SOME ASPECTS OF
THE HOMOLYTIC PSCHORR REACTION

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It is indeed a desirable thing to be well descended,

But the glory belongs to our ancestors.

Plutarch.

To my Mum

ABSTRACT

In furtherance of the study of the mechanism of the Pschorr and related reactions the decompositions of diazotised derivatives of the following 2-aminotriarylmethanols were carried out under three reaction conditions: 2-aminotriphenylmethanol, 2-amino-4'-methyltriphenylmethanol, 2-amino-4'-chlorotriphenylmethanol, 2-amino-4'-methoxy-triphenylmethanols, 2-amino-4'-chloro-4"-methyltriphenylmethanol, 2-amino-3',5'-dichloro-triphenylmethanol and 2-amino-3',5'-dimethyltriphenylmethanol.

The reactions of 2-aminotriarylmethanols, diazotised using amyl nitrite in benzene solution, resulted in products which resembled those of previously reported homolytic arylations. Accordingly, a homolytic mechanism was postulated for reactions under the present conditions. This was the first known application of these reaction conditions to effect intramolecular arylation, previous reports having been of intermolecular arylations only. The cyclisation reactions were accompanied by yields of phenols which were relatively and unexpectedly high in view of the small amount of water expected to be formed in these reactions.

Decompositions were also carried out in aqueous acidic conditions. Where no catalysts were added, the distribution of attack by the reactive intermediates (formed on dediazoniation) upon the various substrates in the reaction mixtures, was almost statistical. Thus 9-phenylfluoren-9-ols substituted in each aromatic system were obtained in almost equal amounts; fluorene-substituted products resulted from cyclisation onto substituted phenyl rings of the 2-aminotriarylmethanols and 9-arylfluorenols from ring closure onto unsubstituted rings. Phenols were obtained in yields slightly lower than those of cyclisation products, possibly as a result of steric effects which did not allow ready reaction between the formed reactive intermediates and water.

The results of copper-catalysed decompositions in aqueous acidic media were explained by postulating the formation of intermediate diazonium salt-copper complexes. Such complexes are expected to react further by expelling nitrogen with consequent formation of cyclic products and phenols.

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I should like to thank my supervisors, Professor G.H. Williams and Dr. R. Bolton, for suggesting the topic of research and their subsequent guidance throughout the ensuing period of investigation. To them, and to the many other investigators whose names appear in the reference section of this thesis, and whose guidance I gratefully acknowledge, I should like to express my appreciation in the words of Adam Curle: "They supplied the shafts of insight which I perhaps misapplied or misconstrued in building my system. I thank them and beg their pardon for possible use of their ideas. I only affirm that they cannot be held accountable for the totality I have attempted to construct." [Curle, A., "Mystics and Militants" (1972) p12, Tavistock Publications.]

My gratitude also goes to the rest of the community at Bedford College, the whole Teaching and Technical Staff of the Chemistry Department, the "workers" in Acland and Tuke laboratories and everyone else I had the pleasure of meeting.

Special thanks are reserved for Mrs. V. Brown for capably typing and presenting this thesis in its present form, and above all, for being a very pleasant person to know and to work with.

I must also mention the British Council without whose financial support this research could not have been possible. I should single out for special mention my past Programme Officers, Angela Truesdale (Mrs) and Debbie Simmons (Miss) for being very true friends during some periods of crisis.

Lastly, I should like to thank all members of my family (both immediate and extended) for their love and well wishes which I carry with me always. To: my late mum (let's hope it was not all in vain), dad, Adelaide, Nina, Eldah, Modie, Mike, Floe, Clara and all the rest, - simply "thanks".

Contents

		Page
Introduction		
1.	Homolytic and Heterolytic Reactions	1
2.1	Homolytic Arylation	4
2.2	Sources of Aromatic Radicals	6
2.2.1	Peroxides and Analogous Substances	6
	a) Diaroyl Peroxides	6
	b) Lead Tetrabenzoate, Phenyl Iodosobenzoate and Silver Halide Dibenzoate	7
	c) The Kolbe Electrolysis	7
	d) Oxidation of Carboxylic Acids	8
2.2.2	Diazo-, Azo- and Related Compounds	8
	a) Diazonium Salts	8
	b) Diazoic Acids and Diazoacetates (the Gomberg Reaction)	9
	c) Acylarylnitrosamines	14
	d) Triazens	21
	e) Arylazotriphenylmethanes	24
	f) Diazonium Tetrafluoroborate and Pyridine	26
	g) Aromatic Amines and Amyl Nitrite	27
	h) Other Related Sources	28
2.2.3	Miscellaneous Sources	29
2.3	Aryl Radicals in Biaryl Synthesis	31
2.4	Mechanisms and Kinetics of Arylation Reactions	34
2.4.1	The Peroxide Reaction	36
2.4.2	Diazo Compounds	45
2.4.3	Quantitative Data of Arylation Reactions	45
	A. The Peroxide Reactions	45
	B. Comparison Between Various Aryl Radical Sources	48
	C. Polarity in Aryl Radicals	50

		Page
2.5.1	Intramolecular Arylation	56
2.5.2	The Pschorr and Related Cyclisation Reactions; Suggested Mechanisms	62
2.5.2.1	The Copper-Catalysed Decompositions	62
	A. Decompositions of Dry Diazonium Salts in Acetone	63
	B. Decompositions in Aqueous Acidic Medium.	67
2.5.2.2	The Uncatalysed Thermal Decomposition in Acidic Solution	73
2.5.2.3	Decompositions under Gomberg Reaction Conditions	78
2.5.2.4	Cyclisations with Acylarylnitrosamines and Triazens	81
3.	Some Aspects of the Homolytic Pschorr Reaction	81
4.	Experimental	83
4.1	Attempted Syntheses of 9-(2-Aminophenyl)fluorene	84
4.2	2-Aminotriphenylmethanol and Derivatives	86
4.2.1	Substituted 2-Aminobenzophenones	86
4.2.2	Substituted Fluorenones	88
4.2.3	Nuclear- and Phenyl-Substituted 9-Phenylfluoren-9-ols	89
4.2.4	2-Aminotriphenylmethanols	92
4.2.5	Deamination Reactions of the 2-Aminotriphenylmethanols	96
	A. Thermal Decompositions in Aqueous-Acidic Solutions	96
	B. Thermal Decompositions in Benzene, the Use of Amyl Nitrite in Diazotisations leading to Intramolecular Cyclisation	101
	C. The Copper-Catalysed Decompositions in Aqueous Acidic Solutions	106
4.2.6	Quantitative Analysis of Reaction Products	110

		Page
5.	Discussion	112
5.1	Synthesis of Intermediates	112
5.1.1	9-(2-Aminophenyl)fluorene	112
5.1.2	2-Aminotriphenylmethanols and Derivatives	116
5.2	Decomposition Reactions of Diazotised 2-Aminotriphenylmethanols	119
5.2.1	Reactions in Benzene, using Amyl Nitrite for Diazotisation	119
5.2.2	Uncatalysed Decompositions in Aqueous Acidic Media	128
5.2.3	Copper-Catalysed Decompositions of Diazotised 2-Aminotriphenylmethanols in Aqueous Acidic Media	140
5.3	Conclusion	148
References		150

INTRODUCTION

1. Homolytic and Heterolytic Reactions

The observation by Waters[1,2] that there are two possible ways in which a covalent molecule may be disrupted during the course of a chemical change has proved to be an important landmark in the study of free-radical chemical reactions. The terms homolysis and heterolysis were first used by Ingold[3] to distinguish between these two modes of bond fission:

Heterolysis

$$AB \longrightarrow A^- + B^+ \qquad (1)$$

and

Homolysis

$$AB \longrightarrow A^\bullet + B^\bullet \qquad (2)$$

where A and B are atoms or groups[4,5].

The intrinsic difference between (1) and (2) for a neutral molecule is that whereas the former results in ions of opposite charge, the latter gives two neutral radical species each possessing an unpaired electron.

Hey and Waters[2] gave simple guiding principles to predict the likely mode of fission in a molecule, viz:

i) neutral radicals are likely to be formed from those molecules which readily undergo thermal self-decomposition at comparatively low temperatures;

ii) photochemical reactions are likely to involve free radical formation;

iii) reactions in solvents containing ions or dipoles, or of high dielectric constant are unlikely to proceed via neutral radicals, whilst reactions in non-polar solvents of low dielectric constant may do so;

and (iv) a non-ionic fission of a covalent link will be improbable it the dipole moment of that link is large.

In energy terms only, homolysis would appear as the favoured mode of fission, since, in heterolysis an extra amount of coulombic energy must be required to separate oppositely charged particles. This is true of gas phase reactions, but in solution the association between solute and solvent molecules leads to a mutual perturbation of their electronic fields, hence ionisation may be favoured.

Williams[4,5] classified organic radicals according to their reactivity as follows: radicals of (i) long life, e.g. triarylmethyls, which are stabilised by resonance; and (ii) short life, e.g. the phenyl and methyl radicals, with no such stabilisation. Subsequent reference to the former group as stable free radicals was later modified to "persistent" free radicals to describe radicals having a lifetime significantly greater than that of methyl under the same conditions[6]. Dermer and Edmison[7] differentiated between radicals in solution, which can be characterised by physical means, and hence assumed by them to be too unreactive to cause direct aromatic substitution; and transient radicals whose presence can only be deduced from their effects. Although their[7] classification of radicals was, in essence, correct, their assumption that stabilised radicals were unreactive towards aromatic substrates was erroneous, such reactions, e.g. the reaction between the relatively stable triphenylmethyl radical and

benzene, being reported later[12].

The fate of the radicals is adequately dealt with in the excellent reviews, some of which are quoted above[2,4,7]. The main ways in which radicals may react are as follows:

(i) dimerisation or combination,

$$R^{\bullet} + R^{\bullet} \longrightarrow RR \qquad (3)$$

(ii) disproportionation by mutual hydrogenation and dehydrogenation

$$2RCH_2CH_2^{\bullet} \longrightarrow RCH_2CH_3 + RCH = CH_2 \qquad (4)$$

(iii) radical transfer,

$$R^{\bullet} + XR' \longrightarrow RX + R'^{\bullet} \qquad (5)$$

(iv) addition to multiple bonds, the first stage of which is expressed by the equation:

$$R^{\bullet} + \quad >C=C< \longrightarrow >\underset{\displaystyle R}{\overset{|}{C}}-\overset{\bullet}{C}< \qquad (6)$$

(v) hydrogen-abstraction reactions e.g. abstraction from a hydrogen-containing solvent:

$$R^{\bullet} + SH \longrightarrow RH + S^{\bullet} \qquad (7)$$

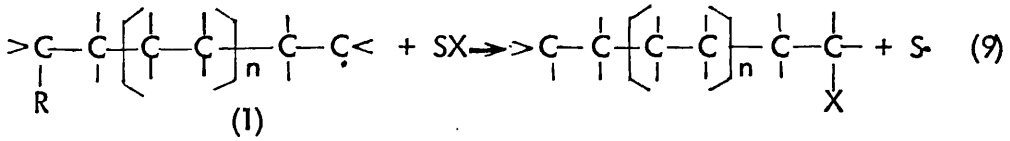
and (vi) substitution reactions, including aromatic substitution which is the main subject of discussion here and can be summarised thus:

$$Ar^{\bullet} + Ar'H \longrightarrow ArAr' + (H^{\bullet}) \qquad (8)$$

In equation (5) the nature of the final product is dependent upon the radical $R'^{\bullet}$. The radical may react again as in equation (5) to give another radical $R''^{\bullet}$, which may or may not be the same as $R'^{\bullet}$. If the same, then a chain reaction is set up and the process repeats itself until

the chain is somehow interrupted. If R'· (or R"·) is relatively unreactive, reaction (5) results effectively in the termination of the reaction, since stationary concentrations of the unreactive radical sufficiently high for reactions of type (3) and (4) to assume predominance are established.

