

HOMOLYTIC SUBSTITUTION IN  
AROMATIC HETEROCYCLES

A thesis presented for the degree of doctor of philosophy

in the Faculty of Science University of London

by

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Bedford College

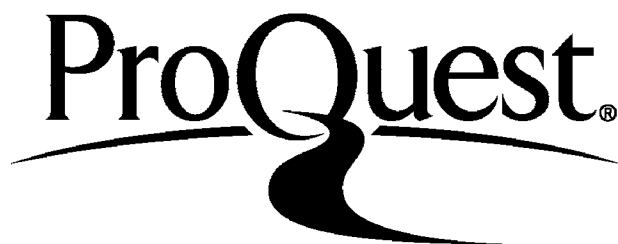
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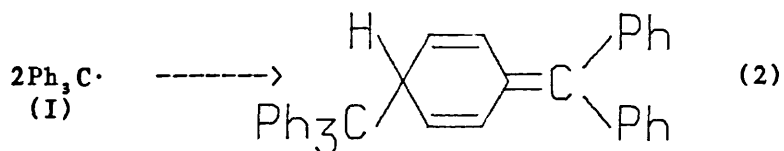
## INTRODUCTION

### I.1

#### Radicals - an introduction

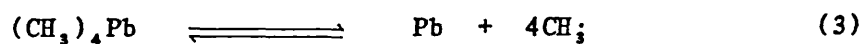
A radical is a species with an unpaired electron.

The classical research papers of Gomberg<sup>1</sup> on the triphenylmethyl radical (I) (reaction 1 and 2), and the study by Lund and



Bodenstein<sup>2</sup> (1906) of the H<sub>2</sub> and Br<sub>2</sub> chain reaction, mark the beginning of organic free-radical chemistry.

Radical kinetics opened up with the radical-mirror removal experiments of Paneth et. al.<sup>3</sup> (1929) (reaction 3) and others<sup>4</sup>.



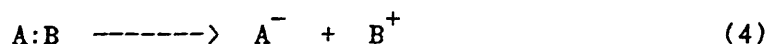
The pyrolysis of tetramethyl lead (900-1200°K; 1 s, residence in quartz furnace) produced species (methyl radicals) which were capable of removing mirrors of lead, antimony and zinc. The rates and products observed made possible the first measurements of radical concentration and of radical reactivity.

The Rice-Herzfield mechanisms<sup>5</sup> (1934) gave a detailed scheme of elementary radical reactions to account for the rates and products of complex pyrolysis reactions.

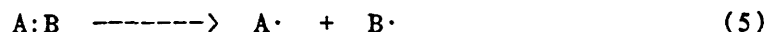
### I.1.1 Radicals and chemical bonding

Ingold<sup>6</sup> (1938) introduced a new terminology to distinguish between the two modes of bond fission<sup>7</sup>.

Heterolytic bond fission (Heterolysis):

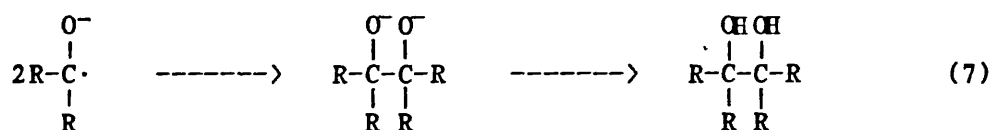
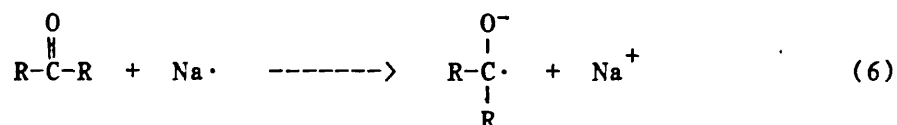


Homolytic bond fission (Homolysis):

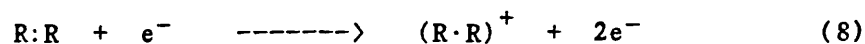


Heterolysis (equation 4) involves the unsymmetrical cleavage of the covalent bond and results in the formation of two ions from a neutral molecule; homolysis (equation 5), on the other hand, by division of the electron pair, results in the formation of two electrically neutral free-radicals.

Radicals need not be neutral. The one-electron reductions of ketones give radical anions (equation 6 and 7).



Radical cations are produced when radicals collide with organic molecules to displace valence electrons (equation 8).



For all linkages A:B, homolysis is the normal mode of fission in the gas phase since this requires less energy than the separation of ionic species<sup>2</sup>. However, in solution, heterolysis is generally favoured since the separation of charged species is assisted by their solvation.

## I.1.2

Thermodynamics of reactivity

A prime need, for mechanistic purposes, is the heat of formation ( $\Delta H_f^{(R\cdot)}$ ) of the radicals which leads to knowledge of the values for  $\Delta H$  for elementary processes.

The value for  $\Delta H_f^{(R\cdot)}$  of benzyl radicals has led to a bond dissociation energy (BDE) ( $\text{PhCH}_2\text{-H}$ ) =  $355 \pm 4$  kJ mol<sup>-1</sup>, which corresponds to a stabilisation energy of  $54 \pm 8$  kJmol<sup>-1</sup>, when compared to the BDE( $\text{CH}_3\text{CH}_2\text{-H}$ ) =  $409 \pm 4$  kJmol<sup>-1</sup>.

If we knew, for each chemical species that might take part in a stoichiometric equilibrium reaction, (a) its heat of formation ( $\Delta H_f^{\circ}(T_0')$ ), and entropy ( $S^{\circ}(T_0')$ ), both at the reference temperature  $T_0'$ , and (b) its heat capacity ( $C_{pT}$ ) over a large temperature range, we could predict the equilibrium constant for that stoichiometric reaction at any temperature<sup>1,2</sup>.

## I.1.3

The role of polar effects in radical reactions

The first observations of the sensitivity of radical reactions to polar substituents were published in 1945-1947. The tendency to form the dipolar resonance structures has been termed the polarisability of the species<sup>3</sup>. Mayo<sup>4</sup>, Price<sup>10</sup>, Bartlett<sup>11</sup>, and their co-workers, postulated that dipolar resonance structures cause the transition states for certain radical reactions to be more stable than expected, and that these polar structures markedly influence the reactivity patterns observed. This has been supported by extensive findings in more recent years<sup>12</sup>.

One of the most informative methods for expressing the quantitative importance of polar effects in radical reactions, is by the applications of the Hammett sigma( $\sigma$ )-rho( $\rho$ ) equation<sup>13</sup> [normally called the Linear Free-Energy Relationship (L.F.E.R.)].

The original explanation of radical reactions by the Hammett equation, was that the transition states of radical reactions involve dipolar charge-separated forms as resonance structures<sup>14</sup>. It was later pointed out that the Hammett correlation of radical reactions also reflects the reactivities of the radicals involved<sup>15,115</sup>.

Effects of BDE and polarity on rho values for radical reactions

Heat of reaction	Effect of Rho	
	Substituent effect on BDE	Dipolar resonance forms
Very exothermic	Not important	Not important
	Moderate effect (gives negative rho)	Large effect (gives positive or negative rho depending on charge type)
Thermonutral	Large effect (gives negative rho)	Not important

Table I

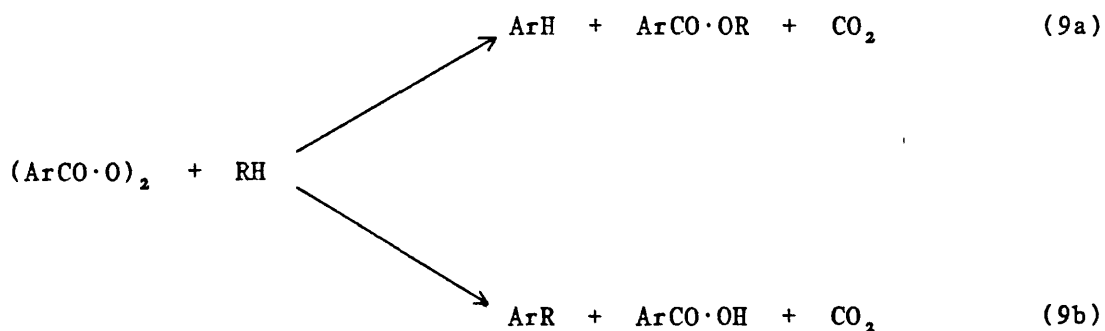
When polar effects on the transition state do become an important factor, it is likely that several characteristics of the radical must be considered in order to rationalise observed rho values<sup>17</sup>, for example, electron affinity and polarisability of the species.

## I.2

Homolytic aromatic substitution

Direct homolytic arylation of an aromatic compound was reported by Gomberg in 1924<sup>18</sup>.

Gelissen and Hermans<sup>19, 20</sup> (1925) who investigated the decomposition of benzoyl peroxide in various aromatic solvents, interpreted the reaction (incorrectly) as proceeding according to their so called 'RH' scheme:-



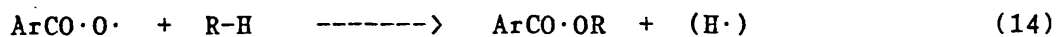
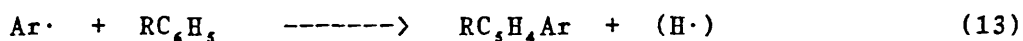
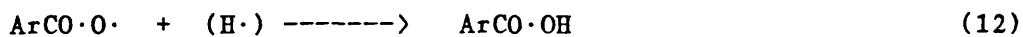
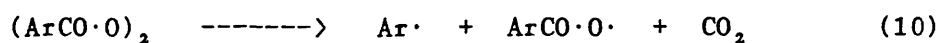
The detailed mechanism was not defined.

Hey<sup>20</sup>, in 1934, pointed out that the results reported by Gomberg could not be fitted into the established pattern of either electrophilic or nucleophilic aromatic substitution, but could be explained in terms of free-radicals (they suggested the phenyl radical) as the attacking species.

Since then a large number of reactions of a similar nature have been brought to light<sup>21</sup>.

I.2.1 Homolytic aromatic substitution with benzoyl peroxide

Hey and Waters<sup>22</sup>(1937) rationalised the decomposition of diaryl peroxides in aromatic solvents in terms of free-radical intermediates in the following scheme, in which equations (10) - (12) reflect the formation of the major products, and equations (13) and (14) show side reactions:



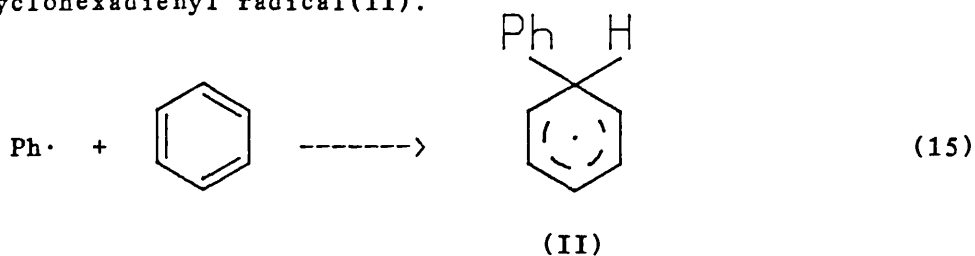
Scheme I

Proposed mode of product formation in the thermolysis of benzoyl peroxide.

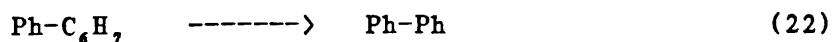
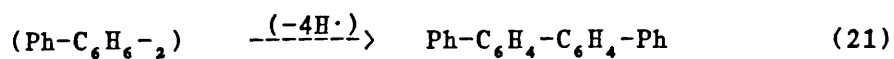
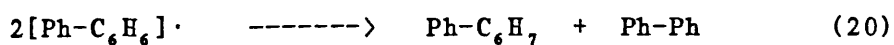
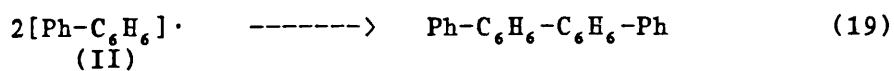
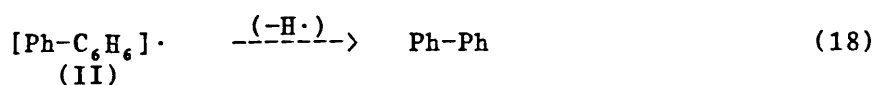
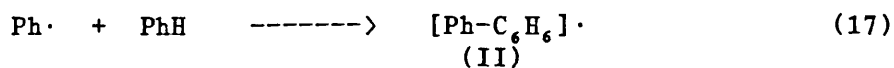


I.2.1.1 The kinetics and mechanism of benzoyl peroxide decomposition

Waters<sup>23</sup> (1941) formulated the initial act in the substitution process as addition to the aromatic ring to form the phenylcyclohexadienyl radical(II).



More recent comprehensive work on the decomposition of benzoyl peroxide in benzene, has now established the following scheme of reactions<sup>127</sup>:-



Scheme II

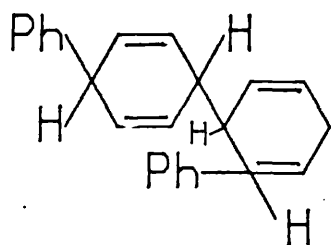
Reactions (21) and (22) require an oxidising agent and do not occur in reactions between benzoyl peroxide and benzene in the absence of oxygen. Among the additional steps established, reactions (19) and (20) represent the dimerisation and disproportionation, respectively, of the radical (II) (page 9) to give hydroaromatic compounds which, in turn, are dehydrogenated according to reactions (21) and (22), to yield biphenyl and quaterphenyls. Thus the following products have been identified<sup>112</sup>. The major products are listed below for the resonance hybrids of radical (II).

$\text{CO}_2$ ,  
(1.77)\*

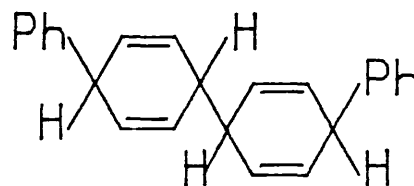
$\text{PhCO}\cdot\text{OH}$ ,  
(0.08)\*

$\text{PhPh}$ ,  
(0.36)\*

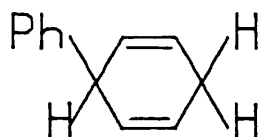
$\text{PhCO}\cdot\text{OPh}$   
(0.03)\*



(0.22) \*



(0.27) \*



(0.18) \*

\*Values in parenthesis represent yields in moles per mole of peroxide

Evidence for the above scheme:-

(i) In the decomposition of benzoyl peroxide in benzene, quaterphenyls were obtained in greater yield than terphenyl. This indicates that terphenyl and quaterphenyl were not formed by successive phenylation<sup>24</sup>.

(ii) The quaterphenyl obtained from the reaction of symmetrically disubstituted benzoyl peroxide with benzene revealed substituents in only two of the aromatic nuclei<sup>25</sup>.

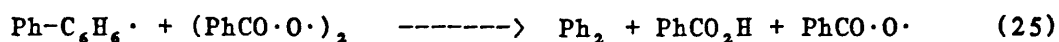
(iii) When decomposition of a very dilute solution of benzoyl peroxide in benzene was carried out in the complete absence of oxygen, hydroaromatic products could be isolated. These were isomeric dihydrobiphenyls and an isomer of tetrahydro-p-quaterphenyl<sup>26</sup>. When oxygen was not rigidly excluded, these hydroaromatic compounds could not be isolated but were apparently oxidised to the corresponding bi- and poly-phenyls.

(iv) In the decomposition of benzoyl peroxide in benzene-1-<sup>14</sup>C, while a little p-terphenyl labelled in one nucleus was found, a much larger yield was obtained of 4,4'-quaterphenyl labelled in two nuclei<sup>27</sup>. The kinetic equation (23)<sup>28</sup> obtained for the primary homolysis process of benzoyl peroxide, represented by P, into two benzoyloxy radicals viz.,

$$-d[P]/dt = k_1[P] + k_2[P]^{3/2} \quad (23)$$

contains the term  $k_2[P]^{3/2}$ , attributable to induced decomposition. This gives rise to variations in the observed rate of decomposition from one solvent to another<sup>29,30</sup>, although among simple aromatic solvents these variations are minor.

Two modes of induced decomposition may occur:-

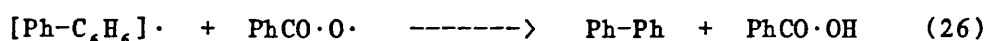


The oxidation of the phenylcyclohexadienyl radicals to biaryls by molecular benzoyl peroxide (reaction 25) is the predominating mode of induced decomposition. Such a process gives 3/2 - order kinetics provided chains are terminated by reaction between like radicals i.e., by dimerisation or disproportionation (reactions 19 and 20). The order of reaction would be unity if termination were by reaction between unlike radicals. Reaction (25) is much more important than reaction (24) as very low yields of phenyl benzoate are obtained<sup>65</sup>.

In many arenes, like benzene and chlorobenzene, other reactions involving the benzoyloxy radical are of minor importance because of the low stationary concentration of the benzoyloxy-radical in such solvents<sup>175</sup>.

For the reaction in benzene, alkylbenzenes, fluorobenzene and chlorobenzene, the rate obeys equation (23), so the chain termination reactions involve dimerisation and disproportionation of the  $\sigma$ -complexes. It is also observed that in high dilution, where secondary radical reactions of the dihydroaromatic products are minimised, the highest yields of quaterphenyls are obtained. When results from this and related experiments were extrapolated to infinitely low concentration of peroxide, almost all of the peroxide could be accounted for as carbon dioxide and the products of dimerisation and disproportionation of the  $\sigma$ -complex, with dimerisation accounting for as much as 75% of the reaction products<sup>31,32,33</sup>.

In bromobenzene, however, abstraction of hydrogen by benzoyloxy radicals becomes the main pathway which produces biaryl by dehydrogenation of  $\sigma$ -complexes<sup>127</sup>. In solvents showing first - order induced decomposition terms (such as bromobenzene), chains are terminated by reaction (26), and consequently,



yields of biaryl and aroic acid are high, and those of the residue are low.

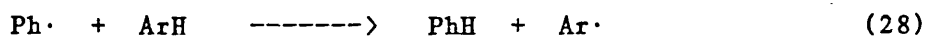
The apparent difference in mechanism between solvents showing 3/2 - order kinetics (chlorobenzene), and solvents showing first - order kinetics (bromobenzene), is due to the greater stability of the benzoyloxy-radical in bromobenzene, probably owing to the more ready formation of a one-electron transfer complex in the solvent. The mechanism in iodobenzene is probably the same as that in bromobenzene but this has not been tested kinetically because of experimental difficulties<sup>34</sup>. However, the high yields of biaryls and low yields of  $\sigma$ -complex dimers obtained in both these solvents confirm the mechanism postulated on the basis of kinetics in bromobenzene.

The reaction in nitrobenzene is more complicated. At very low concentrations of peroxide, the rate law (27) is obeyed indicating that both modes of termination are important.

$$-d[\text{P}]/dt = k_1[\text{P}] + k'_2[\text{P}] + k_{3/2}[\text{P}]^{3/2}$$

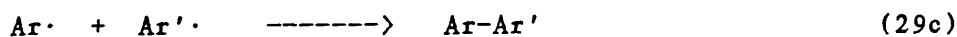
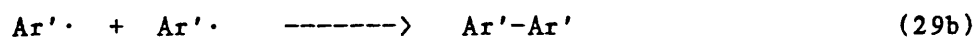
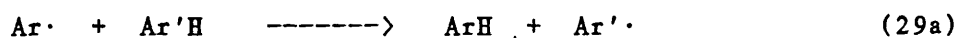
I.2.1.2 Further mechanistic featuresI.2.1.2.1 The nuclear substitution reaction:-

'Simple free-radical phenylation' can, in principle, be achieved

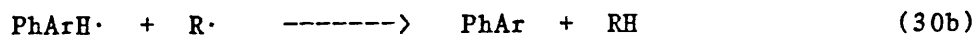
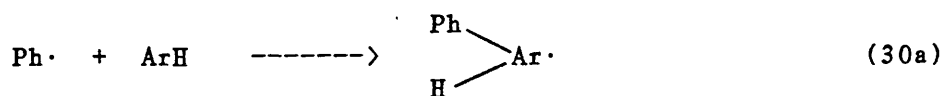


by three possible pathways.

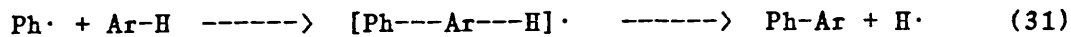
## (I) The abstraction and addition mechanism:



## (II) The addition-abstraction mechanism:

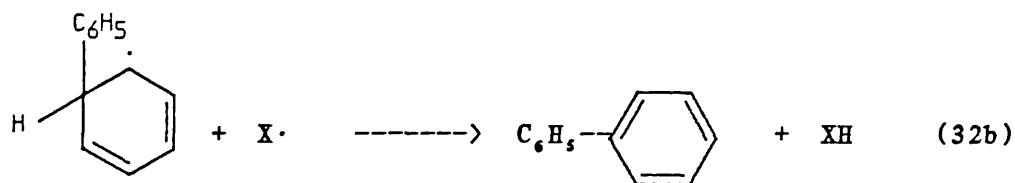
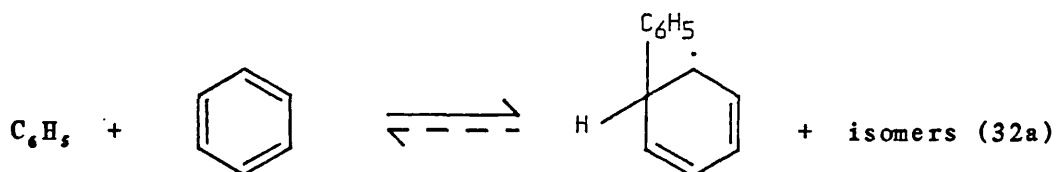


## (III) The synchronous mechanism:



Mechanism (I) is considered unlikely for energetic reasons (high activation energy required for the dissociation of the aromatic C-H bond), and it is ruled out by the absence of symmetrical biaryls (Ar'Ar') in the reaction products.

The absence of a significant change in the hydrogen isotope distribution in the recovered substrates from the reaction in deuterated and tritiated benzene<sup>37</sup>, also argues against mechanisms (I) and (III) and renders freely reversible addition in (II) also unlikely.



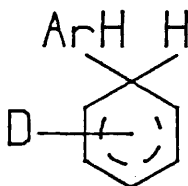
If reaction (32a) was reversible or the rate of the reverse reaction was not much slower than the rate of reaction (32b) (i.e. if reaction (32b) was involved in the rate determining step), then an isotope effect would be found.

Hey and his colleagues<sup>37c</sup> suggested that the acceptable mechanism consistent with this observation is the addition-abstraction mechanism with an irreversible addition step to form the  $\sigma$ -complex. More recently Saltiel and Curtis<sup>38</sup> also reported the absence of a hydrogen isotope effect in the phenylation of deuterated benzene and supported the irreversible addition of phenyl radicals to benzene to form the  $\sigma$ -complex.

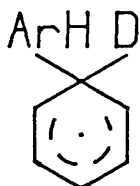
Based on the thermochemical data, Jackson<sup>39</sup> constructed a table to predict the feasibility of the addition reaction to olefins and benzene by free-radicals. It was suggested that the formation of the phenylcyclohexadienyl radical is irreversible at temperatures below 200°C

Eliel and co workers<sup>40</sup> have shown that in the reaction of a benzene-benzeneD<sub>6</sub> mixture with p-chlorobenzoyl peroxide to give a mixture of undeuterated and deuterated p-chlorobiphenyl, whereas the deuterium content of the product corresponded to an isotope effect of 1.3 (i.e., the incoming aryl radical by attaching itself preferentially to a hydrogen-bearing rather than a deuterium-bearing position of the substrate,

i.e., forming:



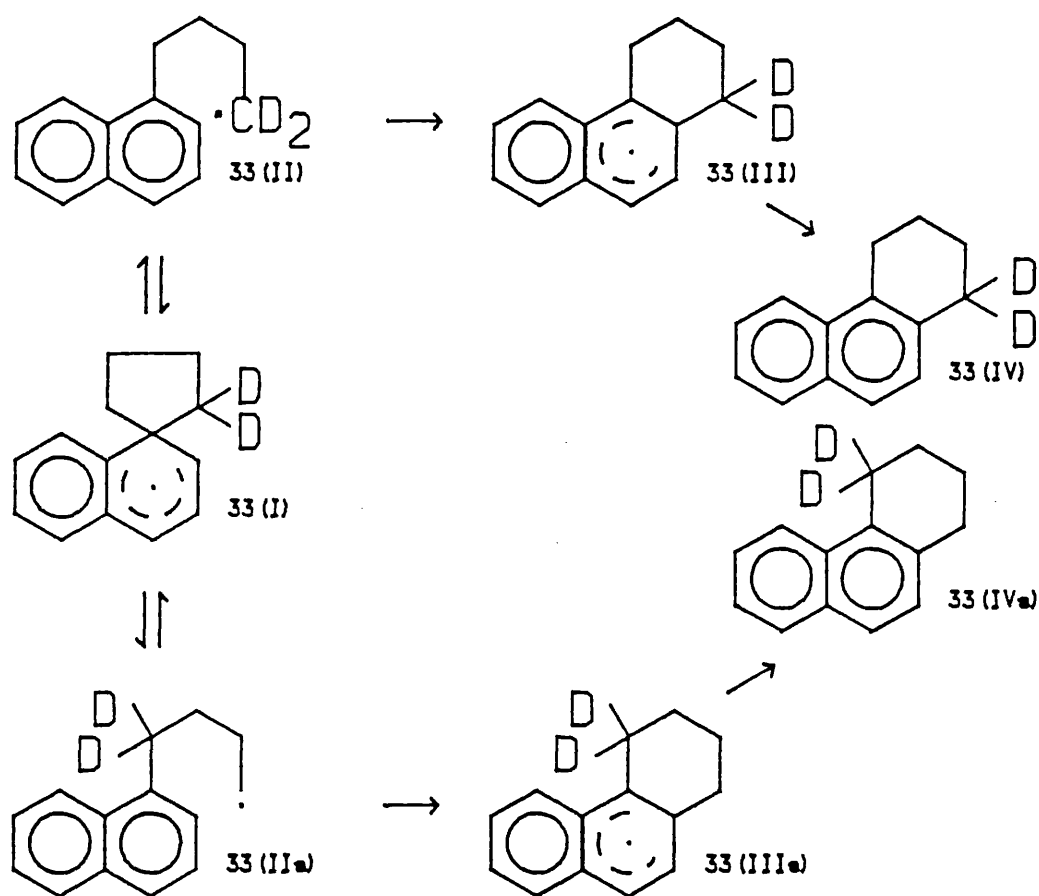
rather than:



alters the deuterium content of the biaryl product), the recovered substrate (benzene-benzeneD<sub>6</sub>) was completely unchanged in isotopic composition. 'The complete absence of such enrichment rules out the possibility of any substantial fraction of the 'product isotope effect' being due to the reversibility of the addition step'<sup>40</sup>.



With the help of isotopically labelled compounds, Julia<sup>41</sup> has shown that the cyclisation of 4-[(1-naphthyl)(1,D<sub>2</sub>)]butyl radical [33(II)] to the spirocyclohexadienyl radical [33(I)] is in competition with the cyclisation to the radical [(33III)(3D<sub>2</sub>)]. The isolation of the two didenterotetrahydrophenanthrenes (IV and IVa) demonstrate that the cyclisation to (33I) is reversible in this case.

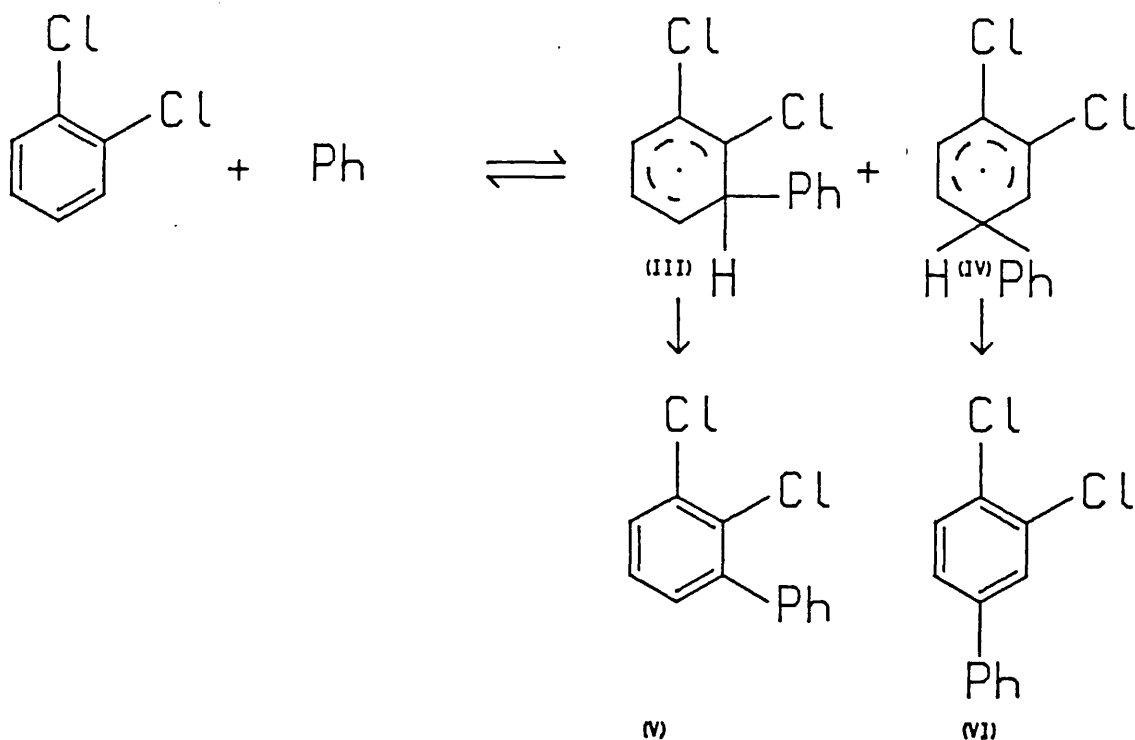


Scheme III

Within the mechanism proposed, the addition step is held to be rate-determining<sup>37,40</sup>, and the hydrogen atom in the  $\sigma$ -radical is never free but lost in a bimolecular hydrogen transfer to another radical in solution. The isolation of dimerisation and disproportionation products of  $\sigma$ -radicals also gives support to this mechanism<sup>26</sup>.

It should be noted that if the reversibility of phenyl radical addition is substantiated, the yield of biaryl depends on the standing concentration of the radicals at equilibrium. This kinetic stability is distinct from the thermodynamic stability where the yield of biaryl is determined by the rate of irreversible formation of the  $\sigma$ -radicals. As yet, there is no unequivocal evidence for reversibility of phenylation in systems involving aroyl peroxides.

Addition of phenyl radicals, generated from benzoyl peroxide, to *o*-dichlorobenzene affords the isomeric phenyldichlorocyclohexadienyl radicals [(III) and (IV)] and thence 2,3- and 3,4-dichlorobiphenyls [(V) and (VI)]<sup>54</sup>.

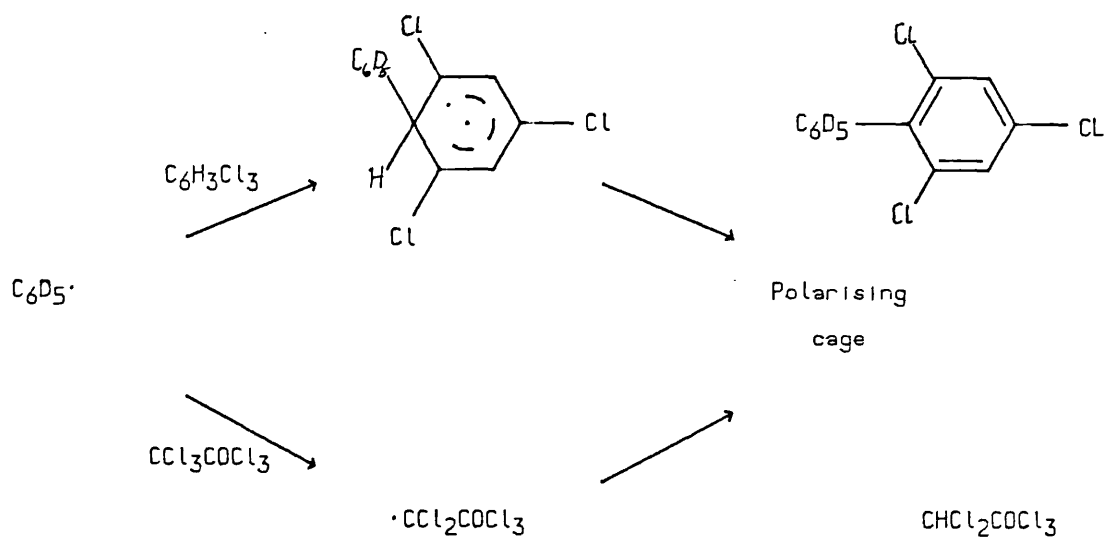


Henriquez and Nonhebel (1975)<sup>54</sup> found that the ratio of (V) to (VI) obtained from the reaction, decreased with increasing temperature but increased on addition of copper(II) salts. They assumed that the radical (III) was more prone to dissociate than (IV) as it was thermodynamically less stable, and on this basis claimed that the change in isomer ratio was evidence for the reversibility of the addition step. The yields of biaryls obtained by these workers was low (22.8% with respect to the phenyl radical, at 120°C), and no effort was made to monitor the side reactions that might affect the yield of biaryls. Though they suggested that the oxidation potentials of the radicals (III) and (IV) would be expected to be similar, no evidence for this was presented.

The low yields of biaryls obtained suggests that a significant proportion of the  $\sigma$ -arylcyclohexadienyl radicals go to products other than biaryls. Selective changes in the rates of these reactions, caused by changes in temperature or the addition of copper(II) salts, could easily account for the change in ratios of the biaryls observed.

Perkins<sup>55</sup>, has suggested that it is 'improbable that appreciable fragmentation of a phenyl-cyclohexadienyl radical would occur in  $10^{-2}$  to  $10^{-1}$  s, a generous estimation for the lifetime of these radicals in normal phenylation reactions', on the basis of the high activation energy for the addition of phenyl radicals to benzene.

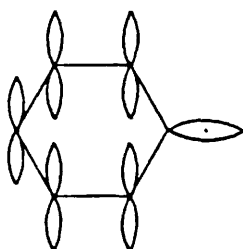
The intermediacy of the cyclohexadienyl radical has been demonstrated by a physical method using chemically induced dynamic nuclear polarisation (CIDNP) techniques<sup>54</sup>. The scheme shown is in agreement with the spectra observed from both the biphenyl and the pentachloroacetone and 1,3,5-trichlorobenzene.



Scheme IV

### I.2.1.3 The nature of the phenyl, benzoyloxy and phenylcyclohexadienyl radicals.

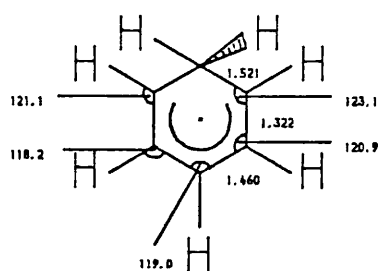
Electron spin resonance (E.S.R.) studies of the phenyl radical in a solid matrix at  $77^\circ C$ , showed that the unpaired electron remains in the  $sp^2$  orbital of the carbon atom at which bond breaking has occurred<sup>21</sup>. This lack of resonance stabilisation is reflected in the highly reactive nature of the phenyl radical.



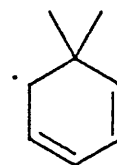
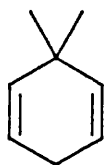
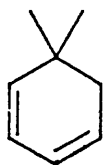
Studies of hydrogen abstraction by the phenyl radical showed an almost complete insensitivity to polar effects<sup>43,44</sup> ( $\rho = -0.1$  in hydrogen abstraction from substituted toluenes would indicate, at the most, a very slight electrophilic character). The numerous studies<sup>21</sup> concerning homolytic aromatic phenylation indicate that the substituent effect is very small because neither the total rates nor the partial rate factors differ greatly from unity. Above all, in the absence of steric effects, all substituents activate the aromatic nucleus to a small extent towards attack by phenyl radicals, such activation being independent of their polar character. The phenyl radical could therefore appear to be almost the ideal nonpolar free-radical.

Two recent facts could, however, indicate that even the reactivity of the phenyl radical can be influenced to some extent by polar effects. The first concerns the homolytic phenylation of heteroaromatic bases in acidic media where the reactivity and selectivity of the ortho and para positions is increased<sup>45,46</sup>. The second fact is connected with the kinetics of decomposition of benzoyl peroxide in the presence of protonated heteroaromatic bases. The increased decomposition has been ascribed to a higher affinity of the phenyl radical towards the protonated base in comparison to the nonprotonated base<sup>21</sup>. Minisci<sup>47</sup> has claimed that the phenyl radical has some nucleophilic character that can only be revealed in the presence of strongly electron deficient substrates, such as the protonated heteroaromatic bases.

Though little is known about the nature of the phenylcyclohexadienyl radical itself, some work has been done on the cyclohexadienyl radical (CHD). The cyclohexadienyl radical is known to be nucleophilic<sup>48</sup>. Birch and Hinde (1980)<sup>49</sup> put forward a structure for the radical (VI) which reflects contributions

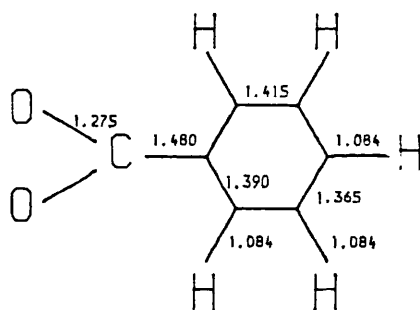


from the valence structures:-



The ground state of the radical corresponds to the unpaired electron occupying a  $\pi$ -type orbital. It is symmetric about the plane perpendicular to the ring plane (passing through  $C_3$ - $C_6$ ). Substituents generally stabilise the radical at positions 1 and 3 and destabilise at positions 6 and 2, acceptors are generally more stabilising than donors. ( $\Delta H_{fo}$  for CHD = 276.6 kJ mol<sup>-1</sup>.)

Though the exact structure for the benzoyloxy radical is not known, the structures of the acetoxy and hydroperoxy radicals have recently been determined<sup>167</sup>. Structurally the acetoxy and hydroperoxy radicals are similar. The O-O bond lengths are essentially the same, and in both cases the OOR bond angle increases 4-5° from the corresponding peroxide. The C-O bond length in the acetoxy radical is the same as in the methyl peroxides. The trend can be extrapolated to predict a structure for the benzoyloxy radical based on the known structure for benzoyl peroxide<sup>52</sup>.



The radical is known to be electrophilic<sup>51</sup>.

I.2.1.3.1 Quantitative studies of phenylationI. Competitive reactions

Provided there is no subsequent diversion, the yield of a reaction product in parallel reactions of the same kinetic order should reflect the rate of the rate limiting step in the formation of that product.

