-Benzyloxy-4-methylbenzimidoyl acetate (91% from ether/hexane)

m.p. 47-48°C (Lit.[135] 82%, 47-48°C)

δ 2.29 (3H,s), 2.36 (3H,s), 5.18 (2H,s), 7.22 (2H,d,J=9Hz), 7.38 (5H,s), 7.62 (2H,d,J= 9Hz)

ν_{max} 1770,1620,1285,1225,1190,1175,1068,1040,1020,815,740,693cm.$^{-1}$

λ_{max},nm (log ε) 260 (4.24)

N-Benzyloxy-4-methoxybenzimidoyl acetate (95% from ether/hexane)

m.p. 61-62°C (Lit.[135] 93%, 61-61.5°C)

δ 2.26 (3H,s), 3.76 (3H,s), 5.19 (2H,s), 6.87 (2H,d,J=9Hz), 7.36 (5H,s), 7.67 (2H,d,J=9Hz)

ν_{max} 1760,1618,1510,1310,1255,1210,1180,1030,970,845,830,758, 710cm.$^{-1}$

λ_{max},nm (log ε) 269 (4.24)

Found: C,68.20; H,5.73; N,4.52. Calculated for $C_{17}H_{17}NO_4$: C,68.22; H,5.73; N,4.68%

N-Benzyloxy-4-dimethylaminobenzimidoyl acetate (96% from ether/hexane)

m.p. 98-99°C

δ 2.26 (3H,s), 2.98 (6H,s), 5.17 (2H,s), 6.64 (2H,d,J=9.0Hz), 7.37 (5H,s), 7.56 (2H,d,J=9.0Hz)

ν_{max} 1765,1620(sh),1600,1525,1210,1185,1050,1025,818,811,740,700cm.$^{-1}$

λ_{max},nm (log ε) 316 (4.38)

Found: C,69.27; H,6.26; N,8.85. $C_{18}H_{20}N_2O_3$ requires: C,69.21; H,6.45; N,8.96%

N-Acetyl-N-benzyloxy-2,4,6-trimethylbenzamide

The acylation of N-benzyloxy-2,4,6-trimethylbenzamide was found to give only the N-acetyl compound under the above conditions. The product (96%) was recrystallised from petroleum ether (60-80°C), m.p. 73-74°C (Lit.[135] 73-74°C).

δ	2.26 (6H,s), 2.33 (3H,s), 2.55 (3H,s), 4.82 (2H,s), 6.92-7.35 (7H,m)
ν_{max}	1710(br),1275,1225,1215(sh),1180,1073,965,853,750,734, 695cm.$^{-1}$
λ_{max},nm	(log ε) 218 (4.30)

5.3.2.5 Preparation of N-Methoxy-4-nitrobenzimidoyl acetate

A solution of N-methoxy-4-nitrobenzamide (0.5g.) in pyridine (3ml.) and acetic anhydride (3ml.) was prepared. After standing at room temperature for 30 minutes, the isolation procedure for N-benzyloxy compounds (Section 5.3.2.4) was adopted. The final product was obtained as pale yellow prisms after recrystallisation (ether/petroleum ether (60-80°C)) m.p. 86-87°C

δ	2.38 (3H,s), 4.05 (3H,s), 7.87 (2H,d,J=9Hz), 8.28 (2H,d,J=9Hz)
ν_{max}	1778,1612,1590,1518,1350,1320,1185,1070,1050,845,758,695cm.$^{-1}$

Found: C,50.31; H,4.05; N,11.49. $C_{10}H_{10}N_2O_5$

requires: C,50.42; H,4.23; N,11.76%

5.3.2.6 Preparation of N-Benzyloxy-4-nitrobenzimidoyl pivalate

Pivaloyl chloride (0.24g.) in dichloromethane (5ml.) was slowly added to a cooled (-70°C), stirred solution of N-benzyloxy-4-nitrobenzamide (0.54g.) in pyridine (3ml.) and dichloromethane (20ml.). After complete addition, the reaction mixture was allowed to warm to room temperature. The solution was poured into ice-water and extracted with chloroform (3 x 40ml.). After washing with saturated sodium bicarbonate (2 x 50ml.), 10% hydrochloric acid (2 x 50ml.) and water (2 x 50ml.), the organic layer was dried ($MgSO_4$). Evaporation of solvent gave an oil which crystallised on standing. Recrystallisation from ether/petroleum ether (60-80°C) gave white needles of N-benzyloxy-4-nitrobenzimidoyl pivalate (93%), m.p. 92-93°C.