Reaction (6) may lead to polymerisation by further addition to olefin molecules to give (1). Termination may be by equations (3), (4) or (7). Alternatively, an added substance (SX) can effect termination (equation 9).



(1) (9)

where S· is relatively unreactive and is removed by either dimerisation or disproportionation.

2.1 Homolytic Arylation

Probably the earliest example of homolytic aromatic substitution was reported, but not recognised as such, by Kuhling in 1895[8]. By allowing sodium p-nitrobenzenediazoate to react with nitrobenzene and toluene Kuhling obtained substitution products, namely 4,4'-dinitrobiphenyl and 2,4'-dinitrobiphenyl from the former, and 2-methyl-4-nitrobiphenyl from the latter compound. In 1897 Bamberger[9] reported the formation of biphenyl from the decomposition of nitrosoacetanilide in benzene. Two papers published by Gomberg[10] in 1924 and 1926 reported processes which conformed to this type of reaction. The anomalous nature of these reactions as compared to the then established pattern of either electrophilic or nucleophilic aromatic substitution was completely overlooked for a further ten years after Gomberg's published results. It was Grieve and Hey[11] who in 1934 drew attention to this anomaly and postulated that these reactions involve intermediate free radicals which are electrically neutral.

In its simplest form homolytic aromatic substitution may be represented as follows:

$$Ar\cdot + Ar'H \longrightarrow ArAr' + H\cdot \qquad (10)$$

an expression of the direction of the reaction only. There is, in fact, no evidence of the intermediacy of a free hydrogen atom.

The subject of homolytic aromatic substitution of homoaromatic substitution has been very comprehensively reviewed[2,4,5,12-15]. More recently interesting new reactions have been developed with heteroaromatic compounds, particularly with protonated bases, which undergo selective and synthetically useful substitutions by nucleophilic radicals. Thus, several pyridine derivatives have been phenylated both in neutral and acidic media. For example, under neutral conditions, 4-substituted pyridines are substituted both in the 2- and 3- positions, whereas in acidic solution, the substitution is almost exclusively at the 2- position[22,23]. From comparing substitution products derived from various radicals, e.g. methyl, phenyl, aryl, carbamoyl, amino cation, ($R_2\overset{+\cdot}{N}H$), α- oxyalkyl, α-amidoalkyl etc., it was concluded that phenyl radicals possess a small but net nucleophilic character[18,22,99].

Several review articles on substitution of heteroaromatic compounds have been published. These deal with such interesting aspects as substitutions of heteroaromatic compounds[15], aromatic and heteroaromatic alkylations[16] and arylation[17], reactivity indexes and transition states for these reactions[18], the behaviour of thiophen towards free radicals[19] and the properties of thiophen radicals[20], the substitutions of protonated heteroaromatic compounds[21] and the applications of some aromatic

substitutions in preparative organic chemistry.

Homolytic arylation reactions have interested chemists mainly for two reasons. Firstly, biaryl synthesis, especially where the two aromatic nuclei are substituted, is of great potential value; in certain cases being the only route to the biaryl. Secondly, such reactions have undoubted theoretical interest for the understanding of the reactivity of both aromatic free radicals and the chemistry of free radicals in general.

2.2 Sources of Aromatic Radicals

2.2.1 Peroxides and Analogous Substances

a) Thermolysis or photolysis of diaroyl peroxides e.g. benzoyl peroxides, results in the formation of aryl radicals.

$$PhCO.O.O.COPh \longrightarrow 2Ph.CO.O\cdot \qquad (11)$$

$$Ph.CO.O\cdot \longrightarrow Ph\cdot + CO_2 \qquad (12)$$

The thermal decomposition of benzoyl peroxide (equation 11) yields two benzoyloxy radicals, some of which undergo decarboxylation to give phenyl radicals. Thus, stationary concentrations of both aroyloxy and aryl radicals are present in the reaction at all times during the reaction[35]. When such decompositions are carried out in an aromatic solvent, which is also the substrate, nuclear substitution by either the aroyloxy or the aryl radicals is, in principle, possible.

The purified peroxides are generally crystalline substances. Their decomposition is convenient to carry out; product isolation is generally easy and yields of biaryl are generally higher (yields in excess of 1 mole biaryl per mole of peroxide have been reported under optimum conditions)

than that from other radical sources[14]. These inherent advantages in the use of peroxides over other radical sources has made them (the peroxides) the most useful and most studied sources of aryl radicals. There is an extensive literature[4,5,7,12,14,15,35] available on these reactions.

Early reported work on peroxide decompositions in a variety of aromatic solvents was carried out by Gelisen and Hermans[24] and Boeseken and Hermans[25]. They showed that, as well as biaryls, the products of such decompositions included carbon dioxide, the aroic acid, and considerable amounts of high-boiling resins, whose significance was not then appreciated. Subsequently the reaction became of great value forming the basis of much work on mechanism as will be discussed in the sections following. Dermer and Edmison[7] reviewed the preparative aspects of the reaction.

(b) Lead tetrabenzoate, phenyl iodosobenzoate and silver halide dibenzoate decompose thermally to give aryl radicals and subsequently biaryl when in aromatic solvents. The decomposition sequence for lead tetrabenzoate is considered to be:

$$Pb(O.CO.Ph)_4 \longrightarrow Pb(O.CO.Ph)_2 + 2Ph.CO.O\cdot \qquad (13)$$

$$PhCO.O\cdot \longrightarrow Ph\cdot + CO_2 \qquad (14)$$

the decomposition temperature being in the range 125-130°C[12]. The other two sources decompose in a very similar manner and within a comparable temperature range.

(c) The Kolbe-type electrolysis of the benzoate anion results in the formation of a phenyl radical thus:

$$PhCOO^- \longrightarrow PhCOO^{\cdot} + e^- \quad (15)$$

$$PhCOO^{\cdot} \longrightarrow Ph^{\cdot} + CO_2 ; \quad (16)$$

the method however being of limited use in non-aqueous media. Successful phenylation of pyridine has been reported[29] using this method.

(d) Russell and Thomson[30] produced aryl radicals from the oxidation of carboxylic acids with a hot solution of potassium persulphate. The process is effectively similar to the Kolbe electrolysis, since it involves the removal of an electron from the carboxylate anion.

2.2.2 Diazo-, Azo- and Related Compounds

(a) Diazonium Salts

Arylation using these sources of radical are most simply carried out by heating an aqueous acidic solution of the diazonium salt in a two phase reaction with organic substrates, e.g.:

$$C_6H_5\overset{+}{N}_2Cl^- + ArH \longrightarrow C_6H_5Ar + N_2 + HCl \quad (17)$$

Under the stated conditions an ionic decomposition mechanism would be easier to rationalise than a homolytic one, since, the only way by which an aryl diazonium cation can give rise to radicals is by reactions yielding ionised nitrogen or water molecules, processes requiring prohibitively high energies[68] (compared to the heterolytic process); i.e.

$$C_6H_5\overset{+}{N}_2 \; X^- \longrightarrow C_6H_5^{\cdot} + (N:::N:)^{\cdot +} \quad (18)$$

and

$$C_6H_5\overset{+}{N}_2 \; X^- + H_2O \longrightarrow C_6H_5^{\cdot} + (H:\dot{O}:H)^+ + N_2 \quad (19)$$

are both unlikely decompositions.

Evidence for a heterolytic mechanism in the thermal decomposition of diazonium salts in acidic aqueous solutions is based on the observation

that the reaction is accurately first order over the full course (10-99%) and is independent of the presence of or absence of a large variety of anions, or of acidity over a considerable pH range[33,65-68]. Biaryl yields of up to 40% based on the amino have been reported in such reactions[10].

Intervention of aryl radicals is more probable when certain metals are added to the diazonium decomposition mixtures. Waters[34] demonstrated the formation of radicals when such metals as antimony, bismuth, lead or mercury were added to an acetone mixture of the diazonium compound. The metals suffered attack during the decomposition despite the mixture being kept neutral with calcium carbonate. Such metals could be considered as functioning as electron donors in the reaction as represented below:

$$ArN_2^+ + e^- \longrightarrow Ar\cdot + N_2 \qquad (20)$$

e^- being the electron donated in a redox reaction between the diazonium salt and the metal.

A comparison can be drawn between these reactions and metal-catalysed decompositions of diazonium salts which also result in the formation of free radicals, e.g. the formation of polyphenyls in the copper-catalysed decomposition of benzenediazonium sulphate (and formate) arises as a result of successive homolytic substitutions[35-37].

Catalysis of the diazonium cation decomposition by metals most likely involves cation reduction as in equation (20). The low oxidation potential of copper and the cuprous cation was discussed by Waters[68,70] and this property makes copper a useful catalyst. The Meerwein reaction involves use of a copper salt, cupric chloride, as catalyst in the decomposition, in 70% aqueous acetone, of an aryldiazonium salt in the

presence of an olefinic compound substrate. The Meerwein arylation proceeds best with the highest yields when the double bond is activated towards the nucleophilic phenyl radical attack by an electron-attracting group Z, such as a carbonyl, cyano, aryl, chloro, etc. The net result is the union of the aryl group with the carbon atom β to the activating group either by substitution of a β-hydrogen atom or by addition of Ar and Cl to the double bond.

$$ArN_2Cl + RCH = CRZ \xrightarrow[salt]{copper} ArCR = CRZ \text{ and/or} \quad (21)$$

$$ArCHRC(R)ClZ \quad (N_2 \text{ evolved})$$

The reaction has been adapted for biaryl preparation[38,39] but yields tend to be low. In a reaction between diazotised p-nitroaniline and nitrobenzene, a mixture of the three isomeric dinitrobiaryls was obtained in a yield of 13%.

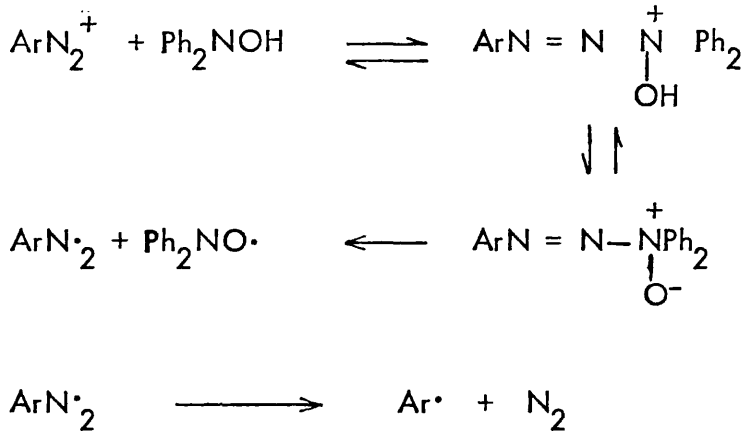
The generally accepted mechanism of the Meerwein reaction involves intervention by an aryl radical Ar· from the diazonium salt, though the manner of its formation and its subsequent reaction are still controversial. Details of some proposed schemes of such reactions are included in two reviews[40,41].