Partial rate factors (p.r.f.) are numerical expressions of reactivity at the o-, m-, and p-, positions (Fo, Fm, Fp) in a monosubstituted benzene derivative, compared with the reactivity of any one position in benzene. The relative proportions in which the ortho-, meta-, and para- isomers are formed in the arylation of the monosubstituted benzene compared with the yield of the arylbenzene (statistically corrected for the existence of two o- two m-, but one p- position) lead to the following expressions for the p.r.f.s of the monosubstituted benzene:

$$F_o = 3\mu K_{PhH}^{PhX}$$

$$F_m = 3\pi K_{PhH}^{PhX}$$

$$F_p = 6\omega K_{PhH}^{PhX}$$



$\frac{k_{PhY}}{k_{PhH}}$  represents the ratio of the total rate of substitution in the monosubstituted substrate compared to that in benzene,  $\mu$ ,  $\pi$ , and  $\omega$  are the isomer ratios for the ortho-, meta-, and para- isomers, respectively. For the remainder of this thesis 'relative rate' shall refer to the reactivity with respect to one of the sites in benzene.

The following results were obtained by allowing benzoyl peroxide to decompose in mixtures of simple aromatic substrates with benzene or nitrobenzene or p-dichlorobenzene.

ArH	$\frac{k_{ArH}}{k_{PhH}}$	Partial rate factors		
		<u>o</u> -	<u>m</u> -	<u>p</u> -
Chlorobenzene	1.14	1.9	0.9	1.2
Bromobenzene	1.47	2.4	1.35	1.35
Fluorobenzene	1.08	1.5	1.1	1.2*
Methylbenzoate	1.89	2.7	1.1	3.6
Benzophenone	4.39	4.13	2.18	7.94**
Benzonitrile	1.92	3.0	1.0	3.5
Toluene	1.81	3.4	1.3	1.5
Anisole	3.18	7.2	1.05	2.5

\*partial rate factors were determined from m-/p- ratio of 1.98/1 given by Lewis and Williams J.CHEM.SOC. B (1969) 120

\*\*relative rate given by authors does not match partial rate factors given, corrected value given.

Results from Bolton, Dailly, Hirakubo, Lee and Williams  
J.CHEM.SOC. PerkinII (1981) 1109.

Table II

## I.2.2

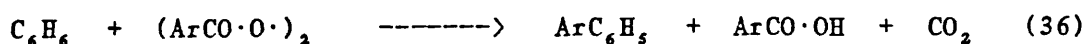
The effect of oxidising agents on homolytic arylation.I.2.2.1 Oxygen

It is known that phenyl radicals are not very reactive towards oxygen<sup>43</sup>. Therefore, the oxygen is thought to abstract hydrogen from the  $\sigma$ -intermediate, presumably by the formation of a hydroperoxide radical, which could bring about the oxidation of another  $\sigma$ -radical.

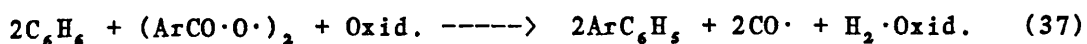


Hydrogen peroxide has been detected in these reactions<sup>67</sup>.

If the dehydrogenation of phenylcyclohexadiene could be effected by a reagent other than the benzoate radicals, this would avoid the wastage of half these radicals in the form of benzoic acid, and might increase the yield of arylbenzene from a maximum of one mole per mole of peroxide<sup>114</sup>:



to a theoretical maximum of two moles per mole of peroxide:



Oxid. = oxidising agent

Some phenol is also formed in this reaction, with higher yields at lower temperatures<sup>67</sup>.



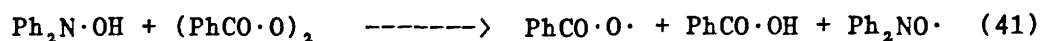
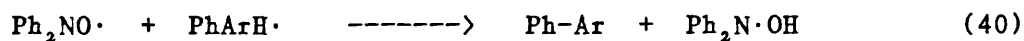
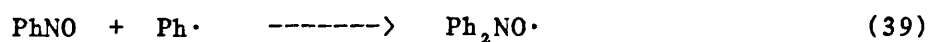
The above observation is attributed to the higher solubility of the gas at lower temperature, and to the more efficient trapping of phenyl radicals by it.

Abramovitch and Saha<sup>68</sup> found no effect of oxygen upon the isomer-ratio, and a slight reduction in the yield of biaryl in the phenylation of pyridine by *o*-tolyl, and *o*-nitrophenyl radicals. Hirakubo *et. al.*<sup>57</sup> found, similarly, that the yield of methoxybiphenyls is not increased if a stream of oxygen is passed through the reaction mixture during the decomposition of benzoyl peroxide in methoxybenzene.

#### I.2.2.2 Nitro-compounds and other electron acceptors.

In reactions involving benzoyl peroxide as the phenylating source, catalytic amounts of nitro-compounds greatly increase the yields of biaryl and aroic acid, and the formation of residues is greatly suppressed. This phenomenon has been referred to as the 'nitro-group effect'<sup>69</sup>.

The effective catalyst is the corresponding nitroso-compound<sup>70, 154</sup> which is formed by reduction of the nitro-compound<sup>36</sup>, and is thought to act as follows (reactions 39-42).



Scheme V

A number of electron acceptors (with the exception of nitro-methane) manifest the same effect. However, there appears to be no simple relationship between the effectiveness of the additive and its reduction potential<sup>71</sup>.

Electron acceptor	Electron acceptor	Benzoyl peroxide	Benzoic acid	Biphenyl
	(mole l <sup>-1</sup> x 10 <sup>3</sup> )	(mole l <sup>-1</sup> x 10 <sup>2</sup> )	(moles per mole peroxide)	
None		8.33	0.28	0.42
None		5.50	0.28	0.50
Nitrobenzene	10.7	8.33	0.70	0.67
<u>m</u> -Dinitrobenzene	8.0	8.33	0.92	0.90
<u>sym</u> -Trinitrobenzene	6.7	5.50	0.95	0.94
Nitromethane	22.0	8.33	0.30	0.28
Tetranitromethane	6.7	5.50	0.69	0.77
Tetracyanoethylene	10.7	8.33	0.74	0.85
<u>p</u> -Chloranil	6.7	5.50	1.00	0.96
Iodine	6.7	5.50	0.54	0.61

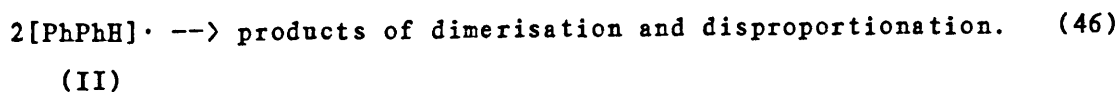
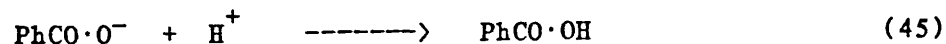
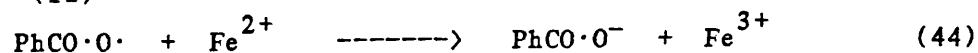
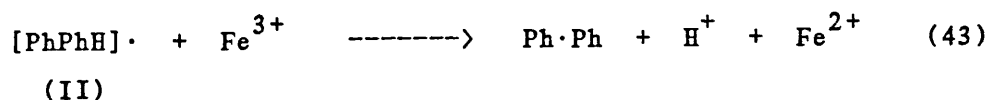
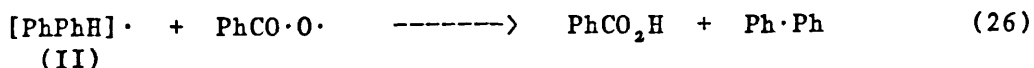
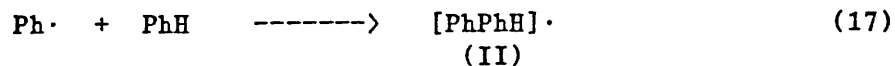
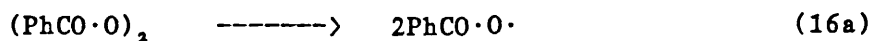
Table III

### I.2.2.3 The effect of transition metal ions.

Metals used in free-radical chemistry are generally in the form of metal complexes. Metal complexes (particularly in the case of transition metals) can readily undergo reactions due to the availability of multiple oxidation states.

#### The mechanism of transition metal catalysis.

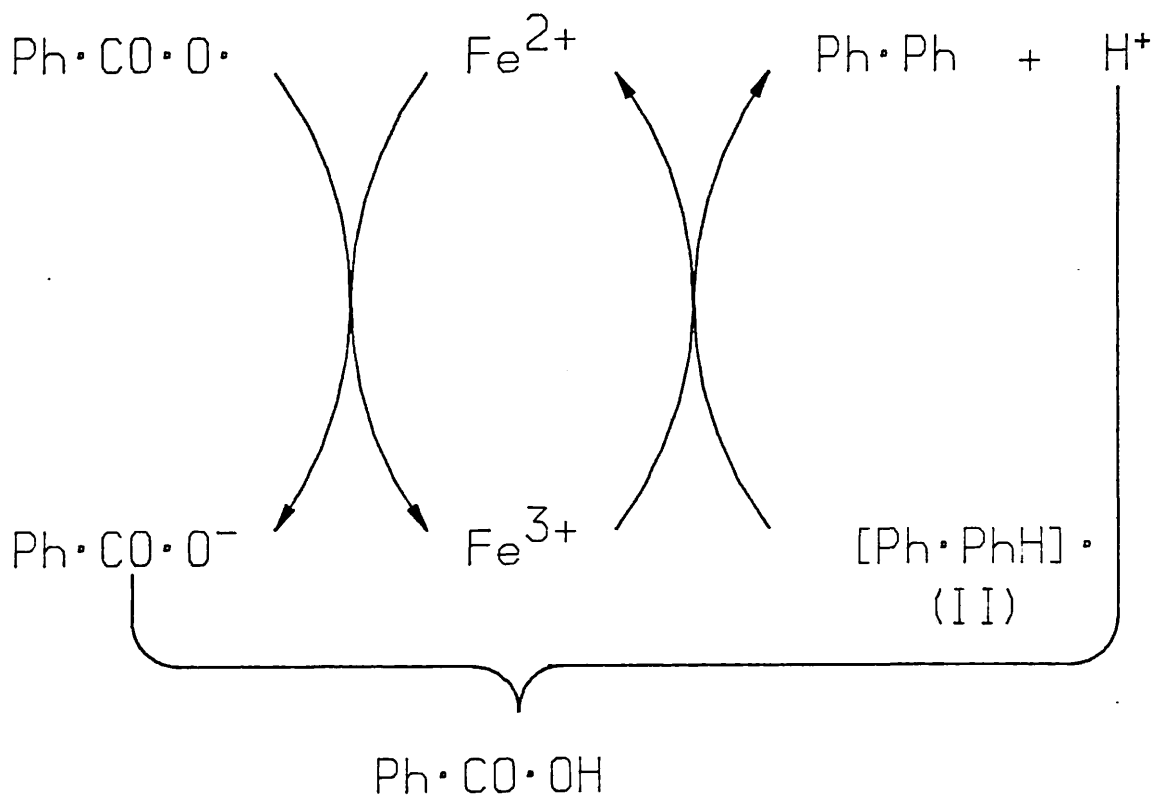
Dailly (1968)<sup>74</sup> carried out the decomposition of benzoyl peroxide in various aromatic solvents, in the presence of ferric benzoate. It was shown that ferric benzoate caused very great increases in biaryl yields. The following mechanism was proposed:



#### Scheme VI

Reaction (26) does not take place to an appreciable level in solvents such as benzene or chlorobenzene, but is important in bromobenzene<sup>57</sup>.

In the presence of ferric benzoate reactions (43), (44) and (45) take over from reaction (46), which then becomes unimportant. The abstraction of hydrogen from phenylcyclohexadienyl radicals by benzoyloxy radicals (reaction 26) can be increased by electron transfer processes<sup>57</sup>. representing the metal as its ion (although in solvents such as arenes this is obviously a simplification), the stoichiometry of such processes can be indicated by the following scheme<sup>72</sup>:-



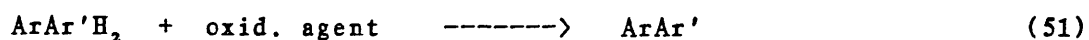
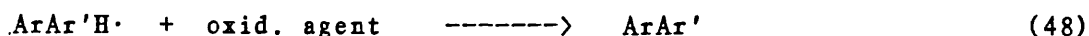
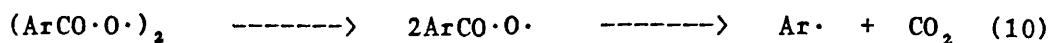
Scheme VII

The regeneration of the metal in its higher valency state is required since quantities of the metal salts, equimolar with that of the peroxide, are not required to give almost theoretical yields of biaryls and benzoic acid. The reaction with iron(III) salts probably proceeds by similar oxidation and proton loss, by the phenylcyclohexadienyl radical, rather than by the mechanism suggested by Hey, Liang and Perkins<sup>73</sup>.

### I.2.3

#### Validity of partial rate factors.

The validity of rate factors derived from data on isomer distribution and substrate competition (where, the relative reactivity of two chemically different substrates is gauged by allowing mixtures of known molar ratios of the two substrates to compete for a single radical reagent) in free-radical aromatic substitution, and of the theoretical discussion based on them, has been seriously questioned, chiefly, and properly, on the basis of certain isotope effects<sup>40</sup> and in the finding of products formed by dimerisation (49) and disproportionation (50) of arylcyclohexadienyl radicals,  $\text{ArAr}'\text{H}\cdot$  (V). Eliel, *et. al.*,<sup>40</sup> found no selectivity in consumption of deuterated and ordinary substrates but a significant product isotope effect, attributed to preferential hydrogen abstraction in (48), (50) and (51), with resulting diversion of  $\text{ArAr}'\text{D}\cdot$  to dimer(49), and perhaps, of  $\text{ArAr}'\text{D}_2$  and  $\text{ArAr}'\text{DH}$  to polymer.



#### Scheme VIII

Isolation of biaryl in the absence of oxygen, which otherwise participates in reaction (51), increases the effect several-fold, indicating the importance of the reactions (50), (51) sequence. Here, clearly, product composition is not a true measure of the relative rates at which Ar'H and Ar'D undergo reaction (47). It was suggested that in a similar way, isomer distribution (and, presumably, competitive data) may not be a true measure of the relative rates of formation of *o*-ArAr'H·, *m*-ArAr'H·, and *p*-ArAr'H· (or ArAr'H and ArAr''H·). Their results, however, could not be repeated by Hirakubo et. al.<sup>57</sup>.

Using gas chromatographic analysis, Morrison, Cazes, Samkoff and Howe<sup>58</sup> have studied the phenylation, by benzoyl peroxide, of four substituted benzenes in both the absence and the presence of oxygen. Their results show that side reactions have no significant effect on isomer distribution and relative reactivities measured by product analysis, and that such data provide valid rate factors for free-radical aromatic substitution (Table IV).



-X	O <sub>2</sub>	yield	Isomer distribution		
			o <sup>-</sup>	m <sup>-</sup>	p <sup>-</sup>
CH <sub>3</sub> O	-	0.50	69.8	14.7	15.6
CH <sub>3</sub> O	+	0.73	69.7	14.5	15.7
Br	-	0.33	56.2	27.3	16.5
Br	+	0.95	55.8	27.8	16.5
NO <sub>2</sub>	-	0.17	62.8	9.5	27.7
NO <sub>2</sub>	+	0.61	63.1	10.1	26.9
t-C <sub>4</sub> H <sub>9</sub>	-	0.72	21.2	49.9	29.0
t-C <sub>4</sub> H <sub>9</sub>	+	1.40	21.2	50.0	28.8

Table IV

Eberhardt and Eliel<sup>56</sup> have found that the presence of oxygen during aroyl peroxide decomposition in benzene dramatically increases the yield of biaryl, evidently speeding up reaction (53), and perhaps reaction (56), at the expense of reactions (54), (55) and other side reactions, and they point out that the isomer distribution determined under these conditions should be a truer measure of rate factors than in previous data. Other workers<sup>57</sup>, however, have not been able to repeat their findings.

Norman<sup>59</sup>, however, noted that the isomer ratio and total rate factors in the decomposition of benzoyl peroxide in anisole are not the same in the presence and the absence of cupric benzoate. Bonnier *et. al.*<sup>60</sup>, also showed that the conclusion drawn by Morrison and co-workers<sup>58</sup> might not be valid in all cases. They found that the isomer ratio of phenylated 4-methylpyridine depends on the concentration of the peroxide. An isotope effect was also reported in the phenylation of the deuterated 4-methylpyridine<sup>61</sup>. They also

reported that the isomer ratio and partial rate factors obtained in the phenylation of pyridinium chloride changed drastically in the presence of catalytic amounts of nitrobenzene<sup>62</sup>. Dou *et. al.*<sup>63</sup>, also reported the variation of isomer ratio with oxidising agent in the phenylation of 4-methylpyridine.

Benzene (ml) added to 4-methyl- pyridine	Peroxide/ 4-methyl- pyridine	Additive	Isomer distribution	
			2-	3-
None	0.16/1	None	53	47
None	"	PhNO <sub>2</sub> (1gm)	45	55
None	0.07/1	None	45	55
None	"	PhNO <sub>2</sub> (1gm)	44.5	55.5
25	"	None	51.5	48.5
"	"	PhNO <sub>2</sub> (1gm)	44.7	55.3
100	"	None	56	44
"	"	PhNO <sub>2</sub> (1gm)	44.5	54.5

Table V

Competitive reactions have often been determined, with nitrobenzene as the standard solvent. Ohta and Tokumaru<sup>64</sup> have pointed out that nitrobenzene is not a suitable standard solvent for competitive studies with substrates having abstractable hydrogen, because the intermediate nitrophenylcyclohexadienyl radical is diverted to products other than nitrobiphenyls.

Hey, Perkins, and Williams<sup>65</sup> have shown that the yield of biphenyl (with respect to initial peroxide concentration), in the decomposition of benzoyl peroxide in benzene, changes with the initial concentration of peroxide and passes through a maximum at a peroxide concentration of 0.12M. There is no reason to assume that the yield of biaryl in any other system should vary with the concentration of the reagent in an identical manner. The relative yields of biaryls within these systems (and presumably the partial rate factors) will, therefore, vary with the reaction conditions used. Indeed, changes in the phenylating agent could alter the partial rate factors if the variation of percentage yields with concentration (or, for that matter any other reaction condition) was not identical within the systems for the phenylating agents concerned.

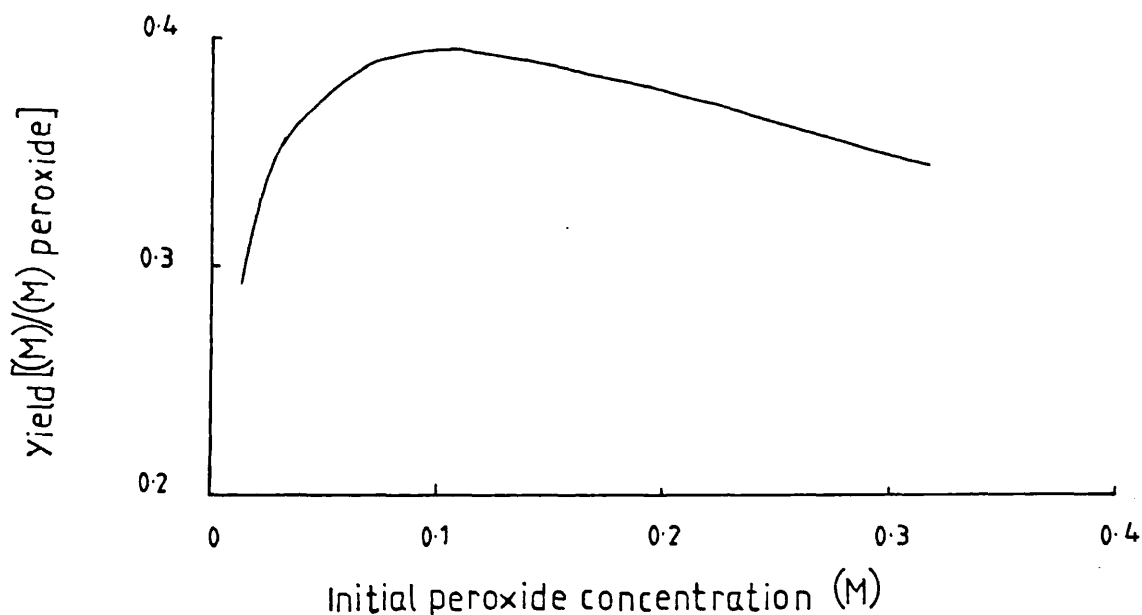


Figure I

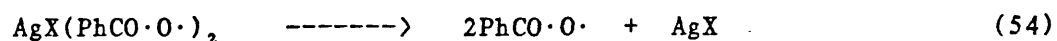
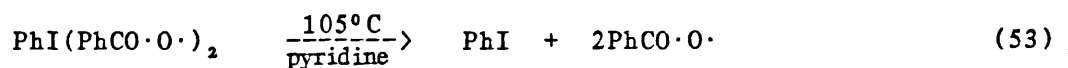
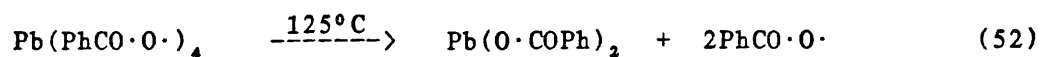
Since partial rate factors are measured under particular reaction conditions, their general use as indices of reactivity must be questioned. However, if they are measured (as for example, by Hirakubo *et. al.*<sup>57</sup>) under conditions such that dimerisation, disproportionation etc., do not occur, and nearly all of the  $\sigma$ -complexes proceed to biaryls, then the partial rate factors are completely valid<sup>66</sup>.

#### I.2.4

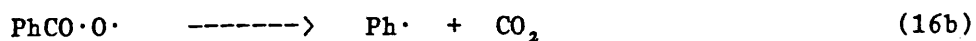
##### Methods of homolytic phenylation.

##### I.2.4.1 Other sources of benzoyloxy radicals: -

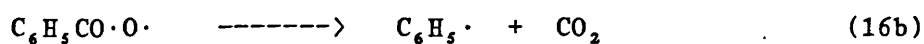
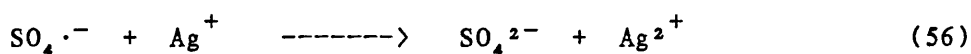
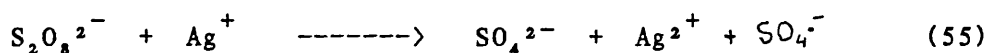
I.2.4.1.1 The decomposition of lead tetrabenzoate<sup>74</sup>, and silver halide dibenzoate<sup>76</sup>:



Phenyl radicals result from the benzoyloxy-radicals by the loss of carbon dioxide.

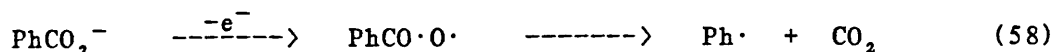


I.2.4.1.2 Decarboxylation of benzoic acid: - Minisci and Clerici<sup>47</sup> extended their work on alkylation of heterocycles, to generate phenyl radicals, by the silver-catalysed decarboxylation of benzoic acid, by peroxydisulphate anion.



They claimed that the reaction was clean, with only negligible amounts of by-products, contrary to experience with some other sources of phenyl radicals.

I.2.4.1.3 Electrolysis of benzoic acid (Kolbe reaction): -

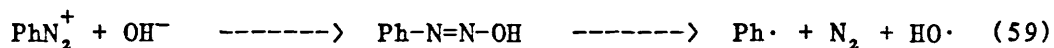


The electrolysis of benzoic acid in pyridine yields, among other products, 4-phenylpyridine and 4-phenylbenzoic acid<sup>77,162</sup>.

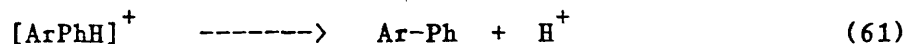
## I.2.4.1.4 Aryldiazonium Salts: -

## I.2.4.1.4.1 Gomberg and Gomberg-Hey Reactions: -

The heterogenous Gomberg and Gomberg-Hey reactions (developed from the work of Bamberger<sup>78</sup> and Kuhling<sup>79</sup>) have been used to provide phenyl radicals. In the former method diazoic acids are used to generate the radicals whereas in the latter method, water insoluble or sparingly insoluble metallic salt derivatives of the diazo-compounds are used.

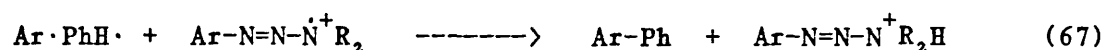
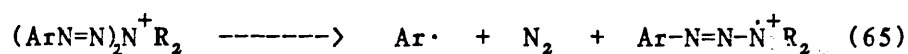
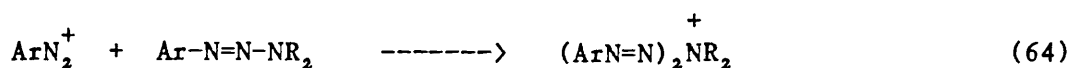
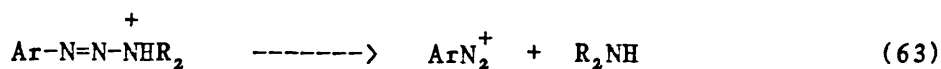
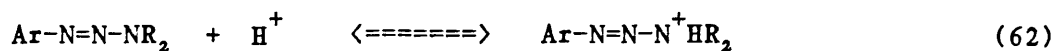


The normal chain-propagation step for the formation of aryl radicals may be reduction of the diazonium cation by an arylcyclohexadienyl cation, forming the biaryl by loss of a proton:

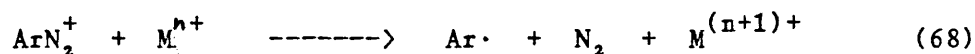


The Gomberg and Gomberg-Hey procedures suffer from the disadvantage that a heterogenous system is used. This can be overcome by diazotising the aromatic amine in situ in an organic solvent, with aryl nitrite, at 60-80°C<sup>80</sup>.

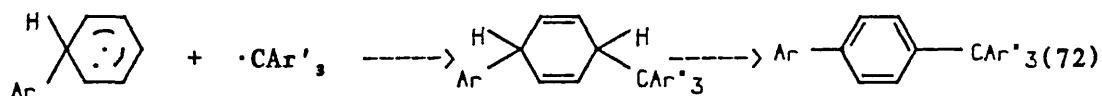
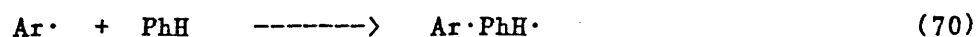
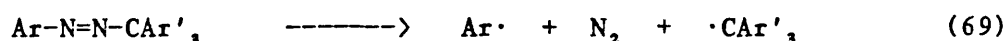
A similar mechanism may also be operative in arylation brought about by the acid-catalysed decomposition of 1-aryl-3,3-dialkyl-triazens<sup>81</sup> or diazoaminobenzenes<sup>82</sup>.



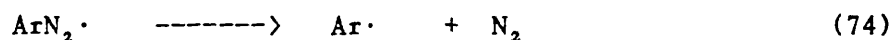
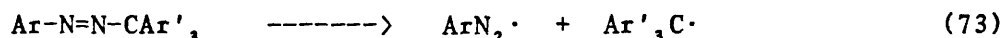
I.2.4.1.4.2 Electron transfer of diazonium cations: Electron-transfer reduction of diazonium cations is an effective way of generating aryl radicals and is brought about by one electron reductants:



I.2.4.1.4.3 Phenylazotriphenylmethane: Phenylazotriphenylmethane decomposes rapidly at 60°C, and is a convenient phenyl radical source. The phenyl radical removes hydrogen from non-aromatic solvents and forms biaryls with aromatic solvents<sup>83</sup>.

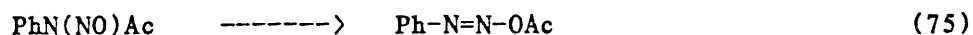


Kinetic studies on this reaction have established that reaction (69) can be represented as a two-step reaction<sup>43</sup>:-



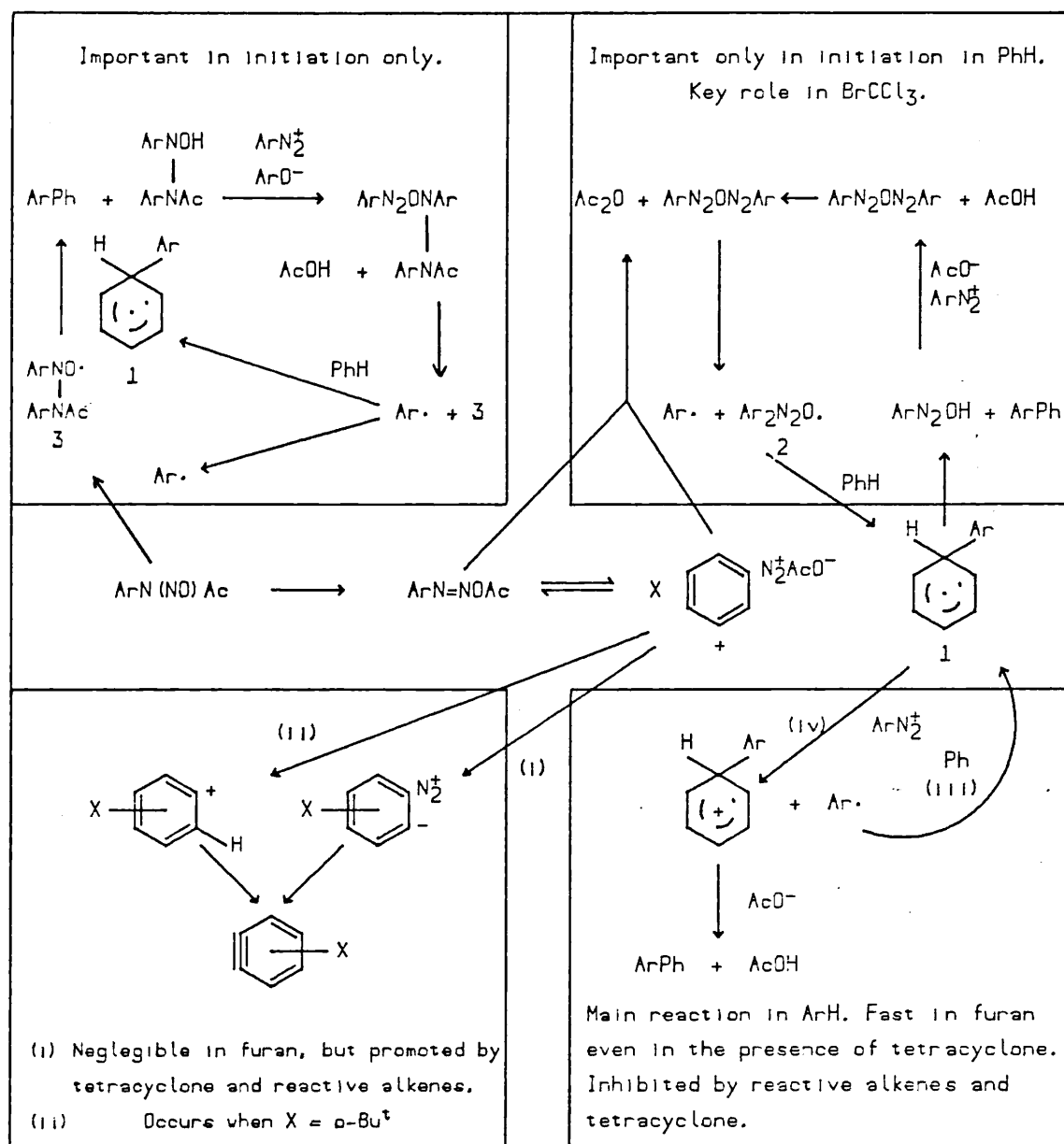
However, the absence of any effect of added triphenylmethyl on the rate of decomposition suggests that the lifetime of the arylazo-radicals must be extremely short, so that the first stage is effectively irreversible.

I.2.4.1.4.4 N-Nitrosoacetanilide (NNA): NNA, prepared by nitrosation of acetanilide with nitrosyl chloride, rearranges in situ to the diazoester<sup>83</sup>:



This rearrangement is the rate determining step. The diazoester undergoes rapid homolysis to phenyl radicals to start chains. The mechanism has long been a subject of controversy<sup>85,86</sup>, but was eventually demonstrated by Cadogan (1971)<sup>87</sup> to be according to the following scheme:

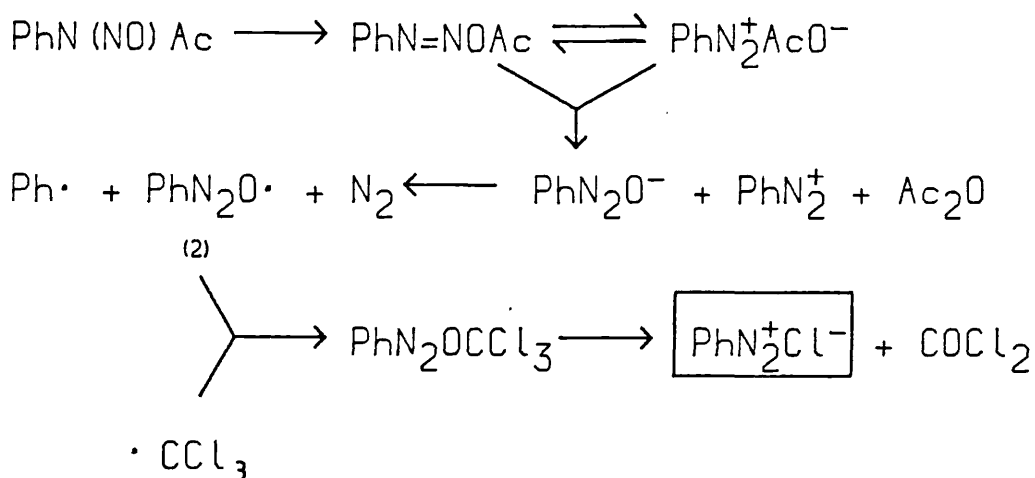




Scheme IX

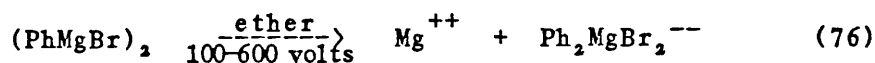
The mechanism for the reaction of N-nitrosoacetanilide (NNA)

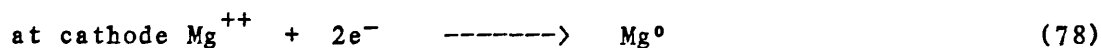
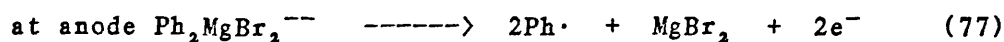
In later publications<sup>8,8</sup> it has been suggested that in bromotrichloromethane, the phenyldiazo-oxy radical [Scheme IX radical (2)] acts as an electron transfer catalyst.



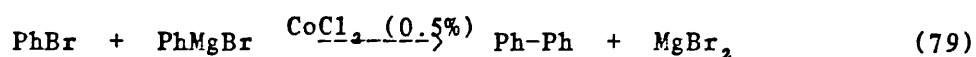
Scheme X

I.2.4.1.5 Phenylmagnesium bromide: Ruchard and Merz<sup>8,9</sup> used phenylmagnesium bromide as a source of phenyl radicals. They electrolysed solutions of phenylmagnesium bromide in ether, using 100 to 600 volts, and identified benzene, biphenyl, p-terphenyl, styrene, ethanol and high molecular weight polymers, at the anode. At high current efficiency, biphenyl was the main product.





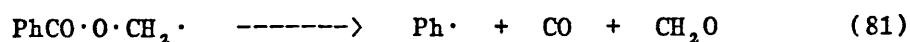
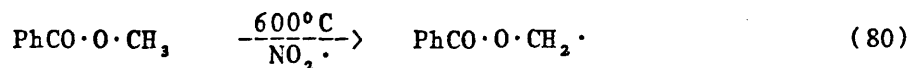
Halogen atoms of aryl halides are displaced by the action of Grignard reagents in the presence of metal salts such as  $\text{CoCl}_2$  and  $\text{MnCl}_2^{90}$ .



It is probable that aryl radicals are intermediates in these reactions.

#### I.2.4.1.6 Pyrolytic methods:

Fienstein and Fields<sup>91</sup> have used nitrobenzene to initiate the decomposition of methyl benzoate in the gas phase, at  $600^\circ\text{C}$ , to obtain phenyl radicals.

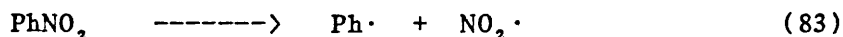


The isomer distributions in these cases differ from those observed using other sources of phenyl radicals, e.g., the gas phase decomposition of nitrobenzene on toluene gives ortho, meta, and para-biaryls in the ratio of 22.5:35.3:42.2, whereas, benzoyl peroxide at  $80^\circ\text{C}$  shows the ratio 65:19:16.

Fields and Meyerson<sup>92</sup> have also allowed toluene to decompose, to obtain phenyl radicals, using a similar process.



However, when nitrobenzene decomposed with pyridine vapour at 600°C<sup>93</sup>, the same isomer distribution, as obtained in the liquid phase with other sources, was obtained.

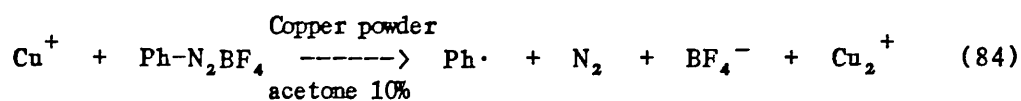


#### I.2.4.1.7 Miscellaneous methods:

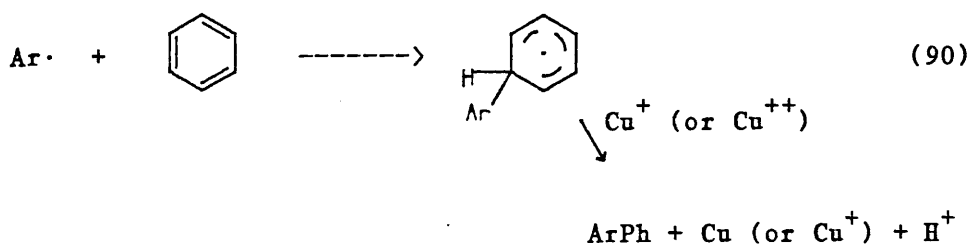
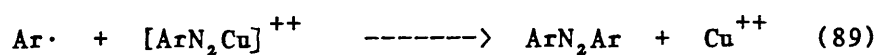
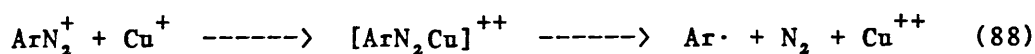
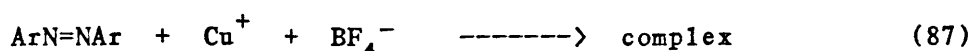
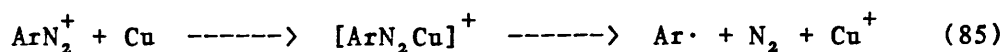
Phenyl radicals produced by irradiation of triphenylbismuth or phenylmercuric iodide usually give the same ratios of isomeric biaryls when they react with aromatic solvents, as do phenyl radicals prepared by other methods<sup>94</sup>.

Phenylation of a solid aromatic compound can be carried out above the melting point, using diazoaminobenzene and aromatic sulphonyl halides. Benzenesulphonyl chloride undergoes rapid homolysis at about 225°C, to give phenyl radicals. Benzene-m-disulphonyl chloride reacts with *p*-dibromobenzene to give 2,5,2',5'-tetrabromo-m-terphenyl, and with 1,3,5-trichlorobenzene to give 2,4,6,2',4',6'-hexachloro-m-terphenyl, while naphthalene-, 1- and 2-, sulphonyl chlorides with naphthalene give the corresponding binaphthyls<sup>95,96</sup>.