δ 1.35 (9H,s), 5.25 (2H,s), 7.42 (5H,s), 7.86 (2H,d,J=9Hz), 7.94 (2H,d,J=9Hz)

ν_{max} 1760,1620(sh),1598,1583,1520,1345,1088,1020,968,853,755,705, 700,690cm.$^{-1}$

Found: C,63.96; H,5.66; N,7.77. $C_{19}H_{20}N_2O_5$

requires: C,64.04; H,5.66; N,7.86%.

5.3.2.7 Preparation of N-Benzyloxy-4-nitrobenzimidoyl benzoates

The general method for the preparation of these compounds consisted of reacting N-benzyloxy-4-nitrobenzamide with one equivalent of the appropriate 4-substituted benzoyl chloride at -70°C (cf. Section 5.3.2.6). The products were isolated using the procedure given in Section 5.3.2.6 and purified by recrystallisation.

Compounds prepared in this way are given below:

N-Benzyloxy-4-nitrobenzimidoyl benzoate (88% from ether/hexane)

m.p. 92-93°C

δ 5.27 (2H,s), 7.38 (5H,s), 7.53-8.33 (9H,m)

ν_{max} 1740,1580,1510,1345,1232,1065,1035,850,753,700cm.$^{-1}$

Found: C,66.75; H,4.16; N,7.31. $C_{21}H_{16}N_2O_5$

requires: C,67.02; H,4.28; N,7.44%.

N-Benzyloxy-4-nitrobenzimidoyl 4-nitrobenzoate (91% from ether/hexane)

m.p. 135-136°C

δ 5.28 (2H,s), 7.35 (5H,s), 7.83-8.38 (8H,m)

ν_{max} 1743,1518,1350,1250,1070,1010,855,750,717,708cm.$^{-1}$

Found: C,59.96; H,3.72; N,9.97. $C_{21}H_{15}N_3O_7$

requires: C,59.86; H,3.59; N,9.97%

N-Benzyloxy-4-nitrobenzimidoyl 4-methylbenzoate (93% from ether/hexane)

m.p. 95-96°C

δ 2.46 (3H,s), 5.25 (2H,s), 7.33 (5H,s), 7.22-8.27 (8H,m)

ν_{max} 1740,1620,1580,1515,1350,1243,1180,1070,1035,865,850,838, 760,742,712,693cm.$^{-1}$

Found: C,67.64; H,4.67; N,7.04. $C_{22}H_{18}N_2O_5$

requires: C,67.52; H,4.67; N,7.20%.

5.3.3 PREPARATION OF REARRANGEMENT PRODUCTS

5.3.3.1. Preparation of N-Acetyl-N-benzyloxybenzamides.

The title compounds were prepared by the general method given below.

The appropriate N-benzyloxybenzamide (1.0g.) was dissolved in benzene and a mixture of acetic anhydride (3ml.) and acetyl chloride (1ml.) added. The solution was then heated under reflux until t.l.c. (silica/chloroform) of the reaction solution showed complete formation of the N-acetyl product.

The isolation procedure given in Section 5.3.2.4 was used to obtain the crude product, which was further purified by recrystallisation.