Stabilised diazonium salts were used in an attempt to increase biaryl yields. For an example, decomposition of diazonium salts stabilised by either naphthalene-1-sulphonic acid, naphthalene-1,5-disulphonic acid or zinc chloride resulted in yields of biaryl of up to 70%[42]. Pettit and Tatlow[43] used diazonium trifluoroacetates as aryl radical sources. Williams[35], in an attempt at a mechanism of the decomposition of stabilised diazonium salts, suggested an equilibrium in solution between the ionic and covalent forms of the trifluoroacetates, the latter dissociating to give aryl radicals.

Other diazonium salts decomposed in arylation reactions included diazonium sulphates,[44,45] and diazonium tetrafluoroborates[46] both of which were used mainly in intramolecular arylation reactions.

A recent report suggests that the nature of the specific solvation of diazonium salts has considerable influence on whether these salts decompose homolytically or heterolytically. A homolytic mechanism seems to be favoured in solvents of high nucleophilicity, e.g. DMSO or HMPA or by addition of added nucleophiles, e.g. diphenylhydroxylamine, (see Scheme XI) whereas in solvents of low nucleophilicity a heterolytic mechanism predominates[142,143].

Scheme XI



b) Diazoic Acids and Diazoacetates (the Gomberg Reaction)

Kuhling's preparations of biaryls by reacting sodium p-nitrobenzenediazoate with nitrobenzene and toluene have already been mentioned (section 2.1). Gomberg and his co-workers[10] adapted this reaction to give a general reaction of preparative value. In its simplest form the reaction consists of the decomposition of diazoic acid (RN_2OH) in a heterogenous aqueous/aromatic medium, the latter participating as substrate and the former as diazonium salt solvent, at temperatures of

0-5°C. Addition of alkali converts the diazotised amine into the covalent diazoic acid (or diazohydroxide) which reacts with the arene present as in equations (22) and (23) below:

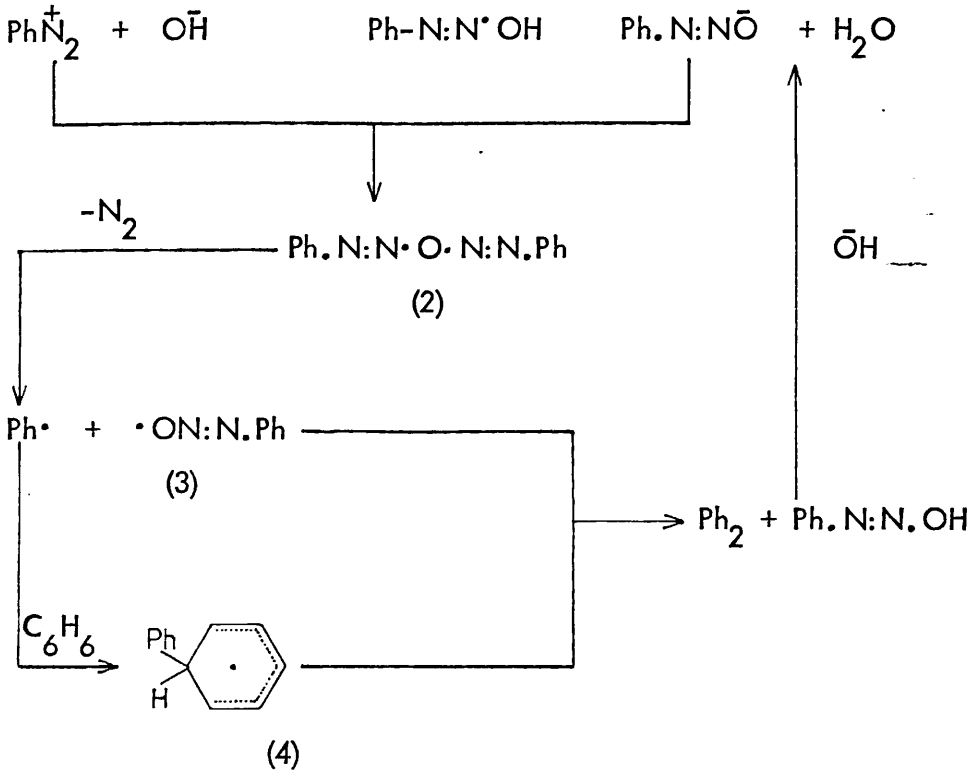
$$Ar'\overset{+}{N}_2Cl^- + NaOH \longrightarrow Ar'N_2OH + NaCl \quad (22)$$

$$ArN_2 = OH + ArH \longrightarrow ArAr' + N_2 + H_2O \quad (23)$$

Biaryl yields are in the range of about 5-40% based on the amine[12]. Grieve and Hey[31] demonstrated that the reaction occurs in the non-aqueous phase by showing that benzoic and anthranilic acids are not attacked by aryl radicals in the Gomberg reaction unless first converted into the water-insoluble esters.

The mechanism of the reaction was established by Ruchardt and Merz[71]. The steps leading to formation of aryl radicals are outlined in Scheme I below. Formation of the anhydride (2) takes place at pH $\sim$ 12, and at lower pH values there may be no diazoate present in the equilibrium mixture, but this depends on the substituent, if any, present in the nucleus; e.g. at pH 8.5 benzenediazonium chloride exists to a certain extent in the diazoate[71]. The reaction was shown to be of second order with respect to the diazonium salt[71].

SCHEME I



The above mechanism is supported by the work of Eliel, Saha and Meyerson[72] on reactions with benzene-d. Their results indicated the formation of a persistent radical intermediate (3) capable of scavenging the phenylcyclohexadienyl radicals (4) before they accumulated to a sufficient concentration for dimerisation or disproportionation to become important (see section 2.3). Electron spin resonance spectroscopy confirmed the presence of PhN:NO· (3) as a persistent radical[73] in the reacting solution.

Arylation of solid aromatic compounds is possible in solvents relatively inert towards the radicals involved[31], e.g. chloroform and carbon tetrachloride, but usually with extended times.

The low yields of biaryl and the formation of large quantities of intractable tars as by-products constitute the major drawbacks of the

Gomberg reaction, both for synthesis and mechanistic studies. Modifications of the original Gomberg reaction aimed at improving yields and obtaining cleaner, more easily isolable products have been reported. Hey and co-workers[32] reported an increase in the yields of o-, m- and p-nitrobiphenyls from 21, 18 and 26% to 45, 45 and 60% respectively when aqueous sodium acetate was used to bring about the decomposition of diazotised nitroaniline in benzene, in place of aqueous sodium hydroxide.

c) Acylarylnitrosamines

The homogenous decomposition of acylarylnitrosamines has probably been the most widely used and studied of the diazo- and related aryl radical sources. Discovered by Bamberger[9], the method was developed as a source of aryl radicals by Grieve and Hey[11]. Their study of the reaction, which revealed the relation between this reaction and the Gomberg process confirmed Bamberger's claim about the existence of tautomerism between the acylarylnitrosamines and the corresponding diazoacetates[47].

$$ArN(NO)COR \rightleftharpoons Ar\text{-}N{=}N\text{-}OCOR \qquad (24)$$

(5)

A similar claim was made by other early investigators[48,49]. Thus acylarylnitrosamines react with aromatic hydrocarbons like alkaline diazo solutions with the formation of biaryls and they couple with β-naphthols and phenols, though surprisingly in the o-position[74], with the latter compounds.

Acylarylnitrosamines can be prepared by acylation of diazoates[9,74-77] or by nitrosation of acylarylamines[50,51,78,79]. Decomposition of these compounds is carried out at moderate temperatures (25-50°) and Hey and co-workers found the reaction to be of first order[2,11,80]. The mechanism

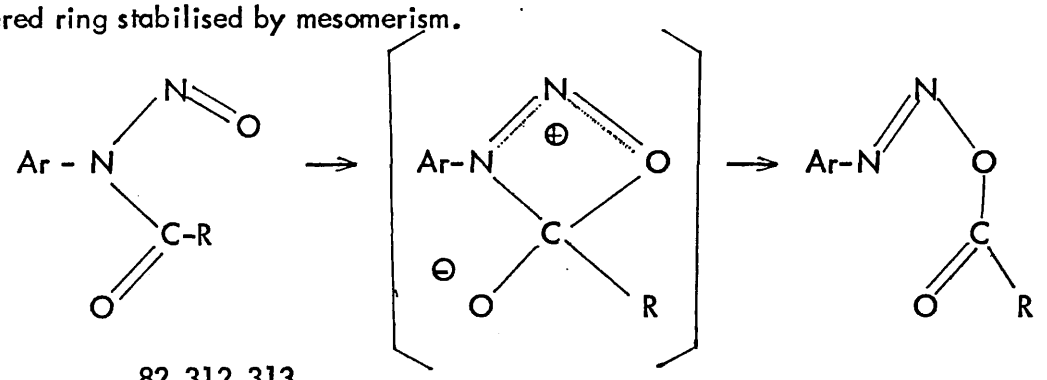
of this decomposition puzzled generations of chemists since Bamberger's discovery that when the reaction is carried out in the presence of benzenes, biaryl and acetic acid are formed (equation 25).

$$ArN(NO).CO.CH_3 + C_6H_6 \longrightarrow C_6H_5Ar + N_2 + CH_3CO_2H \qquad (25)$$

Hey's hypothesis of a mechanism consisting of a rapidly equilibrating tautomerism, acylarylnitrosamine $\rightleftharpoons$ diazoacetate, followed by homolytic fission of the latter into nitrogen, a phenyl, and an acetyl radical (equation 26)[2,11,80] was quickly succeeded by Huisgen's "rolling off" mechanism.

$$Ar - N{=}N{-}O{-}COCH_3 \longrightarrow Ar^{\bullet} + N_2 + \dot{O}{-}COCH_3 \qquad (26)$$

Huisgen's line of thought[81-84] was of a rapid homolytic reaction following the rate-determining rearrangement of the acylarylnitrosamine into the metastable diazoacetate. The rolling off mechanism envisaged the intermediacy of a four-membered ring stabilised by mesomerism.



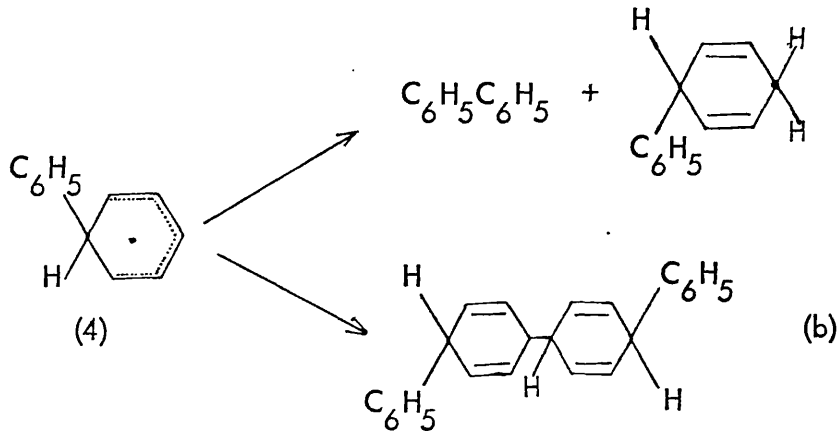
(27)

Subsequent work[82,312,313] on the dependence of the rate of the rearrangement on both the aryl and acyl groups in the acylarylnitrosamine, and on the catalysis of the reaction by bases, led to the formulation of the rearrangement as an intramolecular process involving nucleophilic attack by the oxygen of the nitroso-group on the carbonyl atom as represented above. The main flaw of the two pathways outlined above lay in the fact that acetyloxy radicals, $RCO.O^{\bullet}$, formed according to equation (26), should have given evidence of their presence, as they do in the Kolbe electrolysis, through their typical decarboxylation reaction followed by the formation of products of reactions of methyl radicals, but none of these were

detected in the reaction. Thus for a good part of the 1950's the belief was that homolysis was triggered off only by presenting the diazoacetate molecule with the appropriate solvent molecules, e.g. an alcohol. For the radical intermediates, it was believed, the acceptor was already fixed before the radicals were released from their original molecule and so they never became free in the true sense. That indeed the process was homolytic, was concluded from the aromatic substitution products[85,86] which closely corresponded to those of the then known homolytic processes. The small and remarkably constant percentage of m-nitrobiphenyl in the phenylation of nitrobenzene using this route and common to other homolytic processes was an example of such evidence[4,87].