Aryldiazonium fluoborates, on decomposing in a mixture of 10% acetone and 90% benzene (room temperature, copper powder) react slowly to give precipitates of red complexes of the azo-compounds (ArN:NAr), with ionic copper<sup>97</sup>. In addition, the free azo compounds and small (less than 10%) amounts of biaryls (ArPh) can be isolated.



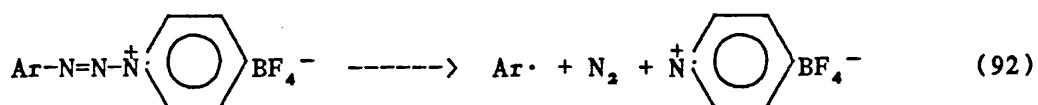
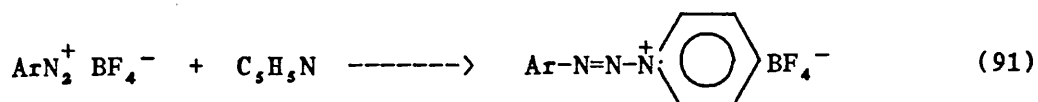
Both copper and copper(I) ion are effective in the reduction of the diazonium cation.



### Scheme XI

Similar reactions occur with p-chlorobenzenediazonium hexafluorophosphate<sup>97</sup>.

With pyridine the following reaction takes place:



## I.3

Free radical reactions of some six membered nitrogen heterocycles.I.3.1 Phenylation of pyridine.

The phenylation of pyridine has been studied by Hey, Stirling and Williams<sup>83</sup>, and others<sup>68,98</sup>. Results for the isomer distribution indicate that the order of positional reactivities is 2-→4-→3- when allowance is made for the two pairs of equivalent sites corresponding to positions 2- and 3-. Yvan's calculation of 'potential barriers', charge density and 'Valence libre' for radical substitution<sup>99</sup> and free valence numbers and frontier electron density calculated by Davies<sup>100</sup>, are in quantitative agreement with the partial rate factors<sup>101</sup> obtained from the decomposition of benzoyl peroxide in mixtures of pyridine and benzene<sup>83</sup>. Charge densities calculated by Davies<sup>100</sup>, are in qualitative agreement with the observed order of reactivities, but the difference between the reactivities of the 2-, and the 4-, positions predicted, is marginal.

r	qr	Fr	f.e.d.
1	1.204	0.110	0.304
2	0.940	0.091	0.403
3	0.986	0.079	0.290
4	0.943	0.086	0.309

r = position in pyridine, qr = charge density at rth position  
 Fr = free valence at rth position, f.e.d. = frontier electron density  
 (Values obtained from Davies<sup>100</sup>)

Table VIa

r	ch	V.1.	B.de.P.
2	0.855	0.387	0.245
3	1.008	0.345	0.254
4	0.904	0.360	0.254

r = position in pyridine, ch = charge at rth position  
 V.1. = Valence libre at rth position, B.de.P. = Barrier de Potential  
 (Values obtained from Yvan<sup>99</sup>)

Table VIb

Theoretical indices of reactivities calculated for pyridine

Abramovitch and Saha<sup>102</sup> have determined the isomer ratios and relative reactivities for the arylation of pyridine by substituted phenyl radicals produced from the corresponding diazonium salts. More nucleophilic aryl radicals, such as, *o*<sup>-</sup> and *p*<sup>-</sup> tolyl, and *o*<sup>-</sup> and *p*-methoxyphenyl radicals gave higher values for the relative substrate reactivity ( $K_{\text{pyridine}}^{\text{benzene}}$ ). On the other hand, the *o*<sup>-</sup> and *p*<sup>-</sup> nitrophenyl, and *o*<sup>-</sup> and *p*<sup>-</sup> bromophenyl radicals, which would be expected to be more electrophilic than phenyl radicals, gave lower values.

Dou and Lynch<sup>103</sup> studied competitive phenylation reactions between pyridine and nitrobenzene both in the presence, and the absence, of acetic acid. They found the relative reactivity in the presence of acetic acid to be 1.66 times that found in its absence.

## Competition between Heteroaromatics(A) and Nitrobenzene(B)

Reactivity in phenylation  
(benzene = 1, nitrobenzene = 2.94)

A	A + B + acetic acid	A + B
Pyridine	1.61	0.97
1-methylpyrazole	1.41	0.57
Thiazole	1.53	0.53

Table VII

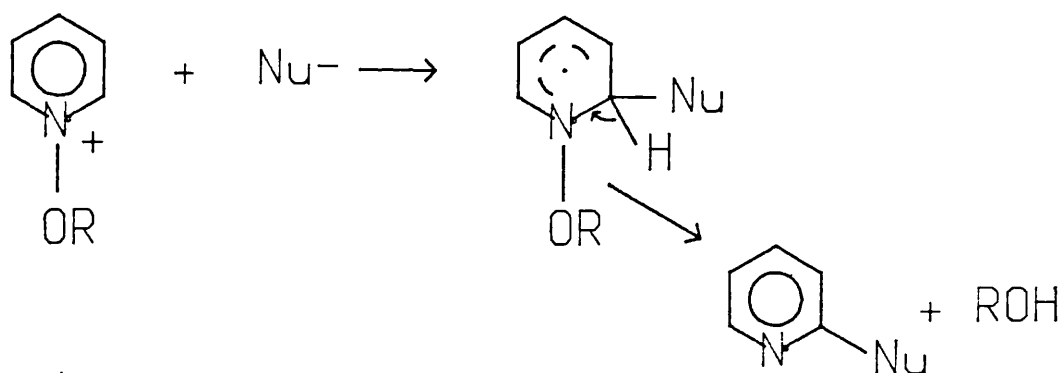
Reactions of heterocycles with phenyl radicals in both acidic and non-acidic media.

Bonnier and Court<sup>104</sup> later found that under the conditions used by Dou and Lynch<sup>103</sup>, pyridine was not completely protonated. They used mixtures of hydrochloric and acetic acid to get complete protonation of pyridine, and used benzoyl peroxide as the radical source. They found the percentage of the meta- isomer was reduced, and those of the ortho- and para-isomers were increased, under acidic conditions. No mechanistic details were given, and the involvement of hydrochloric acid in any other way, apart from the protonation of the molecule, was not suggested. Travecedo and Stenberg(1970)<sup>105</sup> have suggested that hydrochloric acid presumably causes initial hydrogen abstraction by effecting the  $\pi - \pi^*$  excited state during the photoalkylation of pyridine.



The protonated heterocycle might show a mechanism similar to that found in the nucleophilic attack of quaternary pyridinium salts.

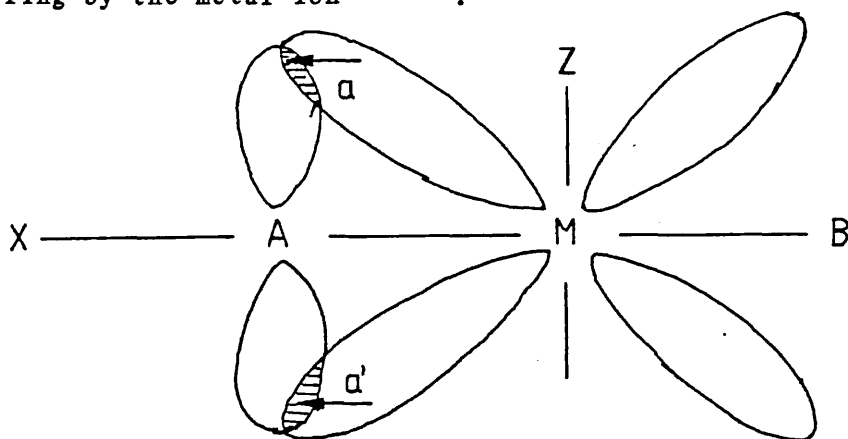
Quaternary pyridinium salts are considerably more reactive towards nucleophiles, and the presence of a good leaving group on the nitrogen atom permits ready fragmentation of the intermediate dihydropyridine to give the desired product<sup>106</sup>.



Scheme XII

Nucleophilic attack on pyridinium salts, however, occurs predominantly at the 2-position<sup>107</sup>. With N-alkoxides attack at the alkoxide group, or ring opening, are often major competing reactions<sup>108</sup>.

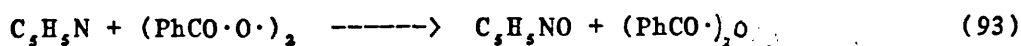
Gritter and Godfrey<sup>109</sup> used phenyl radicals to attack pyridine and pyridine metal complexes. Their results showed an increased yield from substitution in the 4-position of all complexes but one, and from substitution in the 2-position in most cases. The substituent effects were explained by considering a back donation of electrons to the pyridine ring by the metal ion<sup>110,111</sup>.



Ligand A bound by  $p\pi - d\pi$  dative  $\pi$  bonding. The mesomeric effect affects the ortho and para positions preferentially<sup>166</sup>.

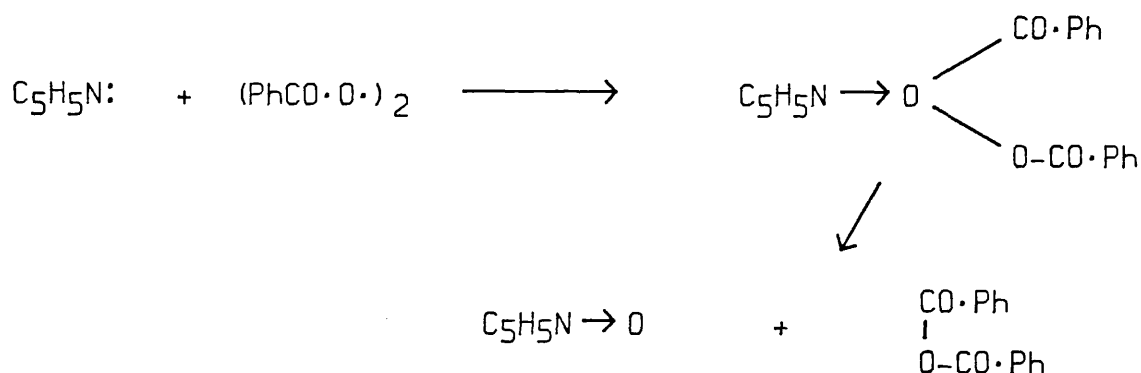
Pausacker<sup>112</sup> allowed benzoyl peroxide to react with pyridine. Among the products formed were phenylpyridines, benzoic acid, pyridine-N-oxide, and bipyridyls. The molar yield of benzoic acid was appreciably higher than that of phenylpyridines. This difference was ascribed to the formation of pyridine-N-oxide and bipyridyls.

It was shown that pyridine-N-oxide was formed by :-



and that pyridine would convert benzoic anhydride to an intermediate which was readily transformed into benzoic acid.

Horner<sup>113</sup>, Imoto and Takemoto<sup>114</sup>, and Martin<sup>156</sup> have stated that benzoyl peroxide initially forms a complex with tertiary amines. On the basis of their structure for this complex<sup>114,156</sup>, the mechanism for pyridine-N-oxide formation may be written as follows:



Scheme XIII

Nozaki and Bartlett<sup>28</sup> measured the rate of decomposition of benzoyl peroxide at 79.8°C in over thirty different solvents. They found that under the same conditions, 77.3% of the benzoyl peroxide, dissolved in pyridine, decomposed, when only 15.5% of the peroxide decomposed in a similar solution in benzene. The different rates of decomposition of the peroxide in the two solvents could be partially responsible for the altered relative yields of the products. Compounds of the type  $\text{Ph}\cdot\text{C}_6\text{H}_4\text{N}\cdot\text{C}_6\text{H}_4\text{N}\cdot\text{Ph}$  were found during the reaction of benzoyl peroxide with pyridine<sup>11,115</sup> (similar to quaterphenyls obtained on the reaction of benzoyl peroxide with benzene).

Coulson<sup>116</sup> has said that the replacement of a C-H bond in an aromatic ring by a nitrogen atom, should lead to an increase in the reactivity of the system. Evidence for this from quantum mechanical calculations was provided by Szwarc and Binks<sup>117</sup> by comparing the

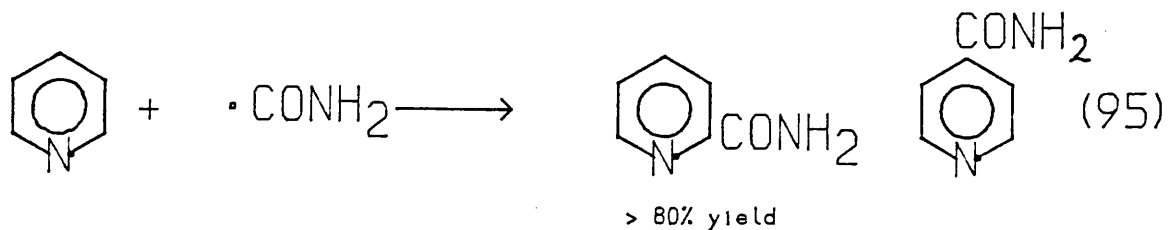
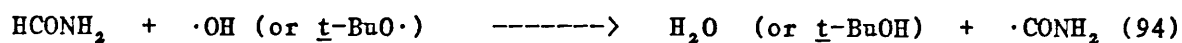
methyl affinities (relative reactivities of aromatic compounds towards methyl radicals<sup>166</sup>) of aromatic hydrocarbons and their heteroaromatic analogues. Earlier, Szwarc and Levy<sup>168</sup> had done experiments to show that the presence of a nitrogen atom in the ring seems to activate the molecule, the effect, however, decreases with the increasing size of the molecule.

Aromatic compound	Methyl affinity
Benzene	1
Pyridine	3
Pyrazine	ca. 18
Naphthalene	22
Quinoline	29

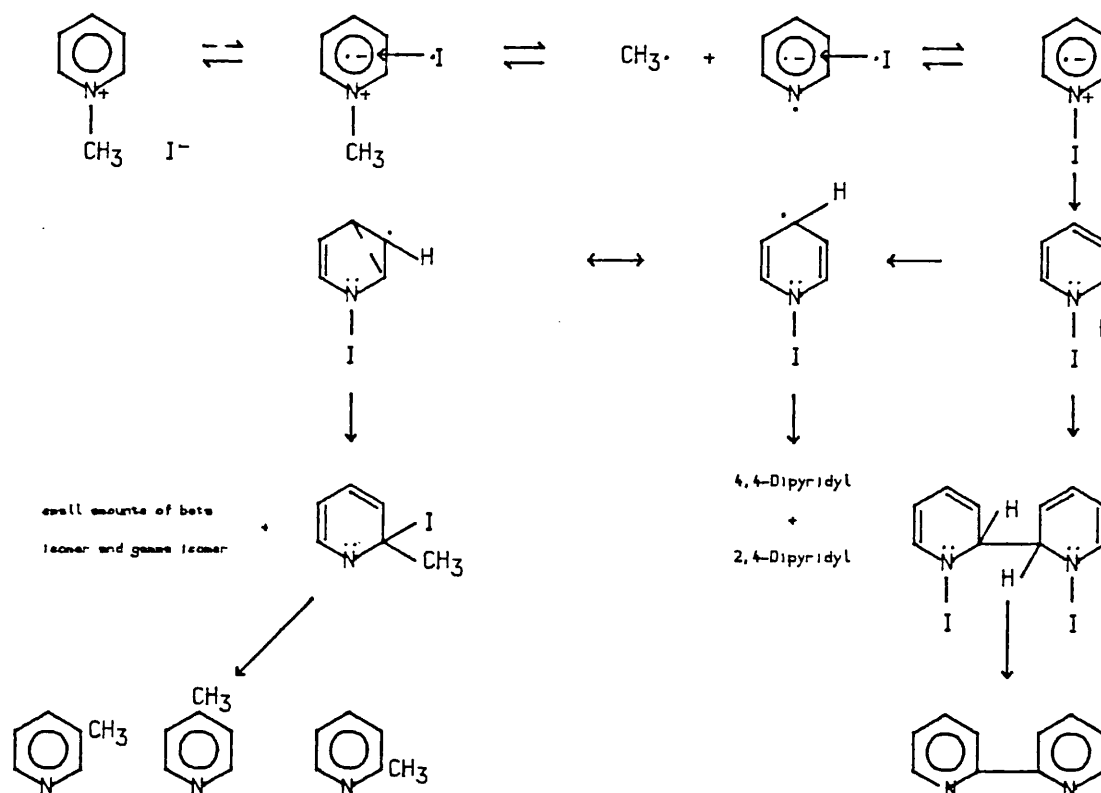
Table VIII

I.3.1.0.1 Other free radical reactions of pyridine.

Most free-radical substitutions of pyridine give primarily 2-substituted derivatives. Photolytic chlorination of pyridine gives 2-chloropyridine in over 70% yield<sup>118</sup>. Similar results are obtained in free-radical acylation<sup>120</sup> and amidation<sup>121,122</sup>, although C-4 substitution is also observed in the last case. The orientation observed in the amidations indicates that  $\cdot\text{CONH}_2$  radicals (from formamide and  $\text{H}_2\text{O}_2 / \text{H}_2\text{SO}_4$  and  $\text{FeSO}_4$ ) have nucleophilic character.



The variation in the product distribution of the Ladenburg rearrangement<sup>121,122</sup> when the halide ion is varied from iodide, to bromide or chloride, has been attributed to the iodide's greater participation in the charge-transfer complex proposed as the first intermediate<sup>123</sup>.



Scheme XIV

Dialkylation products are formed by the radical alkylation of the original charge transfer complex followed by further rearrangement.

Free-radical alkylation (for example, methylation) of pyridine and methylpyridines (as the free bases) occurs at C-2 to a greater extent than does free-radical arylation<sup>48, 124-126</sup>, the methyl radical being more nucleophilic than the phenyl radical for the above systems. However, Minisci's systems are quite different from previous systems studied<sup>169</sup> (where methyl radicals have been used to abstract hydrogen from substituted toluenes), where the methyl radical has been shown to be electrophilic with a  $\rho$  value of  $-0.1$ . It should also be pointed out that abstraction from toluenes, by methyl radicals, is quite exothermic and for this reason the radical will show reduced polar character<sup>13</sup>.

The reactivity of 4-picoline towards the cyclohexyl radical has been investigated. The total rate ratio relative to benzene was large ( $K_{\text{benzene}}^{4\text{-methylpyridine}} = 29$ ; the cyclohexyl radical is known to be very nucleophilic<sup>48, 126</sup>), and the partial rate factors were:  $F_2=81.5$ ;  $F_3=5.6$ ; which are much larger than the partial rate factors found in homolytic aromatic substitution reactions<sup>127</sup>.

The nucleophilic character of alkyl radicals has been further confirmed by use of protonated pyridine as a substrate. The radical  $\text{MeNHC}(\text{CH}_2)_4\text{CH}_2\cdot$  was generated from 2-methyl-3,3-pentamethylene-oxaziran and  $\text{Fe}^{2+}$  in 20% sulphuric acid, in the presence of pyridine, to give products of substitution at C-2 and C-4 (2-34%; 4-66%), and some 1,1'-dimethyl,5,5'-bipyridyl<sup>121</sup>.

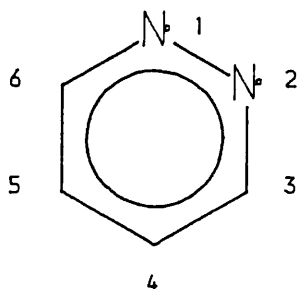
Protonation of pyridine activates the ring toward homolytic alkylation<sup>48, 126, 128</sup>. Thus, while pyridine is not benzylated in nonacidic solution, 2- and 4- benzylpyridine are formed in acidic media, the radicals being generated by thermolysis of dibenzylmercury.

Molecular orbital calculations<sup>100,133</sup> also show the  $\alpha$ -position to be the most favoured point of radical attack. Calculations for the reactivities of the  $\beta$ - and  $\gamma$ - positions, however, do not always correspond to the experimentally determined order of reactivities.

### I.3.2

#### Homolytic substitutions of the diazenes.

##### I.3.2.1 Pyridazine



Data on the reactivity of pyridazine towards free-radicals is complicated by the conflicting nature of the experimental results and the theoretical predictions made of the reactivity of the molecule.

The homolytic phenylation of pyridazine with three different radical sources (benzoyl peroxide, N-nitrosoacetanilide and benzenediazoic acid) has been shown<sup>128</sup> to give 4-phenylpyridazine only. Dou and Lynch<sup>129,130</sup> have reported the formation of 2-, and 4-phenylpyridazines (2- $\rightarrow$ 4-) from the phenylation of pyridazine with benzoyl peroxide in acetic acid.

Substrate	Media	Isomer distribution	
		2-	3- + 4-
Pyridine ''	Acidic	82	18
	Non Acidic	60	40
		3-	4-
Pyridazine ''	Acidic	65	35
	Non Acidic	0	100
		2-	4- + 5-
Thiazole ''	Acidic	84	16
	Non Acidic	58	42

Table IX

The phenylation of some heterocycles in acidic and non-acidic media.

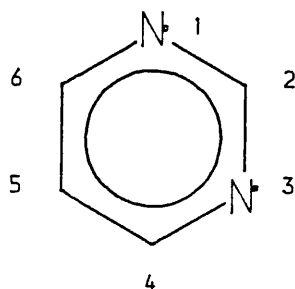
The quoted<sup>27</sup> synthesis of the authentic phenylpyridazines, however, suggests that the authors (Dou and Lynch) have mistaken the 3- isomer for the 2-isomer.

Theoretical predictions for the reactivity of the molecule vary with both the research team the information is obtained from, and the method of calculation used. Different indices of reactivity give inconsistent results even when obtained from the same group of workers.



Theoretical calculations are further weakened in this case as they deal with isolated molecules and ignore intermolecular effects such as hydrogen-bonding. Though the previous assumption, that pyridazine existed in discrete dimers, has been disproved<sup>131</sup>, it is still apparent that a strong association exists between neighbouring molecules<sup>132</sup>. This could lead to both steric and electronic interactions which should be taken into consideration in the calculations.

#### I.3.2.2 Pyrimidine -



The 2-, 4-, and 6- positions in pyrimidine are naturally electron deficient by virtue of the powerful electron withdrawing effect of the nitrogen atoms. In this they resemble, quantitatively, the  $\alpha$ - and  $\gamma$ -positions in pyridine. As the nitrogen atoms in pyrimidine are meta-to each other, their separate effects reinforce each other (as in 1,3-dinitrobenzene) and the resultant effect is greater than in the case of its isomers pyrazine and pyridazine, in which the nitrogen atoms exert electronic effects that partly antagonise one another. The 5-position is not as electron-deficient as the 2-, the 4-, or the 6-position, although it is made slightly so by the general inductive effect. It, therefore, resembles more the  $\beta$ -position of pyridine, and is the nearest to a truly 'aromatic' position in pyrimidine<sup>191</sup>.

Pyrimidine is not truly aromatic because of the depletion of the  $\pi$ -electron layer by the electron-withdrawing nitrogen atoms of the ring. This is seen in its instability to prolonged treatment with alkali.

Electrophilic reagents almost invariably attack pyrimidines at the 5-position, the point most depleted of electrons, but, according to the strength of the reagent, one or more electron-supplying groups are needed in the molecule to permit such substitution.

Although the 2-, 4-, and 6- positions of pyrimidine are suitable for direct nucleophilic attack, only a few examples of the process are known.

Pyrimidine ( $pK_a = 1.3$ ) is a weak base compared with pyridine ( $pK_a = 5.2$ )<sup>135</sup>. This is due to depletion of the  $\pi$ -electrons caused by the insertion of the strongly electron-withdrawing second nitrogen atom.

There is some inconsistency between the positional reactivities predicted by theoretical calculations<sup>100,133</sup> and those obtained experimentally<sup>134</sup>.

r	qr	Fr	f.e.d.
2	0.878	0.092	0.241
4	0.884	0.099	0.437
5	0.973	0.665	0.387

r = rth position in pyrimidine, qr = charge density at rth position  
Fr = free valence number at rth position  
f.e.d. = frontier electron density at rth position

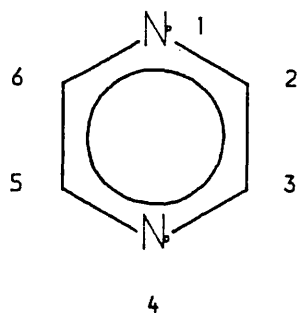
Table X

The reactivities of the various positions in pyrimidine calculated by Davies<sup>100</sup>.

The calculations themselves give different predictions depending upon whether charge densities are used to predict the order of reactivities (2-→4-→5-), or whether free valence numbers (4-→2-→5-), or frontier electron densities (4-→5-→2-) are used.

The arylation of pyrimidine with p-nitrophenyl radicals, produced from the corresponding acylarylnitrosamine, gave the 2- and 4-substituted products<sup>134</sup>. Position 2- in pyrimidine is α- to both of the nitrogen atoms, whereas position 4- is α- to one nitrogen and γ- to the other. Therefore both positions are expected to be activated towards homolytic attack on the basis of additivity<sup>57</sup>, with position 2- being more reactive than position 4-. Position 5-, being β- to both nitrogens would be expected to be the least reactive. This is in fact what has been observed<sup>134</sup>.

#### I.3.2.3 Pyrazine



Very little work has been done on the homolytic substitutions of pyrazine. Theoretical calculations suggest that the reactivity of the identical positions 2-, 3-, 5- and 6- in pyrazine is intermediate between the reactivities of the o- and p- positions of pyridine<sup>100</sup>.

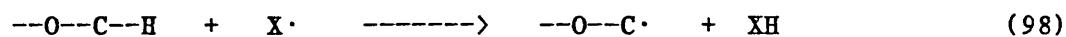
Pyrazine, like benzene and S-triazene, is non-polar, its ring being centro-symmetric. Competition between the nitrogen  $\pi$ -inductive effects accounts for the electron density at the pyrazine nitrogen atoms (0.082e) being smaller than that at the pyridine nitrogen atom<sup>164</sup>.

site	charge density
Pyrimidine (2-)	0.878
Pyrazine (2-)	0.925
Pyrimidine (5-)	0.973

Table XI

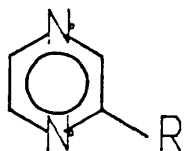
Total charge densities of diazines as calculated by INDO<sup>233</sup> methods.

Hydrogen peroxide, t-butyl hydroperoxide and ammonium peroxydisulphate have been used to produce radicals from the ethers, dioxan, tetrahydrofuran, 1-3,dioxolan and diethyl ether, for the oxyalkylation of protonated heteroaromatic bases<sup>135, 136</sup>.

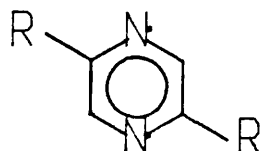


X $\cdot$  = Electrophilic radicals generated thermally, or by redox systems<sup>135</sup>.

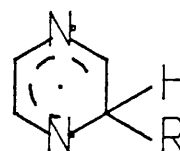
In the reaction between pyrazine and dioxan, mono- and di-derivatives (A) were produced, as well as the dimer (B), supporting the homolytic nature of the reaction which occurs via the dimerisation of the intermediate radical (C) and subsequent oxidation (reaction 99).



(A)

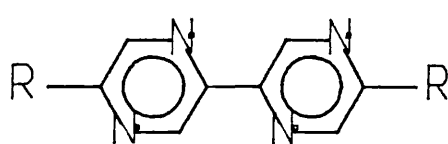


(B)

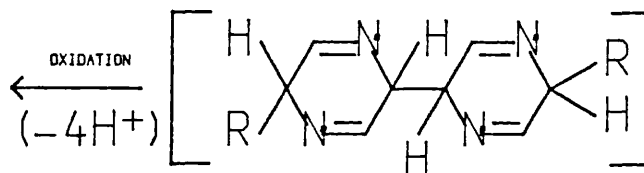


(C)

(99)

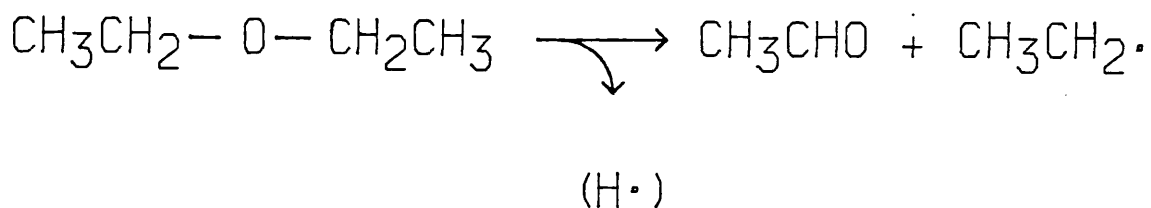


(E)



(D)

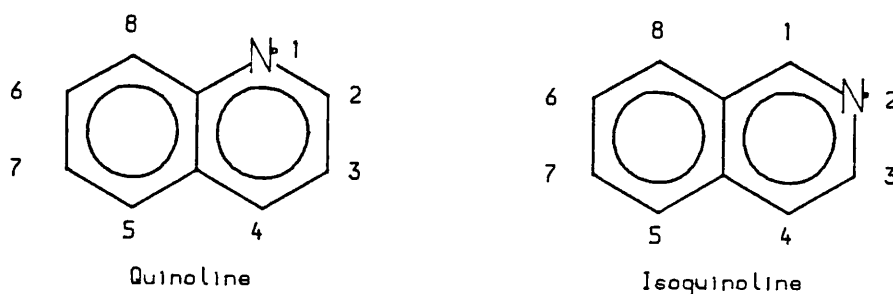
Acyclic ethers partially undergo  $\beta$ -scission with the formation of carbonyl and alkyl compounds. Thus, with diethyl ether, introduction of the oxyalkyl group is accompanied by the formation of appreciable quantities of ethyl and acetyl derivatives. The formation of these latter derivatives is attributed to a  $\beta$ -scission of the  $\alpha$ -oxyalkyl radical:



The ethyl radical attacks the heteroaromatic base directly and selectively<sup>121</sup>, forming the corresponding ethyl derivative. Acetaldehyde initiates homolytic acylation<sup>120</sup>.

Homolytic alkylation<sup>121</sup>, acylation<sup>120</sup>, amidation<sup>122</sup> and  $\alpha$ -amidoalkylation<sup>127</sup>, of heteroaromatic bases, have both synthetic and theoretical importance comparable to Friedel-Crafts' alkylation in the homocyclic series.

## I.3.3

Homolytic substitutions of quinoline and isoquinoline

The homolytic phenylation of quinoline by benzoyl peroxide was reported by Hey and Walker<sup>138</sup> to give 4-phenylquinoline and a smaller amount of the 5-isomer. In a later investigation of this reaction by Pausacker<sup>112</sup>, all of the phenylquinolines were isolated. The percentage isomer distribution was 2-, 6%; 3-, 14%; 4-, 20%; 5-, ~12%; 6-, 8%; 7-, 8%; and 8-, 30%.

The order of positional reactivities (8-→4-→3-→5-→6-, 7-→2-) is in agreement with that predicted from either the free valence numbers<sup>139</sup> or the atom localisation energies<sup>139, 140</sup> for quinoline.

Dou and Lynch<sup>129</sup> have shown that the total relative reactivities ( $K_{\text{benzene}}^{\text{heterocycle}}$ ) of quinoline and isoquinoline, with respect to benzene, towards phenylation with benzoyl peroxide, are increased in acidic solution, but with no change in the isomer ratios. Reiger<sup>141</sup> has used the thermal decomposition of lead tetraacetate and lead

tetrapropionate, in the presence of an excess of the corresponding carboxylic acid, as sources of methyl and ethyl radicals for the alkylation of quinoline and isoquinoline. Quinoline gave the 2- and 4- alkylated products, and isoquinoline gave the 1-alkyl isomer only.

Competitive methylation reactions, where *t*-butyl peroxide was dissolved in mixtures of quinoline or isoquinoline and naphthalene, showed the order of reactivities in non-acidic solution to be isoquinoline(1.52)>quinoline(1.25)>naphthalene(1.00)<sup>170</sup>.

The competitive benzylation of mixtures of pyridine and quinoline or isoquinoline, with dibenzylmercury in acetic acid, gave ratios of relative reactivities, of quinoline and isoquinoline to pyridine, of 16.3:1 and 36.7:1, respectively<sup>142</sup>, which are much greater than the reactivities obtained in non-acidic conditions<sup>128</sup> (pyridine is not benzylated in non-acidic conditions).



## EXPERIMENTAL

### E.1

#### Purification of materials.

##### E.1.1

#### Benzoyl peroxide:

Chloroform was saturated with benzoyl peroxide<sup>101</sup> (B.D.H.) which contained water (30%). The aqueous layer was rejected and the filtered chloroform solution was diluted with three times its volume of ice-cold methanol. The solid which separated was filtered off and the procedure was repeated to give benzoyl peroxide in colourless needles [m.pt. 104.5°C (decomp.); lit. m.pt. 103.5°C<sup>138</sup>].

In another method, warm chloroform was saturated with benzoyl peroxide (B.D.H.), the aqueous later removed, and the chloroform solution cooled in a refrigerator (-5°C). Rhombic colourless crystals of benzoyl peroxide separated out, m.pt. 105.5°C (decomp.). These crystals were slightly more pure (99.7%) by KI test<sup>177</sup> than those obtained by the previous method (99.2% by KI test), but the method was rejected due to the explosive nature of the reagent.

E.1.2

Pyridine:

Dried pyridine (B.D.H.) (stored over potassium hydroxide pellets) was freshly distilled, using calcium chloride guard tubes, under atmospheric pressure before each experiment (b.pt. 114.5-115°C; lit. b.pt. 115.5°C<sup>176</sup>).

E.1.3

Benzene:

Sodium dried benzene (May and Baker), crystallisable, was freshly distilled by a method similar to that used for pyridine.

E.1.4

Pyridazine:

Pyridazine (Aldrich) was distilled under reduced pressure and stored, in a dark bottle, at -5°C (b.pt. 59-60°C/2 mm; lit. b.pt. 208°C<sup>176</sup>).

E.1.5

Benzoic acid:

Benzoic acid (May and Baker) was recrystallised from water to give colourless flat crystals (m.pt. 122°C; lit. m.pt. 122°C<sup>176</sup>).

E.1.6

Quinoline:

Quinoline (B.D.H.) was stored over potassium hydroxide pellets and freshly distilled under reduced pressure before each experiment (b.pt. 111-112°C/15mm; lit. b.pt.114°C/17mm<sup>176</sup>).

E.1.7

Isoquinoline:

Isoquinoline (B.D.H.) was freshly distilled under reduced pressure before each experiment, using an air condenser to collect the solid (m.pt. 24°C b.pt. 128°C/17 mm; lit. m.pt. 24.6°C b.pt. 242°C<sup>176</sup>).

E.1.8

Dioxan:

Dioxan (May and Baker) was distilled under atmospheric pressure and stored in a dark bottle (b.pt. 103°C; lit. b.pt. 101°C/750mm<sup>176</sup>).

E.1.9

Cyclohexane carboxylic acid:

Cyclohexane carboxylic acid (B.D.H.) was distilled under reduced pressure using an air condenser (b.pt. 103-104°C/4 mm; lit. b.pt.105-106°C/4mm<sup>176</sup>).

## E.1.10

## Miscellaneous chemicals:

Pyrazine (Aldrich 99%+ Gold Label), sodium acetate (May and Baker), ammonium peroxydisulphate (May and Baker), sodium benzoate (May and Baker), silver nitrate (B.D.H.), pentafluoronitrosobenzene (Bristol Organics), meta-dinitrobenzene (Harrington Bros.), dibenzyl (Ralph N Emanuel), 4-phenylpyrimidine (Aldrich), sodium methoxide (Aldrich), pyrimidine (Aldrich), 5-aminopyridine (Koch Light), cupric chloride (May and Baker) and ferric chloride (May and Baker), were used as supplied.

## E.2

Preparation of authentic samples and catalysts.

## E.2.1

## Copper(II)benzoate:

Copper(II)benzoate was obtained by mixing equimolar solutions of copper(II)chloride and sodium benzoate in water. Copper(II)benzoate  $[\text{Cu}(\text{C}_7\text{H}_5\text{O}_2)_2 \cdot 2\text{H}_2\text{O}]$  precipitated after double decomposition of the two salts. The solid was filtered, washed with hot water, recrystallised from alcohol, and dried to give a blue crystalline powder.

## E.2.2

## Ferric(III)benzoate:

Ferric(III)benzoate  $[\text{Fe}(\text{C}_7\text{H}_5\text{O}_2)_3]$  was prepared by a similar method using ferric(III)chloride and sodium benzoate. It was dissolved in hot alcohol. A precipitate was obtained on cooling to room temperature. A brown powder of ferric(III)benzoate was obtained on drying the precipitate.

## E.2.3

## 2-Phenylpyridine:

2-Aminopyridine (10gm), in dry benzene (100 ml), was boiled under reflux in a 250 ml three necked round bottomed flask, equipped with a condenser and a calcium chloride guard tube, while amyl nitrite (18 ml)(B.D.H.) was added, dropwise. The solution was boiled under reflux for six hours when the slow evolution of nitrogen ceased. The excess of solvent and pentyl alcohol were removed by rotary evaporator. The residue was extracted with 7N hydrochloric acid and then distilled under reduced pressure. 2-Phenylpyridine (2.7 gm.) was collected as a yellow oil (b.pt.  $132^\circ\text{C}/2\text{ mm}$ ; lit. b.pt.  $268.9^\circ\text{C}^{176}$ ). On reaction with picric acid, orange yellow rhombic crystals of the picrate were obtained (m.pt.  $175^\circ\text{C}$ ; lit. m.pt.  $175^\circ\text{C} - 176^\circ\text{C}$ ).

## E.2.4

## 3-Phenylpyridine:

A similar method<sup>199</sup> involving the diazotisation of 3-aminopyridine, was used. 3-Phenylpyridine was obtained in a 52% yield, as a pale yellow oil (b.pt. 135°C/2 mm; lit. b.pt.269-70°C/749mm<sup>176</sup>). The picrate crystallised as pale yellow needles (m.pt. 159-160°C; lit. m.pt. 159°C -160°C), from acetone.

## E.2.5

## 4-Phenylpyridine:

4-Phenylpyridine was supplied by Ralph N Emanuel and was purified by recrystallisation from water using charcoal. Pure white flaky crystals were obtained (m.pt. 78°C; lit. m.pt. 77-78°C<sup>176</sup>). The picrate crystallised as orange needles (m.pt. 195-196°C; lit. m.pt. 195°C - 196°C) from acetone.

## E.2.6

## 5-Phenylquinoline:

Quinoline was nitrated using sulphuric acid and nitric acid<sup>136</sup>. Nitric acid (density 1.5, 97%) was added gradually to the base in sulphuric acid (density 1.84). After thirty minutes the solution was poured into ice. On partial basification (pH 2.1), the mono-nitro fraction separated out. 5-Nitroquinoline was obtained, as colourless plates, from aqueous ethanol (m.pt. 70°C).

The nitroquinoline was reduced to 5-aminoquinoline using granulated tin and hydrochloric acid<sup>153</sup>.

5-Aminoquinoline was diazotised with amyl nitrite to give 5-phenylquinoline (6.7% yield) as pale yellow needles (m.pt. 82°C; lit. m.pt.82-83°C<sup>176</sup>).