N-Acetyl-N-benzyloxy-4-nitrobenzamide (88% from chloroform/hexane)

m.p. 99-100°C (Lit.[135] 99-100°C)

δ 2.5 (3H,s), 4.87 (2H,s), 7.03-7.73 (9H,m)

ν_{max} 1728,1685,1515,1353,1238,757,743,720,700cm.$^{-1}$

λ_{max},nm (log ε) 263 (4.07)

N-Acetyl-N-benzyloxy-4-cyanobenzamide (93% from chloroform/hexane)

m.p. 152-153°C

δ 2.53 (3H,s), 4.92 (2H,s), 7.72 (5H,s), 7.1-7.8 (4H,m)

ν_{max} 2235,1728,1690,1235,1222,850,840,758,700cm.$^{-1}$

N-Acetyl-N-benzyloxy-4-chlorobenzamide (90% from chloroform/hexane)

m.p. 59-60°C (Lit.[135] 58-60°C)

δ 2.52 (3H,s), 4.88 (2H,s), 7.03-7.70 (9H,m)

ν_{max} 1715,1685,1588,1295,1220,1093,1075,960,845,760,735, 710,692cm.$^{-1}$

λ_{max},nm (log ε) 244 (4.10)

N-Acetyl-N-benzyloxybenzamide (85% from ether/hexane)

m.p. 69-69.5°C (Lit.[135] 69.69.5°C)

δ 2.5 (3H,s), 4.83 (2H,s), 7.27-7.90 (10H,m)

ν_{max} 1728,1700,1600,1289,1178,1025,790,760,700cm.$^{-1}$

λ_{max},nm (log ε) 234 (3.80)

N-Acetyl-N-benzyloxy-4-methylbenzamide (83% from ether/hexane)

m.p. 85-86°C (Lit.[135] 85-85.5°C)

δ 2.43 (3H,s), 2.53 (3H,s), 4.85 (2H,s) 7.13-7.72 (9H,m)

ν_{max} 1705,1685,1600,1370,1290,1230,815,740,695cm.$^{-1}$

λ_{max},nm (log ε) 253 (4.10)

N-Acetyl-N-benzyloxy-4-methoxybenzamide (88% from ether/hexane)

m.p. 64-64.5°C (Lit.[135] 64-64.5°C)

δ 2.48 (3H,s), 3.90 (3H,s), 4.87 (2H,s), 6.86-7.87 (9H,m)

ν_{max} 1710,1685,1600,1295,1270,1250,1182,860,855,770,710cm.$^{-1}$

λ_{max},nm(log ε) 216 (4.28), 277 (4.09)

N-Acetyl-N-benzyloxy-4-dimethylaminobenzamide (85% from chloroform/hexane)

m.p. 90-91°C

δ 2.43 (3H,s), 3.08 (6H,s), 4.88 (2H,s), 6.65 (2H,d,J=9Hz), 7.32 (5H,s), 7.81 (2H,d,J=9Hz)

ν_{max} 1705,1660,1600,1290,1245,1195,1078,983,838,765,700cm.$^{-1}$

Found: C,69.39; H,6.57; N,8.76. $C_{18}H_{20}N_2O_3$

requires: C,69.21; H,6.45; N,8.96%

5.3.3.2 Preparation of N-Acetyl-N-methoxy-4-nitrobenzamide

The title compound was prepared by heating a solution of N-methoxy-4-nitrobenzamide (1.0g.), acetic anhydride (3.0ml.), and acetyl chloride (1.0ml.) in benzene (20ml.) under reflux for five hours. After isolation (Section 5.3.2.4) the product was recrystallised (chloroform/hexane) to give N-acetyl-N-methoxy-4-nitrobenzamide as pale yellow needles (91%), m.p. 118-119°C.

δ 2.53 (3H,s), 3.77 (3H,s), 7.86 (2H,d,J=9Hz),
8.33 (2H,d,J=9Hz)

ν_{max} 1725,1688,1515,1350,1240,1147,1073,988,865,850,748,722cm.$^{-1}$

Found: C,50.55; H,4.31; N,11.77. $C_{10}H_{10}N_2O_5$

requires: C,50.42; H,4.23; N,11.76%

5.3.4 MEASUREMENT OF REARRANGEMENT RATES

It was found that a convenient method to monitor the rearrangement of the O-acylisoimide to the N-acyl isomer was an n.m.r. technique, described in Section 4.1.2.