The detection of persistent radicals[73,88,89] by ESR spectroscopy, and of short-lived species such as the aryl carbonium ion and benzyne[90,91] led to the reinvestigation of the mechanism of the decomposition of acylarylnitrosamines and subsequently to the now accepted pathway.

One flaw of the mechanisms put forward above, i.e. the intermediacy of the acetoxy radical that could not be very satisfactorily justified from experimental evidence, has been mentioned. Another discrepancy of the pathways suggested was that, in other, well characterised homolytic reactions between benzene and phenyl radicals, generated from benzoyl peroxide or phenylazotriphenylmethane (see section 2.4), products of dimerisation (equation 28b) and disproportionation (equation 28a) of the phenylcyclohexadienyl radical (4) are formed as in equation (28).



In the case of N-nitrosacetanilide such by-products are absent, suggesting a very efficient oxidation of the radical (4) to biaryl.

Ruchardt and Freudenberg[92] were the first to put forward the most satisfactory scheme, taking account of all the then available experimental evidence, (Scheme II). The key step of their proposed pathway involved the stable (π-type) phenyldiazoxyl radical, PhN=NO· (3) capable of abstracting hydrogen, and thus cleanly oxidising phenylcyclohexadienyl (4) radical to biphenyl.

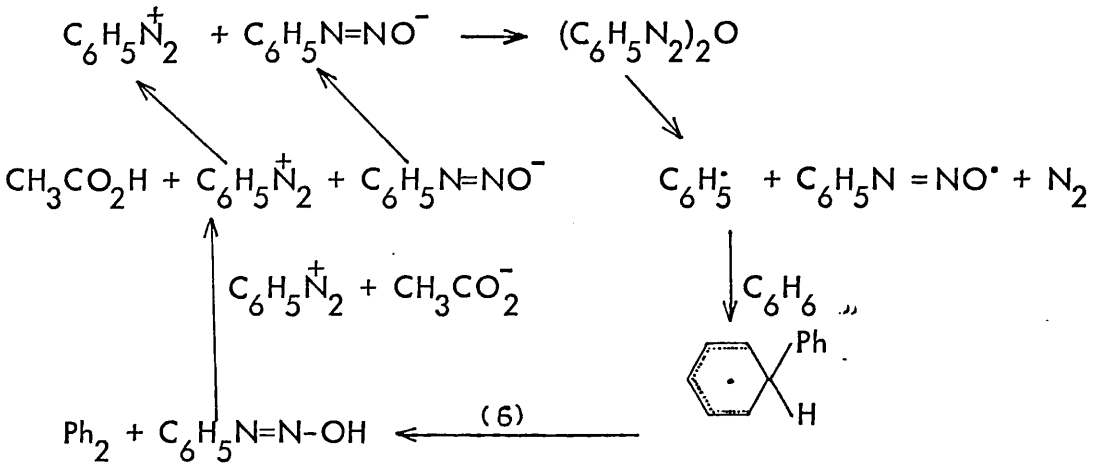
SCHEME II

$$C_6H_5N(NO)COCH_3 \longrightarrow C_6H_5N{=}NO.CO.CH_3 \rightleftharpoons C_6H_5\overset{+}{N}_2\ CH_3CO_2^-$$

Initiation

$$C_6H_5N{=}NO.CO.CH_3 + CH_3CO_2^- \longrightarrow C_6H_5N{=}N\bar{O} + (CH_3CO)_2O$$

Chain Process



The long lived ESR signal which Ruchardt and his co-workers[92,93] attributed to PhN=NO• (6) was later challenged by Hey and Perkins[94] who showed that this ESR signal was that of a nitroxyl (N-phenylacetamido)-phenyl nitroxyl radical (7), produced by scavenging of a phenyl radical by N-nitrosoacetanilide (equation 29).

$$C_6H_5^{\bullet} + C_6H_5N(NO)COCH_3 \longrightarrow \begin{matrix} C_6H_5NO^{\bullet} \\ | \\ C_6H_5NCOCH_3 \end{matrix} \qquad (29)$$

(7)

In consequence Chalfont and Perkins[84] proposed a new mechanism, which differed from Scheme II only in the following:

(a) the initiation step, as different from Scheme II, became:

SCHEME III

$$C_6H_5N = NO.CO.CH_3 \longrightarrow C_6H_5^{\bullet} + N_2 + CH_3CO_2^{\bullet}$$

$$C_6H_5^{\bullet} + C_6H_5N(NO).CO.CH_3 \longrightarrow \begin{matrix} C_6H_5NO^{\bullet} \\ | \\ C_6H_5N\ CO.CH_3 \end{matrix}$$

(7)

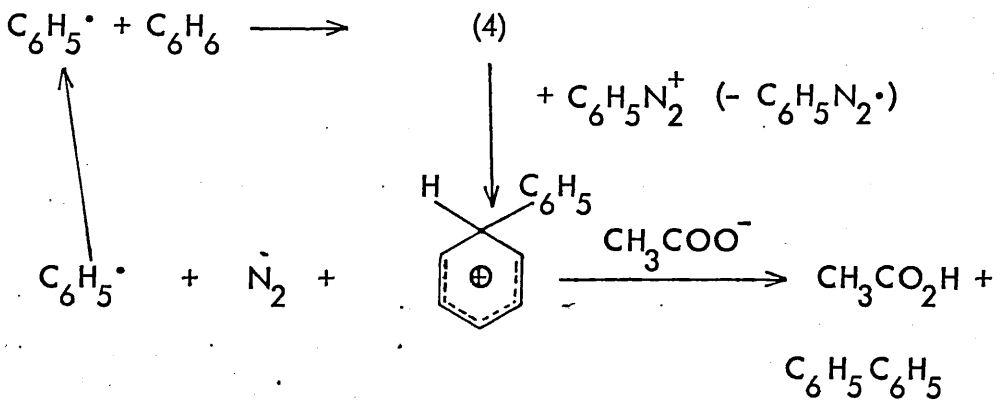
and (b) the oxidising radical became (7) instead of (6) in Scheme II.

The conflicting views regarding the oxidising radical were resolved by the extensive ESR work carried out by Cadogan, Paton and Thomson[89,95]. These workers observed a previously unobserved signal during the decomposition of N-nitrosoacetanilide in organic solvents, which they attributed to (6), in apparent agreement with Freudenberg and Ruchardt's scheme, with the important difference that this was a σ-radical rather than the π-radical postulated in Scheme II. The same workers[89,95] also observed that whereas the signal attributable to (6) appeared in all solvents, that of (7) did not. Cadogan et al[89,95] put forward a scheme, which essentially incorporated aspects of Schemes II and III. In the pathway (Scheme IV) initiation was as depicted in Scheme II (or possibly in certain cases Scheme III), but was likely to be succeeded by an alternative, simpler chain process involving a redox reaction of the intermediate cyclohexadienyl radical (4) with unchanged diazonium cation as summarised below:

SCHEME IV

Initiation $\longrightarrow$ $C_6H_5^{\bullet}$ via Scheme II or sometimes III..

Chain propogation



Evidence in support of a rapid oxidation of the phenylcyclohexadienyl radical by the diazonium cation in an electron-transfer process, and hence Scheme IV, was later provided by Nonhebel and his co-workers[96]. Phenylation of p-xylene under Gomberg conditions gave almost exclusively 2,5-dimethylbiphenyl with less than 1% 4'-dimethylbibenzyl, suggesting a preferential formation, at low temperatures, of the 2,5-dimethylphenylcyclohexadienyl radical followed by a rapid oxidation before dissociation occurs.

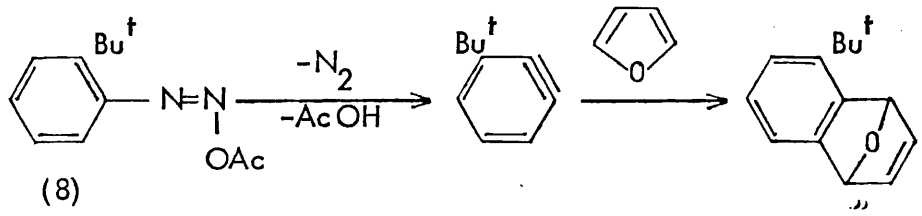
The homogenous decomposition of acylarylnitrosamines at convenient rates at or just above room temperature (25-50°C) in aromatic solvents makes these compounds useful intermediates in kinetic studies. On the other hand, although during many of the reactions up to 90% yields of the nitrogen are found, the yields of biaryls are not high except when the reactions are carried out in dilute solutions. Tarry product contamination sets in when too concentrated solutions are decomposed.

In dilute benzene solution at room temperature under nitrogen, yields of biphenyl of 91% have been reported, but in the presence of oxygen this is reduced to 5-7% with the simultaneous formation of phenol and other phenolic compounds[97].

Both the homolytic process discussed above, and the heterolytic one, which gives rise to aryne intermediates, have been reviewed in very great detail by Cadogan[98]. Aryne intermediates predominate in the reactions of acylarylnitrosamines with bulky substituents at the o-position, e.g. o-t-butyl-N-nitrosoacetanilide (8) and where the substrates are good arynophiles, e.g. furan (see Scheme V) and tetracyclone. These reactions

are of very little relevance here and will not be discussed further.

SCHEME V



(8) (30)

(d) Triazens (Diazoamino Compounds)

Early reported reactions of this group of compounds included the pyrolysis of 1,3-diphenyltriazen (Ph.NH.N:N.Ph),[53,56] which yielded a mixture of substitution products, 2- and 4-biphenylamines. When the decomposition was carried out in paraffin, besides the aforementioned biphenylamines, benzene, aniline, biphenyl and nitrogen were also found. The orientation of isomeric biphenylamine products, in this case, is characteristic of homolytic as well as electrophilic substitution. 1,3-Di-p-tolyltriazen was found to react similarly, decomposing to give isomeric dimethylbiphenylamines, with 4',5-dimethyl-2-biphenylamine as the predominant product[100].

The more frequently used triazens are of the 1-aryl-3,3-dimethyl type (9) and these compounds are prepared by the coupling of diazonium salts with aliphatic secondary amines. Such triazens, which may be liquids or solids, are stable in neutral or alkaline media but decompose into the diazonium ion and the dimethylamine salt in the presence of acid. They may therefore be regarded as stabilised diazo-compounds[55]. Decomposition of these compounds in biaryl synthesis, is carried out by

heating (150-160°) a solution of triazen in aromatic (substrate) solvent, while a slow current of dry hydrogen chloride (or other acidic reagent) is introduced[55,59].

$$\underset{(9)}{Ar.N{:}N.Me_2} + C_6H_5R \longrightarrow ArC_6H_4R + N_2 + NHMe_2.HCl \qquad (33)$$

The assumption made by Saunders[101] that triazen decompositions were homolytic in nature was upheld by later studies[106-109] in which the isomer ratios of biphenyls formed from the decomposition of 1-phenyl-3,3-dimethyltriazen in such aromatic solvents as bromobenzene, chlorobenzene, nitrobenzene and isopropylbenzene were shown to be in agreement with analogous products from known phenyl radical sources, e.g. the Gomberg reaction and pyrolysis of benzoyl peroxide, etc.