#### E.2.7

##### 3-Phenylpyridazine:

3-Phenylpyridazine was made by the method of Gabriel and Colman<sup>201</sup>. 3-Phenylpyridazinone was formed by the condensation of benzoylpropionic acid and hydrazine sulphate. The pyridazinone was chlorinated, aromatised, and subsequently dechlorinated to give 3-phenylpyridazine as light brown flaky crystals (m.pt. 101-102°C; lit. m.pt. 102-103°C<sup>176</sup>). The picrate melted at 127°C (lit. m.pt.127°C<sup>176</sup>).

A change from the literature method was found necessary in the deiodination of 3-phenyl-6-iodopyridazine. Sodium metabisulphite was used to remove excess iodine, and the pyridazine was obtained by extraction with ether.

#### E.2.8

##### 4-Phenylpyridazine:

The method of Stoermer and Fincke<sup>202</sup> gave very low yields (3%) of the pyridazine which was not easy to purify. However, on

decomposition of benzoyl peroxide in pyridazine, using a 1:6 ratio of peroxide to pyridazine and separation of the biaryl products, the distillate of phenylpyridazines was found to consist of almost pure 4-phenylpyridazine. On further purification, clear flaky crystals of 4-phenylpyridazine (99%) were obtained (m.pt. 85°C; lit. m.pt.86-86.5°C<sup>176</sup>). The picrate was crystallised from ethanol to give yellow orange rhombic crystals (m.pt. 128°C). The identity of the compound was confirmed by mass spectroscopy, carbon analysis and nuclear magnetic resonance (N.M.R.) spectroscopy (A.3.4).

#### E.2.9

##### Phenylpyrazine:

o-Bromoacetophenone (35 gm) was refluxed with ethylene diamine (65 ml) for twenty four hours. The golden red solution was kept in a closed system for another eight hours when an orange yellow precipitate came out of solution. The residual bromine and ethylene diamine were removed on washing with water leaving pale yellow crystals of 2-phenyl,3,4,5,6-tetrahydropyrazine. The crude product weighed 23 gm. 2-Phenyl,3,4,5,6-tetrahydropyrazine (8 gm) was ground in a mortar and refluxed with iodine (25 gm) in nitrobenzene (100 ml) for eight hours. A thick dark solution was obtained at the end of the reaction. On addition of sodium metabisulphite the liquid became lighter in colour, but was still very cloudy. Sodium carbonate was added until the solution reached a pH of 9. The solution was repeatedly extracted with toluene (5x30 ml). The toluene extracts were extracted with 7N hydrochloric acid (3x30 ml). The acidic solution was neutralised with sodium carbonate and extracted with toluene (3x30 ml).



The toluene extracts were dried with anhydrous magnesium sulphate, and on distillation under reduced pressure yielded 1.8 gm (23% yield) of phenylpyrazine as a pale brown solid (m.pt. 68°C with sintering). The identity of the compound was confirmed by N.M.R., mass spectroscopy and carbon analysis (A.3.5).

## E.2.10

## 2-Phenylpyrimidine:

The method of Moisack, Peukert and Schoenleben<sup>203</sup> was used in this synthesis. The only alterations from the literature method were in the use of thionyl chloride in place of phosgene, and benzamidine ammonium benzenesulphonate<sup>204</sup> in place of benzamidine hydrochloride. The pyrimidine melted at 37 - 38°C (lit. m.pt. 37 - 38°C<sup>134</sup>) and had a b.pt. of 100°C/5 mm.

## E.2.11

## 4-Phenylpyrimidine:

4-Phenyl-2-thiouracil (m.pt. 257°C<sup>205</sup>) was desulphurised to give 6-hydroxy-4-phenylpyrimidine (m.pt. 270°C). The hydroxyphenylpyrimidine was chlorinated<sup>206</sup> to give 6-chloro,4-phenylpyrimidine, which was dechlorinated by boiling with 55% hydrogen iodide and red phosphorus. On purification of the product 4-phenylpyrimidine was obtained (m.pt. 64°C; m.pt. of picrate, 162-163°C)

However, a purer form was later supplied by Aldrich Chemicals and this was used for analytical purposes.

## E.2.12

## 5-Phenylpyrimidine:

Ethylphenylmalonate<sup>207</sup> was condensed with urea (B.D.H.), using sodium methoxide, to give 5-phenylbarbituric acid<sup>235</sup>. The barbituric acid was aromatised via oxidative chlorination to give 5-phenyl-2,4,6-trichloropyrimidine<sup>237</sup>. The trichloro- derivative was later dechlorinated using hydrogen iodide and phosphorus in glacial acetic acid, to give 5-phenylpyrimidine as a clear yellow oil (m.pt. 24-27°C, b.pt. 111-132°C/2 mm; lit. m.pt. 23-27°C<sup>236</sup>, b.pt. 120-140°C/0.01mm<sup>237</sup>). The picrate melted at 117-119°C (lit. m.pt. 120°C<sup>134</sup>).

The identity of all the above mentioned compounds were confirmed by analytical methods, such as, mass spectroscopy, N.M.R., carbon analysis and infra-red spectroscopy. The results are given in the appendix (Section A.3).

## E.3

Experimental conditions.

## E.3.1

## Decomposition of benzoyl peroxide:

## E.3.1.1 Pyridine:

Reactions were carried out in 250 ml round bottomed flasks with ground glass joints which were fitted with Liebig condensers and calcium chloride guard tubes.

Flasks containing pyridine (75 gm) were placed in the thermostat for one hour before the addition of the reagent. The addition of benzoyl peroxide was effected with stirring and the sides of the flask were immediately washed down with a further 25 gm of the solvent. The reagent dissolved easily, and the flasks were removed from the bath after twenty four hours, the reaction being assumed to be complete.

The method used for competitive experiments was identical except for changes in the chemical composition of the solvent.

Catalysts (50 mg) were added before the addition of benzoyl peroxide.

#### E.3.1.2 Quinoline:

Quinoline (14 gm) was phenylated with benzoyl peroxide (0.525 gm) at 80°C, using the method used for pyridine. Additives (2-3 mg) were used in the catalysed experiments.

#### E.3.1.3 Isoquinoline:

Isoquinoline (14 gm) was phenylated with benzoyl peroxide (0.525 gm) by the same method as used for quinoline, however, since isoquinoline is a solid at room temperature, the base was warmed to about 27°C, which facilitated easy transfer to the reaction flask.

The decomposition of benzoyl peroxide in quinoline and isoquinoline gave low yields of biaryl. The experiments were repeated using 10 gm of the base, in order to increase the peroxide to base ratio.

#### E.3.1.4 Pyridazine:

Pyridazine (1 gm) and benzene (5 gm) were allowed to react with benzoyl peroxide (0.35 gm) in a 25 ml round bottomed flask fitted with a Liebig condenser and a calcium chloride guard tube. Due to the small bulk of the reactants preheating was not necessary. Benzoyl peroxide and the catalysts were poured down the flask, carefully avoiding contact with the neck. The solvent was then poured down the sides of the vessel. The flask was shaken until all the peroxide had dissolved, and then immersed into the oil bath. The reactants took about 10 minutes to reach the bath temperature. About 2.5 mg of additives were used in the catalysed experiments. The flasks were removed after twenty four hours.

#### E.3.1.5 Pyrazine:

Pyrazine (0.50 gm) and benzoyl peroxide (0.35 gm) were carefully poured into a 10 ml round bottomed flask fitted with a Liebig condenser and a calcium chloride guard tube (about 2.5 mg of additives were also added along with the rest of the solids in the catalysed experiments). Benzene (2.5 gm) was poured down the wall of the flask. The flask was shaken until the pyrazine and benzoyl peroxide had completely dissolved in the solvent, and then immersed into the oil bath. The reactants reached the bath temperature in less than ten minutes.

## E.3.1.6 Pyrimidine:

Benzoyl peroxide (0.35 gm) was allowed to decompose in a mixture of benzene (2.5 gm) and pyrimidine (0.5 gm) for twenty four hours by a method identical to that used for pyrazine.

## E.3.2

## Oxidative decarboxylation of benzoic acid:

Phenylation by oxidative decarboxylation of benzoic acid, by ammonium peroxydisulphate, was attempted using the method of Minisci<sup>197</sup> for decarboxylating aliphatic carboxylic acids. However, the low solubility of benzoic acid in water made it a two phase reaction. To overcome this, the method of Anderson and Kochi<sup>180</sup>, which involves dimethylsulphoxide (DMSO) as a co-solvent, was used. However, the amount of DMSO found necessary to dissolve all the benzoic acid was found to form an explosive mixture with ammonium peroxydisulphate. This could be due to the oxidation of DMSO to the sulphone by the persulphate<sup>209</sup>.

The use of acetone as a co-solvent gave rise to a high number of side products and very low yields.

Later, a method devised for phenylation of protonated 4-substituted pyridine, by the oxidative decarboxylation of benzoic acid by persulphate<sup>47</sup>, was used in a modified form.

A one-phase system could not be obtained using the quoted experimental conditions. At elevated temperatures, where higher solubility was achieved, the benzoic acid steam distilled, and collected as white needles on the neck of the flask.

To a solution of pyridine (0.01 mole) and silver nitrate (0.03) in 10% sulphuric acid (0.01 mole) and benzoic acid (0.05 mole), heated at 70°C under reflux with vigorous stirring, was added, over about ten minutes, a solution of ammonium persulphate (0.03 mole) in water (15 ml), between 85°C and 95°C, under reflux.

After the emission of carbon dioxide had ceased (about one hour), the stirring and heating were continued for 20 minutes. The condenser had to be cleared every 12-13 minutes with a glass rod as benzoic acid collected in the condenser. The solution was poured into ice and 30% w/w ammonia, and extracted with chloroform. The organic layer was washed with 10% sodium hydroxide and water, dried with anhydrous magnesium sulphate, and analysed by gas liquid chromatography (g.l.c.).

In order to determine whether the extent of protonation affected the orientation of attack by the phenyl radical on the heterocycle, the use of buffers was attempted during the phenylation to control the pH. However, the buffers precipitated silver from the solution and the method was abandoned.

Eventually, the reaction was carried out by adding various amounts of sodium carbonate to the reaction mixture and measuring the pH as the reaction progressed. Sodium benzoate was used in place of benzoic acid in subsequent experiments. When benzoic acid was used, the reaction mixture formed a single phase only at pH's above 7.5. Using sodium benzoate a single phase could be obtained even at a pH as low as 1.5.

### E.3.3

Oxidative decarboxylation of acetic acid and propionic acid:

The oxidative decarboxylation of acetic acid and propionic acid by persulphate, were done by the method of Minisci et. al.<sup>197</sup>.

The silver nitrate had to be dissolved before the addition of benzoic acid or persulphate, as the catalyst refused to dissolve if added later. Some silver nitrate precipitated out of solution on the addition of pyrazine. The phenomenon was not observed with any of the other bases.

### E.3.4

Oxidative decarboxylation of cyclohexane carboxylic acid:

The method used was similar to that used for the decarboxylation of benzoic acid. The solubility of cyclohexane carboxylic acid in water is also very low, but as it does not steam distil as readily as benzoic acid, the reaction could be carried out at 100-102°C, when appreciable solubility was obtained.

Friedel Crafts' alkylation of pyridine using cyclohexene and concentrated sulphuric acid, gave very poor yields of a mixture of cyclohexylpyridines which could not be separated into individual isomers. The reaction products were, therefore, aromatised using iodine and red phosphorus, and the aromatised products compared with the known specimens of phenylpyridines using g.l.c.

Similar methods were used for the cyclohexylation of pyridazine, pyrazine and pyrimidine.

### E.3.5

The reaction of pyrazine with dioxanyl radicals:

This reaction was undertaken, partly as an extension of the work done on alkylation, and partly because it was the most well documented work done by Minisci *et. al.*<sup>197</sup>. Published details of the reaction products included N.M.R. spectra which could be directly compared with those obtained by us. The results obtained were in very close agreement with those reported in the literature. However, other experiments done by the same authors, which we attempted to duplicate (e.g. the attack of the ethyl radical on protonated pyridine via the oxidative decarboxylation of propionic acid), did not correlate in any way with the results quoted. Details of the analytical methods for the latter experiment were not published and therefore could not be compared with our methods. Correspondence with the authors did not produce a response.



## E.4

Analytical methods.

## E.4.1

Analysis of the reaction products obtained from the decomposition of benzoyl peroxide in pyridine<sup>210</sup>:

The bulk of the unreacted pyridine was removed by distillation at atmospheric pressure. Esters in the residue were saponified with boiling sodium hydroxide (2N, 100 ml), for four hours. The unsaponifiable material was thoroughly extracted with toluene (3x50 ml). The toluene extracts were washed with water (25 ml) and dried (anhydrous magnesium sulphate). The sodium hydroxide solution, combined with the aqueous washings, was worked up for benzoic acid as follows:

· Benzoic acid estimation: The alkaline extracts of the saponification mixture were made just acid with hydrochloric acid and then neutralised by the addition of sodium hydrogen carbonate. The mixture was heated to boiling, and the flocculent precipitate of silicic acid, which arises from the attack of sodium hydroxide on the glass during the saponification, was filtered off.

The filtrate, when cold, was extracted with methylene chloride (2x20 ml), to remove phenols. The solution was then acidified with hydrochloric acid, and then saturated sodium chloride. The precipitated benzoic acid was thoroughly extracted with methylene chloride (4x30 ml). The aqueous layer was rejected and the combined

extracts, after being dried (anhydrous calcium chloride), were allowed to evaporate at room temperature. The residue of benzoic acid had a m.pt. of 119-120°C (not depressed on admixture with an authentic specimen).

The accuracy of this method was tested by carrying out the procedure on known amounts of benzoic acid when quantitative recovery was achieved.

The toluene extracts of the unsaponifiable material, combined with toluene washings of the magnesium sulphate (75 ml), were reduced to 70 ml by distillation through a 25 cm column. The solution was poured on to an alumina column (2x25 cm) and eluted successively with toluene (100 ml) and ether (100 ml).

Ether and toluene were removed from the eluate by distillation through the 25 cm column, and the residue (10 ml) was transferred quantitatively to a 25 ml B10 pear-shaped flask fitted with a side arm and a fractional distillation head. The entire apparatus was weighed before each experiment. Most of the remaining solvent was removed by distillation at reduced pressure (25 mm). The dark residue was distilled over a metal bath (150°C) at a pressure of about 0.2 mm. The bulk of the biaryls distilled over at a temperature of 126-128°C. The last traces of biaryls were distilled into the receiver by raising the temperature of the bath to 170°C and cautiously warming the flask with a naked flame. At this stage, a small drop of dark red material remained on the thermometer bulb. The partly solid biaryl fraction was weighed and redistilled. In not a single case was more than a trace of solvent or any coloured material obtained on the second distillation. The weight of the residue was obtained by weighing the

apparatus after the first distillation and subtracting the weight of the clean apparatus. Attempts to identify the individual components of the residue were unsuccessful except for the detection of p-terphenyl.

The presence of each isomer and their approximate ratios were demonstrated in the following manner; a mixture of phenylpyridines (2.5 gm), dissolved in ethanol (10 ml), was added to a hot solution of picric acid (2.9 gm) in ethanol (38 ml). The mixture was heated to boiling and filtered hot. The residue was fractionally crystallised from acetone and yielded, first, 4-phenylpyridine picrate in yellow needles (m.pt. 196°C; lit. m.pt. 195-196°C<sup>210</sup>), and then the picrate of 2-phenylpyridine in yellow prisms (m.pt. 176°C; lit. m.pt. 175-176°C<sup>210</sup>). Evaporation of the filtrate and crystallisation of the residue from acetone gave 3-phenylpyridine picrate in feathery yellow needles (m.pt. 160°C; lit. m.pt. 159-160°C<sup>210</sup>).

The above methods were slow and inaccurate, especially in the estimation of the isomer ratios of the phenylpyridines. Quicker and more accurate results were obtained by g.l.c.

Nine feet glass (silanised) columns of internal diameter 0.25 in were used in the analysis. A 1% F.F.A.P. (on chromosorb Q 100-120 mesh) column was found to be the most suitable for the analysis of phenylpyridines. A 2% P.E.G.A. on celite 545 (AW) column was found to be the most suitable for analysis of the phenyldiazines.

Both columns were initially pressure packed (35 p.s.i.) under nitrogen, prebaked at 50°C for four hours, at 150°C for a further six hours and at 185°C for a further fourteen hours. No column bleeding was apparent at the end of this treatment. The columns were purged with nitrogen (oxygen free) and sealed before storage.

## D.1

### DISCUSSION

#### D.1.1

##### The decomposition of benzoyl peroxide in pyridine.

Only biphenyl, 2-, 3-, and 4-phenylpyridines and benzoic acid were detected (g.l.c.).

However, no biphenyl was detected in the experiments including additives. Although previous workers<sup>112</sup> have reported the presence of bipyridyl in their reaction mixtures on the basis of (a) a rose-red colouration formed on treatment of the phenylpyridine mixture with ferrous sulphate and (b) the high nitrogen content of the phenylpyridine fraction, we have found no evidence for this product. The rose-red colouration given by 2,2'-dipyridyl with ferrous sulphate is similar to the colour given by a mixture of pure 2- and 3-phenylpyridines with ferrous sulphate. The infra red spectra of the 2,2'-dipyridyl-iron complex and phenylpyridine-iron complexes are also very similar.

The isomer ratios obtained vary slightly from previous findings, giving a higher percentage of 4-phenylpyridine.

Expt. no.	Additive	Phenylpyridine yield (gm)	Isomer distribution			Benzoic acid yield (gm)	Total* yield %
			o-	m-	p-		
1	none	2.97	48.2	33.5	18.3	2.60	91.16
2	"	2.85	47.6	33.8	18.6	2.75	
3	"	2.75	48.4	33.8	17.8	2.44	
ave	"	2.84	48.1	33.7	18.2	2.59	
4	CopperII	1.96	47.2	34.8	18.0	3.58	94.70
5	"	2.23	46.6	34.9	18.5	3.58	
6	"	2.12	47.3	34.3	18.4	3.42	
ave	"	2.10	47.1	34.6	18.3	3.36	
7	IronIII	1.67	45.3	29.0	25.7	2.28	69.44
8	"	1.59	45.0	28.4	26.6	2.51	
9	"	1.45	45.5	29.1	25.4	2.54	
ave	"	1.57	45.3	28.8	25.9	2.44	
10	M.D.B.**	2.61	45.6	36.4	18.0	2.63	89.60
11	"	2.77	46.1	35.3	18.6	2.78	
12	"	2.75	45.7	37.0	17.3	2.41	
ave	"	2.71	45.8	36.2	18.0	2.61	
13	P.F.N.B.***	2.62	47.8	35.3	16.9	3.25	95.03
14	"	2.57	48.9	34.6	16.5	3.23	
15	"	2.43	48.0	34.9	17.8	2.61	
ave	"	2.54	48.0	34.9	17.1	3.03	

\* Yield with respect to  $C_6H_5$ .

\*\* meta-dinitrobenzene

\*\*\* pentafluoronitrosobenzene

Table XII

The decomposition of benzoyl peroxide in pyridine at 80°C.

The following sources of error are inherent in the method of analysis employed:

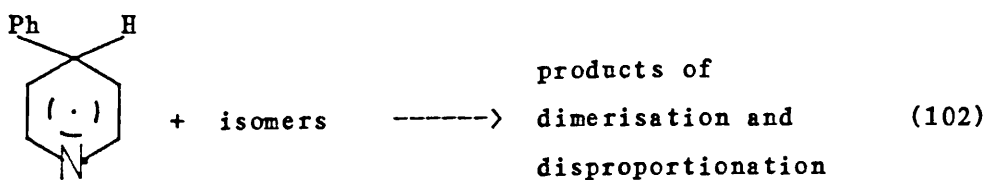
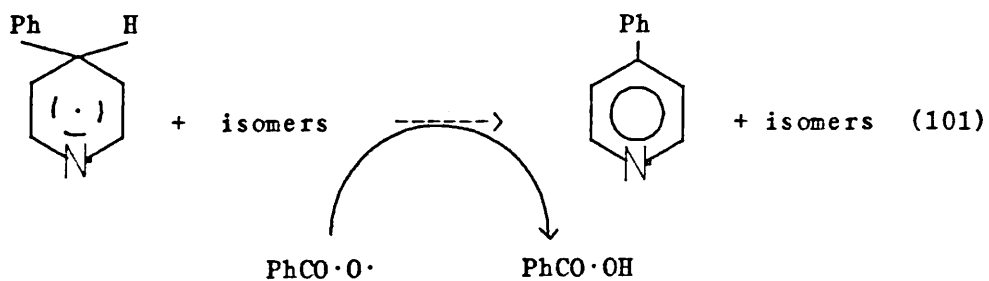
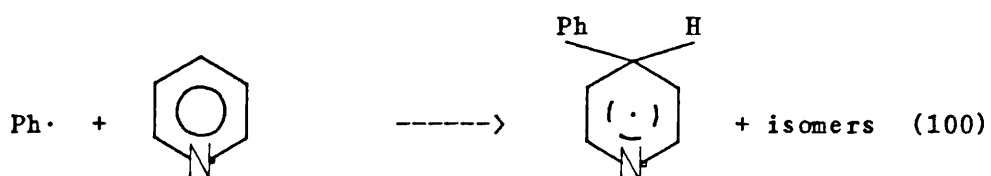
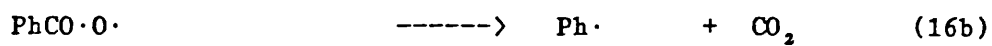
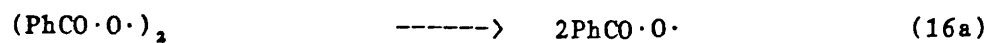
(1) Methods involving purification of the phenylpyridines by reduced pressure distillation selectively remove the least volatile isomer, 4-phenylpyridine, (2-phenylpyridine 133-4°C/2mm., 3-phenylpyridine 135-6°C/2mm., 4-phenylpyridine 136-9°C/1mm.)

(2) Methods involving removal of excess solvent by distillation alter the relative amounts of the phenylpyridines. Appreciable quantities (between 7 to 9 percent) of the total biaryl fraction are found in the recovered solvent, which is preferentially enriched with 2- and 3-phenylpyridines, the extent of which varies with the dryness of the solvent before distillation.

Our method involves direct (g.l.c.) analysis of the crude reaction product and avoids these artefacts.

Various workers have reported the phenylation of pyridine without making detailed mechanistic studies. Absolute rate constants have been reported for reactions of phenyl radicals in the gas phase (~300°C)<sup>143</sup>. De Tar<sup>152</sup> has used computer techniques to assign rate constants to the elementary steps in the reaction of benzoyl peroxide with benzene [ $k_H$ (the rate of hydrogen abstraction by phenyl radicals) =  $2 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ ,  $k_{PhH}$ (the rate of addition of phenyl radicals to benzene) =  $2 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$ ]. Recent values obtained by Kryger *et al*<sup>144</sup> ( $k_H = 3.3 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ ,  $k_{PhH} = 10.3 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ ) are estimated to give a precision of about  $\pm 50\%$ . The values obtained by Pausacker are probably low due to their assumption of low values for rate constants of radical-radical reactions, e.g.,  $1 \times 10^8$  for alkyl-alkyl combination, for which values of 0.4 to  $\sim 3 \times 10^9$  have since been measured<sup>147,171</sup>.

A reaction scheme analogous to that determined for the decomposition of benzoyl peroxide in benzene can be postulated.



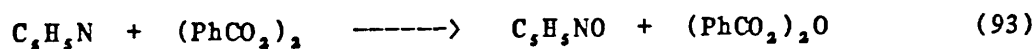
Scheme XV

Compounds of the type  $C_6H_5 \cdot C_5H_5N \cdot C_5H_5N \cdot C_6H_5$ , are formed during the reaction of benzoyl peroxide with pyridine. This is similar to the formation of quaterphenyl from the reaction of benzoyl peroxide with benzene<sup>24</sup> and of disubstituted quaterphenyls from substituted benzoyl peroxides and benzene<sup>25</sup>.

The above scheme however, can only achieve a maximum theoretical yield of benzoic acid of one mole per mole of benzoyl peroxide. Since the yields of benzoic acid observed are consistently higher than that permitted by Scheme XV, some mechanism whereby benzoic acid may be formed without the concomitant production of phenylpyridines must be present.

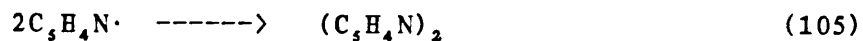
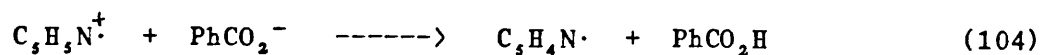
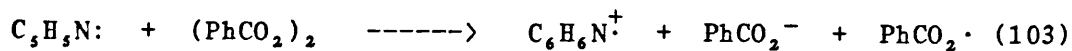
Though a detailed quantitative study has not been done on the decomposition of benzoyl peroxide in pyridine it has been found that, under the same conditions, 77.3% of the benzoyl peroxide dissolved in pyridine decomposed when only 15.5% of the peroxide decomposed in a similar solution in benzene<sup>11</sup>.

Pausacker<sup>112</sup> attributed the accelerated decomposition of benzoyl peroxide in pyridine to secondary mechanisms which compete with its homolysis (equations 93 and 103-105). It was suggested that the reaction went according to (a) Scheme XIII, the net reaction being:





and (b) Scheme XVI :

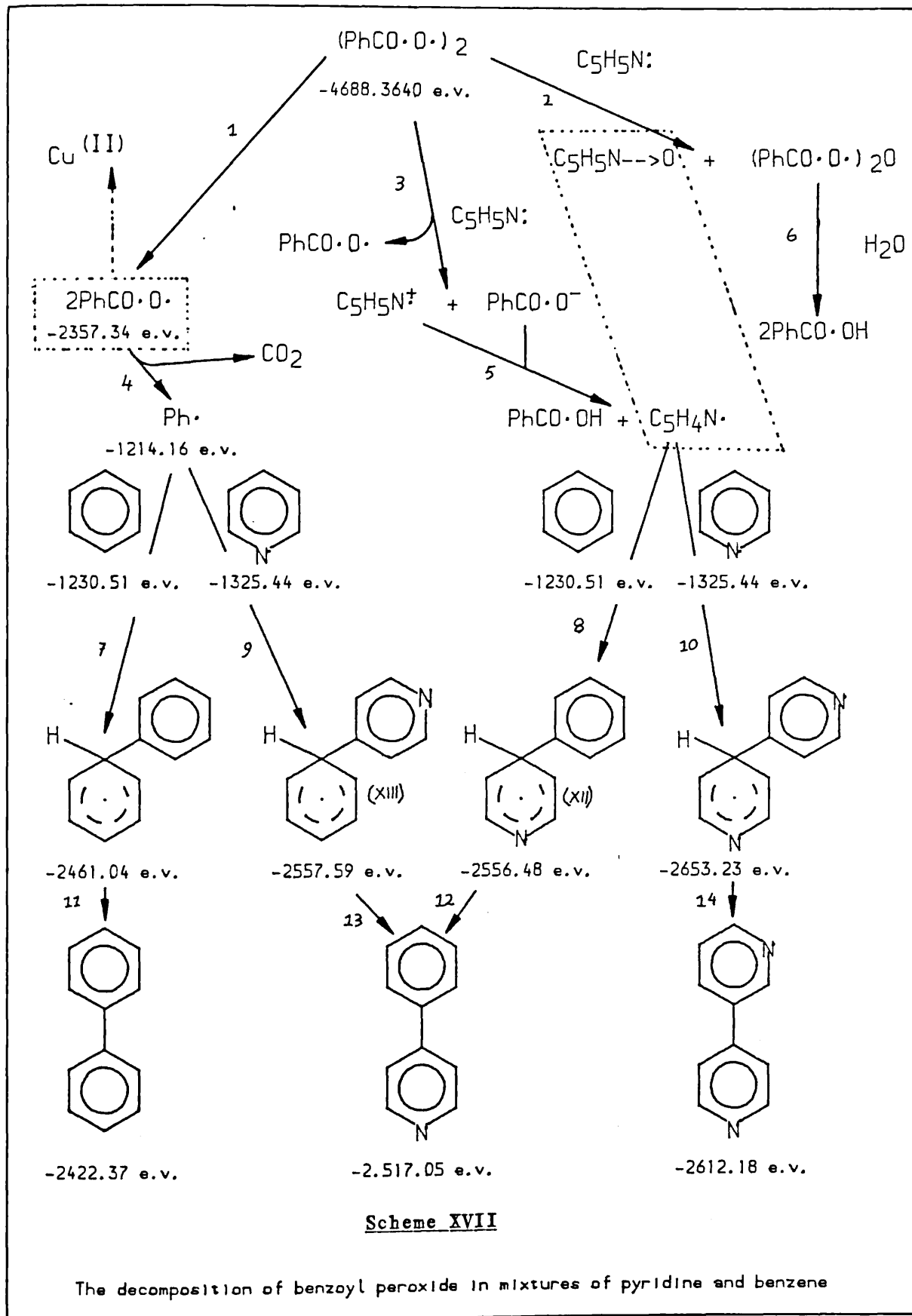


Scheme XVI

The induced decomposition of benzoyl peroxide in pyridine.

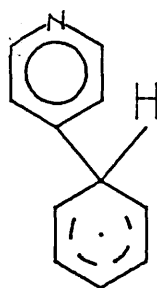
and were used to explain the high yield of benzoic acid obtained in pyridine.

Similar mechanisms have been suggested to explain the high yield of benzoic acid in 4-methylpyridine (1.32mole/mole peroxide), in comparison with the yield in mixtures of 4-methylpyridine and benzene (0.34 mole/mole peroxide)<sup>60</sup>. The following scheme can lead to varying amounts of benzoic acid being formed from one mole of benzoyl peroxide depending upon its mode of formation.



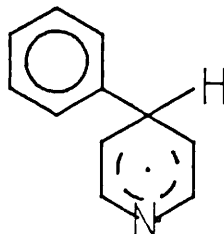
Evidence for the formation of pyridine-N-oxide has been given by Pausacker<sup>112</sup> and Hey and Walker<sup>138</sup> but could not be verified by us, as pyridine-N-oxide is not detectable by our g.l.c. columns. Though water was excluded from the reaction mixture during the incubation, the rapid rate of hydrolysis of benzoic anhydride in pyridine<sup>172</sup> would enable the anhydride to be converted to benzoic acid by the uptake of water by the reaction mixture prior to the g.l.c. analysis. The part of the scheme corresponding to Scheme XVI involves the formation of either bipyridyl or phenylpyridines. Since the stationary concentration of pyridinyl radicals should be low (the existence of significant cage effects in these systems has been discounted<sup>144</sup>), it is more likely that pyridinyl radicals will react with solvent molecules and lead to the corresponding sigma-complexes. The fact that biphenyl is only formed in one set of experiments (experiments 1-3) and then only in very small amounts (2.6mg.) also argues against the presence of strong cage effects.

It is interesting to note that attack of benzene by pyridinyl radicals leads to a sigma-complex (VIII)



(VIII)

which is different from the sigma-complex (VII)



formed by attack of phenyl radicals on pyridine, though subsequent oxidation of both leads to phenylpyridines. The biaryl isomer formed in the case of attack of benzene by pyridinyl radicals, will depend upon which isomeric pyridinyl radical is attacking benzene, whereas in the case of attack of pyridine by phenyl radicals it will depend upon which position of the pyridine molecule the radical attacks. Selectivity, therefore, will be determined during the hydrogen abstraction step in the former case, whereas it will be determined during the formation of the sigma-complex in the latter case.

INDO<sup>233</sup> Calculations (appendix) show that the decomposition of benzoyl peroxide to give two molecules of benzoyloxy radicals (reaction 1) is endothermic by 7.23 e.v. with respect to the induced decomposition by pyridine (reactions 3 and 5). The formation of radical(VIII) (equation 9) is more exothermic than the formation of radical(VII) (equation 8) by 17.27 e.v. The formation of 4-phenylpyridine via radical(VIII) (equation 13) is also more exothermic (1.1 e.v.) than its formation via radical(VII) (equation 12). Attack of benzene by 4-pyridinyl radicals should therefore more readily lead to biaryl formation than the attack of phenyl radicals on the 4-position of pyridine. In competitive experiments, therefore, scheme XVI would be more important than scheme XV leading to greater biaryl yields. In reactions where pure pyridine is the solvent, attack of pyridine by pyridinyl radicals will lead to bipyridyls and the

corresponding products of dimerisation and disproportionation of the sigma-complexes. Reactions of phenyl and pyridinyl radicals involving radical-radical attack leading to biaryl formation will be negligible due to the low stationary concentration of these radicals and the absence of significant cage effects.

The formation of 3-,4'-bipyridyl from radical IX (reaction 14) is exothermic by 1.61 e.v. with respect to the formation of 4-phenylpyridine from radical VIII (reaction 13). On thermodynamic grounds, therefore, bipyridyl should be formed both in competitive experiments where benzene is present and also in pure pyridine. We have, however, failed to detect any bipyridyl in our reaction products.

Nitrosobenzene and nitroxides in general are well known radical scavengers<sup>154</sup>. Pyridine-N-oxide, by scavenging pyridinyl radicals can prevent the radical from forming biaryls. The absence of bipyridyl suggests that biaryl formation takes place entirely according to Scheme XV.

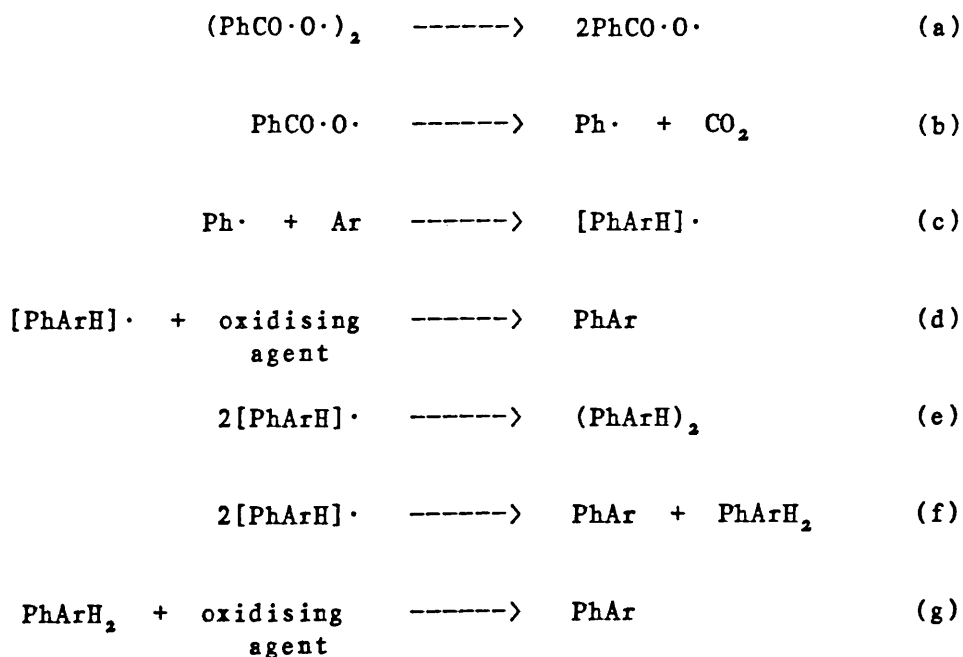
It is interesting to note that since the total yields have been evaluated in terms of the theoretical maximum yields of phenyl radicals, diversion of sigma-radicals or biaryls derived from phenyl radical attack would affect the overall yields whereas the diversion of the corresponding products derived from pyridinyl radical attack would leave the yields unaffected. Diversion of these latter products could, therefore, still lead to the high yields of phenylated derivatives observed and could lead to yields greater than 100%, as calculated on the basis of total benzoyl peroxide used (where benzene is used as a co-solvent). The formation of phenylpyridines or other detectable products containing phenyl derivatives arising from attack of pyridinyl radicals on benzene (reaction 9 and 13) will lead to an

apparent increase in yields. However, since reaction (9) is prevented by scavenging of pyridinyl radicals by pyridine-N-oxide, these complications do not arise, and the yield determined on the basis of the theoretical yield of phenyl radicals from benzoyl peroxide is still valid.

#### D.1.1.1

##### The effect of oxidising agents on the decomposition of benzoyl peroxide in pyridine.

It was held that oxidising agents such as nitro- compounds<sup>69,153</sup>, metal benzoates<sup>36,154,146</sup>, and oxygen<sup>56,58</sup>, participate in the decomposition of benzoyl peroxide in a number of aromatic solvents. In the following scheme steps (d) and (g) involve such interactions:

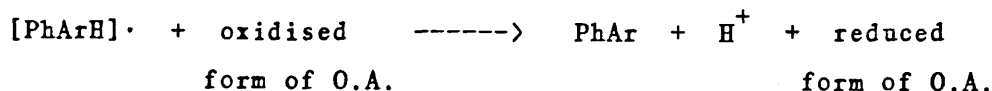


#### Scheme XVIII

\*The effect of oxygen has since been refuted in the decomposition of benzoyl peroxide in benzene<sup>57</sup>

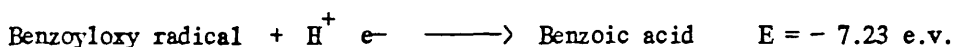
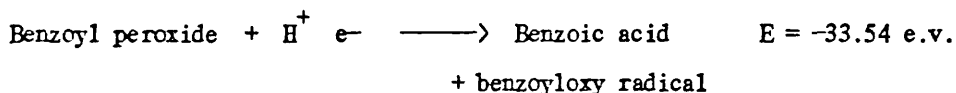
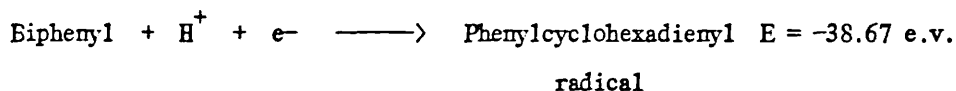
In the absence of any external agent, the oxidising agents could be benzoyl peroxide or the benzoyloxy radical<sup>60</sup>.

The stoichiometric form of step (d) is:



O.A. stands for oxidising agent

The redox potential for the half reactions involved in this step have not been determined experimentally, but the redox potentials calculated by INDO<sup>2,3</sup> methods for the biphenyl/sigma-complex and the known oxidising agents are given below:



The values obtained are absolute thermodynamically and cannot be directly compared with  $E^0$  values which are relative to the hydrogen electrode. The fact that transition metal complexes (in their oxidised form), nitro and nitroso compounds increase the yield of biphenyl in the phenylation of benzene by benzoyl peroxide, suggests that the redox potentials of these couples are lower (more positive) than that of the benzoyloxy radical / benzoic acid couple.

The values for the biaryl/sigma couple for the pyridine system have been similarly calculated. It was generally not possible to calculate the redox potentials of the oxidants normally present in these systems as their exact nature is not known, but the high yield of phenylpyridines in the decomposition of benzoyl peroxide in pyridine means that the positions of these oxidants in the redox potential table must be lower than that of the oxidants present in benzene.

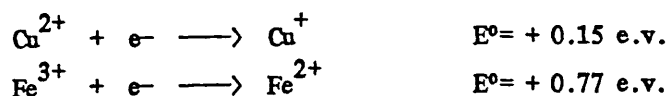
The values obtained from our calculations are given in the following table.