5.3.4.1 N.m.r. procedure

The appropriate substrate (0.2mM.) was placed in an n.m.r. tube, which was then placed in a holder calibrated to indicate the depth of the tube equivalent to an internal volume of 0.5ml.* In a dry-box in an atmosphere of dried nitrogen gas, the catalyst was added by volume from a microlitre syringe, and the total volume of the solution was made up to the indicated mark with the required solvent.

After careful sealing to ensure no ingress of water, the n.m.r. spectrum of the reaction solutions was recorded and the tube then immersed in a thermostatted bath containing polyethylene glycol at 60 $\pm$ 0.2°C. At timed intervals, the tubes were removed and, after arresting the reaction by cooling in ice-water, the n.m.r. spectrum was

* The assumption of constant dimensions of the many n.m.r. tubes used in the course of this work was verified by placing tubes of known weight in the holder and, after addition of water to the calibration mark, reweighing. The errors were found to be very small ($\gtrsim$1.5%).

Table 5.3

BENZYLIC METHYLENE AND ACETYL CHEMICAL SHIFTS OF O- AND N-ACETYLATED N-BENZYLOXYAMIDES IN $CDCl_3$/TMS

Compound	$-O-CH_2$(Hz)	$-CH_3CO$(Hz)
4-NMe_2PhC(OCOMe):$NOCH_2$Ph	310	136
4-NMe_2PhCON(COMe)OCH_2Ph	293	146
4-MeOPhC(OCOMe):$NOCH_2$Ph	311	136
4-MeOPhCON(COMe)OCH_2Ph	292	149
4-MePhC(OCOMe):$NOCH_2$Ph	311	137
4-MePhCON(COMe)OCH_2Ph	291	152
PhC(OCOMe):$NOCH_2$Ph	314	138
PhCON(COMe)OCH_2Ph	290	150
4-ClPhC(OCOMe):$NOCH_2$Ph	314	138
4-ClPhCON(COMe)OCH_2Ph	293	151
4-CNPhC(OCOMe):$NOCH_2$Ph	316	140
4-CNPhCON(COMe)OCH_2Ph	295	152
4-NO_2PhC(OCOMe):$NOCH_2$Ph	317	140
4-NO_2PhCON(COMe)OCH_2Ph	292	150

recorded. In order to minimise timing errors, reagent concentrations were adjusted, as far as was possible, to ensure that the reaction half-life was at least two hours. After running the spectra, the signals were integrated at least three times, and the tube was replaced in the oil-bath at 60°C.

5.3.4.2 Analysis of Kinetic Data

The extent of reaction could be ascertained directly either by observing the benzylic methylene signal or, with the exception of the 4-methylbenzamide derivative, by monitoring the acetyl signal.

Since it was impractical to leave the control settings (e.g. R_f power, amplitude, phase) on the Varian T60 n.m.r. machine entirely constant for a complete kinetic run, the observed signal of the substrate (e.g. $-OCH_2$, CH_3CO) for any particular scan was related to the overall combined integral i.e. total benzylic methylene or acetyl integral.

The substrate concentration, therefore, at any time 't' ($[S_t]$) could be determined from Equation (68), where S_o represents the initial substrate concentration.

$$S_t = [S_o] \times \left(\frac{-OCH_2{}^{sub}}{-OCH{}^{total}} \right)$$

$$= [S_o] \times \left(\frac{CH_3CO^{sub}}{CH_3CO^{total}} \right) \quad \ldots\ldots(68)$$

In Equation (68), $-OCH_2{}^{sub}$ and CH_3CO^{sub} represent the integrals of the substrate; $-OCH_2{}^{total}$ and CH_3CO^{total} represent the sum of the methylene and acetyl integrals of the substrate and product. The observed kinetic behaviour with various catalysts is shown in Table 5.4 - 5.10.