Table I below gives the results of the phenylation reactions on chlorobenzene.

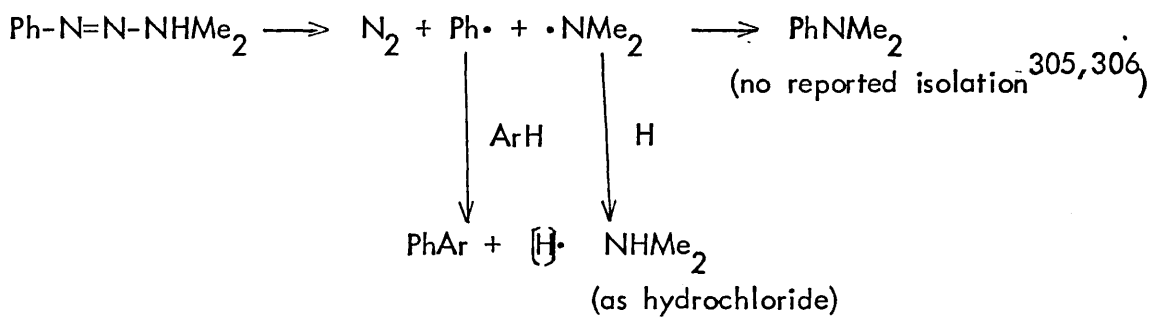
Table I - Phenylation of Chlorobenzene

Method	o-	m-	p-	Ref.
Gomberg	64.6	21.7	13.7	102
Benzoyl Peroxide	57.5	26.6	15.9	103
Silver iodide dibenzoate	60.0	24.0	16.0	104
Phenylhydrazine-silver oxide	64.9	22.1	13.0	105
Phenylazotriphenylmethane	58.2	27.9	13.9	103
Diazoaminobenzene (1-phenyl-3,3-dimethyltriazen)	59.8	23.7	16.5	59

From the above results, and the formation of 2,3-dimethyl-2,3-diphenylbutane in the decomposition of diazoaminobenzene in isopropylbenzene, Hardie and Thomson[59] concluded that the pyrolysis of these triazens.

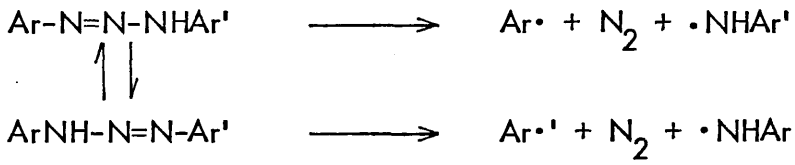
generates anilino and phenyl radicals, the latter proceeding to attack the solvent. The reaction can be represented thus:

SCHEME VI (adapted from a scheme by Hardie and Thomson[59])



Since 1,3-diphenyltriazens are tautomeric, (Scheme VII), it is expected that decomposition of their unsymmetrical derivatives would yield two different aryl radicals and hence two groups of biaryl derivatives. This was confirmed by Hardie and Thomson[59].

SCHEME VII



The two advantages of this reaction over other radical sources are:

(a) the reactions are carried out in homogenous media (cf. the Gomberg reaction) resulting in "clean" products in comparatively high yields (usually >50%) with negligible by-product formation; and,

(b) the reaction is effected at elevated temperatures, which permit the use of a wider range of compounds including substrates which are solid at ambient temperatures.

Conversely, the method is inapplicable to benzene and a few other

low-boiling aromatic solvents.

(e) Arylazotriphenylmethanes

These compounds dissociate in organic solvents at 60-80° to give aryl radicals (equations 34 and 35)[61,62].

$$Ph\text{-}N{=}N\text{-}CPh_3 \longrightarrow PhN{=}N\cdot + \cdot CPh_3 \quad (34)$$

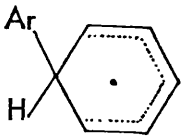
$$Ph\text{-}N{=}N\cdot \longrightarrow Ph\cdot + N_2 \quad (35)$$

Cohen and Wang[110] showed that the rate of decomposition is independent of initial concentration and obeys first-order kinetics. Further kinetic work by Huisgen and Nakaten[111] revealed that radicals were involved (analysis of the ratio of isomeric products) but that no chain mechanism operated. The formulation of a step-wise homolysis as in equations (34) and (35) above followed investigation of the kinetics of reaction of substituted arylazotriarylmethanes[112], but later work[113] revealed the absence of any effect of added triphenylmethyl on the rate of decomposition. The two-step mechanism might suggest that added triphenylmethyl, by reversing (34), reduces the observed rate of decomposition. A possible rationalisation of this could be the formation of arylazo radicals of extremely short life so that the first stage is effectively irreversible.

A suggestion was made that radicals might not be formed in the decomposition, but that formation and dehydrogenation by triarylmethyl radicals of the arylcyclohexadienyl radical (4) takes place rapidly in a solvent cage. The suggestion got support from the absence of isotope effects, and the absence of dihydrophenyls in the reaction products; but the isolation of all possible isomeric crossed products (10) from the

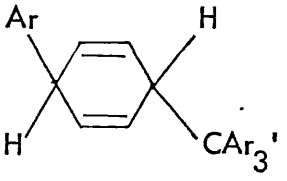
decomposition of a mixture of two appropriately substituted arylazotriaryl-methanes proved this suggestion incorrect.

SCHEME VIII

a) $Ar^{\bullet} + PhH \longrightarrow$ 

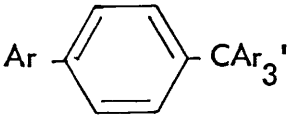
(4)

b) $(4) + \bullet CAr_3' \longrightarrow ArPh + HCAr_3'$

c) $Ar\ (4) + \bullet CAr_3' \longrightarrow$ 

cis & trans

-2H



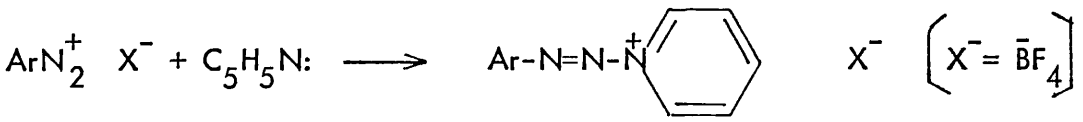
(10) (minor product)

The scheme above shows the formation of the various products in the decomposition of arylazotriarylmethane. A confirmation of the intervention of free radicals in this reaction was that iodine and carbon tetrabromide, highly efficient radical traps, inhibited the reaction even at low concentration[117].

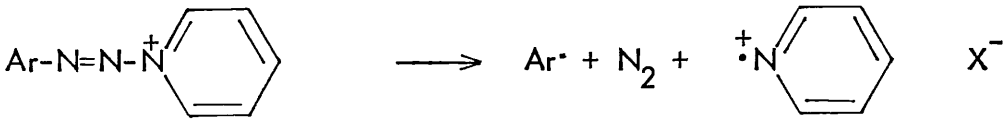
(f) Diazonium Tetrafluoroborate and Pyridine

Aryldiazonium tetrafluoroborate together with one equivalent of dry pyridine has been found to be a convenient radical source[118]. The process bears a close resemblance to the Gomberg reaction, with pyridine (pK_a 5.21) acting as the base in the formation of the salt (11), which could be regarded as similar to diazo-anhydride in the Gomberg process. Aryl radicals are supposed to arise as in Scheme IX below:

SCHEME IX[118]



(11)



(12)

The formation of (11) finds support since no nitrogen is apparently evolved until one equivalent of base has been introduced[119].

Biphenyls, pyridinium tetrafluoroborate and nitrogen were the only products of the above decomposition at 75°C in aromatic substrate. No phenylpyridines, fluorobenzene, or boron trifluoride were detected; this in contrast to the products of the thermal decomposition of benzenediazonium tetrafluoroborate in the same aromatic solvents in the absence of pyridine, when the normal "Schiemann" product, fluorobenzene, is formed in 90-95% yield, boron trifluoride and nitrogen are copiously evolved and fluorobiphenyls (0.5-0.8%) and biaryls (3-5%) constitute only minor products.

With pyridine added, as above, biaryl yields are in the region 30-40%[118]. Comparison of the biaryl isomer distribution, and the relative rates of attack, from this reaction and from the thermolysis of benzoyl peroxide, showed reasonable agreement[118]. Formation of bibenzyl in 10% yield in the phenylation of toluene provided further evidence of free radical intervention[118].

(g) Aromatic Amines and Amyl Nitrite

This route was developed independently by two groups of workers[120,121]. They showed that when aniline in benzene is boiled under reflux with butyl or amyl nitrite, biphenyl is formed in yields of up to 65%. Similarly, substituted biphenyls were prepared and yields were as follows: 4-chlorobiphenyl (53 %), 4-methoxybiphenyl (33%), and such other biaryls as 3-phenylpyridine (52%) and phenylquinoline (35%).

Prior to the development of this method alkyl nitrites had been used to generate diazonium and diazo- compounds. Griess[122] and Meyer and Ambuhl[123] had reported the formation of diazoamino compounds from diazotisation reactions with amyl nitrite and ethyl nitrite in alcohol solutions. Since it has been shown that thermal decomposition of diazoamino compounds results in aryl radicals it could be argued that formation of aryl radicals here, could occur in similar manner. Such an argument can be countered by consideration of the low temperatures needed in the amyl nitrite reaction[121]. Further, no products arising from the arylamino radicals, ArNH· are detected. Knoevenagel[124] reported a method of diazotisation using ethyl and amyl nitrite, but did not go so far as to investigate the products of decomposition of the diazonium compounds formed.

Literature on the mechanism of diazotisation, and subsequent decomposition to form radicals, using alkyl nitrites is limited. Cadogan[125] suggested that the products of the diazotisation reaction are those shown in equation (34):

$$ArNH_2 + RONO \longrightarrow Ar\overset{+}{N}_2\ \bar{O}R + H_2O \qquad (34)$$

and hence radical formation would occur as in the Gomberg reaction. However, the reaction is more complex. An E.S.R. signal which had first been mistakenly attributed[126] to a phenyldiazoxyl, PhN=N-O• (no specification as to whether a σ or π radical) led to some confusion. This was later shown[95,126,127,128] to consist of two overlapping signals from phenylpentylnitroxyl (13) and diphenylnitroxyl (14). Product (13) results from spin trapping of a phenyl radical by pentyl nitrite (Scheme X) and (14) is considered[126,127,128] to arise by the decomposition of phenylpentyl-nitroxyl (13) to nitrosobenzene, which in turn traps a phenyl radical, also as in Scheme X.