	4-phenylpyridine	+ H <sup>+</sup>	+ e <sup>-</sup>	→	Sigma-radical	E = -40.55 e.v.
-ve	2-phenylpyridine	+ H <sup>+</sup>	+ e <sup>-</sup>	→	Sigma-radical	E = -40.10 e.v.
	3-phenylpyridine	+ H <sup>+</sup>	+ e <sup>-</sup>	→	Sigma-radical	E = -39.58 e.v.
	biphenyl	+ H <sup>+</sup>	+ e <sup>-</sup>	→	Sigma-radical	E = -38.67 e.v.
E	benzoyl peroxide	+ H <sup>+</sup>	+ e <sup>-</sup>	→	Benzoic acid + benzoyloxy radical	E = -33.54 e.v.
+ve	benzoyloxy rad.	+ H <sup>+</sup>	+ e <sup>-</sup>	→	Benzoic acid	E = - 7.23 e.v.
	Ph <sub>2</sub> N-O·	+ H <sup>+</sup>	+ e <sup>-</sup>	→	Ph <sub>2</sub> NOH	E = + 5.98 e.v.

Table XIII

We have taken the diphenyl nitroxide as a model for the reactive species of nitro and nitroso compounds in general.

The standard electrode potentials for the Cu<sup>2+</sup>/Cu<sup>+</sup> and the Fe<sup>3+</sup>/Fe<sup>2+</sup> couples are:



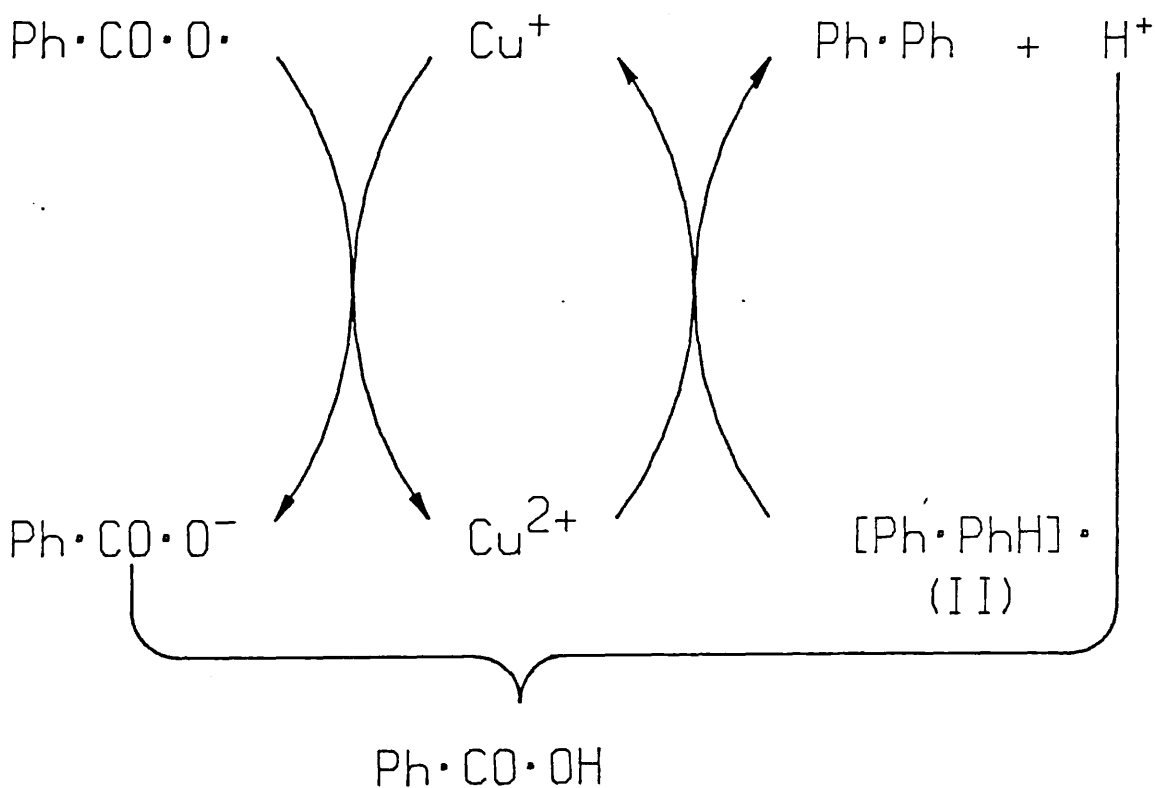


Associations between benzoyl peroxide and pyridine has previously been suggested<sup>112,60</sup>. Benzoic acid forms strong associations with pyridine under our reaction conditions<sup>66</sup>. These factors affect the redox potentials of these oxidising agents in pyridine.

D.1.1.1.1

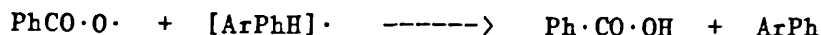
The effect of Copper(II)benzoate

Even in the absence of additives, the yield of residues is low and that of biaryls is high, so copper(II) has less scope in which to assist the oxidation of sigma-radicals to biaryls in this system. A possible mechanism applied to pyridine for the catalysis by copper<sup>72</sup> drawn by analogy to the reaction in  $(PhCO\cdot O)_{2}Pb$  is given below.

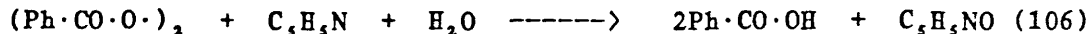


Scheme VII

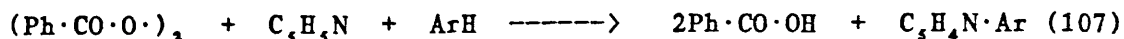
The net reaction of Scheme VII being:



Reid and Kovacic<sup>148</sup> have suggested that copper(II) complexes with benzoyloxy radicals. The complex is said to have a stabilising effect on the radical. As a result the stationary concentration of total benzoyloxy radicals (complexed and uncomplexed) increases, but that of free benzoyloxy radicals (and hence phenyl radicals) is decreased. Theoretically, a maximum of one mole of benzoic acid and one mole of biaryl can be formed from one mole of benzoyl peroxide according to Scheme XV. However, if the induced decomposition by pyridine (Scheme XVI and Scheme VIII) is considered, Scheme VIII can lead to two moles of benzoic acid per mole of benzoyl peroxide provided benzoic anhydride can be hydrolysed before the final analysis,



and Scheme XVI can lead to two moles of benzoic acid and one mole of biaryl per mole of benzoyl peroxide provided benzoyl peroxide can react with the sigma radicals before decomposing to phenyl radicals and carbon dioxide. Stabilisation of benzoyloxy radicals would reduce this decomposition.

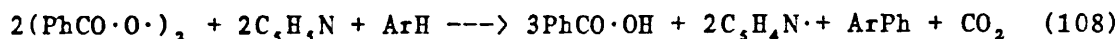


However, since pyridine-N-oxide (Section D.1.1) prevents the formation of biaryls formed by attack of pyridinyl radicals on the arenes, Scheme XVI would only yield one mole of benzoic acid and no biaryl from one mole of benzoyl peroxide. The phenyl group in the

phenylpyridines formed by Scheme XVI would of course come from the solvent and not from benzoyl peroxide.

Stabilisation of benzoyloxy radicals would increase the rates of reactions 1 and 3 but reduce the rate of reaction 4. If benzoyloxy radical was made super stable, however, there would be no biaryl formation.

It appears therefore that copper(II)benzoate aids reactions 1 and 3 but the stabilisation of benzoyloxy radicals is not sufficient to prevent its decomposition. Hence Scheme XVI becomes more important than Scheme XV in the presence of copper(II)benzoate. The benzoyloxy radical formed by reactions 1 and 3 reacts according to Scheme XV and is not involved in reactions 13 and 14. Since Scheme XVI gives a maximum yield of 1.5 moles of benzoic acid and 0.5 moles of biaryl when reactions 9 and 10 are not involved:



an overall increase of benzoic acid yield and a decrease of biaryl yield is observed in the presence of copper(II)benzoate.

#### D.1.1.1.2

##### The effect of Iron(III)benzoate.

A possible oxidative catalysis by iron(III)benzoate could follow a similar mechanism to that suggested for copper(II)benzoate (Scheme VII). However, the high yields of biaryl suggest that the oxidising agents already present in the system are well down the EMF table (more

positive values), the similarity between the  $\text{Cu}^{2+}/\text{Cu}^+$  and  $\text{Fe}^{3+}/\text{Fe}^{2+}$  couple free energies then imply that iron(III) is ineffective as a catalyst.

Gritter and Godfrey<sup>109</sup> have shown that pyridine complexes with iron, and a number of other metals showed enhanced reactivity to attack in the 4-position of pyridine in all cases (except nickel) and in the 2-position in most cases (section I.3.1.). Iron also forms complexes with phenylpyridines readily (section D.1.1) and iron dipyridyl complexes are known<sup>112</sup>.

The molecular orbital (MO) theory (Section D.16) can be used to predict the reactivities of the various positions in pyridine. In general the reactions of aromatic species will be charge- or orbital-controlled in view of the extensive interaction with the  $\pi$  - system<sup>149</sup>.

Though charge densities predict that the odd electron will attack the o-position more readily than the p-position ( $q_2=3.8212$ ,  $q_4=3.9074$ ), the coefficient for the lowest unoccupied molecular orbital (LUMO) is greater at the p-position ( $c_4=0.5619$ ) than at the o-position ( $c_2=0.3632$ ). This means that reagents which involve complexation with the  $\pi$ -system react in the p-position, whereas, reagents which experience a large Coulombic (electrostatic) interaction tend to react in the o-position (Section D.16.5).

Complexation of iron with pyridine increases the relative reactivity of the p-position in pyridine (Table XII). Similar considerations determine the almost exclusive formation of 4,4'-dipyridyl derivatives (e.g. 'paraquat') by reduction via free radicals<sup>150</sup> (or radical anions).

Position in pyridine	Coefficient of LUMO	Electron charge density	Free valence number	L.E.(E.E.) (A.U.)	L.E.(T.E.) (A.U.)
<u>ortho</u> -	0.3612	3.8212	0.4339	-107.7667	-0.6468
<u>meta</u> -	0.2139	4.0023	0.4211	-106.0592	-0.6254
<u>para</u> -	-0.5619	3.9074	0.4233	-105.7708	-0.6610

Theoretical indices of reactivity of the various positions of pyridine as calculated by INDO<sup>2,3</sup> methods.

Table XIV

L.E.(E.E.) = Localisation energy (calculated from electronic energy)

L.E.(T.E.) = Localisation energy (calculated from total energy)

Though back-donation and orbital control can account for the increased relative reactivity of the p-position in pyridine in the presence of iron(III)benzoate, they cannot explain the overall reduction in phenylpyridine yield. It is possible that by complexing with pyridine, iron competes with benzoyl peroxide for the pyridine nucleus, but since only catalytic amounts of ferric benzoate (50mg) are present, such an effect cannot have a significant effect unless the iron complexes, involving pyridine as ligands, have a high coordination number.

Since the formation of biaryls is the main source of hydrogen for the formation of benzoic acid, the reduction in the yields of biaryl is accompanied by a reduction in the yields of benzoic acid.

The localisation energy (L.E.) calculated from the difference between the sum of the total electronic energies of the phenyl radical and pyridine, and the total electronic energy of the sigma-complex corresponding to attack at a specific position, predicts the order of reactivities to be of the order 2- > 4- > 3-. When total energies are used to calculate the L.E. (as indeed they should be), the reactivity of the 3-position is predicted to be greater than that for the 4-position. The difference between these predictions is due to the greater nuclear repulsion energy in the sigma-complex corresponding to attack at the 4-position.

In previous calculations of L.E. calculations have been made on the Wheland intermediate<sup>188</sup> neglecting the nature of the attacking species. This would lead to accurate results when the attacking species is the hydrogen radical. However, when the attacking species is a species like the phenyl radical, there will be extensive  $\pi$ -overlap between the aromatic rings. The greater number of atoms in the phenyl radical will lead to both greater nuclear repulsion energies and total electronic energies (which explains the unrealistically high values for the L.E. as calculated by total electronic energies alone). This means that the difference in L.E.s will be small with respect to the total energies. The predictions will, therefore, be sensitive to the geometry used for the sigma-complex. Since this has not been established, the predictions made on the basis of L.E.s should be viewed with caution. The fact that the total energies of the sigma-complexes are lower (L.E.s are negative) than the sum of the energies of the reactants, means that our model

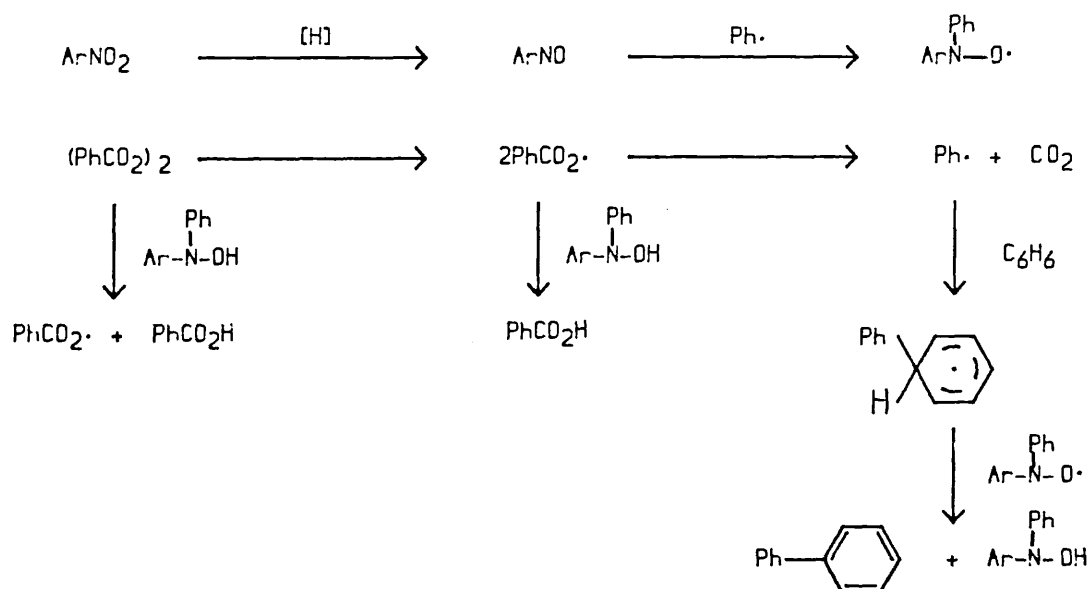
being stable with respect to the reactants, is probably close to the structure of the true 'Wheland intermediate' and not a transition state. This can be attributed to the possibility of  $\pi$  - overlap between the phenyl ring and the pyridine ring which would not have been the case if a hydrogen atom had been used in place of the phenyl radical, as had been originally suggested by Wheland<sup>118,119</sup>.

#### D.1.1.1.3 The effect of meta-dinitrobenzene

It has been suggested<sup>154</sup> that the nitro- group has to be initially reduced to the nitroso- group before it can be effective in catalysing biaryl formation.

Reduction of a small amount of nitrobenzene to nitrosobenzene (probably by phenylcyclohexadienyl radicals) and subsequent radical addition gives diphenyl nitroxide. This stable nitroxide was considered responsible for oxidising the phenylcyclohexadienyl radicals.

The suggested mode of action<sup>154</sup> in the phenylation of benzene by benzoyl peroxide is given below:



For catalysis to take place the redox potential for the nitroxide/ hydroxylamine couple must be lower than that of the biphenyl/ phenylcyclohexadienyl radical couple. This is found to be the case.

-ve	4-phenylpyridine + H <sup>+</sup> + e <sup>-</sup> → Sigma-radical	E = -40.55 e.v.
	2-phenylpyridine + H <sup>+</sup> + e <sup>-</sup> → Sigma-radical	E = -40.10 e.v.
	3-phenylpyridine + H <sup>+</sup> + e <sup>-</sup> → Sigma-radical	E = -39.58 e.v.
E	biphenyl + H <sup>+</sup> + e <sup>-</sup> → phenylcyclohexadienyl radical	E = -38.67 e.v.
	benzoyl peroxide + H <sup>+</sup> + e <sup>-</sup> → benzoic acid + benzoyloxy radical	E = -33.54 e.v.
	benzoyloxy radical + H <sup>+</sup> + e <sup>-</sup> → benzoic acid	E = - 7.23 e.v.
+ve	Ph <sub>2</sub> N-O· + H <sup>+</sup> + e <sup>-</sup> → Ph <sub>2</sub> N-OH	E = + 5.98 e.v.

Redox potential table based on total energies calculated by INDO<sup>2,3</sup> methods.

Table XIII



The Table confirms that nitroso- compounds can oxidise phenylcyclohexadienyl radicals to biphenyl, and are capable of oxidising the sigma-complexes in the pyridine system to the corresponding biaryls.

Again, the position of the oxidants normally present in the pyridine system decides whether meta-dinitrobenzene will have any effect in this system. As before, the high yield of biaryl in the absence of additives suggests that these oxidants lie lower in the redox potential table than meta-dinitrobenzene.

As a result, the yield of both biaryls and benzoic acid are largely unaffected by meta-dinitrobenzene.

#### D.1.1.1.4

##### The effect of pentafluoronitrosobenzene

The mechanism of sigma-radical oxidation is presumably the same as in the case of nitro- compounds, except of course in that the initial reduction of the nitro- compound to the nitroso- compound is no longer necessary. This should make the nitroso-group more efficient an oxidant than the nitro- group. However, the same arguments used to explain the ineffectiveness of meta-dinitrobenzene as a catalyst in this system, apply in the case of pentafluoronitrosobenzene.

Nitrosobenzene, and so, by extension, pentafluoronitrosobenzene, scavenges phenyl radicals to form aryl nitroxides<sup>173</sup>. The latter interacts with benzoyloxy radicals, and as a result, fewer benzoyloxy radicals react with benzene and more benzoic acid is formed<sup>60</sup>.

## D.1.1.1.5

Competitive reactions between benzene and pyridine in the phenylation of benzoyl peroxide in the absence of additives.

The yield of phenyl-4-methylpyridine was found<sup>60</sup> to be the same whether phenylation occurred in 4-methylpyridine, or a benzene-4-methylpyridine mixture (5:1,v/v). This suggests that benzene does not compete effectively with 4-methylpyridine for the phenyl radicals. Similarly, we have found that the yield of phenylpyridines (Table XV) arising from phenylation of mixtures of benzene and pyridine does not change as violently as the changes in the relative amounts of the two substrates suggest.

Expt. no.	Pyridine /benzene v/v	Phenyl pyridine yield**	Biphenyl yield	Rel. rate	Isomer dist.* /p.r.f.			Benzoic acid yield	Total yield (%)
					2-	3-	4-		
1-3	1/0	2.84	none	-	48.1	33.7	17.8	2.59	91.16
16-18	2/1	2.22	0.53	1.90	46.5 /2.65	35.2 /2.01	18.3 /2.07	2.39	86.09
19-21	1/1	1.69	0.81	1.89	50.8 /2.88	31.7 /1.80	17.5 /1.98	2.23	79.38
22-24	1/2	1.36	1.08	2.28	55.7 /3.81	27.8 /1.90	16.5 /2.26	2.06	75.30
25-27	0/1	-	1.46	-	-	-	-	1.77	55.15

\* percentage

\*\* (gm)

| (gm)

|| with respect to phenyl radical

The decomposition of benzoyl peroxide (5.25gm) in a mixture of benzene and pyridine (100ml) at 80°C under nitrogen for 24hr.

Table XV

Among the side reactions cited as invalidating isomer distributions and rate factors, the main ones are reactions of the arylcyclohexadienyl radicals which do not yield biaryls. It has been shown that in the phenylation of 4-methylpyridine such reactions can be selective<sup>60</sup>, the workers suggest that to avoid this source of error an efficient oxidising agent should be added to benzoyl peroxide at least in the case of pyridine derivatives. They have also observed such selective side reactions in the phenylation of quinoxaline and methoxypyridines. This disagrees with the work of Morrison and Cazes<sup>58</sup> but is in accordance with results on the reaction of benzoyl peroxide with anisole<sup>159</sup>. Therefore, the conclusions of reference 58 do not apply to all substrates. We however, have clearly shown (Table XII) that the oxidants normally present in the pyridine system is efficient in oxidising the sigma-radicals and lead to high yields of biaryls.

In experiments 16 to 24 in Table XV the isomer distribution of the phenylpyridines changes towards an increase of the ortho-isomer as the amount of benzene is increased.

As the amount of benzene is increased, the concentration of the sigma — complexes derived from pyridine decreases, while the concentration of available oxygen remains the same (the solubility of oxygen in benzene and pyridine are similar<sup>160</sup>). It is currently believed that oxygen does not increase the yield of biphenyl in the decomposition of benzoyl peroxide in benzene<sup>57</sup>. It is also believed that in the decomposition of benzoyl peroxide in 4-methylpyridine, oxygen does catalyse the oxidation of sigma-complexes to biaryls<sup>60</sup>. If a similar catalytic effect exists in pyridine, the greater ratio of oxygen to sigma-complexes derived from pyridine in reactions involving high benzene to pyridine ratios would account for the increase in the

relative rate of phenylation of pyridine with respect to benzene. However, the fact that other known oxidants, e.g., ferric and cupric benzoates and nitro- and nitroso-compounds, are known to be less effective in pyridine than in benzene argues against this mechanism.

Side reactions involved in the formation of biaryls from sigma-complexes derived from 4-methylpyridine are known to be selective<sup>60</sup>. It has been suggested that this could be due to the increased rate of oxidation of sigma-complexes involving delocalisation of the odd electron on the nitrogen atom.

In the case of pyridine this would increase the yields of the 2- and the 4-phenylpyridines preferentially, resulting in an increase in their isomer ratios relative to the meta-isomer and also the relative rate of phenylation of pyridine with respect to benzene ( $K_{\text{benzene}}^{\text{pyridine}}$ ).

Another cause for the change in relative rates and isomer distribution could be due to steric reasons<sup>161</sup>. Nitrogen-nitrogen interactions are present in pyridine solutions. This could cause a steric hindrance for attack at the ortho-position. These interactions are reduced as the amount of benzene is increased, leading to an increase in both the relative rate of formation and the percentage yield of the 2-phenylpyridine.

A detailed study of the addition step in the phenylation of pyridine has not been done, but it is known that the addition step in the alkylation of pyridine is reversible<sup>163</sup> when t-butylperoxide is used as the source of methyl radicals. If the addition step in the

phenylation of pyridine was reversible then the ortho-isomer would be more likely to dissociate<sup>44</sup> than the meta- and para- isomers. Steric factors involving N-N interactions (Section D.15) would aid the dissociation at low benzene to pyridine ratios, the effect would be relieved at high benzene to pyridine ratios. The fact that the isomer ratio for the 2-isomer increases at the cost of both the 3-, and the 4- isomer suggests that the steric factor is more important than the selective oxidation by available oxygen.

The yield of benzoic acid decreases as the amount of benzene is increased. Two factors contribute to this change.  $K_{\text{benzene}}^{\text{pyridine}} > 1$ , therefore, greater benzene / pyridine ratios will lead to lower biaryl yields, and hence, a decrease in the availability of (H·) (from sigma-radical oxidation) required for the formation of benzoic acid. Higher benzene / pyridine ratios will increase the relative importance of Scheme XV over Scheme XVI. As Scheme XV can yield a maximum of one mole of benzoic acid per mole of benzoyl peroxide, and Scheme XVI can yield 1.5 moles of benzoic acid per mole of benzoyl peroxide, this will lead to reduced benzoic acid yields.

#### D.1.1.1.6

##### Competition between benzene and pyridine in the phenylation of benzoyl peroxide in the presence of Cu(II)benzoate.

The reasons for the small, but definite, increase in the ratio of the 2-, to the 3- and 4-phenylpyridines, as the benzene to pyridine ratio is increased, in the presence of copper(II) (Table XVI), are probably the same as those in the absence of copper(II) (experiments 31-33 do not fit in with this trend).

Expt. no.	Pyridine /benzene v/v	Phenyl pyridine yield**	Biphenyl yield	Rel. rate	Isomer dist.* /p.r.f.	Benzoic acid yield	Total yield (%)
4-6	1/0	2.10	none	-	47.1 34.6 18.3	3.36	94.7
28-30	2/1	1.72	0.56	1.39	48.5 33.1 18.4 /2.03 /1.47 /1.66	3.03	91.2
31-33	1/1	1.43	0.95	1.36	43.6 35.9 20.5 /1.78 /1.47 /1.66	2.70	86.5
34-36	1/2	1.09	1.23	1.60	52.7 30.5 16.8 /2.53 /1.46 /1.61	2.54	82.6
37-39	0/1	-	1.52	-	- - -	2.49	69.8

\* percentage

\*\* (gm)

| (gm)

|| with respect to phenyl radical

The decomposition of benzoyl peroxide (5.25gm) in a mixture of benzene and pyridine (100ml) at 80°C under nitrogen for 24hr. Copper(II)benzoate (30mg) was added.

Table XVI

The catalytic effect of copper(II) on the phenylation of benzene has previously been shown (Section D.1.1.1.) to be greater than that in the phenylation of pyridine. Consequently, the relative rates for phenylation of pyridine are lower in the presence of copper(II)benzoate.

Previous workers<sup>60</sup> had found that the observed change in isomer ratios with change in benzene/pyridine ratio was eliminated in the presence of Cu(II)benzoate, though in a reduced form.

Since copper(II) increases the yield of benzoic acid in the phenylation of both benzene<sup>154</sup> and pyridine (Table XV) by benzoyl peroxide, the increased benzoic acid yields obtained when copper(II) is added to mixtures of benzene and pyridine is not surprising.

The above explanations are probably an oversimplification. The solvent effect upon the equilibrium constant for the copper(II)-pyridine complex is not known. Since copper(II) complexes with both benzoyloxy radicals<sup>148</sup> and pyridine<sup>109</sup>, there may be competition between benzoyloxy radicals and pyridine for copper(II). In the phenylation of 4-methylpyridine by benzoyl peroxide, the total yield of biaryl is increased when nitrobenzene is added to mixtures of 4-methylpyridine and benzene. However this is not the case when no benzene is added to 4-methylpyridine. In this case nitrobenzene does not increase the oxidation of the sigma-complexes, but competes with 4-methylpyridine for phenyl radicals so that the yield of methylphenylpyridines is lower. Such complexities make it difficult to explain the results of experiments 31-33, where the percentage of the ortho-isomer is lower than that obtained in both higher (experiments 28-30), and lower (experiments 34-36) pyridine to benzene ratios.

The results obtained in the phenylation of pyridine are in complete contrast to the effects observed in the phenylation of substituted benzenes by benzoyl peroxide, where the use of catalysts increased the ortho-yield. The following reason has been suggested for the increased ortho-yields obtained in substituted benzenes.

It is expected, on steric grounds, that the ortho-substituted phenylcyclohexadienyl radical has a greater tendency to dissociate than the other isomers. The catalyst, by removing the sigma-complex prevents the backward reaction. This argument would of course not apply in our system as copper(II) is not found to be an effective oxidant in pyridine.

## D.2

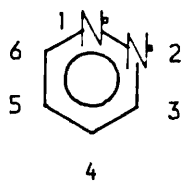
### The decomposition of benzoyl peroxide in pyridazine.

The relative rate of attack of phenyl radicals on the pyridazine molecule (Table XIX) is in general greater than that for pyridine (Table XVIII), however, the relative rate changes with both changes in the benzene to pyridazine ratio and changes in the initial peroxide concentration.

The biaryl fraction consists of almost entirely (>99.97%) 4-phenylpyridazine. 3-phenylpyridazine (upto ~ 0.03%) was detected, but changes in the yield of this isomer could not be accurately determined.

Theoretical predictions give conflicting predictions for pyridazine. Whereas Davies' calculations<sup>100</sup> show the 4-position to be the most favoured point of attack on the basis of free valence numbers, the calculations show the 3-position to be the most favoured point of attack on the basis of electron charge densities.



	r	q <sub>r</sub> a	pr <sub>s</sub> b	F <sub>r</sub> c
	1	1.132	0.638	0.103
	2		0.673	
	3	0.932	0.655	0.086
	4	0.936	0.671	0.088

r = position in pyridazine.

q<sub>r</sub> = charge density at atom r.

pr<sub>s</sub> = bond order between the r and s atoms, s being adjacent to r in a clockwise direction round the ring.

F<sub>r</sub>c = free valency at the atom r.

Theoretical indices of reactivity as calculated by Davies<sup>100</sup>

Table XVII

Our own INDO<sup>233</sup> and CNDO<sup>232</sup> calculations (appendix) are consistent in predicting the 3-position to be the more favoured point of attack according to free valence numbers, charge densities and localisation energies (calculated on the basis of total electronic energies, when the nuclear repulsion energy is taken into consideration, the 4-position is predicted to be the most reactive). However, the LUMO for pyridazine has a greater coefficient at the 4-position (0.4120) than at the 3-position. As in the case of pyridine (Section D.1.1.2), where complexation with iron(III) leads to reactivities determined by orbital control, the reactivities observed in pyridazine appear to be orbital controlled rather than charge controlled (Section D.16.6).

r	qr	Fr	c	L.E.(E.E.) (A.U.)	L.E.(T.E.) (A.U.)
3	3.8638	0.4282	0.1565	-116.1078	-0.6674
4	3.9522	0.4211	0.4120	-115.5466	-0.7129

r = position on pyridazine

qr = electron charge density

c = coefficient of LMO for pyridazine on atom r

L.E.(E.E.) = Localisation energy (calculated from total electronic energy)

L.E.(T.E.) = Localisation energy (calculated from total energy)

Theoretical indices of reactivity as calculated by INDO<sup>233</sup> methods.

Table XVIII

One possible cause for this discrepancy could be the selective diversion of the sigma-complex formed by attack at the 3-position to side products at a much greater rate than the corresponding reactions of the 4-isomer. There is no evidence for this.

Though pyridazine is known to undergo ring opening reactions in alkaline medium, 3-phenylpyridazine is stable under our reaction conditions (due to the small amount of 3-phenylpyridazine available, errors of upto  $\pm 15\%$  are possible in our determination of stability, i.e. no more than 15% of the total 3-phenylpyridazine will have been destroyed during the analytical process,).

Another possible reason for the difference between the theoretical predictions and the experimental findings is in the possible inaccuracy of the model used for the calculations. The model

used is an isolated pyridazine molecule (the sigma-complex in the case of localisation energy calculations). Such a model is adequate for evaluating intramolecular interactions but cannot take into account intermolecular interactions.

It has been suggested<sup>64</sup> that pyridazine exists as dimers, though this has since been contested<sup>65</sup>, there is still evidence for the existence of strong N-N interactions (Section D.15) in pyridazine. These interactions could cause changes in the electronic structure of the pyridazine molecule in solution and also cause some steric hindrance to attack at the 3-position. However, models based on pyridazine dimers also predict the 3-position to be more reactive than the 4-position on the basis of free valence numbers and electron charge densities, but again the coefficients of the LUMO predict attack at predominately the 4-position. The differences between the coefficients are much more exaggerated in this case. The coefficient for the 4-position (0.3383) in the pyridazine dimer is in fact less than that of the 4-position in pyridazine (0.4120), but the coefficient for the 3-position in the dimer (0.0036) is very much lower than the coefficient for the 3-position in pyridazine (0.1565).

Using the additivity principle suggested by Williams<sup>57</sup> we can (using the partial rate factors from experiments 19-21) calculate the expected partial rate factors of the 3- and the 4- positions of pyridazine to be 5.18 and 3.56 respectively. The relative rate of phenylation of pyridazine with respect to benzene would be 2.92.

Expt. no.	Additive (5mg)	4-Phenyl pyridazine yield (mg)	Biphenyl yield (mg)	Rel. rate	Partial rate factor	Benzoic acid yield*	Ester yield (mg)	Total yield (%)
40-42	None	32.94	96.15	1.73	5.20	74.50	13.50	52.3
43-45	Copper*	24.89	94.20	1.34	4.02	82.78	10.12	51.9
46-48	Iron**	28.62	112.25	1.29	3.86	62.80	8.50	50.8
49-51	M.D.B.	23.78	110.69	1.08	3.24	50.26	10.54	46.2
52-54	P.F.N.B.	35.86	102.41	1.77	5.32	46.65	12.24	46.3

\* (mg), | with respect to phenyl radical,

The decomposition of benzoyl peroxide (0.35gm) in a mixture of pyridazine (1gm) and benzene (5gm), at 80°C, under nitrogen. In experiments 43-54, 5mg of additives were used.

Table XIX

Though the relative rates observed in Table XIX are lower than this predicted value, this is largely due to the greatly reduced reactivity of the 3-position since the reactivity of the 4-position is in fact, greater than that predicted by the additivity rule. The reactivity of the 3-position of pyridazine is therefore a special case where some significant factor, other than those normally encountered in the phenylation of aromatic compounds, is involved.

## D.2.1

The effect of additives on the decomposition of benzoyl peroxide in pyridazine.

None of the catalysts have a significant effect in these reactions. In fact, the highest total yield is obtained in the uncatalysed experiment. The biaryl yield is slightly increased in the presence of pentafluoronitrosobenzene, though the total yield is lower than that obtained for benzene alone.

In contrast to the pyridine reactions there were a number of products formed in the phenylation of pyridazine. Not all the peaks obtained by g.l.c. could be identified. On saponification with sodium carbonate, two of the peaks disappeared. These peaks were attributed to esters.

Pyridazine is considerably more polar than pyridine, the retention times obtained by g.l.c. for pyridazine and its derivatives under our conditions are considerably greater than those obtained for the corresponding derivatives of pyridine, pyrazine or pyrimidine. Products like pyridazine dimers could easily escape detection by the methods employed. The yield of detectable products therefore does not represent the total reaction. The low reactivity of the 3-position could also contribute towards the low yields obtained.

Due to economic considerations relatively large amounts of benzene (benzene to pyridazine ratio ~5:1) were present in all the reaction mixtures. The phenylation of benzene affords much lower yields of phenylated aromatic products than is obtained in the aromatic heterocycles. As a result the reaction mixtures gave low overall yields.

-ve	4-phenylpyridazine	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma-complex	E = -41.85 e.v.
	3-phenylpyridazine	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma-complex	E = -40.48 e.v.
	biphenyl	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma-complex	E = -38.67 e.v.
E	benzoyl peroxide	+ H <sup>+</sup> + e <sup>-</sup>	→ benzoic acid + benzoyloxy radical	E = -33.54 e.v.
+ve	benzoyloxy radical	+ H <sup>+</sup> + e <sup>-</sup>	→ benzoic acid	E = - 7.23 e.v.
		Cu <sup>2+</sup> + e <sup>-</sup>	→ Cu <sup>+</sup>	E° = +0.15 e.v.
		Fe <sup>3+</sup> + e <sup>-</sup>	→ Fe <sup>2+</sup>	E° = +0.77 e.v.
		Ph <sub>2</sub> N-O· + H <sup>+</sup> + e <sup>-</sup>	→ Ph <sub>2</sub> N-OH	E = + 5.98 e.v.

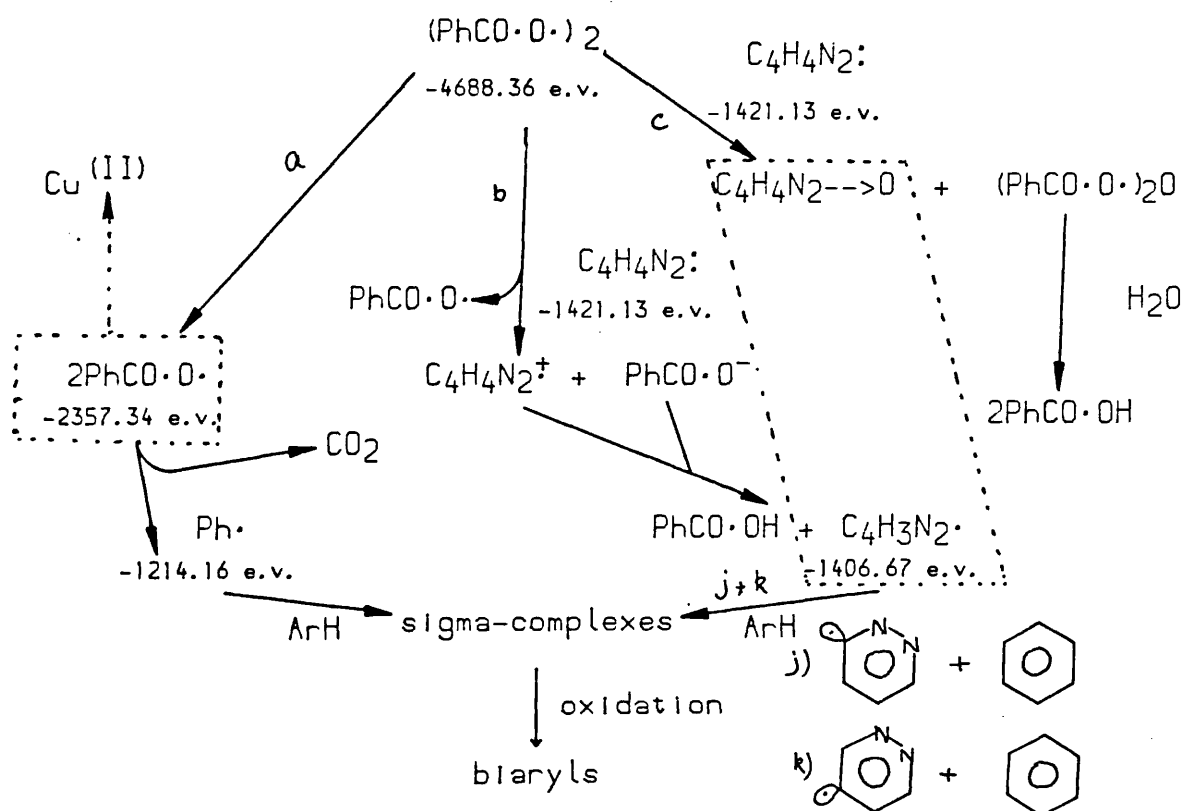
Table XX

The redox potentials of some intermediates in homolytic phenylation

The effective oxidants present in the pyridazine system must have a redox potential greater (more positive) than  $-40.48\text{e.v.}$ . Since the additives fail to enhance the biaryl yield despite the overall yield being low the effective oxidants must have a redox potential greater than  $+5.98\text{e.v.}$

#### D.2.1.1 The effect of copper(II)benzoate.

The yield of benzoic acid is increased in the presence of copper(II)benzoate. A mechanism for the decomposition of benzoyl peroxide in pyridazine similar to that obtained for pyridine (Scheme XVII) can be postulated.



The decomposition of benzoyl peroxide in mixtures of pyridazine and benzene

Scheme XIX

As in the case of pyridine, nitroxides or products thereof, formed by this mechanism could go undetected. The large number of unidentifiable products, and the low yields of products attributable to attack by phenyl radicals mean that large amounts of bipyridazinyls could also be present in the system. The residue obtained by reduced pressure distillation of the basic fraction gave, on carbon analysis 68% carbon, 27% nitrogen and 5% hydrogen which would allow some pyridazine dimer or its reduced form to be present in the residue. However, if reaction (k) takes place, reaction (j) should also take place. This would lead to higher yields of 3-phenylpyridazine. It is assumed therefore, that trapping of pyridazinyl radicals by pyridazine-N-oxide is efficient in pyridazine and does not allow pyridazinyl radicals to form biaryls. As in the case of pyridine (section D.1.1.1.) copper, by diverting benzoyloxy radicals would increase the stationary concentration of benzoyloxy radicals and eventually lead to increased benzoic acid yields and to reduced phenylpyridazine yields.

#### D.2.1.2 The effect of iron(III)benzoate.

Though the absolute yield of phenylpyridazines in the presence of iron(III)benzoate is greater than that obtained for copper(II)benzoate, the biphenyl yield is increased to a greater extent than the phenylpyridazine yield thereby decreasing  $K_{\text{benzene}}^{\text{pyridazine}}$ . According to Table XXI iron(III)benzoate will not be effective as an oxidant in this system. The back donation of electrons towards iron should be higher for the diazines than for pyridine<sup>166</sup>, but since very little 3-phenylpyridazine is formed, a change in isomer distribution cannot be detected.