Table 5.4

PYRIDINE/ACETIC ANHYDRIDE CATALYSED REARRANGEMENT OF $4\text{-}NO_2PhC(OCOMe):NOCH_2Ph$

$T = 60^{\circ}C$ Solvent = $PhNO_2$

$[Sub] = 0.4M$ $[Ac_2O] = 0.2M = [py]$

R_T(mns)	$-OCH_{2sub}$	$\sum -OCH_2$	$[Sub]_M$.	% Reaction	$10^6 k_{obs}(s^{-1})$
0	30	30	0.4	-	
1023	26	29.5	0.353	11.8	2.04
1618	24.5	30.0	0.326	18.5	2.08
2464	21.0	30.0	0.280	30.0	2.41
3018	20.0	30.0	0.267	33.3	2.23
3931	17.0	29.0	0.234	41.5	2.26
4472	17.0	31.0	0.219	45.3	2.23
5384	14.0	30.0	0.186	53.5	2.35
6020	13.0	31.0	0.168	58.0	2.40
6752	11.5	30.5	0.151	62.3	2.40
8187	9.0	28.5	0.126	68.5	2.34
9613	8.0	31.0	0.103	74.3	2.34
11048	6.0	29.0	0.083	79.3	2.37
12492	5.0	30.0	0.067	83.3	2.39

k_{obs}(mean) = 2.30×10^{-6}

k_{obs}(graphical) = 2.30×10^{-6}

Table 5.5

PYRIDINE-CATALYSED REARRANGEMENT OF
$4\text{-}NO_2PhC(OCOMe):NOCH_2Ph$

T= 60°C Solvent = $CDCl_3$

[Sub] = 0.4M [Pyridine] = 0.8M

R_T(mns)	$-OCH_{2sub}$	$\sum -OCH_2$	[Sub]M.	%Reaction	$10^6 k_{obs}(s^{-1})$
0	34.0	34.0	0.4	-	
1374	27.0	33.0	0.327	18.3	2.43
2822	21.0	33.0	0.255	36.3	2.22
3379	20.0	33.0	0.242	39.5	2.47
4247	17.0	33.0	0.206	48.5	2.60
5700	13.0	32.0	0.163	59.3	2.63
7582	11.0	33.0	0.133	66.8	2.41
8688	8.0	31.0	0.103	74.3	2.59
11411	5.0	30.0	0.067	83.3	2.61

k_{obs}(mean) = $2.50 \times 10^{-6} s^{-1}$

k_{obs}(graphical) $\simeq$ $2.59 \times 10^{-6} s^{-1}$

k_{cat} = 3.24×10^{-6} $1M^{-1}s^{-1}$

Table 5.6

PYRIDINE-CATALYSED REARRANGEMENT OF
$4\text{-}NO_2\text{-}PhC(OCOMe):NOCH_2Ph$

$T = 60^{\circ}C$ Solvent = $PhNO_2$

[Sub] = 0.4M [Pyridine] = 0.4M

R_T(mns)	$-OCH_{2sub}$	$\sum -OCH_2$	[Sub]M.	% Reaction	$10^6 k_{obs}(s^{-1})$
0	33.0	33.0	0.4	-	
164	32.00	33.0	0.3888	15.5	3.12
1144	25.0	33.0	0.303	24.3	4.04
1688	21.5	33.0	0.260	35.0	4.23
2705	17.0	33.0	0.206	48.5	4.08
3108	15.0	33.0	0.182	54.5	4.22
4017	12.5	33.5	0.149	62.8	4.09
4420	11.0	35.0	0.125	68.8	4.36
5737	7.5	31.0	0.098	75.5	4.12
7080	6.0	32.0	0.075	81.3	3.94