SCHEME X[98]

$$Ph^{\bullet} + RONO \longrightarrow Ph(RO)NO^{\bullet} \longrightarrow RO^{\bullet} + PhNO \quad \left[R=C_5H_{11}\right]$$

(13)

$$PhNO + Ph^{\bullet} \longrightarrow Ph_2NO^{\bullet}$$

(14)

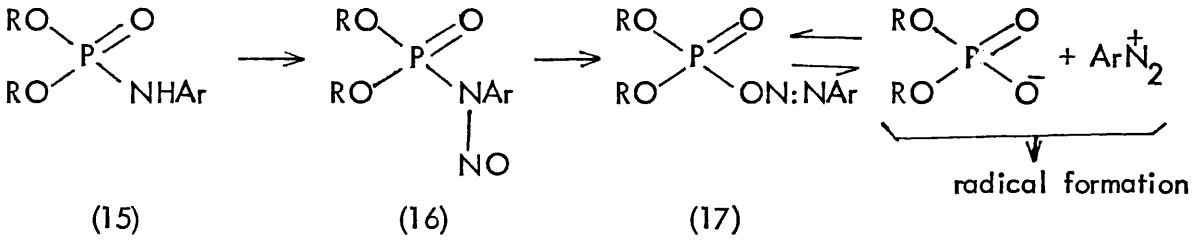
(h) Other Related Sources

Diazoanhydrides $(ArN_2)_2O$, made by careful addition of acetic acid to potassium diazotate, react very vigorously with aromatic substrates[60].

The biaryl yields, however, were low.

Bunyan and Cadogan[129] showed that nitrosation of N-arylphosphoramidate (15) by nitrosylsulphuric acid or nitrosyl chloride gives an unstable N-nitroso-compound (16) which undergoes a rapid rearrangement to the corresponding diazo-phosphate (17) and subsequently to aryl radicals (Scheme XI).

SCHEME XI



(15) (16) (17)

Other less important sources of aryl radicals are discussed in several reviews[5, 7, 12], e.g. oxidation of phenylhydrazine to the diazonium compound with metallic oxides, preferably silver oxide[64].

2.2.3 Miscellaneous Sources

By far the greatest amount of work carried out to date, both synthetic and mechanistic, has been on the radical sources discussed above. Included here are a few other sources, the use of which has been somewhat curtailed either by cost, safety, general availability and application, or whose potential has yet to be realised.

Photolysis of aryl halides[130], especially iodides and of organometallic compounds[131] gives aryl radicals. The photolysis of iodobenzene in cumene gives a mixture of isomeric isopropylbiphenyls in the same ratio as is obtained in the decomposition of benzoyl peroxide in cumene, together

with the dimer 2,3-dimethyl-2,3-diphenylbutane. Wolf and Kharasch[132] developed this method into one of general biaryl synthesis and a yield of 91% p-terphenyl was obtained from the photolysis of 4-iodobiphenyl in benzene. The reaction can be successfully applied to iodophenols and iodobenzoic acids. Other reported arylations have included 2,4,6-tri-iodophenol with benzene (75%)[12], phenylation of xylenols[133], preparation of binaphthyls[134] and quaterphenyls[135]. Diphenylmercury and triphenylbismuth have been used as radical sources[131]. Tetraphenyl-lead was also photolysed in cumene to give isomeric products as indicated above[12].

The photolytic reactions are clean, but suffer from the disadvantage of being limited in scope. Some substances, e.g. nitrobenzene, are opaque to ultraviolet radiation, so that no photolysis of the radical source occurs[131]. In other cases, the substrates, e.g. halogenobenzenes, are apt to be photolysed,[131] resulting in complex product mixtures.

The photolysis of 4-bromobiphenyl in benzene has been reported, but the product distribution was different to that in the photolysis of 4-iodobiphenyl. γ-Radiolysis of bromobenzene and iodobenzene has also been reported[136] with the former giving phenylation products with an isomer distribution consistent with the normal homolytic pattern, but in the latter no biphenyl formation was reported.

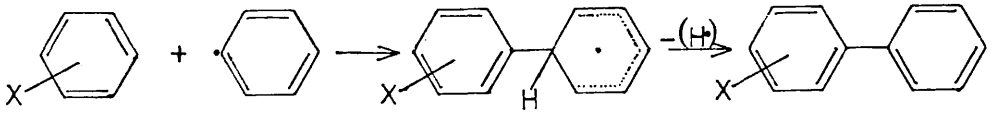
Nonhebel, Tedder and Walton[137] have, in a recent publication, discussed the topic of photolysis from the point of view of bond strengths, dissociation energies and radical formation.

Other radical sources, like the Grignard reagents[12], in the presence

of catalytic quantities of cobaltous halides, and organotitanium[138,139,140,141] compounds are known, and have occasionally been used to generate aryl radicals.

2.3 Aryl Radicals in Biaryl Synthesis

Biphenyl can be formed by substitution of a phenyl radical in benzene (see equation 10). If either the phenyl radical or benzene is substituted, isomeric biphenyls result, e.g. a mixture of o-, m- and p-substituted biphenyls result from the reaction between a phenyl radical and a mono-substituted benzene substrate (equation 31).



(31)

Two important considerations in evaluating a synthetic route are:

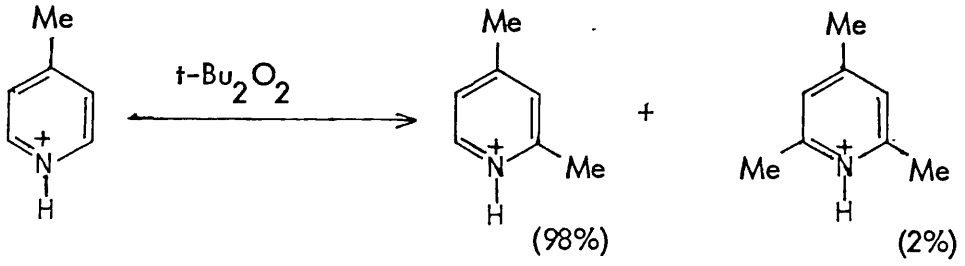
(a) the amount of required product formed, and,

(b) the ease of separation of products from by-products, if present.

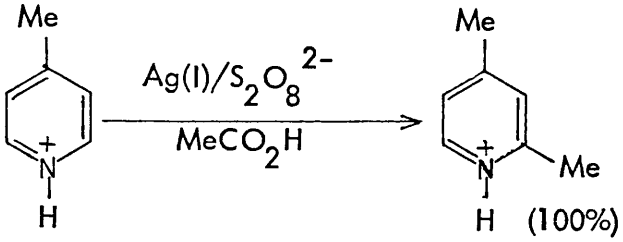
The lack of interest early synthetic chemists showed in homolytic arylation arose mainly from the very low positional and substrate selectivity exhibited by such reactions. The o-isomer was found to predominate in the product mixture, but workers in the 1930's found that in many reactions the p-isomer was sufficiently insoluble for it to be crystallised from the mixture, albeit in low yield[2,31]. Thus such preparative routes were only resorted to where no alternative to the biaryl existed.

In recent years homolytic biaryl synthesis has gained importance for a variety of reasons including the following: The greater range of radical sources has, in certain cases, led to higher product yields, better substrate and positional

selectivity and cleaner products, e.g. the high positional selectivity exhibited by the protonated 4-substituted pyridines (equations 32 and 33)[22,23].



(32)



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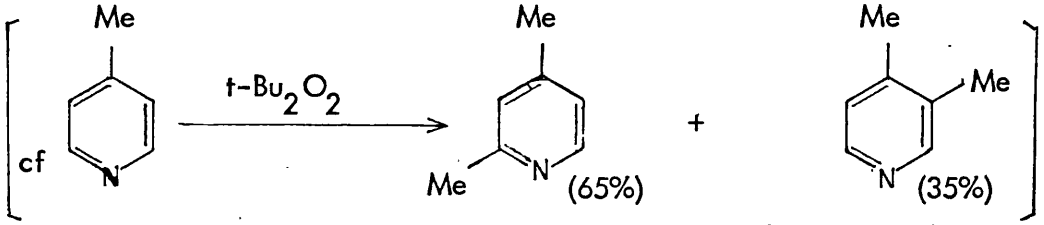
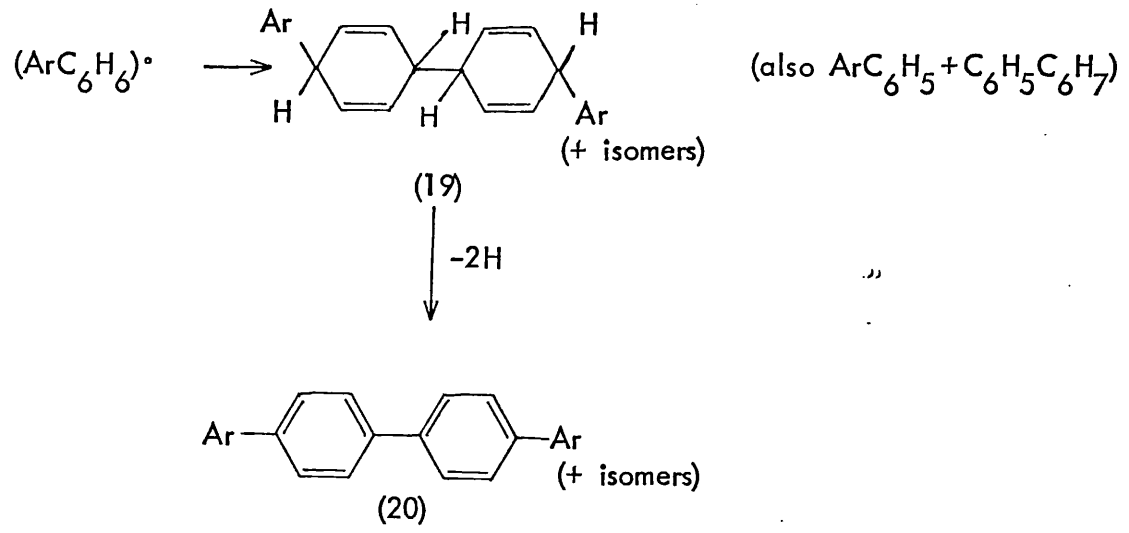


Arylation reactions under the same conditions should presumably show a comparable degree of positional selectivity.

Coupling reactions constitute useful synthetic routes. Such compounds as some of the isomeric quaterphenyls result from coupling of two σ-complexes followed by chemical dehydrogenation of the σ-complex dimer (19). High potential quinones[158-160] such as o-chloranil are extensively used in the dehydrogenation.

SCHEME XII



Extrapolation of data from observed peroxide decomposition reactions led to a suggestion[158,161,162] that at infinite dilution of the peroxide in aromatic substrate, almost all of the peroxide could be accounted for as carbon dioxide and the products of dimerisation and disproportionation of the arylcyclohexadienyl radicals (Scheme XII), with dimerisation accounting for as much as 75% of the reaction.

Intramolecular arylation reactions, e.g. the Pschorr phenanthrene synthesis, are the main subject of this thesis, and are now established synthetic routes. More detailed discussion on these will be given in later sections. The synthesis of the antileukemic phenanthroindolizidine alkaloid, tylocrebrine[163] is an example of an intramolecular arylation reaction which has become of industrial importance.

2.4 Mechanisms and Kinetics of Arylation Reactions

An account of the development of the various theoretical approaches to the rationalisation of the phenomena of homolytic aromatic substitution was given by Williams[144].

Early investigations clearly distinguished homolytic from heterolytic aromatic substitution by the one very important property: the independence of orientation in homolytic reactions on the electronic requirements of substituents already present in the aromatic substrate. The approach was qualitative only and inevitably contained distortions and oversimplifications. Improved spectroscopic and chromatographic methods which became available after the 1950's led to the accumulation of much quantitative data and, hence, more detailed mechanistic studies. These studies seem to have concentrated on three reactions: The Peroxide Reaction, the Acylnitrosamine and the Phenylazotriphenylmethane Reactions. E.S.R. techniques have been very important in the elucidation of the mechanisms of the last two reactions. More recently, determination of absolute rate constants for the addition of phenyl radicals to aromatic substrates by optical pulse radiolysis and time-resolved E.S.R. experiments in aqueous solutions has been reported[145]. Until then only approximate rate constants for the addition step were available.

$$Ar^{\bullet} + Ar'H \longrightarrow (ArArH)^{\bullet}$$

The addition step is very rapid, with rate constants of the order of 7×10^6 $M^{-1}s^{-1}$ (corrected to zero ionic strength)[145]. E.S.R. studies show that phenyl radicals in a variety of matrices at 77°K have the unpaired electron in the sp^2-orbital in a σ-type radical[146]. The lack of resonance explains its high reactivity.