The reduced yields of benzoic acid, in the presence of iron(III)benzoate, is unexpected since the phenylpyridazine yields are increased. It is possible that the hydrogen abstraction from sigma-radicals is effected by species other than the benzoyloxy radical in this case. After all, on the basis of its position in the redox potential table, better electron acceptors than benzoyloxy radical are present in the system. However, on the basis of the results of all other experiments where the yield of benzoic acid is generally accompanied by high biaryl yields, this appears unlikely.

#### D.2.1.3 The effect of meta-dinitrobenzene.

Nitrobenzene competes with 4-methylpyridine for phenyl radicals<sup>60</sup>. Meta-dinitrobenzene may have a similar effect in the phenylation of pyridazine, and certainly the yield of phenylpyridazine is considerably lowered in the presence of meta-dinitrobenzene. The reduction in yield of phenylpyridazines can theoretically be accounted for by  $2.90 \times 10^{-2}$  mmoles of benzoyl peroxide. Since about  $2.98 \times 10^{-2}$  mmoles of meta-dinitrobenzene is present in the system, this could satisfactorily account for the change in yield observed.

The reduced yield of phenylpyridazine partially contributes towards the reduction of benzoic acid yield, though free meta-dinitrobenzene should catalyse the formation of benzoic acid in benzene, its involvement in competition with phenyl radicals will prevent the normal catalytic activities demonstrated in benzene.

#### D.2.1.4 The effect of pentafluoronitrosobenzene.

The effect observed is the opposite to what was observed in the case of pyridine, where, the biaryl yield was decreased and the benzoic acid yield increased. In the case of pyridazine, the yield of biaryls is slightly increased but there is a significant drop in the yield of benzoic acid ( Table XIX).

Nitrosobenzene is known to scavenge phenyl radicals to form diphenyl nitroxide<sup>175</sup>, whether pentafluoronitrosobenzene has a similar effect on benzoyloxy radicals is not known. Of the additives studied, pentafluoronitrosobenzene is the most efficient oxidising agent (Table XX). The low yields obtained in the phenylation of pyridazine, by benzoyl peroxide, suggest that the oxidants normally operative in this system have a redox potential only slightly greater than +5.98e.v., pentafluoronitrosobenzene, therefore, could still be important in the electron transfer chain, and divert electrons from the benzoyloxy radical to the effective oxidants in the system.

#### D.2.2

#### Competition between benzene and pyridazine on phenylation by benzoyl peroxide.

The results in Table XXI are consistent with two separate trends. (a) The relative rate increases when the concentration of peroxide is decreased (experiments 58-60 and 61-63). (b) The relative rate decreases with an increase in the benzene/pyridazine ratio (experiments 61-63 and 64-65).

Comparison between the other sets of experiments is not as simple because more than one change (peroxide concentration and benzene/pyridazine ratio) might have been made, but the trends confirm the above observation.

Expt. no.	Solvent ratio* w/w	4-Phenyl pyridazine yield (mg)	Biphenyl yield (mg)	Rel. rate	Partial rate factor	Benzoic acid yield	Ester yield (mg)	Total yield (%)
55-57	0.5/2.5	31.08	78.36	2.14	6.42	85.34	5.73	51.0
58-60	0.5/5.0	17.73	129.30	1.39	4.17	80.43	4.76	56.7
61-63	0.5/5.0	13.46	54.61	2.48	7.44	67.41	6.60	73.1
64-66	0.5/10.0	7.34	179.33	0.83	2.49	48.49	25.23	56.6
67-69	0/0.6	-	94.25	-	-	76.20	5.61	43.7

\* pyridazine/benzene, | (mg), || with respect to phenyl radical, Only 0.167gm of benzoyl peroxide was used in experiments 61-63.

The decomposition of benzoyl peroxide (0.35gm) in mixtures of benzene and pyridazine, in varying molar ratios, under nitrogen at 80°C.

Table XXI

Benzoyl peroxide is known to form complexes with tertiary amines<sup>113,114</sup>. It has been suggested that the change in relative rate, observed when pyridine is phenylated by benzenediazonium tetrafluoroborate, is due to complexation of pyridine with the arylating agent. The complex has a greater reactivity than the free heterocycle, since the concentration of the complex is greater when the concentration of arylating agent is greater, the relative rate of phenylation of the heterocycle with respect to the rate of phenylation of benzene, will increase as the concentration of the arylating agent is increased. A similar mechanism may be operating in this system.

The yield of biphenyl in the decomposition of benzoyl peroxide in benzene (80°C), maximises at a peroxide concentration of about 0.12M<sup>65</sup>. If the yield of phenylpyridazine in benzene-pyridazine mixtures used maximises at a concentration higher than the concentration at which the yield of biphenyl maximises, then  $K_{\text{benzene}}^{\text{pyridazine}}$  will increase as the concentration of phenylating agent increases, from the optimising concentration for benzene, to the optimising concentration for pyridazine.

We have already shown that the coefficient of the LUMO of the carbon atoms in the pyridazine dimer is almost entirely on the position corresponding to the 4-position of pyridazine. Since no discrete dimer is present, the association probably involves loose  $\pi - \pi$  overlap. Such an overlap would increase the extent of orbital control (Section D.16.6) in the reaction, and increase the reactivity of 4- and 4-' positions of the dimer relative to the 4-position in pyridazine. As more benzene is added, this association would decrease (there would still be considerable association since the yield of 3-phenylpyridazine is still negligible), leading to reduced reactivity and reduced relative rates of phenylation.

The yield of benzoic acid decreases as (a) the initial concentration of peroxide decreases and (b) the ratio of pyridazine/benzene decreases. As the benzoyl peroxide concentration is decreased, the concentration of benzoyloxy radicals will also decrease, leading to lower absolute yields of benzoic acid. However, as the benzoyl peroxide concentration decreases, the ratio of peroxide to heterocycle will decrease. Reactions (b) and (c), will therefore, increase with respect to reaction (a). This will lead to the higher benzoic acid yields, with respect to benzoyl peroxide, observed.

## D.2.3

Competition between pyridazine and benzene for phenyl radicals in the presence of copper(II)benzoate.

Expt. no.	Pyridazine /benzene w/w	4-Phenyl pyridazine yield (mg)	Biphenyl yield (mg)	Rel. rate	Partial rate factor	Benzoic acid yield*	Ester yield (mg)	Total yield (%)**
70-72	1/2.5	33.24	54.74	1.54	4.62	86.89	8.23	45.7
73-75	0.5/2.5	29.89	80.07	1.89	5.67	86.83	2.23	49.6
76-78	0.5/2.5	15.42	45.38	1.72	5.16	69.23	1.93	67.2
43-45	1/5.0	24.89	94.20	1.34	4.02	23.47	10.12	51.9
79-81	1/10.0	8.57	157.03	0.55	1.66	56.97	2.32	53.6

\* (mg)

\*\* with respect to phenyl radical

Only 0.175gm of benzoyl peroxide was used in experiments 76-78.

The decomposition of benzoyl peroxide (0.35gm) in mixtures of benzene and pyridazine under nitrogen at 80°C. Copper(II)benzoate(5mg) was added.

Table XXII

There are no marked differences between the results obtained in the absence of copper and those in the presence of copper. The trends observed in Table XXI can also be found in Table XXII.

The effect of change of peroxide concentration (experiments 73-75 and 76-78), and change of benzene to pyridazine ratio (experiments 76-78 and 43-45), are not as drastic in the presence of copper(II)-benzoate.

The only experiments that can be directly compared, are experiments 55-57 in Table XXI and experiments 73-75 in Table XXII. As in the case of pyridine, the inclusion of copper(II)benzoate results in a decrease in the relative rate of phenylation of pyridazine with respect to benzene. This is because copper(II)benzoate is an effective catalyst in the phenylation of benzene but an ineffective catalyst in pyridazine. Hence, only the yield of biphenyl will be increased in the presence of copper(II)benzoate, leading to reduction of  $K_{\text{pyridazine/benzene}}$ .

Since copper complexes with pyridazine<sup>174</sup>, it will compete with benzoyl peroxide for pyridazine, the concentration of benzoyl peroxide-pyridazine complex will, therefore, be lower in experiments where copper has been added. The change in relative rates directly attributable to this complexation, between benzoyl peroxide and pyridazine (Section D.2.2), will also be lower.

Since copper(II) already gives higher yields of benzoic acid than in the uncatalysed experiments (experiments 43-45), reduction of benzoyl peroxide concentrations does not increase the yield of benzoic acid, with respect to peroxide concentration, as much as in the absence of copper(II).

The change in relative rates with increased relative amount of benzene and heterocyclic compound differs for pyridine and pyridazine. We have earlier (Section D.2) suggested that N-N interactions are present in both pyridine and pyridazine and cause steric hindrance to attack at the position ortho- to nitrogen in both these heterocycles. As the benzene/heterocycle ratio is increased, the relative amounts of such dimeric species will fall in both cases, thereby facilitating attack at the ortho-position. However, since the partial rate factor at the 2-position is high in pyridine, and the partial rate factor in the 3-position is minute in pyridazine, this decrease causes an increase in relative rate in pyridine, but not in pyridazine.

On this basis, an increase in the benzene/heterocycle ratio increases the relative rate only in the cases where the position ortho- to nitrogen is readily attacked but not in other cases.

### D.3

#### The decomposition of benzoyl peroxide in pyrazine.

##### D.3.1

#### Theoretical predictions for the reactivity of pyrazine.

Due to the symmetry in the pyrazine molecule, all the carbon atoms in the molecule are equivalent. The reactivity parameters calculated by INDO<sup>233</sup> methods predict a partial rate factor for each of the positions in pyrazine similar to the partial rate factor for the 2-position of pyridine.

Free valence	=	0.4313
Total Charge Density	=	3.8685
Coefficient for LUMO	=	0.2948
Localisation energy (Elec. En.)	=	-114.1992 A.U.
Localisation energy (Tot. En.)	=	-0.6884 A.U.

Table XXIII

Reactivity of pyrazine as calculated by INDO<sup>233</sup> methods.

## D.3.2

The effect of additives in the decomposition of benzoyl peroxide in pyrazine.

Pyrazine is a much weaker base than pyridine<sup>155</sup> and normally behaves as a monoacidic base<sup>157</sup>.

On the basis of additivity (Section D.2),  $K_{\text{pyrazine benzene}}$  should be 3.46.

Expt. no.	Additive (5mg)	Phenyl pyrazine yield (mg)	Biphenyl yield (mg)	Rel. rate	Partial rate factor	Benzoic acid yield	Ester yield (mg)	Total yield (%)
82-84	none	93.60	74.15	6.40	9.6	76.00	19.72	62.4
85-87	Copper*	115.52	85.77	6.82	10.23	102.59	3.3	74.7
88-90	Iron**	86.89	73.97	5.95	8.93	73.23	7.78	57.9
91-93	M.D.B.†	93.68	75.65	6.28	9.42	84.50	3.6	59.4
94-96	P.F.N.B.‡	77.28	73.87	5.29	7.94	79.23	3.71	54.6

Benzoyl peroxide (0.35gm) was decomposed in mixtures of benzene(2.5gm) and pyrazine(0.5gm), under nitrogen at 80°C. Experiments 85-96 had additives (5mg).

| (mg), || with respect to phenyl radical, \* copper(II)benzoate, \*\* ferric benzoate, † meta-dinitrobenzene, ‡ pentafluronitrosobenzene,

Table XXIV



The relative rates observed in Table XXIV are higher than those predicted by the additivity rule.

The ratio of pyrazine to benzene (1:5) in these experiments is less than that used with pyridine. Since benzene competes ineffectively with 4-methylpyridine (Section D.1.1.1.5), the yield of biphenyl will not be as high as the benzene to pyrazine ratio suggests. This will lead to higher apparent relative rates. The increase in relative rates obtained are however much higher than those obtained in the case of pyridazine. However, the surprisingly low reactivity of the 3-position of pyridazine makes it a special case, the partial rate factor of the 4-position of pyridazine is higher than the predicted value by a similar amount to that observed in pyrazine.

Since the yields of biaryl and benzoic acid in pyrazine and benzene mixtures are higher than that obtained in pure benzene. There must be oxidising agents present in this system which are more efficient than the oxidising agents present in benzene. The redox potential of the sigma radical/phenylpyrazine couple can be compared to that of the known oxidants present in the system (Table XXV).

	phenylpyrazine	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma complex	E = -41.33 e.v.
-ve	biphenyl	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma complex	E = -38.67 e.v.
E	benzoyl peroxide	+ H <sup>+</sup> + e <sup>-</sup>	→ benzoic acid + benzoyloxy radical	E = -33.54 e.v.
+ve	benzoyloxy radical	+ H <sup>+</sup> + e <sup>-</sup>	→ benzoic acid	E = - 7.23 e.v.
	Ph <sub>2</sub> N-O·	+ H <sup>+</sup> + e <sup>-</sup>	→ Ph <sub>2</sub> N-OH	E = + 5.98 e.v.
	Cu <sup>2+</sup>	+ e <sup>-</sup>	→ Cu <sup>+</sup>	E <sup>0</sup> = +0.15 e.v.
	Fe <sup>3+</sup>	+ e <sup>-</sup>	→ Fe <sup>2+</sup>	E <sup>0</sup> = +0.77 e.v.

Table XXVI

Since the additives [except copper(II)] are not effective in increasing biaryl yields the effective oxidants must have a redox potential higher than +5.98 e.v.

The redox potentials of the  $\text{Cu}^{2+}/\text{Cu}^+$  and the  $\text{Fe}^{3+}/\text{Fe}^{2+}$  couples cannot be directly compared with the redox potentials for the other couples given in the table (Section D.1.1.1). The values given are relative to the hydrogen electrode and relate to specific aqueous solutions of copper ions. If the increased phenylpyrazine yield in the presence of copper(II)benzoate is due to the additive oxidising the corresponding sigma complexes more efficiently than the oxidants normally present in the system, then the position of the  $\text{Cu}^{2+}/\text{Cu}^+$  couple in our system will be more positive than that of the normal oxidants.

#### D.3.2.1 The Effect of Copper(II)benzoate.

Copper(II)benzoate is the only additive that increases the yields of biaryls. Since copper(II)benzoate is ineffective in catalysing the oxidation of other heterocyclic sigma complexes to their corresponding biaryls (Tables XII and XIX) it appears that in the presence of pyrazine, the  $\text{Cu}^{2+}/\text{Cu}^+$  couple (probably complexed to pyrazine in some form) has a higher redox potential than in the other systems. The phenylpyridazine/sigma complex couple must have a redox potential which is intermediate between +5.98 e.v. and the value of the  $\text{Cu}^{2+}/\text{Cu}^+$  couple. However, whether their relative positions is due to an unusually positive value of the  $\text{Cu}^{2+}/\text{Cu}^+$  couple in this case or the unusually negative value of the pyrazine/sigma complex is not known.

Copper generally forms yellow or orange complexes with pyrazine<sup>174</sup>, but copper(II)benzoate dissolved partially in experiments 85-87 to give a blue colour very similar to the colour obtained when it is dissolved in benzene.

The increased yields of benzoic acid in the presence of copper(II)benzoate is again due to complexation of copper(II) with benzoyloxy radicals (Sections D.1.1.1.1 and D.2.1.1).

#### D.3.2.2 The effect of iron(II)benzoate.

Iron(II)benzoate is ineffective as an oxidant in this system. As in the case of pyridine and pyridazine, iron(II)benzoate reduces the benzoic acid yields. Back donation of  $\pi$ -electrons from pyrazine to iron will be greater for pyrazine than for pyridine. As in the case of pyridine (Section D.1.1.1.2), iron(II) may compete with benzoyl peroxide for pyrazine. This will reduce the yield of phenylpyrazine and hence the yield of benzoic acid.

#### D.3.2.3 The effect of meta-dinitrobenzene.

Meta-dinitrobenzene is ineffective as a catalyst in this system.

#### D.3.2.4 The effect of pentafluoronitrosobenzene.

Nitrosobenzene, and by extension pentafluoronitrosobenzene, scavenges phenyl radicals to form diphenylnitroxide (diphenylpentafluoronitroxide in the latter case). Diphenylnitroxide interacts with benzoyloxy radicals leading to increased benzoic acid yields at the expense of both biaryls and esters.

All the additives reduce the formation of esters. Whether this is due to a reduced formation of esters, or increased side reactions of the esters is not known.

## D.3.3

Competition between pyrazine and benzene in their phenylation by benzoyl peroxide.

Two trends are apparent in these reactions.

Expt. no.	Pyrazine /Benzene mMol/mMol	Phenyl pyrazine yield (mg)	Biphenyl yield (mg)	Rel. rate	Partial rate factor	Benzoic acid yield	Ester yield (mg)	Total yield (%)
82-84	6.25/64.1	93.60	74.15	6.40	9.6	76.00	19.72	62.4
97-99	"	67.73	107.27	6.48	9.72	62.74	10.29	58.6
100-102*	"	30.05	58.63	5.28	7.92	57.16	19.93	83.8
103-105	6.25/128.21	44.39	121.77	7.39	11.09	38.04	12.40	50.2
67-69	0/76.92	-	94.25	-	-	76.20	5.60	43.7

| (mg), || with respect to phenyl radical,

\* 0.167gm of benzoyl peroxide were used in these experiments,

The decomposition of benzoyl peroxide (0.35gm) in mixtures of benzene and pyrazine (in varying molar ratios,) under nitrogen at 80°C for 24hrs.

Table XXVII

(a) The relative rate decreases as the initial concentration of peroxide decreases (experiments 97-99 and 100-102).

Benzoyl peroxide can form complexes with pyrazine (Section D.2.2).

As the concentration of the peroxide decreases, the concentration of the complex also decreases. If the complex is more reactive towards phenyl radicals than the free substrate, then this will also cause a decrease in  $K_{\text{benzene}}^{\text{pyrazine}}$ .

If, as seems likely, the yield of biphenyl formation and the yield of phenylpyrazine formation optimises at different peroxide concentration, then variation of peroxide concentration within these peroxide concentrations will cause significant changes in  $K_{\text{benzene}}^{\text{pyrazine}}$ .

(b) The relative rate increases as more benzene is added (experiments 100-102 and 103-105). Pyrazine is much less volatile than either benzene, or pyridine (pyrazine is a low melting point solid). This suggests that some forms of intermolecular associations are present in pyrazine which are stronger than those present in benzene or pyridine. Such interactions (probably involving the nitrogen atoms) can cause steric hindrance to substitution reactions. All of the carbons in pyrazine are ortho- to one of the nitrogen atoms and are likely to be affected by such interactions. As benzene is added these interactions will decrease leading to higher values for  $K_{\text{benzene}}^{\text{pyrazine}}$ . Complexation of the above type have been suggested by Rondestvedt and Blanchard<sup>178</sup>.

Benzene does not compete effectively with 4-methylpyridine (Section D.1.1.1.5). Similar ineffectiveness is seen in the case of pyridine and pyridazine, and is presumably the case with nitrogen heterocycles in general. Hence an increase in the benzene to pyrazine

ratio will not lead to increased biphenyl yields, and will lead to an increase in  $K_{\text{benzene}}^{\text{pyrazine}}$ .

The yield of benzoic acid decreases as the benzoyl peroxide decreases. Such a change would be expected on the basis of the kinetics of benzoic acid formation in the decomposition of benzoyl peroxide in benzene<sup>65</sup>. However, in the presence of pyrazine, a decrease in benzoyl peroxide concentration results in an increase in the ratio of pyrazine to benzoyl peroxide. This will lead to greater induced decomposition of benzoyl peroxide (c.f. Scheme XVII), and hence greater benzoic acid yields. Thus, though the absolute yield of benzoic acid is reduced from 62.74 mg (experiments 97-99) to 57.16 mg (experiments 100-102), as the benzoyl peroxide concentration is reduced, the yield of benzoic acid, with respect to phenyl radicals obtainable from benzoyl peroxide, is increased from 17.77% (experiments 97-99) to 34.26% (experiments 100-102).

The yield of benzoic acid decreases as the ratio of benzene to pyrazine increases. There are two reasons for this. (a) The biaryl yield, and presumably the formation of sigma-complexes, decreases with an increase in benzene to pyrazine ratio. Since hydrogen abstraction from sigma-complexes, by benzoyloxy radicals, is a major source of benzoic acid, this will lead to reduced yields of benzoic acid. (b) As the benzene to pyrazine ratio is increased, the extent of induced decomposition of benzoyl peroxide by pyrazine will also decrease. As this decomposition leads to greater yields of benzoic acid than the mode of decomposition analogous to Scheme XV, the overall yield of benzoic acid will be reduced.

The changes in yields of esters, with changes in either peroxide concentration, or solvent ratio, is erratic. Since the exact nature of these esters is not known it is difficult to draw any conclusions from these changes.

## D.4

The decomposition of benzoyl peroxide in pyrimidine.

## D.4.1

The effect of additives in the decomposition of benzoyl peroxide in pyrimidine.

The additivity rule (Section D.2) predicts that  $K_{\text{pyrimidine benzene}}$  should be 5.21 on the basis of the partial rate factors calculated for pyridine (experiments 19-21, Table XV).

Expt. no.	Additive	Phenyl pyrimidine yield**	Biphenyl yield	Rel. rate	Isomer dist.* /p.r.f.	Benzoic acid yield	Ester yield mg	Total yield (%)
106-108	none	11.54	39.21	1.49	42.33 53.41 4.26 /3.78 /2.39 /0.38	39.31	4.52	46.6
109-111	copper†	13.06	42.31	1.57	41.39 52.29 6.32 /3.90 /2.46 /0.60	44.23	2.73	50.89
112-114	iron††	12.90	41.04	1.60	42.66 54.89 2.45 /4.10 /2.63 /0.24	39.13	4.52	47.92
115-117	M.D.B.‡	13.81	40.23	1.73	38.23 55.76 6.01 /3.97 /2.89 /0.62	40.08	3.22	47.99
118-120	P.F.N.B.§	11.21	39.23	1.45	39.46 54.21 6.33	42.16	3.09	47.64

Benzoyl peroxide (0.175gm) was decomposed in mixtures of benzene(1.25gm) and pyrimidine(0.25gm), under nitrogen at 80°C  
Experiments 109-120 had additives (5mg).

\* percentage, \*\* mg, | mg, || with respect to phenyl radical,  
† copper(III)benzoate, ††iron(III)benzoate, ‡meta-dinitrobenzene,  
§pentafluoronitrosobenzene,

Table XXVIII

In contrast to the experiments with the other heterocycles (pyridine, pyridazine and pyrazine),  $K_{\text{benzene}}^{\text{heterocycle}}$  for pyrimidine is lower than that predicted by the additivity rule.

	2-phenylpyrimidine	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma complex	E = -42.25
	5-phenylpyrimidine	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma complex	E = -42.20
	4-phenylpyrimidine	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma complex	E = -41.68
-ve	biphenyl	+ H <sup>+</sup> + e <sup>-</sup>	→ Sigma complex	E = -38.67 e.v.
E	benzoyl peroxide	+ H <sup>+</sup> + e <sup>-</sup>	→ benzoic acid + benzoyloxy radical	E = -33.54 e.v.
+ve	benzoyloxy radical	+ H <sup>+</sup> + e <sup>-</sup>	→ benzoic acid	E = - 7.23 e.v.
	Ph <sub>2</sub> N-O·	+ H <sup>+</sup> + e <sup>-</sup>	→ Ph <sub>2</sub> N-OH	E = + 5.98 e.v.
	Cu <sup>2+</sup>	+ e <sup>-</sup>	→ Cu <sup>+</sup>	E° = +0.15 e.v.
	Fe <sup>3+</sup>	+ e <sup>-</sup>	→ Fe <sup>2+</sup>	E° = +0.77 e.v.

Table XXIX



The redox potentials of the phenylpyrimidine/sigma-complexes are more negative than those for the other biaryl/sigma-complexes studied [except for the 4-phenylpyridazine/sigma-complex couple ( $E = -41.85$  e.v.), which has a more negative value than that for the 4-phenylpyrimidine/sigma-complex couple ( $E = -41.68$  e.v.)]. The free valence numbers, the total charge densities, and the localisation energies calculated by INDO<sup>233</sup> methods, also predict a greater reactivity for pyrimidine than for pyridine.

r	qr	Fr	c	L.E.(E.E.) (A.U.)	L.E.(T.E.) (A.U.)
2	3.6890	0.4514	0.0081	-117.1092	-0.7243
4	3.7850	0.4369	0.5565	-116.2427	-0.6991
5	4.0472	0.4220	0.0054	-115.3406	-0.7040

r = position on pyrimidine

qr = total electron charge density

c = coefficient of LMO for pyrimidine on atom r

L.E.(E.E.) = Localisation energy (calculated from electronic energy)

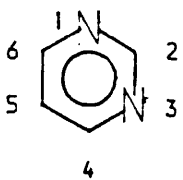
L.E.(T.E.) = Localisation energy (calculated from total energy)

Table XXX

Reactivity parameters for pyrimidine as calculated by INDO<sup>233</sup> methods.

It appears, therefore, that the redox potentials of the oxidants normally present in pyrimidine, must have a redox potential value more negative than that of the oxidants normally present in the other heterocycles. The fact that the additives do have some catalytic effect in pyrimidine confirms this hypothesis.

The additivity rule (Section D.2) predicts that for pyrimidine,  $F_2 = 8.29$ ;  $F_4 = 5.70$ ;  $F_5 = 3.24$ . Though the numerical values for the partial rate factors obtained are lower than those predicted, the order of reactivities (2-→4-→5-) predicted is the same as the order observed experimentally. This is the same order that is predicted by the free valence numbers and total electron charge densities obtained by INDO calculations (Table XXX). However, theoretical calculations by Davies<sup>100</sup> predict the order of reactivity to be 2-→4-→5- on the basis of electron charge densities, but an order of 4-→2-→5- on the basis of free valence numbers.

	r	qr	Fr	f.e.d.
2	2	0.878	0.092	0.241
4	4	0.884	0.099	0.437
5	5	0.973	0.084	0.387

r = position on pyrimidine

qr = electron charge density at rth position

f.e.d = frontier electron density for pyrimidine

Theoretical parameters of reactivity as calculated by Davies<sup>100</sup>.

Table X

Despite both methods (our own and that of Davies<sup>100</sup>) showing a high coefficient of the frontier electron density on the 4-position, it is the 2-position that is found to be the most reactive. This suggests that the phenylation of pyrimidine by benzoyl peroxide (in our system) is charge controlled rather than orbital controlled (Section D.16.6).

#### D.4.1.1 The effect of copper(II)benzoate.

Contrary to what was observed in the other heterocycles (pyridine, pyridazine and pyrazine) copper(II)benzoate is an effective catalyst in the phenylation of pyrimidine. The  $\text{Cu}^{2+}/\text{Cu}^{+}$  redox couple in this system must have a redox potential more positive than that of the oxidants present in the uncatalysed system. The mode of catalysis by copper(II) is presumably analogous to Scheme VIII.

Copper(II) increases the yield of biaryl by oxidising the corresponding sigma complexes. This leads to increased yields of benzoic acid. Since copper complexes with benzoyloxy radicals, it will facilitate the induced decomposition of benzoyl peroxide by pyrimidine (c.f. Scheme XVII). This mechanism leads to enhanced benzoic acid yields.

The proportion of 5-phenylpyrimidine is increased in the presence of copper(II). Copper also had a similar effect in the phenylation of pyridine where the proportion of the meta-isomer was increased. It has been shown<sup>60</sup> that in the phenylation of 4-methylpyridine by benzoyl peroxide, the different sigma radicals have different rates of oxidation, which can be selectively altered. Copper(II) by selectively increasing the rate of formation of the 5-isomer would increase the yield of 5-phenylpyrimidine. The reason for such selectivity is not known and has not been generally observed in aromatic phenylation.

Steric factors can contribute to the change of isomer distribution observed. We have previously suggested that copper competes with benzoyl peroxide for the heterocycle. Such competition probably involves copper and the nitrogens of the heterocycle (since similar competition is not observed in benzene). The 5-position, being far away from the nitrogens, would not be affected by copper. If the addition step in the phenylation of pyrimidine is reversible, then the steric factor will have a greater effect. This, however, does not explain the small, but definite, increase in the isomer ratio of 3-phenylpyridine that is observed on the addition of copper(II)benzoate. The reasons for this enhancement are therefore still unclear.

#### D.4.1.2 The effect of iron(III)benzoate.

The position of the usual oxidising agents in pyrimidine (previous section) means that iron(III), like copper(II), will be an effective oxidant in this system. However, whereas copper(II)benzoate causes an increase in the isomer ratio of 5-phenylpyrimidine, iron(III)benzoate causes an increase in the isomer ratio of 2-, and 4-phenylpyrimidines.

This change in isomer ratios is similar to that observed in the phenylation of pyridine, where (Section D.1.1.3) iron(III)benzoate increased the isomer ratio of 4-phenylpyridine. As in the case of pyridine, back donation of  $\pi$ -electrons<sup>109</sup> from pyrimidine will cause an increased reactivity of the ortho-, and para-positions. Back donation will be more extensive for the diazines than for pyridine. As in the case of pyridine where the para-position was the most strongly affected, the 4-position in pyrimidine, which is para-to one nitrogen and ortho- to the other, is more affected than the 2-position of pyrimidine which is ortho- to both nitrogens.

As in the cases of pyridine, pyridazine and pyrazine, the benzoic acid yield is reduced in the presence of iron(III)benzoate, this is particularly unusual in the case of pyrimidine as the increased yields of biaryls should lead to an increased yield of benzoic acid. It appears that iron(III)benzoate is involved in transferring electrons from sigma-radicals such that some of the hydrogen obtainable from the oxidation of sigma-radicals is diverted to recipients other than benzoyloxy radicals. It is important to note that though the additives may not be the eventual oxidants (electron acceptors) in the oxidation of sigma-radicals to biaryls, it is still thermodynamically feasible that they are involved as electron transfer catalysts, particularly the transition metals.

#### D.4.1.3 The effect of meta-dinitrobenzene.

The yield of phenylpyrimidines is increased by meta-dinitrobenzene but the yield of biphenyl and benzoic acid is not significantly affected. Since the redox potentials of the phenylpyrimidine/sigma-complexes are more negative than the redox potential of the biphenyl/phenylcyclohexadienyl complex the additives will catalyse the formation of phenylpyrimidines more readily than the formation of biphenyl. However, this effect should only be observable if the redox potential corresponding to the additives is more positive than the redox potential corresponding to the oxidants normally present in the system, but only if this difference is small. When the difference is large, the formation of all biaryls should be facilitated. When the redox potential corresponding to the oxidising species is very low on the redox potential table (has large positive values), the free energies involved in the oxidation will be large in all cases and selectivity will not be observed.

The change in isomer ratio observed (experiments 109-111) where copper(II)benzoate was added (the yield of 5-phenylpyrimidine is increased at the cost of 2-phenylpyrimidine), is also observed in meta-dinitrobenzene, this is probably due to steric interference to attack at the position ortho- to nitrogen as a result of interaction of the additives with the nitrogen in pyrimidine. The reversal of this effect in the case of iron(III)benzoate is due to the back donation of  $\pi$ -electrons which increases the yield of the ortho- and meta- positions.

#### D.4.1.4 The effect of pentafluoronitrosobenzene.

Since pentafluoronitrosobenzene does not require initial reduction before it can operate as an oxidant, we would expect it to be more effective in increasing the yields of biaryls than meta-dinitrobenzene. The catalytic effect is probably counteracted by the fact that nitrosobenzene, and by extension, pentafluoronitrosobenzene, scavenges phenyl radicals to form diphenylnitroxide (N-phenyl,N-pentafluorophenylnitroxide in the case of pentafluoronitrosobenzene). This results in reduced yields of biaryls, and the benzoic acid thereof.

## D.4.2

Competition between benzene and pyrimidine on phenylation by benzoyl peroxide.

An increase in peroxide concentration does not have a significant effect on  $K_{\text{benzene}}^{\text{pyrimidine}}$  (experiments 121-123 and 124-126), though the percentage yield (with respect to phenyl radicals) of biaryls are reduced and that of benzoic acid is increased in the reactions with higher concentrations of benzoyl peroxide.

Expt. no.	Peroxide conc. $\times 10^3$	Pyrimidine /benzene w/w	Phenyl pyrimidine yield**	Biphenyl yield	Rel. rate	Isomer dist.* /p.r.f.	Benzoic acid yield	Ester yield mg	Total yield (%)
121-123	9.8	0.5/5	8.73	42.38	2.09	42.45 53.64 3.91 /5.32 /3.36 /0.49	25.23	4.30	40.6
106-108	37.76	0.25/1.25	11.54	39.21	1.49	42.33 53.41 4.26 /3.78 /2.39 /0.38	39.31	4.52	46.6
124-126	34.53	0.25/1.75	14.81	74.51	2.21	42.63 52.34 5.03 /5.65 /3.47 /0.67	63.54	6.43	42.7
127-129	35.93	0.25/5.25	20.31	144.31	2.99	42.43 49.23 8.34 /7.61 /4.42 /1.50	133.29	11.21	43.8

The decomposition of benzoyl peroxides in various concentrations in mixtures of benzene and pyrimidine under nitrogen at 80°C for 24hrs.

\* percentage, \*\* mg, | mg, || with respect to phenyl radical,

Table XXXI

Hence even if complexation between pyrimidine and benzoyl peroxide does occur, the reactivity of the complex does not differ significantly from that of 'free pyrimidine'.

The yield of biaryls and benzoic acid with respect to initial peroxide concentration decreases with decrease in the concentration of peroxide. This is consistent with the kinetics of benzoyl peroxide normally observed in benzene<sup>65</sup>. It appears that the extent of phenylpyrimidine formation varies in the same way as the formation of biphenyl with peroxide concentration.

Since the redox potentials of the oxidants present in pyrimidine are similar to the redox potentials of the oxidants present in benzene, i.e. they are close to -7.23 e.v. on the thermodynamic scale, it is expected that pyrimidine will behave in a similar fashion to benzene as regards phenylation. Though the mechanisms for phenylation need not be identical.

$K_{\text{benzene}}^{\text{pyrimidine}}$  increases as the ratio of benzene to pyrimidine is increased (experiments 106-108, 124-126 and 127-129). As observed in pyridazine and pyridine (Section D.2) N-N interactions cause an increase in  $K_{\text{benzene}}^{\text{heterocycle}}$  with increase in the ratio of benzene to heterocycle only when the partial rate factor for the position ortho to nitrogen is high, hence  $K_{\text{benzene}}^{\text{heterocycle}}$  is increased in the cases of pyridine ( $F_0 = 2.88$  experiments 19-21), pyrazine ( $F_2 = 9.62$  experiments 82-84 and 97-99) and pyrimidine ( $F_2 = 5.49$  experiments 121-123 and 124-126), but not in the case of pyridazine ( $F_3 = \sim 0$  experiments 55-81).



The increase in  $K_{\text{benzene}}^{\text{pyrimidine}}$  with increase in benzene to pyrimidine ratios, however, does not result in an increase in the isomer ratios of 2-, and 4-phenylpyrimidines, though the partial rate factors of all three isomers are increased. This is contrary to what is expected as the increase in reactivity is mainly due to the increased reactivity of the 2-position and, to a lesser extent, the 4-position.

The yield of the phenylpyrimidines is affected not only by the rate of attack of the various positions in pyrimidine, but also by the rate of oxidation of the sigma-radicals formed thereby. It appears, therefore, that as the rate of attack by phenyl radicals increases, the rate of oxidation of the sigma-complexes becomes limiting. Hence, since the rate of formation of the sigma-complexes corresponding to 2-phenylpyrimidine (and, to a lesser extent, the 4-phenylpyrimidine,) is increased most dramatically, these intermediates will be oxidised less efficiently than the less abundant intermediate formed by attack at the 5-position. Though the absolute yield of 2-phenylpyrimidine is increased, its ratio with respect to the other phenylpyrimidines is lowered.

This assumes that the oxidising agents can distinguish between the sigma-complexes, which of course they must do, due to the differences in the redox potentials involved (Table XXIX).

In contrast to the experiments with pyridine, pyridazine and pyrazine, the yield of benzoic acid increases with the increase of benzene to pyrimidine ratios. There is, however, a marked difference between the experiments done with pyrimidine and those done with the other heterocycles. Whereas an increase in benzene to heterocycle ratio is accompanied by a decrease in the benzoyl peroxide concentration in pyridine, pyridazine and pyrazine, the peroxide concentration is approximately maintained in the case of pyrimidine. The reactions are in effect done on a bigger scale leading to greater

absolute yields. The overall yield, with respect to the moles of benzoyl peroxide initially present, does not vary a great deal, but it increases as the number of moles of benzoyl peroxide increases. This change in peroxide concentration must partially contribute to the higher yields of benzoic acid observed.

## D.5

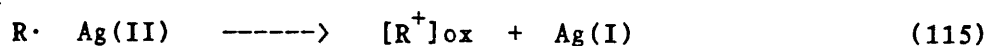
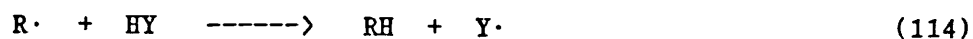
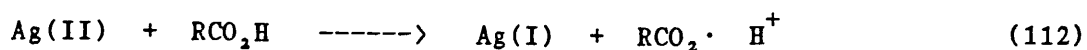
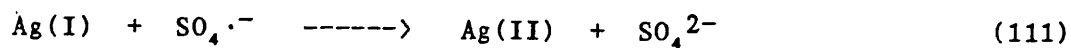
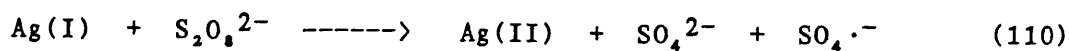
The decarboxylation of benzoic acid by ammonium persulphate in pyridine.

The decarboxylation of carboxylic acids to generate alkyl or aryl radicals was reported by Starnes Jr.<sup>179</sup> using oxygen and di-*t*-butylperoxide. Benzoic acid was decarboxylated to give yields ranging from 36% to 0.2% of biaryl at 170-180°C, using *ortho*-dichlorobenzene as the substrate. Kochi and Anderson<sup>180</sup> used persulphate and silver(I) to decarboxylate aliphatic carboxylic acids. Minisci *et. al.*<sup>47</sup> later used the second method for the decarboxylation of benzoic acid to generate phenyl radicals. Kinetic studies show that the rate of carbon dioxide evolution and persulphate disappearance are first order in silver(I) but zero order in carboxylic acid<sup>180</sup>.

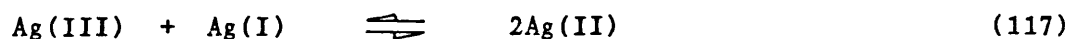
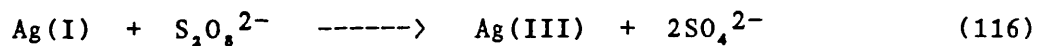
$$d[\text{CO}_2]/dt = -n d[\text{S}_2\text{O}_8^{2-}]/dt = k_2 [\text{Ag(I)}] (\text{S}_2\text{O}_8^{2-}) (\text{RCO}\cdot\text{OH})^0 \quad (109)$$

The kinetic equation given follows a general pattern for the silver-catalysed oxidation, by persulphate, of a variety of other reducing agents including oxalate, thiosulphate and hydrogen peroxide<sup>181</sup>.