$k_{obs}(mean) = 4.14 \times 10^{-6}\ s^{-1}$

$k_{obs}(graphical) = 4.17 \times 10^{-6}\ s^{-1}$

$k_{cat} = 1.04 \times 10^{-5}\ 1M^{-1}s^{-1}$

Table 5.7

ACETATE-CATALYSED REARRANGEMENT OF 4-CNPhC(OCOMe):$NOCH_2Ph$

Solvent: $CDCl_3$ $T = 60^{\circ}C$

$[Sub] = 0.4M$ $[Me_4\overset{+-}{N}OAc] = 0.15M$

R_T(mns)	$-OCH_{2sub}$	$\sum -OCH_2$	[Sub]M.	% Reaction	$10^4 k_{obs}(s^{-1})$
0	28	28	0.40	-	
5	24	28.5	0.336	16.0	5.81
9	22	30.0	0.293	26.8	5.76
14	20	31.5	0.254	36.5	5.41
19	16.5	30.5	0.216	46.0	5.39
24	14.5	31.5	0.184	54.0	5.39
29	12.5	31.5	0.158	60.5	5.31
33	10.5	30.5	0.138	65.5	5.39
38	9.0	30.5	0.118	70.5	5.35
43	8.0	31.5	0.102	74.5	5.31
48	7.0	31.5	0.089	77.8	5.22
55	5.5	31.5	0.070	82.5	5.28

k_{obs}(mean) = $5.42 \times 10^{-4}\ s^{-1}$

k_1(graphical) = $5.60 \times 10^{-4}\ s^{-1}$

k_{cat} = $3.73 \times 10^{-3}\ 1M^{-1}s^{-1}$

Table 5.8

ACETYL BROMIDE CATALYSED REARRANGEMENT OF
$4\text{-}NO_2PhC(OCOMe):NOCH_2Ph$

$T = 60^{\circ}C$ Solvent = $PhNO_2$

[Sub] = 0.4M. [AcBr] = 1.36M.

R_T(mns)	$-OCH_{2sub}$	$\sum -OCH_2$	[Sub]M.	% Reaction	$10^5 k_{obs}(Ms^{-1})$
0	29	29	0.4	-	
12.5	26	28	0.371	7.3	3.81
33.5	23	29	0.317	20.8	4.12
58.0	18	29.5	0.244	39.0	4.48
68.0	15.5	29.0	0.214	46.5	4.57
78.0	13.0	28.0	0.186	53.5	4.58
87.0	11.5	29.0	0.158	60.5	4.63
97.0	9.5	29.5	0.129	67.8	4.66
107.0	7.5	28.0	0.107	73.3	4.56
122.0	5.5	28.5	0.077	80.8	4.41

k_{obs}(mean) = $4.42 \times 10^{-5}\ Ms^{-1}$

k_{obs}(graphical) = $4.60 \times 10^{-5}\ Ms^{-1}$

k_{cat} = $3.38 \times 10^{-5}\ s^{-1}$

Table 5.9

ACETYL BROMIDE CATALYSED REARRANGEMENT OF
4-NO_2PhC(OCOMe):$NOCH_2$Ph

T = 60°C Solvent = $CDCl_3$

[Sub] = 0.4M. [AcBr] = 0.68M.

R_T(mns)	$-OCH_{2sub}$	$\sum -OCH_2$	[Sub]M.	% Reaction	$10^7 k_{obs}(Ms^{-1})$
0	25.5	28	0.364		-
409	24.0	28	0.344	5.5	8.15
1633	19.5	28.5	0.272	25.3	9.38
2833	15.0	27.5	0.220	39.6	8.48
4161	10.0	27.5	0.144	60.4	8.74
4702	8.0	26.0	0.124	65.9	8.51
5577	6.0	29.0	0.083	77.2	8.40
6150	3.0	25.0	0.048	86.8	8.56

k_{obs}(mean) = 8.60×10^{-7} Ms^{-1}

k_{obs}(graphical) = 8.72×10^{-7} Ms^{-1}

k_{cat} = 1.28×10^{-6} s^{-1}

TABLE 5.10

ACETYL BROMIDE CATALYSED REARRANGEMENT OF
4-MeOPhC(OCOMe):NOCH$_2$Ph

T = 60°C Solvent = CCl_4

[Sub] = 0.4M. [AcBr] = 0.4M.