The intermediacy of the arylcyclohexadienyl radical (4 in Scheme VIII) is now generally accepted, and its intervention has been demonstrated using CIDNP techniques[147]. Earlier, the products of its disproportionation and dimerisation had been isolated. However, the irreversibility of the addition of the aryl radical to the aromatic substrate is still contested. The addition of hydrogen atoms to benzene has an activation energy of about 3kcal $mole^{-1}$ and is exothermic by about 28 kcal $mole^{-1}$.[148] Addition of phenyl radicals is less exothermic (ΔH, $\sim$ 18kcal $mole^{-1}$) and presumably has a larger activation energy. It is therefore most improbable that appreciable fragmentation of (4) would occur within the lifetime of these radicals in normal phenylation reactions since it would have an activation energy of at least 21 kcal $mole^{-1}$.

Absence of isotope effects in free radical phenylations has been observed and quoted by many authors in support of an irreversible arylcyclohexadienyl radical formation[12,14,15]. For example, phenyl radicals do not normally appear to discriminate between benzenes and benzene-d_6[150-153]. Some workers have, however, reported[6] detecting kinetic isotope effects. A group of Japanese workers reported[154,155] such an effect in phenylations in dimethyl sulphoxide at room temperature; however, the reproducibility of their observation was not good. A very large isotope effect was found in the phenylation with phenylazotriphenylmethane at the crowded 2-position of m-dinitrobenzene, but not at the crowded positions of 1,3,5-tri-t-butylbenzene[154,155]. The isotope effect, in the addition of benzoyloxy radicals to aromatic substrates, easily observable in the presence of oxygen, is well documented[15,137]. This observation has led to the generally accepted view that this addition is reversible.

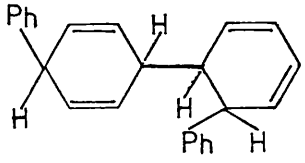
The phenylcyclohexadienyl radicals can react further in three ways:

(a) they can disproportionate to give biphenyl and dihydrobiphenyl (18),

$$2\ (PhC_6H_6)\cdot \longrightarrow PhC_6H_7 + PhC_6H_5 \qquad (36)$$

(18)

(b) they can dimerise to give tetrahydroquaterphenyl,

$$2\ (PhC_6H_6)\cdot \longrightarrow$$  (37)

(+ isomers)

and (c) they can be oxidised to biphenyl (see equation 31). It is evident that the route of reaction of the phenylcyclohexadienyl (also called the σ-complex) is dependent on its environment. For an example, dihydrobiphenyl formation (equation 36) is most likely to occur in dilute solutions. Even more important is the presence or absence of an oxidant in the reaction. Dimerisation and disproportionation products found in arylation reactions where peroxides and phenylazotriphenylmethanes are used as radical sources are absent where N-nitrosoacetanilide is used because of the formation in the latter reaction of a very efficient oxidant (see Schemes II, III and IV). For this and other reasons, which should manifest themselves later, discussions of the mechanisms of arylation reactions whereby the different sources are used will be given separately.

2.4.1 The Peroxide Reaction

Excellent reviews exist[2,4,5,12,14,15,156,157] on the elucidation of the mechanism of this reaction. For this reason, discussion of the mechanism of the reaction here will concentrate mainly on those aspects general to arylation.

The decomposition of aroyl peroxides to give aryl radicals was

discussed in section 2.2.1. The kinetics of the reaction, especially of the reaction of benzoyl peroxide in benzene, has been studied extensively. Nozaki and Bartlett[164] were the first to observe an induced reaction leading to a kinetic order of 1.5 in peroxide, which accompanies the first-order primary homolysis into benzoyloxy-radicals (equation 38):

$$-d[P]/dt = k_1[P] + k_2[P]^{3/2} \quad (38)$$

where P represents the peroxide. The induced decomposition which contributes the term $k_2[P]^{3/2}$ leads to a variation in the observed rate of the reaction, in changing from one solvent to another. Kinetics of the form as represented in equation (38) relate to systems in which chains are terminated by either dimerisation or disproportionation involving like radicals[14].

Further investigations[162,165-168] correlated kinetic results, and variation in yields of biaryls, esters, aroic acids, dihydrobiaryls, and residue, with the initial peroxide concentration, and led to the identification of the σ-complex as the most important chain carrier (equation 39).

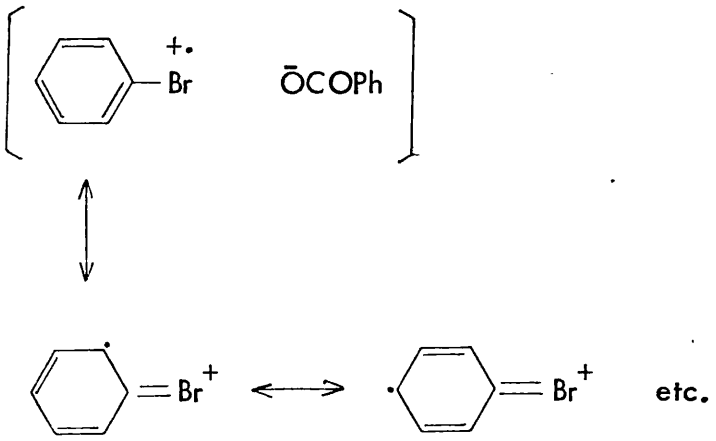
$$PhArH^{\cdot} + (Ph.CO.O)_2 \longrightarrow PhAr + PhCO_2H + Ph.CO.O^{\cdot} \quad (39)$$

In termination reactions involving unlike radicals, e.g. the peroxide decomposition in bromobenzene, the kinetic law becomes that in equation (40), with the induced reaction being first order with respect to the peroxide[14].

$$-d[P]/dt = k_1[P] + k'_1[P] \quad (40)$$

The reason for the different termination mode in bromobenzene is thought[14,166] to be the greater degree of stabilisation of the benzoyloxy radicals in that solvent resulting from formation of charge-transfer complexes because of the greater polarisability of the bromine atom (Scheme XII, cf. sequence 41-53). The desirability of this mode of chain termination lies in the fact that much biaryl and no dimer results from it.

SCHEME XII[14]

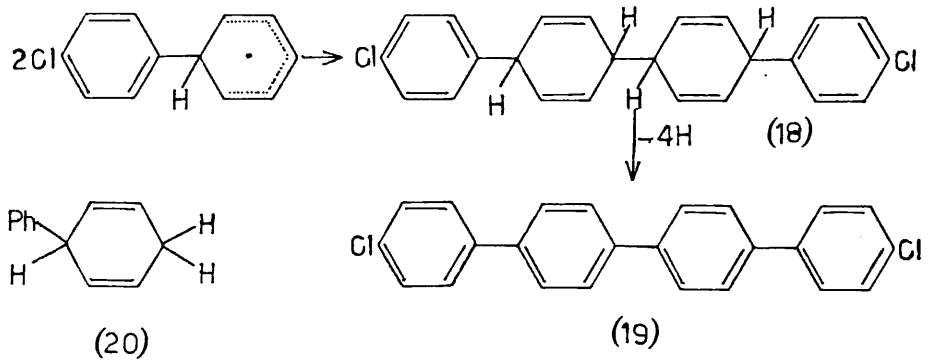


The kinetic studies of the decomposition of benzoyl peroxide led to the formulation of the following peroxide reaction sequence[12,14]:

$(Ph.CO.O)_2$	$\longrightarrow$	$2Ph.CO.O\cdot$	(41)
$Ph.CO.O\cdot$	$\longrightarrow$	$Ph\cdot + CO_2$	(42)
$Ph.CO.O\cdot + P$	$\longrightarrow$	$P + Ph.CO.O\cdot$	(43)*
$Ph\cdot + ArH$	$\longrightarrow$	$(PhArH\cdot)\ \sigma\cdot$	(44)
$Ph.CO.O\cdot + ArH$	$\longrightarrow$	$(Ph.CO.O.C_6H_6)\cdot\ \sigma'$	(45)*
$\sigma\cdot + P$	$\longrightarrow$	$PhAr + Ph.CO_2H + Ph.CO.O\cdot$	(46)
$\sigma\cdot' + P$	$\longrightarrow$	$Ph.CO.O.Ar + PhCO_2 + Ph.CO.O\cdot$	(47)*
$\sigma\cdot + Ph.CO.O\cdot$	$\longrightarrow$	$PhAr + PhCO_2H$	(48)*
$\sigma\cdot' + Ph.CO.O\cdot$	$\longrightarrow$	$Ph.CO.O.Ar + PhCO_2H$	(49)*
$2\,\sigma\cdot$	$\longrightarrow$	$PhAr + PhArH_2$	(50)
$2\,\sigma\cdot$	$\longrightarrow$	$(PhArH)_2$	(51)
$2\,\sigma\cdot'$	$\longrightarrow$	$Ph.CO.O.C_6H_7 + Ph.CO.O.C_6H_5$	(52)*
$2\,\sigma\cdot'$	$\longrightarrow$	$(Ph.CO.O.C_6H_6)_2$	(53)*

with reactions marked with an asterisk regarded as of minor importance when the reaction is carried out at 80°C.

The identification of high-boiling, resinous materials formed during the reaction, as comprising mainly of the σ-complex dimer (see reaction 51) was first made by Lynch and Pausacker[27] and Walling[169]. The possible formation of positional and geometrical isomers, together with further transformation of the dihydroquaterphenyls (equation 37) was appreciated. Confirmation came through the isolation of a symmetrically disubstituted quaterphenyl (19) from the decomposition of a symmetrically disubstituted peroxide in benzene[170] and oxidation of the product with o-chloranil (equation 54) and shortly afterwards isolation of tetrahydroquaterphenyl (18) as well as dihydrobiphenyl (20) from the benzoyl peroxide-benzene reaction[171].



(54)

(20) (19)

Isolation of (20) further established the σ-complex as capable of behaving as a perfectly normal free radical, with sufficient resonance stabilisation in the cyclohexadienyl system for reaction with the benzene solvent to be energetically unfavourable[15].

The discussion so far has taken for granted the fundamental fact that the biaryls formed are those in which one aryl group is derived from the peroxide and the other from the aromatic substrate. This in fact was amply shown by the accumulated evidence from the work done by Hey[61], which

evidence also pointed to hydrogen abstraction from the substrate as not occurring. Thus, it was shown that symmetrical biaryls are not formed in these reactions (equation 56).

$$Ar\cdot + Ar'H \quad \not\longrightarrow \quad ArH + Ar\cdot' \qquad (55)$$

$$Ar'\cdot + Ar'\cdot \quad \not\longrightarrow \quad Ar'Ar' \qquad (56)$$

Naphthalene, on the other hand, is an exception to this generalisation. Nuclear hydrogen abstraction occurs extensively, resulting in the formation of 1,1'-, 2,2'-binaphthyl, 1,2'-binaphthyl, benzoyloxylation products and, of course, the expected 1- and 2-phenylnaphthalene in the proportions 79.1% and 20.9% respectively[14], when the benzoyl peroxide decomposes in molten naphthalene.