The following reactions have been suggested<sup>1,2</sup>

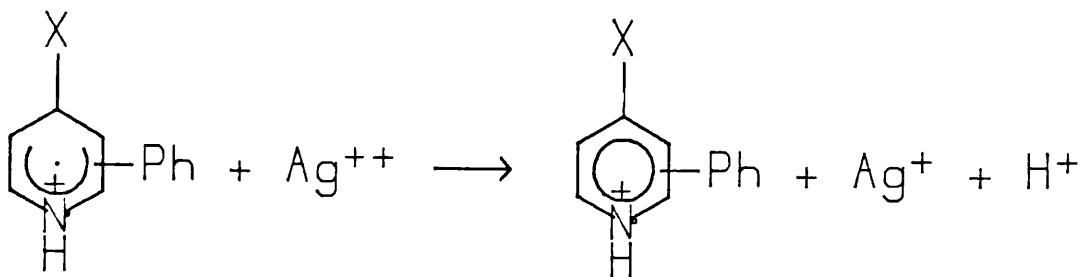


The sequence 110,111 cannot be kinetically distinguished from the formation of a silver(III) species (equation 116) which undergoes rapid syn-proportionation (equation 117).



The equilibrium constant for equation 117 lies far to the right, although it has only been studied in concentrated solutions of mixed mineral acids, the only medium in which these high oxidation states of silver are stable<sup>1,3</sup>.

Minisci *et. al.*<sup>47</sup> have suggested that the sigma-complex is efficiently rearomatised by the aromatic source either through an electron transfer by  $\text{Ag}^{++}$ ,



or through an oxidation by persulphate or by intermediate radicals, 'giving clean reactions, only negligible amounts of by products being formed'. No yields were quoted for these experiments, so no direct comparison between their results and those obtained by us can be made.

Media	Isomer distribution			Ref
	2-	3-	4-	
acidic	68.9	5.58	25.52	current work
acidic	79-82	18-21		184
non acidic	61-63	37-39		184
acidic	64.5	4.5	31	47
non acidic	55	31	14	47

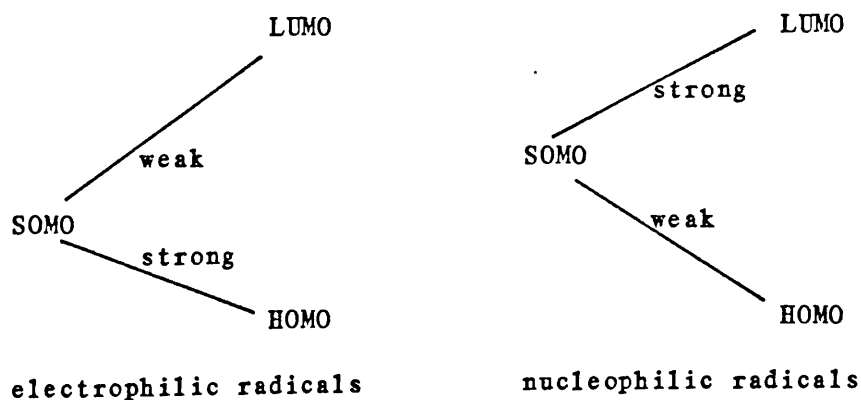
Table XXXII

Dou and Lynch<sup>184</sup> obtained a total yield of phenylated products of 0.36-0.4 moles per mole of peroxide, but the yields of biaryls were not given.

The enhancement of the rate of attack at the 2- and the 4-positions in acidic media, were interpreted by Minisci<sup>47</sup>, to show that the phenyl radical has nucleophilic character. However, Rondestvedt and Blanchard<sup>178</sup>, in their postulation of the preliminary complex, have suggested that 'the phenyl radical is somewhat electrophilic' and tends to become associated with sites of high electron density. The fact that the phenyl radical attacks at the ortho- and the para-positions has been used as a basis of their argument. On this evidence there is some ambiguity about the nature of the phenyl radical.

Radicals should be very 'soft'<sup>185</sup> entities, since most of them are not charged, and in most chemical reactions they react with uncharged species.

Electrophilic radicals generally have a low energy SOMO and nucleophilic radicals generally have a high energy SOMO, so electrophilic radicals generally interact less strongly with the LUMO of the substrate than nucleophilic radicals.

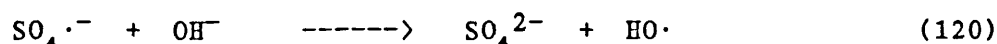
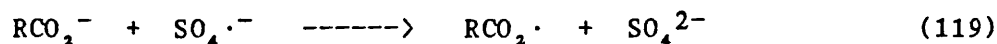


D.6

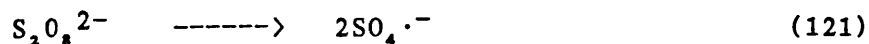
The decarboxylation of sodium benzoate by ammonium persulphate in pyridine at varying pH.

Sodium benzoate was used instead of benzoic acid as it is more soluble in acidic media. The pH was varied by adding known amounts of sodium carbonate (10%).

Ag(II), in reaction (112), reacts with benzoic acid and not benzoate ions, and gives rise to benzoyloxy radicals which, in turn, form phenyl radicals. Hence, benzoate ions must be capable of forming benzoyloxy radicals, to give rise to phenyl radicals in this system. The sulphate ion radical, formed by reaction (110), has been invoked (in alkaline media) in the oxidation of acids, by the Fichter procedure<sup>187</sup>.



It can also be generated directly by the thermolysis of persulphate.



The reaction has an activation energy of 126 Kjoules/mole and is accelerated by strong mineral acids as well as trace metal ions<sup>187</sup>. It appears likely, however, that Ag(II) will react with carboxylate anions, in a reaction analogous to reaction (112), to give the corresponding carboxy radical, since the reaction works well with acids that dissociate readily under the reaction conditions.



No 3-phenylpyridine was formed in these experiments. A decrease in acidity resulted in a decrease in the overall yield of biaryl, and a decrease in the percentage yield of 2-phenylpyridine.

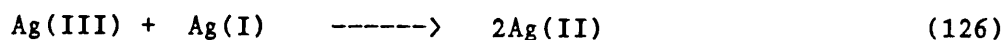
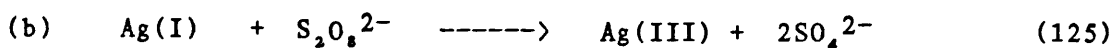
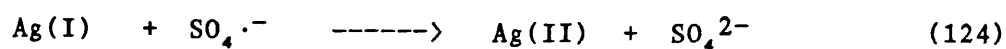
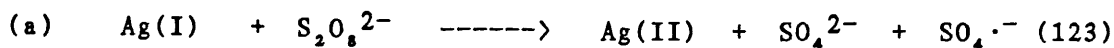
Expt. no	sodium carbonate (ml)	pH		phenyl pyridine yield (mg)	isomer distribution (%)		
		init.	final		2-	3-	4-
133-135	none	7.5	1.5	28.86	90.2	-	9.8
136-138	10	10.5	7	2.14	80.6	-	19.4
139-141	60	11.5	9	1.53	27.9	-	72.1
142-144	90	11.5	10.5	1.22	21.2	-	78.8

The decarboxylation of sodium benzoate (0.05 mole) by ammonium persulphate (0.03 mole) and silver nitrate (0.03 mole) in the presence of pyridine (0.01 mole) and varying amounts of sodium carbonate (10%).

Table XXXIII

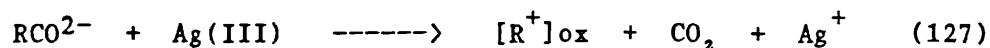
The reduction in total biaryl yield cannot be accounted for by the reduction in yield of 2-phenylpyridine alone. One possible reason for the reduction of the biaryl yield at high pH might have been an instability of the phenylpyridines towards boiling aqueous sodium carbonate, a selective loss of 2-phenylpyridine could also account for the change in isomer ratios observed. However, all three phenylpyridines were found to be stable to boiling with aqueous sodium carbonate (10%) at 90°C., for two hours.

The reaction may involve two different methods of oxidation.



Method (b) would not operate at high pH as the silver(III) species is stable only under acidic conditions. Provided method (b) was important this would cause a reduction in biaryl yields.

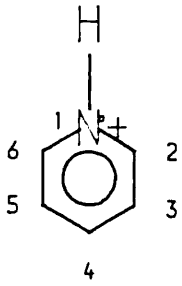
Silver(III) may be directly involved in the oxidation of the carboxylate ion



The coefficients for the LUMO for the pyridinium ion is identical to that for pyridine, however the total charge densities on the carbon atoms is reduced, i.e., the carbon atoms are more positive than the corresponding atoms in pyridine. Therefore, conditions where there is extensive interaction with the base will lead to a relatively greater reactivity of the para-position.

Since the charge density alters with respect to pyridine by +0.0174, +0.0365, +0.0722, for the ortho-, meta-, and para-positions respectively, the increase in reactivity is expected to be in the order of para->meta->ortho-, though the overall reactivity should still be ortho->para->meta-.



	r	c	Fr	qr
	2-	0.3632	0.4643	3.8035
	3-	0.2140	0.4233	3.9658
	4-	0.5619	0.4484	3.8352

r = rth position in protonated pyridine

c = coefficient of LUMO

Fr = free valence number at position r

qr = total charge density at position r

Table XXXIV

Reactivity parameters of protonated pyridine as calculated by INDO<sup>233</sup> methods.

The fact that only ortho-, and para-phenylpyridines are formed suggests that the phenyl radical is extremely nucleophilic under the reaction conditions.

Pyridine and bipyridyl stabilise  $Ag^{2+}$  in aqueous media, the competition between various bases for  $Ag^{n+}$  ( $n = 2$  or  $3$ ) and  $H^+$  would also allow an explanation for the change in isomer ratios observed with change in pH. At low pH, the high concentration of  $H^+$  will reduce complexation of pyridine with  $Ag^{n+}$  as  $H^+$  will compete for  $Ag^{n+}$ . This will reduce the extent of orbital control (Section D.16.6) in the reaction, consequently, the para- position in pyridine will no longer be preferentially attacked. It is also likely that protonated

pyridine due to the charge repulsion between  $\text{Ag}^{n+}$ , and the nitrogen in pyridine. However, the proximity of  $\text{Ag}^{n+}$ ,  $\text{RCO}_2^-$  and the ortho-position of pyridine, will make an acceleration of the attack by phenyl radicals likely, particularly at the ortho-position. The latter effect should reduce the extent of orbital control.

Since both protonated and unprotonated pyridine is present in the system at the same time, and phenyl radicals attack both species, the overall yield of the phenylpyridines will depend on the rate of attack of phenyl radicals on protonated pyridine and on unprotonated pyridine. If  $\text{KP}_a^O$  represents the proportionality constant for attack on the ortho position of protonated pyridine by phenyl radicals,  $\text{KP}_a^P$  represents the proportionality constant for attack on the para position of protonated pyridine by phenyl radicals,  $\text{KP}_b^O$  represents the proportionality constant for attack on the ortho position of unprotonated pyridine by phenyl radicals,  $\text{KP}_b^P$  represents the proportionality constant for attack on the para position of

unprotonated pyridine by phenyl radicals, then, we will obtain four linear equations that will represent the formation of sigma-radicals and subsequent biaryl formation, these simultaneous equations can be solved to determine the values for K by comparing the yields at two known pH values. This of course assumes that the values of K are constant, or nearly so, within that pH range. Though we do not know this, by comparing reactions conducted at similar pH, we can reduce the errors of estimation. Since the rates are obtained relative to one another, they are not absolute values and have no units. They can however be freely used to compare the reactivities of the reactions concerned within the relevant pH values. The method of analysis is elaborated in the appendix.

The results obtained are given below:

proportionality constant	value	pH range
$K_{\text{Pyridine}}^{\text{O}}_{\text{a}}$	$4 \times 10^{-4}$	7 - 10.5
$K_{\text{Pyridine}}^{\text{P}}_{\text{a}}$	$5 \times 10^{-5}$	7 - 10.5
$K_{\text{Pyridine}}^{\text{O}}_{\text{b}}$	$3 \times 10^{-5}$	7 - 10.5
$K_{\text{Pyridine}}^{\text{P}}_{\text{b}}$	$9 \times 10^{-6}$	7 - 10.5

Assuming that the yield of phenylpyridines reflects the rate of attack on the corresponding position in pyridine, these proportionality constants are valid and can be used to compare the reactions studied quantitatively.

#### D.7

The decarboxylation of sodium benzoate by ammonium persulphate in pyridazine at varying pH.




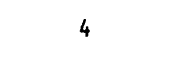
As in the case of pyridine, there is a marked difference between the positional selectivity obtained by attack by phenyl radicals in aromatic solution and that obtained by attack in aqueous media (section D.1.2).

Expt. no	sodium carbonate (ml)	pH		phenyl pyridazine yield (mg)	isomer distribution (%)	
		init.	final		3-	4-
145-147	none	7	2-1	37.25	27.0	73.0
148-150	10	10.5	6.5	30.38	26.8	73.2
151-153	60	11.5	9	12.31	15.0	85.0
154-156	90	11.5	10.5	3.41	14.8	85.2

The decarboxylation of sodium benzoate (0.05 mole) by ammonium persulphate (0.03 mole) and silver nitrate (0.03 mole) in the presence of pyridazine (0.01 mole) and varying amounts of sodium carbonate (10%)

Table XXXV

Analogy with the pyridine system is also observed in the reduction of biaryl yields with increase in pH. This is due to the reduced reactivity of the pyridazine molecule with respect to the protonated form of pyridazine towards nucleophilic species (the total electron charge density on the carbon atoms on pyridazine are reduced on protonation).

	r	qr	Fr	c
	3	3.8121	0.4600	-0.1565
	4	3.9252	0.4252	-0.4120
	5	3.8729	0.4417	0.4120
	6	3.8299	0.4440	0.1565

r = position on protonated pyridazine,

qr = electron charge density at rth position,

c = coefficient of LUMO for protonated pyridazine on atom r,

Table XXXVI

Since only one of the nitrogen atoms (nitrogen 1) is protonated, the total electron charge densities and the free valence numbers for positions 3 and 6, and 4 and 5 are not identical, as the positions are no longer equivalent. Due to the electron withdrawing effect of the proton, the positions nearest to nitrogen are relatively more depleted ( $qr_3 < qr_6$ ,  $qr_5 < qr_4$ ). The free valence for these positions are relatively increased ( $Fr_3 > Fr_6$ ,  $Fr_5 > Fr_4$ ). Hence, apart from the overall reactivity of the molecule towards nucleophilic species increasing with respect to pyridazine, the positions nearest to the protonated nitrogen will also experience increased reactivity. The average of these values have been taken as the time averaged values for the 3-6 pair and the 4-5 pair and will be the same, as both nitrogens in pyridazine are identical and are as likely to be protonated.

Since the coefficient for the LUMO is unchanged on protonation, reaction of the 4-position will be favoured over the 3-position when the molecule is involved in complexation involving the  $\pi$ -orbitals (the coefficient of the LUMO is present entirely in the pz orbital).

The observed experimental results are entirely consistent with the theory. As the pH is increased, the extent of protonation decreases, hence the overall reactivity decreases (pyridazine has a lower reactivity than protonated pyridazine), as the concentration of  $H^+$  goes down, complexation of pyridazine with  $Ag^+$  increases ( $H^+$  is in competition with  $Ag^+$  for pyridazine), this leads to greater charge control and hence a greater reactivity of the position with the greatest coefficient in the LUMO of pyridazine, i.e. the 4-position.

As in the case of pyridine (Section D.6), The yields of phenylpyridazines and the pKa value of pyridazine have been used to calculate the rate constants for the attack of phenyl radicals on protonated and unprotonated pyridazine.

proportionality constant	pH range (initial)	value
Kpyridazine <sup>3</sup> <sub>a</sub>	7 - 10.5	$4 \times 10^{-1}$
Kpyridazine <sup>4</sup> <sub>a</sub>	7 - 10.5	2
Kpyridazine <sup>3</sup> <sub>b</sub>	7 - 10.5	$4 \times 10^{-3}$
Kpyridazine <sup>4</sup> <sub>b</sub>	7 - 10.5	$2 \times 10^{-4}$

D.8

The decarboxylation of sodium benzoate by ammonium persulphate and silver nitrate in pyrazine at varying pH.

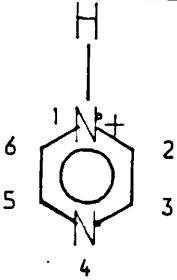
Pyrazine is a symmetrical molecule, hence, there is no change in the isomer ratios with changes in pH. As in the case of pyridine and pyridazine, however, the yield of biaryl decreases with an increase in pH.

Expt. no.	sodium carbonate (ml)	pH		phenyl pyridazine yield	yield w.r.t. pyrazine	yield w.r.t. phenyl
		init.	final			
169-171	none	7	2-1	7.40	0.47	0.09
172-174	10	10.5	6.5	5.96	0.38	0.08
175-177	60	11.5	9	2.07	0.13	0.03
178-180	90	11.5	10.5	0.48	0.03	0.01

The decarboxylation of sodium benzoate (0.05 mole), by ammonium persulphate (0.03 mole) and silver nitrate (0.03 mole), in the presence of pyrazine (0.01 mole), and varying amounts of sodium carbonate (10%).

Table XXXVII

The coefficient of the LUMO of the carbon atoms in pyrazine are not significantly altered on protonation. As in the cases of pyridine and pyridazine, the total charge density on the carbon atoms are reduced, there is also an increase in free valence numbers but the change is marginal.

	r	qr	Fr	c
	2	3.8467	0.4625	0.2955
	3	3.8402	0.4343	0.2927
	5	3.8407	0.4343	0.2993
	6	3.8432	0.4634	0.2919

r = rth position in protonated pyrazine  
 qr = total charge density at rth position  
 Fr = free valence at rth position  
 c = coefficient of LUMO at rth position

Parameters obtained from INDO<sup>223</sup> calculations on protonated pyrazine.

Table XXXVIII

D.9

The decarboxylation of benzoic acid by ammonium persulphate and silver nitrate in pyrimidine.

The isomer ratios of phenylpyrimidines obtained from attack of protonated pyrimidine by phenyl radicals is different from the ratios obtained from the attack of the unprotonated base.

Expt. no.	mg	Biaryl yield		% w.r.t. acid	Isomer ratio		
		mMole	% w.r.t. base		2-	4-	5-
181	4.42				7.3	92.7	-
182	4.46				6.7	93.3	-
183	4.01				5.9	94.1	-
ave	4.28	0.027	0.27	0.05	6.8	93.2	-

Benzoic acid (0.025 mole) was decarboxylated, by ammonium persulphate (0.0175 mole) and sulphuric acid (0.005 mole), in a solution of pyrimidine (0.005 mole) and water (13 ml) at 85-95°C under reflux. Silver nitrate (0.0175 mole) was used as a catalyst.

Table XXXIX

Of all the heterocycles studied, pyrimidine is the only one that has nitrogens meta- to one another. The properties of pyrimidine have been discussed on this basis (Section I.2.3.2.2.). Protonated pyrimidine likewise differs from the protonated forms of the other heterocycles studied. Whereas the coefficient of the LUMO for the carbon atoms in pyridine, pyridazine and pyrazine (and their protonated forms) all have large values in the pz orbital and zero values in the s, px, and py orbitals, in the case of protonated pyrimidine, the values are entirely on the s, px, and py orbitals, the pz orbital having zero values. [The coefficient of the LUMO of unprotonated pyrimidine lies entirely in the pz orbital.]

atom	orbital	coefficient
C <sub>2</sub>	s	0.0560
"	px	-0.0866
"	py	0.0838
"	pz	0.0000
C <sub>4</sub>	s	-0.0171
"	px	-0.0074
"	py	0.0257
"	pz	0.0000
C <sub>5</sub>	s	-0.0418
"	px	0.1279
"	py	-0.0237
"	pz	0.0000
C <sub>6</sub>	s	0.0398
"	px	-0.0915
"	py	0.0786
"	pz	0.0000

The eigenvectors for the carbon atoms in pyrimidine as calculated by INDO<sup>233</sup> methods

Table XXXX



The observed change is not due to a change in the shapes of the orbitals themselves, but due to a change in the orbital energies such that the energy of the seventeenth orbital, which corresponds to the the shape of the LUMO in unprotonated pyrimidine, is at a higher energy level than the LUMO in protonated pyrimidine.

The results observed in Table XXXIX cannot be easily explained by the coefficients of the LUMO of pyrimidine, since the precise orientation of attack by phenyl radicals is not known.

The free valence for the carbon atoms in protonated pyrimidine is increased with respect to the free valence in pyrimidine. Of this increase 71.6% goes to the 4-position, 27.6% goes to the 2- position and 0.8% goes to the 5- position. This will cause an increased yield in the 4-position and some increase in the 2-position.

	r	qr	Fr
	2	3.6729	0.4718
	4	3.7286	0.4635
	5	4.0074	0.4226
	6	3.7625	0.4631

r = position on protonated pyrimidine

qr = electron charge density at rth position

Free valence numbers and total electron charge densities  
calculated by INDO<sup>2,3</sup> methods.

Table XXXXI

The total electron charge density in the carbon atoms in protonated pyrimidine is decreased with respect to the values in unprotonated pyrimidine. Of this decrease, 58.8% is in the 4-position, 29.3% is in the 2-position and 11.9% is in the 5-position. This will result in an increased reactivity mainly in the 4-position and 2-position and some increase in the 5-position.

Though the change in free valence and total charge density will contribute to the observed change in reactivity, it cannot account for the complete absence of the 5-isomer, particularly since in absolute terms the reactivity of the 5-position should also increase. However, as we have seen with pyridine pyridazine, and pyrazine, the reactivity of the heterocycles in aqueous acidic media is generally low though the relative proportions of the arylated or alkylated isomers is as expected on the basis of the reactivities of the various positions in the heterocycle.

D.10

The decarboxylation of cyclohexylcarboxylic acid by ammonium persulphate in pyridine.

Though the cyclohexyl radical is expected to be much more nucleophilic than the phenyl radical, the overall yields of cyclohexylated pyridines was not much greater than the yields of phenylpyridines obtained on phenylation by the decomposition of benzoic acid or sodium benzoate in pyridine.

Expt. no.	mg	Biaryl yield		% w.r.t. acid	Isomer ratio		
		mMole	% w.r.t. base		2-	3-	4-
157	464.28				41.53	9.26	49.21
158	481.39				41.20	9.08	49.72
159	433.82				41.69	8.95	49.36
ave	459.8	2.86	28.56	5.71	41.5	9.1	49.4

Cyclohexyl carboxylic acid (0.05 mole) was decarboxylated by ammonium persulphate (0.03 mole) and sulphuric acid (0.01 mole) in a solution of pyridine (0.01 mole) and water (25 ml). Silver nitrate (0.03 mole) was used as a catalyst.

Table XXXXII

The relative yields of the three isomeric cyclohexylpyridines correspond to the coefficients of the LUMO for pyridine [the coefficients of the LUMO for pyridine and protonated pyridine are identical (Table XIV)].

Values for the cyclohexylation of unprotonated pyridine could not be obtained in the literature. Cyclohexyl radicals derived from cyclohexane via hydrogen abstraction by triplet states of ketones can attack benzene to ultimately yield cyclohexylbenzene<sup>190</sup>.

Shelton and Uzelmeier<sup>192</sup> photolysed di-tert-butyl peroxide in cyclohexane, in the presence of various aromatic solvents, to form cyclohexyl radicals which subsequently attacked the aromatic solvent.

If meta/ortho + para ratios are measured, the cyclohexyl radical appears to be more nucleophilic than the phenyl radical in this system, however, if the meta/para ratios are measured, both radicals appear to have similar nucleophilicities.

As expected, the change of carboxylic acid does not affect the extent of protonation of the base (the initial pH is between 7-6.5 and the final pH 2-1 in all cases where no sodium carbonate is added). This is because sulphuric acid is a much stronger acid than any of the organic acids used, so the relative strengths of the organic acids have little effect.

## D.11

The decarboxylation of cyclohexane carboxylic acid by ammonium persulphate in aqueous pyridine and acetone.

The presence of acetone increases the solubility of cyclohexane carboxylic acid in aqueous protonated pyridine, but since the solubility of the acid in the system at around 95°C is high anyway, this does not result in an increased yield of biaryl (yield in water = 5.7%, yield in acetone and water = 1.4%).

Expt. no.	mg	Biaryl yield			Isomer ratio		
		mMole	% w.r.t. base	% w.r.t. acid	2-	3-	4-
160	102.37				16.39	58.57	25.04
161	109.42				16.64	59.34	24.02
162	114.66				16.55	58.19	25.26
ave	108.8	0.676	6.76	1.4	16.5	58.7	24.8

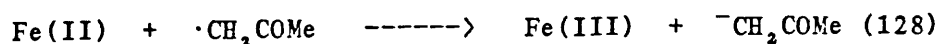
Cyclohexyl carboxylic acid (0.05 mole) was decarboxylated by ammonium persulphate (0.03 mole) and sulphuric acid (0.01 mole) in a solution of pyridine (0.01 mole), acetone (25ml) and water (25 ml). Silver nitrate (0.03 mole) was used as a catalyst.

Table XXXVIII

There is considerable change in both yields and isomer ratios in the presence of acetone. The biaryl yield is lowered. The isomer ratio of meta-cyclohexylpyridine increases while the ratio of the ortho- and para- isomers decrease.

The reactions in acetone are complicated. Acetone enolisation is an important part of sigma-complex formation in the reaction between meta-dinitrobenzene and acetone<sup>193</sup>. Addition of large amounts of water sharply decreases the rate of complex formation. With small amounts of water in solution, the decrease in the complex formation rate is associated with both the enolisation equilibrium shift and with stabilisation due to specific solvation of the sigma-complex by water. A negative salt effect is observed in the formation of sigma-complexes of meta-dinitrobenzene and MeCOCH<sub>2</sub>K. This is due to the differing stabilities of the acetone carbanion in the reaction system. The effect of the salt anion on complex formation is small<sup>193</sup>.

Acetone shows competitive inhibition in the reaction between Fe<sup>3+</sup> and H<sub>2</sub>O<sub>2</sub><sup>194</sup>. No complex is formed between acetone and Fe<sup>3+</sup>, instead there is a binding of the secondary Fe<sup>3+</sup>-H<sub>2</sub>O<sub>2</sub> complex by acetone, one acetone molecule binding upto nine molecules of the secondary complex. Acetonyl radicals react with Fe<sup>2+</sup> ions:



The above reaction is negligible when pH = 1, but significant when pH = 7<sup>195</sup>.

It is apparent, therefore, that interactions between acetone, metal ions and water are involved and can be sensitive to changes in pH.

The complexation of silver ions with pyridine leads to increased yields of cyclohexylpyridines and, in particular, ortho-cyclohexylpyridine, acetone by acting as an inhibitor (as in the case of the  $\text{Fe}^{3+}$ ,  $\text{H}_2\text{O}_2$  system<sup>194</sup>), can reduce both the overall yield of biaryl and the isomer ratio of the ortho-cyclohexylpyridine isomer. Acetone may also be involved in reducing the  $\pi$ -overlap between pyridine molecules, thereby reducing the yield of the para-isomer (Section D.1.1.1.2).

## D.12

The decarboxylation of benzoic acid by ammonium persulphate in aqueous pyridine and acetone.

The complex interactions between acetone, water and metal ions, have been discussed (Section D.11). The effect of acetone on the phenylation of pyridine is similar to its effect on the cyclohexylation of pyridine.

Expt. no.	Biaryl yield				Isomer ratio		
	mg	mMole	% w.r.t. base	% w.r.t. acid	2-	3-	4-
163	16.03				18.27	56.69	25.04
164	17.86				18.69	56.39	24.92
165	14.02				18.39	56.25	25.36
ave	16.0	0.103	1.03	0.21	18.5	56.4	25.1

Benzoic acid (0.05 mole) was decarboxylated by ammonium persulphate (0.03 mole) and sulphuric acid (0.01 mole), in a solution of pyridine (0.01 mole), acetone (25 ml) and water (25 ml). Silver nitrate (0.03 mole) was used as a catalyst.

TABLE XXXIV

The oxidation of  $\text{H}_2\text{O}_2$  by  $\text{Fe}^{3+}$  is similar to the oxidation of  $\text{Ag}^+$  with persulphate involving  $\text{H}_2\text{O}_2$ <sup>196</sup>. The mechanism proceeds with the oxidation of  $\text{H}_2\text{O}_2$  to molecular oxygen with disintegration of the persulphate O-O bond. Electrons are transferred from the oxidising substance to the persulphate without the displacement of the oxidiser oxygen atoms. Competitive inhibition of the  $\text{Ag}^+$  and persulphate reaction by acetone (as in the case of the  $\text{Fe}^{3+}$  and  $\text{H}_2\text{O}_2$  system) could take place, resulting in decreased biaryl yields.

D.13

The methylation of pyridine by the decarboxylation of acetic acid by ammonium persulphate and silver nitrate.

This reaction was primarily conducted as a control experiment, and was the only experiment by Minisci *et. al.*<sup>120, 121, 123, 137, 197</sup> where distributions were given.

Expt. no.	Methylpyridine yield				Isomer ratio		
	mg	mMole	% w.r.t. base	% w.r.t. acid	2-	3-	4-
166	306.76				54.52	4.32	41.16
167	282.23				54.94	4.39	40.67
168	295.45				54.93	4.45	41.62
ave	294.8	3.17	31.7	6.34	54.5	4.4	41.1

Acetic acid (0.05 mole) was decarboxylated by ammonium persulphate (0.03 mole) and sulphuric acid (0.01 mole), in a solution of pyridine (0.01 mole), acetone (25 ml) and water (25 ml). Silver nitrate (0.03 mole) was used as a catalyst.

Table XXXV

A 51.5% yield of 2,4-dimethylpyridine was also reported, but we did not attempt to identify this isomer. Though the authors reported a hundred percent conversion of the heterocyclic base, over 10% unreacted base was obtained in our experiments. The reported isomer distributions for the methylpyridines were: 2-, 47%; 3-, 0%; 4-, 53%.

Though our results do not completely agree with those reported by Minisci et. al.<sup>197</sup>, they are consistent with the results obtained for the cyclohexylation and phenylation of pyridine.

The meta-/ ortho- + para- ratio for the methylpyridines is lower than that obtained in the previous cases. The initial pH in these experiments was 5.5, though the final pH was again 1-2. Since pyridine is protonated to a greater extent in this system, nucleophilic radicals, like the methyl radical<sup>124</sup>, will attack the ortho- and para- positions of pyridine more readily than the meta-position.

D.14

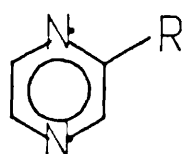
The attack of pyrazine by dioxanyl radicals generated from dioxan by ammonium persulphate.

The abstraction of hydrogen from the  $\alpha$ -position to the oxygen of alcohols and ethers occurs frequently and is a readily available source of  $\alpha$ -oxyalkyl radicals<sup>135</sup>. In the case of cyclic ethers, the oxyalkyl radical attacks the heterocyclic substrate without undergoing  $\beta$ -scission.

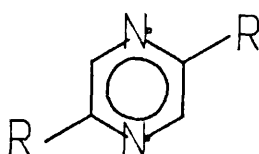
Dioxanyl radicals have been generated by (a) t-butyl-hydroperoxide (75% in di-t-butyl peroxide) and ferrous sulphate and (b) ferrous sulphate and hydrogen peroxide, in the



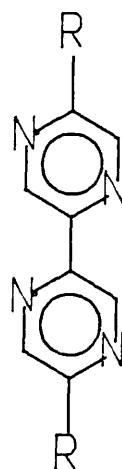
presence of pyrazine<sup>135</sup>, giving a yield of 38% 2-dioxanylpyrazine (A), 20% of the disubstituted derivative (B) and 10% of the dimer (C).



(A)



(B)



(C)

The yields are based on the heteroaromatic base, but which of the two sources of dioxanyl radicals were used in the experiments was not quoted.

Expt. no.	Dioxanyl pyrazine yield				Isomer ratio	
	mg	mMole	% w.r.t. pyridine	% w.r.t. dioxan	di-2-,5-,	mono-2-
184	1.84				33.67	66.33
185	1.91				33.24	66.76
186	1.65				33.29	66.71
ave	1.8	7.24	36.2	1.81	33.4	66.6

Dioxanyl radicals were generated from dioxan (0.04 mole), by ammonium persulphate (0.06 mole), in a solution of pyrazine (0.02 mole), in fifty percent sulphuric acid (0.03 mole).

Table XXXVI

No attempt was made to isolate the dimer (C). The ratio of (A) to (B) is similar to that obtained by the methods used by Minisci et. al.<sup>137</sup>. This suggests that 'free dioxanyl' radicals are the attacking species in all these cases.

D.15

The N-N interactions:

We have suggested that N-N interactions are responsible for some of the anomalies observed in the heterocycles, for example, the increased reactivity of the 4-position in pyridine in the presence of iron(III)benzoate (Section D.1.1.3).

The presence of such interactions are confirmed by comparing the boiling points of these heterocycles with their homolytic analogues, or isomers, where such associations are absent due to the presence of substituents in the vicinity of the nitrogen atoms.

Pyridines substituted at the 2- or 6- position have a lower boiling point than those without a substituent at the corresponding position, e.g., 2-methylpyridine (b.pt. 129°C) and 2-ethylpyridine (b.pt. 149°C), both boil about 15°C lower than the corresponding 3- or 4-substituted isomers. Dimethylpyridines with no  $\alpha$ -substituent boil at  $174 \pm 4^\circ\text{C}$ , and with one substituent at  $159 \pm 2^\circ\text{C}$ , while 2,6-lutidine boils at 144°C. Thus, for 2,6-lutidine, this position is completely blocked, and the degree of association of this compound is close to that of the corresponding benzene derivative, m-xylene (b.pt. 139°C).

D.16

The perturbation treatment of chemical reactivity.

Chemical reactivity is usually discussed in terms of the transition state theory<sup>16</sup>, but this method has severe limitations<sup>16</sup> in that neither the activation energy nor the activation entropy can be calculated to within reasonable limits of accuracy, except for the simplest of reactions (e.g.  $H + H_2$ ). The principle of conservation of orbital symmetry, which delienates in a simple way those reactions which can occur and those which cannot, has been particularly successful in dealing with concerted reactions<sup>210</sup>. These rules are part of a wider scheme of treating chemical reactions<sup>211</sup>, and of estimating potential energy surfaces in an approximate way.

. On the approach of two interacting systems, the combined wave function of the perturbed system is given by appropriate combinations of the wave functions of the two unperturbed molecules<sup>211</sup>. By considering the interaction of each pair of orbitals separately, the total perturbation energy can be found.

The orbitals may interact in various ways depending on their symmetry and their relative energies. In the perturbation method, this is represented by a Hamiltonian operator  $H'$ , which is a modification of that of the initial system  $H_0$ , thus:

$$H = H_0 + H'$$

The Shrodinger equation may be solved by the usual variational treatment leading to a set of simultaneous equations:

$$\begin{vmatrix} \alpha_1 - E & \beta \\ \beta & \alpha_2 - E \end{vmatrix} = 0 \quad (129)$$

for the energy  $E$ , due to the interaction of orbitals  $\Psi_1$  and  $\Psi_2$  of energy  $\alpha_1$  and  $\alpha_2$ , respectively,  $\beta$  is the resonance integral for the specific interaction:

$$\langle \Psi_1 | H | \Psi_2 \rangle$$

#### D.16.1

##### Degenerate orbitals

When  $\alpha_1 = \alpha_2$ , e.g., for the interaction of two identical atoms or radicals, solution of the Schrodinger equation (with neglect of overlap) gives:

$$E_+ = \alpha + \beta, \quad E_- = \alpha - \beta \quad (130)$$

The combination of two orbitals, thus gives rise to splitting, to give bonding and anti-bonding orbitals (Fig 3). For two electrons the bond energy is  $2\beta$ .

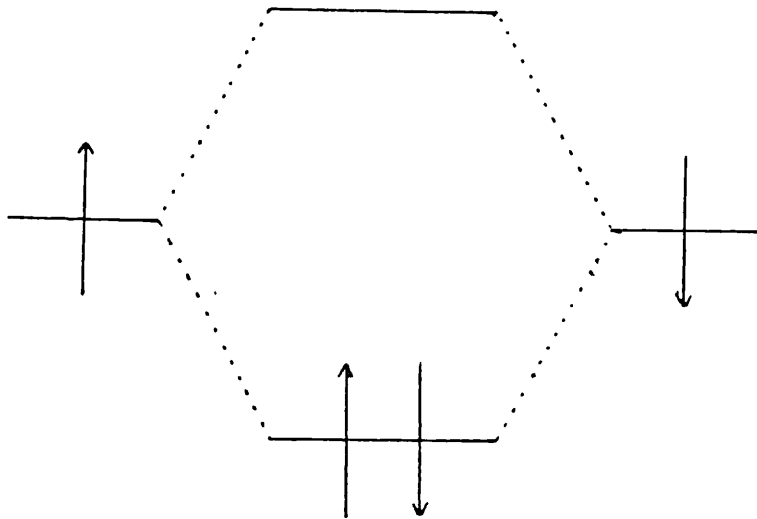


Fig. 3

Interaction of two singly occupied degenerate orbitals.

This is known as a first order perturbation.

If the orbitals are doubly filled, then according to equation (130),

$$\Delta E = 2\beta - 2\beta = 0$$

This cannot be exact since the interaction of two closed shells e.g. two helium atoms, leads to a net increase in energy, i.e. a repulsion. This can be introduced indirectly by retaining the overlap integral  $S$  in the solution of equation (129) which gives

$$E_+ = \frac{\alpha + \beta}{1 + S} \quad \text{and} \quad \frac{\alpha - \beta}{1 - S} = E_- \quad (131)$$

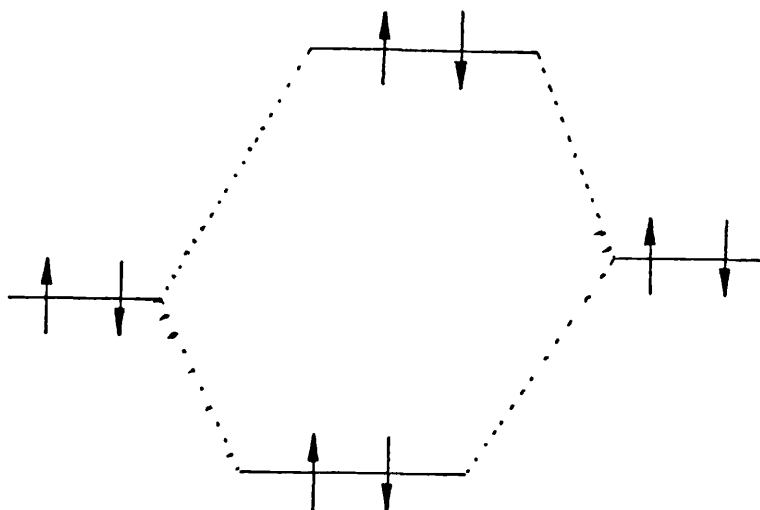


Fig.4.

Interaction of two doubly occupied degenerate orbitals.

This relates the repulsion energy of closed shells to the overlap integral, which is amenable to calculation<sup>231</sup>.

D.16.2

Non-degenerate orbitals

Usually  $\alpha_1 \neq \alpha_2$ , i.e., the interacting orbitals are non-degenerate. This corresponds to the interaction of an electron donor (a 2-electron orbital) of energy  $\alpha_1$ , with an unoccupied level of an electron acceptor, of energy  $\alpha_2$ .