R_T(mns)	$-OCH_2$	$\sum -OCH_2$	[Sub]M.	% Reaction	$10^5 k_{obs}(s^{-1})$
0	33	33.0	0.4		
149	26	30.5	0.341	14.8	1.79
308	23	32.0	0.288	28.0	1.78
440	20	32.5	0.246	38.5	1.64
750	14	32.0	0.175	43.7	1.84
1040	10	32.0	0.125	68.8	1.86
1240	8	32.0	0.100	75.0	1.86
1480	6	31.5	0.076	81.0	1.87
1750	4.5	32.5	0.055	86.3	1.89

k_{obs}(mean) = $1.82 \times 10^{-5} s^{-1}$

k_{obs}(graphical) = $1.88 \times 10^{-5} s^{-1}$

5.3.5 PREPARATION OF LABELLED SUBSTRATE

A solution of N-benzyloxy-4-cyanobenzamide (0.45g.) in pyridine (3ml.) was prepared, and C^{14}-labelled acetic anhydride (0.185g.) added. The reaction was followed by n.m.r., and when the reaction was complete, the labelled product was isolated as described in Section 5.3.2.4. The final product (0.500g., 94%) was obtained as fine white needles m.p. 82.5-83°C. Infra-red and n.m.r. spectra were superimposable with those of N-benzyloxy-4-cyanobenzimidoyl acetate previously prepared.

5.3.6 PYRIDINE-CATALYSED REARRANGEMENT OF LABELLED SUBSTRATE IN THE PRESENCE OF UNLABELLED SUBSTRATE

A solution of N-benzyloxy-4-cyanobenzimidoyl C^{14}-acetate (0.09g.), N-benzyloxy-4-nitrobenzimidoyl acetate (0.09g.), pyridine (0.03g.) in deuterochloroform (0.5ml.) was prepared and held at 60°C until n.m.r. spectra indicated complete rearrangement.

The reaction was then poured into water (10ml.) and extracted into chloroform. After washing with dilute hydrochloric acid and water, the solution was dried ($MgSO_4$) and evaporation of solvent gave a white crystalline solid.

The pure products were obtained by (silica/chloroform) the crude sample to give N-acetyl-N-benzyloxy-4-cyanobenzamide and N-acetyl-N-benzyloxy-4-nitrobenzamide. The purity of the products was checked by i.r. spectroscopy and melting point determination.

5.3.7 ACETATE-CATALYSED REARRANGEMENT OF N-BENZYLOXY-4-CYANOBENZIMIDOYL 1-C^{14}-ACETATE

A solution of the substrate (0.059g.), tetramethylammonium acetate (0.009g.) in chloroform (to 0.5ml.) was held at 60°C, until n.m.r. analysis showed complete reaction. The reaction mixture was then poured into ice-water, extracted with chloroform, and washed with saturated sodium bicarbonate solution and water. After drying ($MgSO_4$), the solvent was removed in vacuo to give a white crystalline solid, which was purified by t.l.c. (silica/chloroform). The n.m.r. and i.r. spectra of this purified sample were superimposable with those of an authentic sample.

5.3.8 ASSAYING PROCEDURE FOR LABELLED PRODUCTS

In order to determine the amount of 'scrambling' of the C^{14}-label in the pyridine- and acetate-catalysed rearrangements, the products were assayed using a liquid scintillation counter. Scintillation solution (diphenyloxazole (10g.) and 1,4 bis 2-(4-methyl-5-phenyloxazoyl) benzene (0.25g.) in xylene (1l.)) was added (5ml.) to a known weight of the purified product, and the solution then assayed by scintillation counting.

5.3.8.1 Analysis of Results

In order to calculate the percentage scrambling between the 4-cyano and 4-nitro compounds, the results were evaluated using specific activities (Equation (69)). In Equation (69), S_o represents

$$S_o = \frac{A_o}{W_o} \qquad \text{.....(69)}$$

the specific activity and A_o is the activity of a known weight (W_o) of the compound in question. The specific activities of the products were then compared with the value determined for the labelled 4-cyano substrate.

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