Solution of equation (129)\* then gives<sup>148.2</sup>

$$E = \frac{\alpha_1 + \alpha_2 \pm \sqrt{(\alpha_1 - \alpha_2)^2 + 4\beta^2}}{2} \quad (132)$$

\*The solution given in reference 148.2 was incorrect. The corrected version is given.

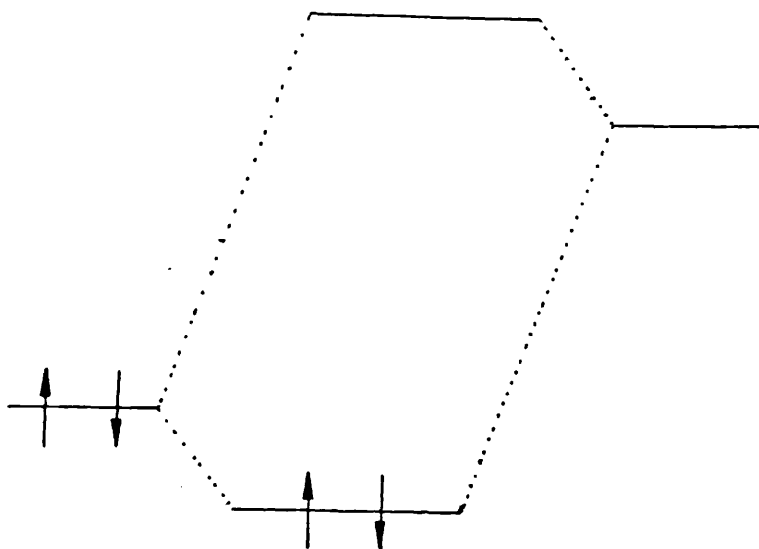


Fig.5.

Interactions of a doubly occupied orbital of energy  $\alpha_1$  with an occupied orbital of energy  $\alpha_2$ .

If  $\alpha_1 \gg \alpha_2$ ,

$$E = 2\alpha_1 + 2\beta^2/(\alpha_1 - \alpha_2)$$

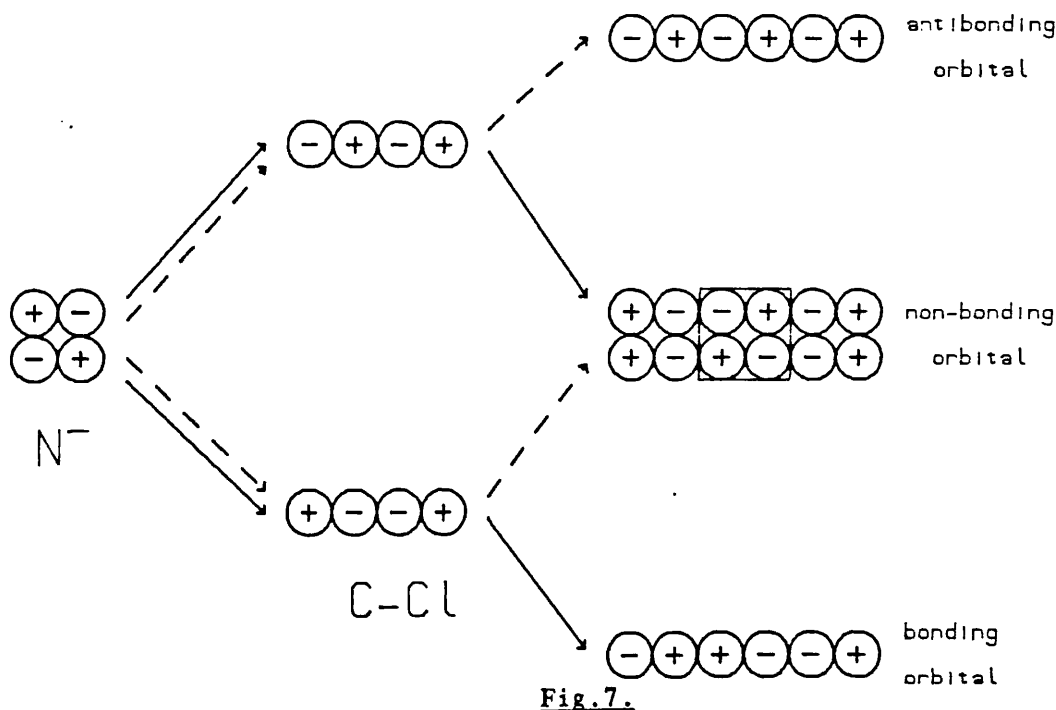
(133)

Thus

$$\Delta E = 2\beta^2/(\alpha_1 - \alpha_2)$$

The energies calculated by these procedures refer to small interactions only, as under these conditions the wave function of the combined system can be adequately represented by a combination of the ground state functions. A chemical reaction proceeding through a transition state, however, involves considerable displacement of the nuclei, and we must determine therefore under what conditions the initial perturbation represents the chemical reactivity.

An empirical treatment of nucleophilic reactivity<sup>214</sup> is formulated by the following rules: (1) The position of the largest density in the HOMO or LUMO is also the position most likely to weaken the bonds, with neighbouring atoms, for electron releasing or electron attracting interaction, respectively. (2) The energy difference between the orbitals of donor and acceptor decrease as the reaction proceeds. (3) The coefficients in these orbitals increase (to the ultimate value of unity) as the reaction proceeds. These changes are more pronounced for  $\sigma$ -bonds than for  $\pi$ -bonds, in view of the greater influence of the overlap integral in saturated systems, and lead to re-hybridisation, as in the formation of an  $S_N2$  transition state. The reaction progress involves the conversion of the initial orbitals into 3 molecular orbitals characterising the transition state as shown by the correlation diagram for a C-Cl bond in figure 7.



Correlation diagram for the interaction of an electron donor with a C-Cl bond.



It is seen that the interaction of the nucleophile orbital with the antibonding orbital of the electrophile transforms into the non-bonding orbital (expressed originally<sup>215</sup> as a resonance hybrid of  $N^-RX$  and  $NRX^-$ ). The initial perturbation thus directs the formation of the transition state.

In aromatic chemistry, the rate of electrophilic substitution of a range of polycyclic alternant hydrocarbons is related logarithmically to the basicity<sup>216</sup>, as represented by the protonation equilibria in HF. Similarly, the relative reactivity of two similar aromatic compounds, e.g., toluene and benzene, towards different electrophiles, gives a measure of the extent of interaction in the transition state, as assumed in the rule of Brown and Nelson<sup>217</sup>. Since the selectivities (defined as reactivity relative to that of benzene) given in this way, vary from ca. 1.5 to  $10^4$ , a wide range of transition state structures, as found for  $S_N2$  and  $E_2$  reactions, must occur. The transition state may, thus, differ considerably in structure from a Wheland intermediate<sup>218</sup>.

### D.16.3

#### Radical Abstraction reactions

Radical reactions may be treated in the same way as nucleophilic substitutions, but here the interaction with occupied orbitals must be considered.

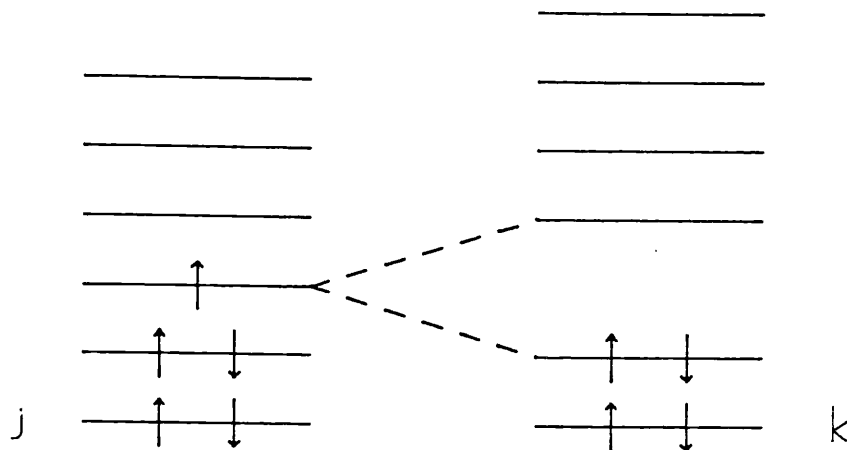


Fig. 8.

Interaction of a singly occupied orbital j with the HOMO and LUMO orbitals k.

In general, the interaction of the singly occupied j level with the HOMO and LUMO k orbitals will determine the perturbation energy.

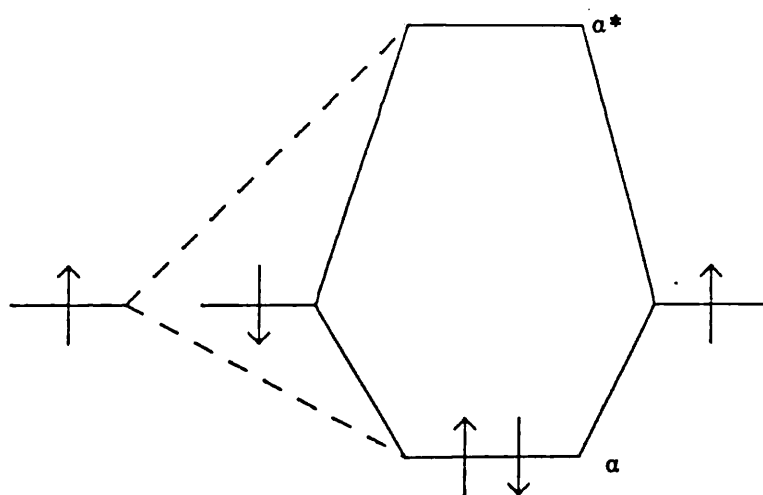
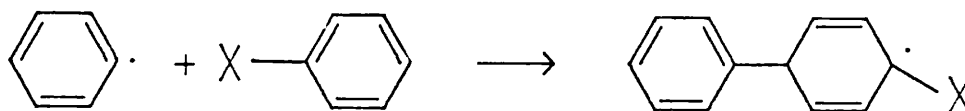


Fig. 9

The interaction of a radical with the C-H bond of a saturated hydrocarbon.

If we consider the interaction of a radical  $R\cdot$  with a saturated hydrocarbon  $R'CH_2-H$  (Fig.9), the C-H bond is originally formed by the combination of C and H atomic orbitals, as shown in Figure 9. Owing to the overlap term [equation 131], the energy of  $\sigma^*$  is usually very high and consequently  $R\cdot$  interacts more strongly with  $\sigma$  than with  $\sigma^*$ . In other words, radicals behave as weak electrophiles. This is not necessarily the case for other types of radical reactions. Addition to aromatic systems is assisted by both electron donating and electron attracting substituents, for example:



This is because  $\pi^*$  orbitals are usually lower in energy than  $\sigma^*$  orbitals, and, hence, the interactions of the lone electron with  $\pi$  and  $\pi^*$  levels are comparable.

#### D.16.4

#### The influence of polarity

So far we have concentrated mainly of the reactions of non-polar  $\pi$  systems and molecules of weak polarity, e.g. radicals, where orbital interactions normally determine the course of the reaction. For polar molecules, the energy of Coulomb interaction (equation 134) may become important and Coulomb and orbital terms may be in opposition<sup>219</sup>.

$$\Delta E = q_r q_s \gamma_{rs} 1.2 + 2 \sum_j^{\text{occ}} \sum_k^{\text{unocc}} \frac{C_j^2 C_k^2 \beta_{rs}^2}{a_j - a_k} \quad (134)$$

The equation is derived from a polyelectronic perturbation treatment and is an approximate equation for the perturbation energy<sup>219</sup>.

If a nucleophile is represented by a doubly filled atomic orbital ( $C_{rs} = 1.0$ ) equation 134 becomes:

$$\Delta E = q_r q_s \gamma_{rs} + 2 \frac{C_j^2 \beta_{rs}^2}{a_j - a_k} \quad (134a)$$

For certain restricted series of reagents these two terms change in the same direction with a change in structure of the nucleophile. For example, considering the substitution of an electron attracting substituent A in an alkoxide ion



This has the effect of (i) reducing the formal negative charge on the nucleophile and (ii) reducing the energy of the 'nucleophilic' orbital, (j), leading to decreased orbital interaction. Under these conditions the two nucleophiles show the same relative reactivity order to all electrophilic centres.

This is however not always the case, and the nucleophilic order may change with the nature of the electrophile<sup>220</sup>.

This may be understood by comparing alkylation and acylation. The first term of equation 134 is small for alkyl halides, and hence the reactivity order<sup>221</sup> follows the perturbation given by the second term, e.g.  $I^- > Br^- > Cl^- > F^-$  (Figure 10), i.e., it is orbital controlled.

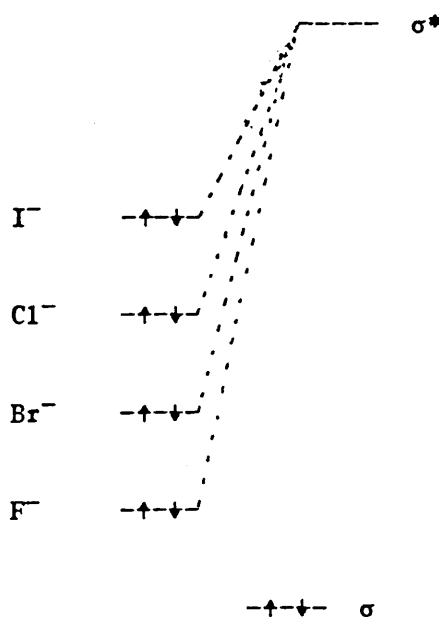


Fig.10. Orbital interactions in alkyl halides.

On the other hand, in acylation, the first term in equation 134 is large in view of the high positive charge on the carbonyl carbon atom, and although the orbital term is also increased, since a  $\pi^*$  level is lower than a  $\sigma^*$  level, the first term is dominant and leads to a reverse nucleophilic order (this provides a theoretical basis for the concept of 'hard' and 'soft' acids and bases<sup>222</sup>), i.e., to charge control<sup>219</sup>.

## D.16.5

Positional reactivity

The perturbation method is particularly useful in the prediction of the relative reactivity of two or more nucleophilic centres in a given nucleophile towards a range of electrophilic reagents. This is because the coefficients on atoms of the various orbitals of alternant hydrocarbons and their heteroaromatic analogues usually change in a regular way. The influence of the heteroatom can be introduced as a perturbation as in the method of Coulson and Longuet-Higgins<sup>22</sup>, which modifies the form of the wave function.

## D.16.6

Charge and orbital control

In general the reactions of the aromatic species will be charge or orbital controlled in view of the extensive interaction with the  $\pi$ -system.

The charge densities ( $C_{rj}$ ) on o- and p- carbon atoms of toluene (also for aniline, anisole etc.) can be represented diagrammatically (Figure 11.). Alternation leads to the conclusion that

$$q_{\underline{o}} > q_{\underline{p}} \text{ but } q_{\underline{p}}^f \gg q_{\underline{o}}^f$$

Thus strong perturbation (as measured by a large Brønsted coefficient, or a large reaction selectivity), should lead to exclusive p-substitution (as in Friedel Crafts acylation), weaker perturbation should lead to greater o-substitution.

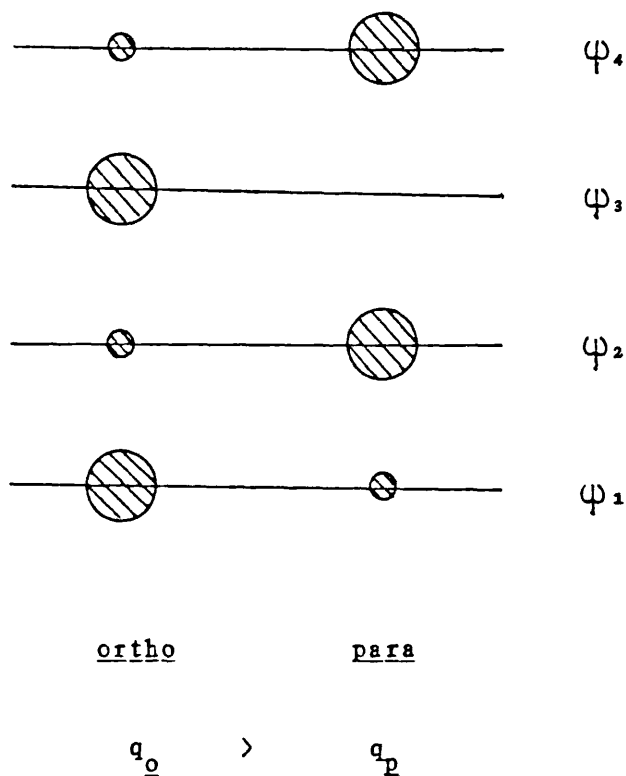


Fig.12. Charge densities on the o- and p-carbon atoms in toluene.

The available experimental data<sup>224</sup> for toluene (in homogenous solution) are in general agreement with those predictions. The above treatment is an over-simplification of the process, and in particular all the orbitals 1--> 4 should be considered. This leads to interesting results in the case of pyridine-N-oxide, where calculations of the total perturbation energy (equation 134) with gradually changing values of (j-- k) show a change in reactivity from  $C_2- > C_4- > C_3-$ . Electrophilic substitution has been observed in these three positions with change in electrophile<sup>225</sup>.

Michael addition to unsaturated ketones may be attributed to the large coefficient on the LUMO on the terminal carbon ( $C_3 = 0.435$ ,  $C_1 = 0.303$ ). The charge densities are in the opposite direction however ( $q_1^+ = 0.286$ ,  $q_3^+ = 0.392$ ), and hence reactions involving strong Coulombic interaction, e.g., reduction with  $AlH_4^-$  or  $BH_4^-$ , proceed at the carbonyl group.

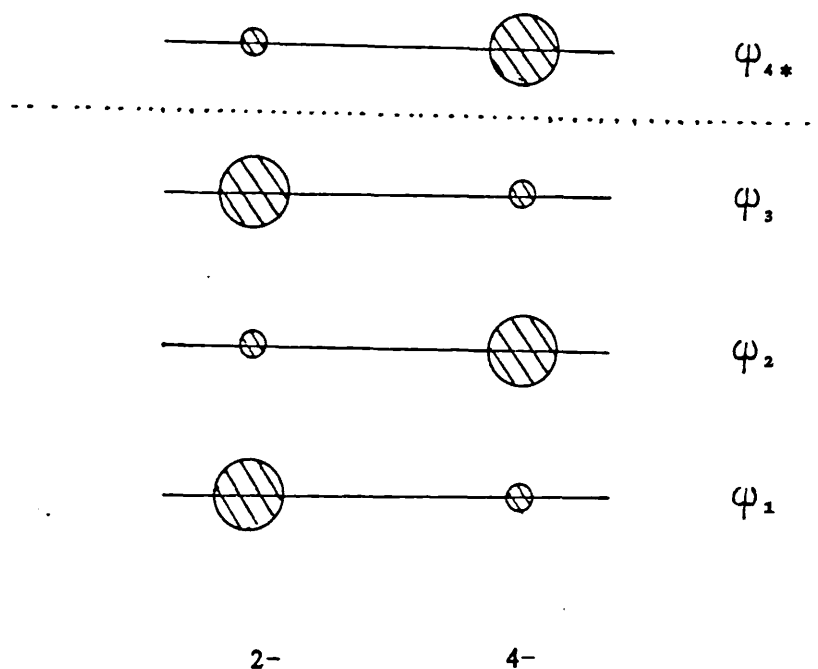


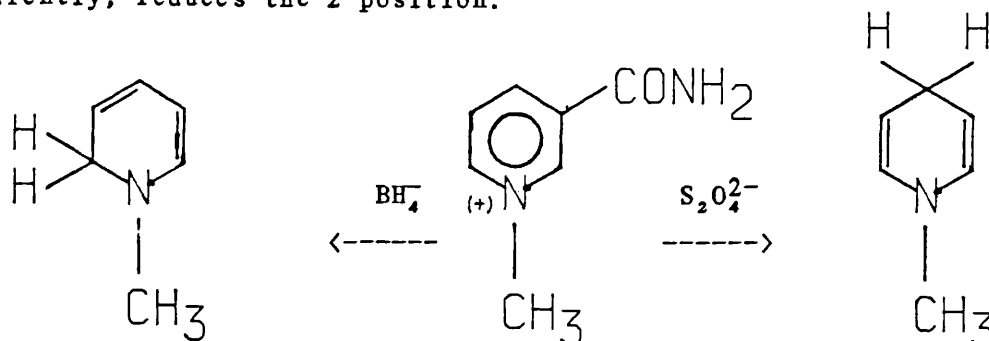
Fig. 13. Charge densities in positions 2- and 4- of pyridine.

Similarly in the reduction of pyridine and pyridinium salts<sup>226</sup>, the LUMO is used in the initial stages of bond formation.

Figure 13 shows that the coefficients on  $C_2$  and  $C_4$  alternate such that for the LUMO,  $C_4^0 > C_2^0$ , but  $q_2^+ > q_4^+$ . This means that reagents which interact strongly, react in the 4-position, whereas reagents which experience a large Coulombic (electrostatic) interaction tend to react in position 2.



Experimentally<sup>227</sup> it is found that  $S_2O_4^{2-}$ , which forms a strong complex, reduces the 4-position, whereas  $BH_4^-$ , which cannot interact covalently, reduces the 2-position.



#### D.17

##### SUMMARY

A study has been made of the reactivity of nitrogen containing aromatic heterocycles towards free radicals.

Oxidising agents [copper(II)benzoate, iron(III)benzoate, meta-dinitrobenzene and pentafluoronitrosobenzene] have little effect on the biaryl yield in the phenylation of pyridine, pyridazine or pyridazine, but have some catalytic effect in the phenylation of pyrimidine.

It is suggested that this difference is due to the difference between the redox potentials of the electron acceptors normally present in the system.

Relative rates of attack and isomer distributions obtained in the competitive phenylation of benzene with the heterocycles were found to vary with (a) both the initial peroxide concentration, and (b) the relative amounts of benzene and the heterocycle. This could be due to the complexation between the reagent and the heterocycle, and in some cases, with the catalyst. Increased complexation leads to selectivity determined by charge control and follows the order of the coefficients of the LUMO of the carbon atoms in the substrate. Where complexation is low, the reactivity is dictated by electron charge density, the radical preferentially attacking the site of lowest electron density. The relative rate is also affected by the relative reactivities of the free and the complexed substrates.

The phenyl radical is nucleophilic in aqueous acidic media, as are the cyclohexyl and methyl radicals.

Total electronic energies, nuclear binding energies, free valence numbers, localisation energies and the redox potentials (thermodynamic, not relative to the hydrogen electrode) for the biaryl / sigma-radical couples have been calculated by INDO<sup>233</sup> and CNDO<sup>232</sup> methods (Appendix). The reactivities observed correspond with the calculated order of reactivities in all cases except for pyridazine. This is attributed to the extensive nitrogen-nitrogen (N-N) interactions in pyridazine. Calculations on model pyridazine dimers which simulate the N-N interactions in pyridazine, give correct predictions for reactivity. N-N interactions are found to affect the reactivities of the other heterocycles, but to a lesser extent.

Changes in the rates of phenylation and methylation, with the extent of protonation of the heteroaromatic bases, have been studied, and qualitative values for the reaction rates estimated.

## APPENDIX

### A.1

Determination of proportionality constants: The relative rates of attack of the heterocycles by phenyl radicals in aqueous acidic media have been evaluated by the following method:

1. The pKa of the base has been used to determine the ratio of the base to the protonated base at the appropriate pH.

$$\text{pH} = \text{pKa} + \text{Log} \frac{(\text{B})}{(\text{A})} \quad (1)$$

Since pKa and pH are known for each experiment (B)/(A) can be easily determined.

$$\text{antilog} (\text{pH} - \text{pKa}) = \frac{(\text{B})}{(\text{A})} \quad (2)$$

Let  $(\text{B} + \text{A}) = (\text{B}) + (\text{A}) = \text{P}$  (the initial heterocycle concentration) (3)

Substituting for (B) in equation 2:

$$\text{antilog} (\text{pH} - \text{pKa}) = \frac{\text{P} - (\text{A})}{(\text{A})} \quad (4)$$

Thus numeric values for number of moles of the acidic (A) and the basic (B) forms of the heterocycle present in the reaction mixture can be determined.

Let  $k_a$  be the proportionality constant for the rate of biaryl formation from A. (No assumptions as to the exact nature of the reaction or the rate limiting step are made at this stage).

Assuming:                    yield of biaryl derived from A =  $k_a \times A$  (number of moles of A, the total volume is constant),

and :                         yield of biaryl derived from B =  $k_b \times B$

We get (for the 2-isomer):

$$\text{biaryl}_2 = (k_{a_2} \times A) + (k_{b_2} \times B) \quad (5)$$

Since numerical values for  $\text{biaryl}_2$  (yield of the 2-isomer), A, and B are known a simple linear equation in  $k_{a_2}$  (rate of attack for the acidic form at the 2-position) and  $k_{b_2}$  (rate of attack for the basic form at the 2-position) is obtained. Different numerical values for the coefficients A, B, and  $\text{biaryl}_2$  are obtained at a different pH. These simultaneous equations can be solved for numerical values of  $k_{a_2}$  and  $k_{b_2}$ . The units for A and B are in moles, but since the reaction is assumed to have gone to completion, in the absence of results for the yield of biaryl formation with respect to time, meaningful units for the proportionality constants cannot be assigned. The values are meaningful when used to compare the relative reactivities of the various species and the various positions within the system.

## A.2

The INDO and CNDO programs.

The programs used, perform the standard LCAO RHF MO calculation using a basis of N AOs for a molecule containing  $2*N(\text{DOCC}) + N(\text{SOCC})$  electrons, i.e., a set of N(DOCC) doubly occupied MOs and N(SOCC) singly occupied (open shell) MOs. If N(SOCC) is zero, the program merely omits the open shell section and performs the simple closed-shell calculation. The input arguments to the routine (in addition to N, N(DOCC), N(SOCC)) are H, COUL, and EXCH; the matrices of one-electron integrals ('core integrals') Coulomb integrals (ii,jj) and 'exchange' integrals (ij, ij), respectively.

The program assumes that these integrals are over an orthogonalised basis (i.e., OAOs or OHAOs) and, in the case of valence-only calculations, that the one-electron integrals contain precautions against variational collapse. Output is E, the total electronic energy, EPS the orbital energies, and P(TOT) and P(OPEN), the charge and bond-order matrices. P(TOT) is the total charge and bond-order matrix with contributions from open and closed shells, and where relevant, P(OPEN) is the open-shell contributions to P(TOT).

If any set of approximations is used to generate H, COUL and EXCH (including of course, 'EXCH = 0'), the program will enable this set of approximations to be tested within the MO model [including the approximation implicit in the use of COUL, EXCH: i.e.  $(ij, kl) = 0$  unless it is of Coulomb or exchange type].

Most existing methods use empirical data, overlap integrals and, s-type Coulomb integrals of ref. 228. These numbers are generated using the overlap integral program of reference 229 together with program GAMMA from reference 230. Also<sup>231</sup> the program PAIRS enables any approximation method to be tested in the wider context of a many-determinant model of molecular electronic structure (where the electron-pair model is relevant, of course).

The most widely used approximation methods use the 'invariance principle' and make use of empirical quantities for some elements of the one-electron Hamilton matrix. 'Empirical' values were found with respect to experiment or ab initio calculation (or parts of both). Thus, the results of these calculations do not refer to an explicitly-stated orbital basis and the interpretation of, for example, the charge and bond-order matrix is rather ambiguous. Using an explicit OAO or OHAO basis and no 'invariance principle' the way is open to investigate NSI schemes in both the MO and many-determinant formulations.

The skeletons of the programs used in our calculations are given below:

CNDO (J.A.Pople and G.A.Segal J.CHEM.PHYS., (1965) 43 S136)

(i) All elements of EXCH are zero:  $EXCH(I,J) = 0, \quad I \neq J$

(ii) Elements of COUL are given by the Coulomb integral

between the s-type AO on which the two AOs are based:

$$\begin{aligned} \text{COUL (I,J)} &= \int dv_1 \int dv_2 \phi_i^a(1)^2 \frac{1}{r_{12}} \phi_j^b(2)^2 \\ &= \int dv_1 \int dv_2 [ns^a(1)]^2 \frac{1}{r_{12}} [n's^b(2)]^2 \end{aligned}$$

- (iii) Off-diagonal elements of H are proportional to the corresponding overlap integrals

$$\begin{aligned} H(I,J) &= \beta_{\alpha\beta}^{\phi} S_{ij} \quad (I \neq J) \\ &= \frac{S_{ij}}{2} (\beta_{\alpha}^{\phi} + \beta_{\beta}^{\phi}) \end{aligned}$$

the proportionality constants  $\beta_{\alpha\beta}^{\phi}$  are characteristic of an atom pair  $\alpha, \beta$  and are obtained by fitting the ab initio calculations.

- (iv) Diagonal elements of H are taken from observed atomic data and 'corrected' for the presence of other nuclei:

$$H(I,I) = W_i^a + \sum_{\beta \neq \alpha} U_{\alpha\beta}$$

where  $U_{\alpha\beta}$  is a spherically-averaged nuclear attraction integral:

$$U_{\alpha\beta} = -Z_{\beta} \int dv_1 [ns^a(1)]^2 \frac{1}{rb}$$

(later papers use  $U_{\alpha\beta} = -Z_{\beta} * \text{COUL (I,J)}$ )

The atomic data  $W_i^\alpha$  are obtained either from atomic ionisation potentials (IP) and/or electron affinities (EA):

$$W_i^\alpha = -(\text{IP})_i - (Z - 1) * \text{COUL} (I, I)$$

or

$$W_i^\alpha = -[(\text{IP})_i + (\text{EA})_i] - (Z_a - 0.5) * \text{COUL} (I, I)$$

- (v) Interpretation of the orbital basis are ambiguous.  
Some workers assume AOs, some assume OAOs.

INDO (J.A.Pople, D.L. Beveridge and P.A. Dobosh  
J.Chem.Phys. (1967) 47 2026)

- (i) Elements of EXCH are included if  $\phi_i$  and  $\phi_j$  are on the same centre. Non-zero elements of EXCH are taken from atomic data.
- (ii) One-centre elements of COUL are taken from experimental data, otherwise the elements of COUL are obtained from the CNDO routines.



- (iii) The off-diagonal elements of H are evaluated as in CNDO except that the auxiliary formula

$$H(I,J) = W_{ij}$$

is used for one-centre off-diagonal elements for which  $S_{ij} = 0$ . The  $W_{ij}$  are determined from atomic data.

- (iv) The diagonal elements of H are the same as in the CNDO method: using

$$U_{\alpha\beta} = -Z_{\beta} * \text{COUL}(I,J).$$

The definition of the  $W_i^{\alpha}$  is slightly different from the CNDO W-values due to the inclusion of the atomic exchange integrals.

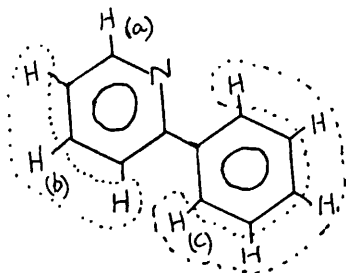
- (v) As for CNDO.

### A.3 IDENTIFICATION OF COMPOUNDS.

#### A.3.1 2-Phenylpyridine.

##### A.3.1.1 N.M.R.: -

- (a) doublet at 8.63ppm,  
integration, 1 proton.



(b) complex peak with multiple splitting at 8.02ppm, integration, 3 protons.

(c) complex peak with multiple splitting at 7.42ppm, integration, 5 protons.

A.3.1.2 Mass Spectra: -

(a) mass of M+ ion =155

A.3.1.3 Carbon Analysis: -

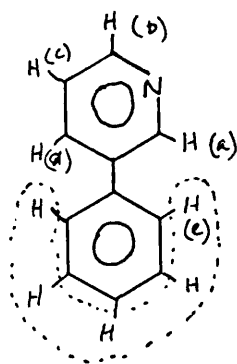
(a) nitrogen = 9.1%

(b) carbon = 85.0%

(c) hydrogen = 5.4%

A.3.2 3-Phenylpyridine.

A.3.2.1 N.M.R.: -



(a) singlet at 8.85ppm, integration, 1 proton.

(b) doublet at 8.58ppm, integration, 1 proton.

(c) triplet at 7.86ppm, integration, 1 proton.

(d) doublet at 7.72ppm, integration, 1 proton.

- (e) complex peak with multiple splitting at 7.43ppm, integration, 5 protons.

A.3.2.2 Mass Spectra: -

(a) mass of M<sup>+</sup> ion =155

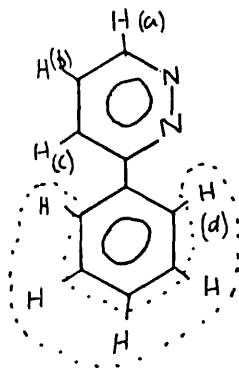
A.3.2.3 Carbon Analysis: -

(a) nitrogen = 9.3%

(b) carbon = 85.1%

A.3.3 3-Phenylpyridazine.

A.3.3.1 N.M.R.: -



(a) doublet at 9.18ppm, integration, 1 proton.

(b) triplet at 8.12ppm, integration, 1 proton.

(c) doublet at 7.80ppm, integration, 1 proton.

(d) complex peak with multiple splitting at 7.56ppm, integration, 5 protons.

A.3.3.2 Mass Spectra: -

(a) mass of M<sup>+</sup> ion =156

## A.3.3.3 Carbon Analysis: -

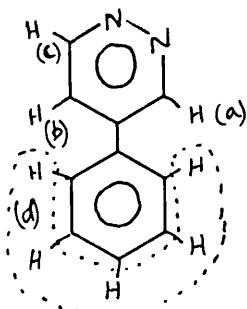
(a) nitrogen = 18.0%

(b) carbon = 76.2%

(c) hydrogen = 5.1%

## A.3.4 4-Phenylpyridazine.

## A.3.4.1 N.M.R.: -

(a) singlet at 9.09ppm,  
integration, 1 proton.(b) broad doublet at 8.08ppm,  
integration, 1 proton.(c) doublet at 9.16ppm,  
integration, 1 proton.(d) complex peak with multiple  
splitting at 7.49ppm,  
integration, 5 protons.

## A.3.4.2 Mass Spectra: -

(a) mass of M<sup>+</sup> ion =156

## A.3.4.3 Carbon Analysis: -

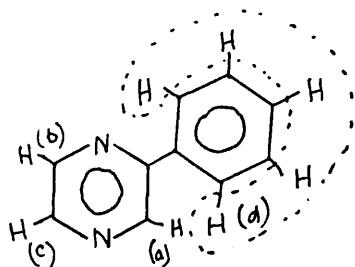
(a) nitrogen = 9.7%

(b) carbon = 84.2%

(c) hydrogen = 5.2%

## A.3.5 2-Phenylpyrazine.

## A.3.5.1 N.M.R.: -



(a) singlet at 9.06ppm,  
integration, 1 proton.

(b) doublet at 8.65ppm,  
integration, 1 proton.

(c) doublet at 8.52ppm.  
integration, 1 proton.

(d) complex peak with multiple  
splitting at 7.56ppm,  
integration, 5 protons.

## A.3.5.2 Mass Spectra: -

(a) mass of M<sup>+</sup> ion =156

## A.3.5.3 Carbon Analysis: -

(a) nitrogen = 9.3%

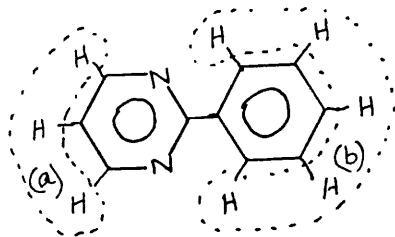
(b) carbon = 85.1%

(c) hydrogen = 5.2%

## A.3.6 2-Phenylpyrimidine.

## A.3.6.1 N.M.R.: -

(a) complex peak at 8.73ppm,  
integration, 3 protons.



(b) complex peak at 7.84ppm,  
integration, 5 protons.

A.3.6.2 Mass Spectra: -

(a) mass of M<sup>+</sup> ion =156

A.3.6.3 Carbon Analysis: -

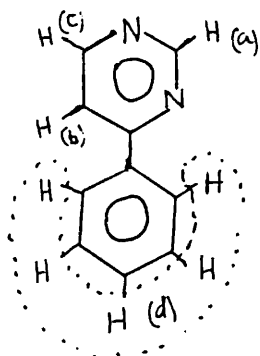
(a) nitrogen = 9.1%

(b) carbon = 84.8 %

(c) hydrogen = 5.6%

A.3.7 4-Phenylpyrimidine.

A.3.7.1 N.M.R.: -



(a) singlet at 9.30ppm,  
integration, 1 proton.

(b) doublet at 8.18ppm,  
integration, 1 proton.

(c) doublet at 9.21ppm,  
integration, 1 proton.

(d) complex peak with multiple  
splitting at 7.62ppm,  
integration, 5 protons.

A.3.7.2 Mass Spectra: -

(a) mass of M<sup>+</sup> ion =156

A.3.7.3 Carbon Analysis: -

(a) nitrogen = 9.0%

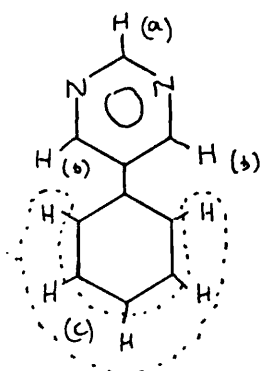
(b) carbon = 84.6 %

(c) hydrogen = 5.0%

Some residue was also obtained.

A.3.8 5-Phenylpyrimidine.

A.3.8.1 N.M.R.: -



(a) singlet at 9.28ppm,  
integration, 1 proton.

(b) singlet at 9.08ppm,  
integration, 2 protons.

(c) complex peak with multiple  
splitting at 7.58ppm,  
integration, 5 protons.

A.3.8.2 Mass Spectra: -

(a) mass of M<sup>+</sup> ion =156

A.3.8.3 Carbon Analysis: -

(a) nitrogen = 9.1%

(b) carbon = 84.6%

(c) hydrogen = 5.0%

Some residue was also obtained.

A.3.9 Retention Times obtained by g.l.c.

Compound	Column	Temp. °C.	Inlet pressure p.s.i.	Flow rate ml.min <sup>-1</sup>	Ret. time min.	Rel.Ret.*	Response (Area/Area)**
Biphenyl	10%FFAP	151	18	35	3.9	0.619	1.40
Dibenzyl	"	151	18	35	15.5	1.0	1.0
3-Phenylpyridazine	"	151	18	35	47.3	9.76	0.68
4-Phenylpyridazine	"	151	18	35	67.9	12.01	0.69
Phenylpyrazine	20%PEGA	178	18	43	10.2	1.62	0.74
2-Phenylpyrimidine	"	178	18	43	21.0	7.08	0.77
4-Phenylpyrimidine	"	178	18	43	12.8	4.30	0.77
5-Phenylpyrimidine	"	178	18	43	18.5	6.21	0.77
2-Methylpyridine	"	115	9.5	24	7.0	1.24	0.83
3-Methylpyridine	"	115	9.5	24	11.2	1.98	0.83
4-Methylpyridine†	"	115	9.5	24	11.7	2.07	0.80
Benzoic acid††	10%FFAP	151	18	35	24.8	3.94	0.28

\* retention time with respect to dibenzyl.  
\*\* area of peak for compound/area of peak for same weight of dibenzyl.  
† Small hump at retention time of 10.5 min. obtained for this compound even after extensive purification.  
†† Broad peak with considerable tailing.

The retention times and responses with respect to dibenzyl obtained for some of the compounds analysed by g.l.c.

TABLE XXXVII



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