Relatively small amounts of esters (varies according to reaction conditions) found in the products of the peroxide reaction (see equations 47, 49, 52 and 53) indicate the intermediacy of aroyloxy radicals. Higher ester yields result from the arylation of the more reactive naphthalene substrate[15].

A large number of these arylation reactions have been investigated and results therefrom interpreted by use of partial rate factors.

Partial rate factors, Fo, Fm and Fp are numerical expressions of reactivity at the o-, m- and p- positions respectively, in the mono-substituted benzene derivative C_6H_5R compared with the reactivity at any one position in benzene[12,114]. The method of their determination is based upon the competition between two substrates present in large excess and the extent of the change in reactivity due to the presence of a

substituent in the substituted benzenes. Measurements are thus made of:

a) the quantity $\frac{C_6H_5R}{C_6H_6}K$, i.e. the total rate ratio of substitution in C_6H_5R to that in C_6H_6, with benzene conveniently assigned an arbitrary value of unity, and,

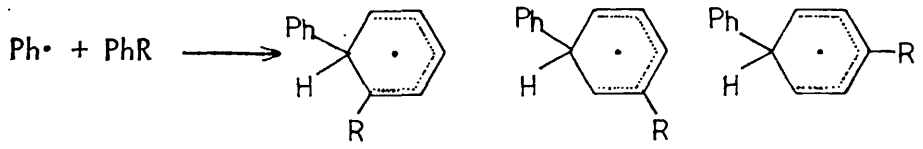
b) the proportions in which o-, m- and p-isomers are found in the arylation of C_6H_5R, and if such proportions be symbolised ω, μ and π respectively, then the particular rate factors for the three positions are given by the equations[14,144]:

$$Fo = 3\omega \frac{C_6H_5R}{C_6H_6} K \quad (57)$$

$$Fm = 3\mu \frac{C_6H_5R}{C_6H_6} K \quad (58)$$

$$Fp = 6\pi \frac{C_6H_5R}{C_6H_6} K \quad (59)$$

Relative reactivity and isomer distribution measurements would appear to be based on the assumption that the rates of formation of binuclear products are related directly to the rates of formation of σ-complexes. However, appreciation that σ-complexes do not necessarily proceed to biaryl, but may instead dimerize, disproportionate or undergo other radical reactions raised doubts concerning the validity of the assumption stated above. Thus, it seems unreasonable to expect that oxidation to biaryl should account for exactly the same fraction of each of the three isomeric radicals in equation (60) particularly where R is a bulky or polar group[15].



Indeed, results reported[172-174] between 1954 and 1964, and compiled into a table by Hey[12] underlined the pronounced steric effect on the reaction at the o-position of such bulky groups as isopropyl and t-butyl in the decomposition of benzoyl peroxide in various aromatic substrates. Further, an isotope effect was observed in the binuclear product, but not in the unconsumed substrate[150-152], in the phenylation of (^{2}H) benzene, indicating that the oxidation to biaryl (dehydrogenation) was in competition with side reactions. This, and the observation that bubbling oxygen through the peroxide reaction suppresses side reactions and considerably enhances biaryl yield led Eliel and his co-workers[175,176] to doubt the validity of measured partial rate factors. The reaction, with oxygen added, was reported by a later group of workers[177] to be greatly sensitive to minor temperature changes, possibly because of variation of oxygen solubility with temperature. A temperature variation of 5°C was reported as resulting in a 55 mole per cent change in biphenyl yield[177].

The observation of the effect of oxygen upon the peroxide reaction has turned out to be a basis for further investigation. A lot of work has subsequently been done into ways of maximising the oxidation of the σ-complex to biaryl, at the same time suppressing diversionary reactions. Williams and co-workers[178] have reported the most recent and comprehensive survey of such oxidising additives.

Nevertheless Morrison and Cazes[179], who studied phenylation of

substituted benzenes by benzoyl peroxide in both the absence and the presence of oxygen showed that, even though biaryl yields are increased as much as threefold by oxygen, isomer distribution and relative reactivities remain unchanged. They concluded that side reactions are not selective, a conclusion also reached by another group of workers[181], who reported an increase in yield of fluorobiphenyls of 65% when an aromatic nitro-compound was included in the reaction and yet noticed no significant change in isomer distribution. Cazes[180] also showed that both the isomer distribution and relative reactivity remained constant over a twenty-fold change in concentration.

The above observations and conclusions did not seem valid in all cases. For example, thermal decomposition of benzoyl peroxide in 4-methylpyridine was reported[182] not to give the same isomer distribution with and without oxidising agents present. Bonnier and Court found that in the phenylation of methylpyridinium hydrochloride[183], and later of neutral methylpyridine[184], the isomer distributions and partial rate factors were drastically changed in the presence of catalytic amounts of nitroso-benzene. Williams and co-workers observed an increase in the abundance of the o-isomer in the high yield reactions over what had been previously found, with a corresponding decrease in the relative yields of the m- and p-isomers[178]. The small but consistent reduction of o-isomer yield from residue-forming reactions (i.e. in the absence of oxidants, e.g. iron (III) benzoate) had been observed earlier[14]. For the sake of comparison, the results reported by Williams and co-workers[178] and by Morrison and Cazes[179] are tabulated in section 2.4.3.

A brief discussion of the action of oxidising additives may be of some interest. These include nitroso- and nitro-arenes[168,181], transition metal complexes,[185-189] quinones[190] and of course oxygen[176,179].

Two mechanisms of the 'nitro-group effect' of increasing biaryl yields have been put forward. The first mechanism attributed this effect to the conversion of the nitro-compounds into nitroxides which effect dehydrogenation of the intermediate arylcyclohexadienyl radicals thus[191]:

SCHEME XIII

$$ArNO_2 \longrightarrow ArNO \xrightarrow{Ph^\bullet} ArN(O^\bullet)Ph$$

$$Ph^\bullet + PhH \longrightarrow \left[PhPhH\right]^\bullet$$

$$\left[PhPhH\right]^\bullet + ArN(O\bullet)Ph \longrightarrow Ph_2 + ArN(OH)Ph$$

A later mechanism, based on comparing yields of reactions where substituted nitro- and dinitrobenzenes were additives, suggested that the 'nitro-group effect' involved the oxidation of arylcyclohexadienyl radicals by an electron-transfer mechanism:[192,193]

SCHEME XIV

$$ArNO_2 + \left[PhPhH\right]^\bullet \longrightarrow ArNO_2^{\bar{\bullet}} + \left[PhPhH\right]^+$$

$$\left[PhPhH\right]^+ \longrightarrow Ph_2 + H^+$$

$$ArNO_2^{\bar{\bullet}} + (PhCO_2)_2 \longrightarrow ArNO_2 + PhCO_2^\bullet + PhCO_2^-$$

The latter mechanism bears some resemblance to that suggested for transition metal catalysis, which may be summarised thus:

$$\left[ArAr'H\right]\cdot + Fe^{3+} \longrightarrow ArAr' + H^{+} + Fe^{2+} \qquad (61)$$

$$ArCO\cdot O\cdot + Fe^{2+} \longrightarrow ArCOO^{-} + Fe^{3+} \qquad (62)$$

$$ArCOO^{-} + H^{+} \longrightarrow ArCO_2H \qquad (63)$$

where iron (III) benzoate is used. The regeneration of the metal in its higher oxidation state (equation 62) is assumed since only catalytic (not stoichiometric) amounts of metal salts are used in the reaction[178].

2.4.2 Diazo Compounds

Arylation using diazo-sources is distinguished from that using peroxides by the intervention of very efficient oxidising radicals in the former (see Schemes I, II, III, IV and XI). The consequence of this is an apparent absence, in the products of the former reactions, of hydroaromatic products deriving from dimerisation and disproportionation of the arylcyclohexadienyl intermediates. The mechanisms of arylation by acylarylnitrosamines (section 2.2.2.c) or by the Gomberg method (section 2.2.2b) have been discussed already).

2.4.3 Quantitative Data of Arylation Reactions

The next section presents a comparison of the isomer distribution and partial rate factors for phenylation by a variety of sources.

A. Peroxide Reactions

Table 2: Relative Rates, Isomer Ratios and Partial Rate Factors for the Phenylation of Benzene Derivatives with Benzoyl Peroxide at 80°

R in C_6H_5R	Rate Ratio	Isomer Distribution			Partial Rate Factors			Ref.
		o-	m-	p-	Fo	Fm	Fp	
Cl	1.06	50.1	31.6	18.3	1.6	1.0	1.2	172
	1.14	54.6	27.2	18.2	1.9	0.9	1.2	178
	1.43[b]	57.6[b]	26.1[b]	17.3[b]	2.5[b]	1.1[b]	1.5[b]	178
Br	1.29	49.3	33.3	17.4	1.9	1.3	1.3	172
	1.14	56.2	27.3	16.5	1.9	0.9	1.1	179
	1.11[a]	56.2[a]	28.8[a]	16.0[a]	1.9[a]	0.96[a]	1.07[a]	179
	1.47	54.2	30.5	15.3	2.4	1.35	1.35	178
	1.53[b]	54.2[b]	29.5[b]	16.0[b]	2.3[b]	1.35[b]	1.5[b]	178
F	1.03	54.1	30.7		1.7	0.95	0.86	172
	1.08	48.2	51.8*		1.5	1.1	1.2	178
	1.23[b]	55.0[b]	45.0*[b]		2.0[b]	1.1[b]	1.1[b]	178
I	1.32	51.7	31.6	16.7	2.0	1.3	1.3	172
NO_2	2.94	62.5	9.8	27.7	5.5	0.86	4.9	172
	2.95	63.2	9.7	27.1	5.6	0.86	4.8	179
	2.85[a]	62.8[a]	9.7[a]	25.7[a]	5.4[a]	0.83[a]	4.4[a]	179
Me	1.23	66.5	19.3	14.2	2.5	0.71	1.0	172
	1.81	62.6	24.0	13.4	3.4	1.3	1.5	178
	1.64[b]	60.9[b]	21.6[b]	17.5[b]	3.0[b]	1.1[b]	1.7[b]	178
OMe	1.99	69.8	14.7	15.6	4.2	0.88	1.9	179
	2.01[a]	69.8[a]	14.5[a]	15.8[a]	4.2[a]	0.87[a]	1.9[a]	179
	3.18	75.8	11.0	13.2	7.2	1.05	2.5	178
	1.78[b]	70.1[b]	16.6[b]	13.3[b]	3.7[b]	0.9[b]	1.3[b]	178
	1.08[c]	68.8[c]	20.1[c]	11.1[c]	4.3[c]	1.3[c]	1.4[c]	178
CN	3.7	60.0	10.0	30.0	6.5	1.1	6.5	173
	1.92	52.3	17.4	30.3	3.0	1.0	3.5	178
	1.82[b]	57.1[b]	15.6[b]	27.3[b]	3.1[b]	0.83[b]	3.0[b]	178

Table 2 (continued)

R in C_6H_5R	Rate Ratio	Isomer Distribution			Partial Rate Factors			Ref.
		o-	m-	p-	Fo	Fm	Fp	
Et	0.90	53.0	2.8	19.0	1.4	0.76	1.0	172
t-Bu	0.64	24.0	49.0	27.0	0.46	0.94	1.0	172
	0.63	21.2	49.9	29.0	0.40	0.94	1.1	179
	0.61[a]	21.2[a]	50.0[a]	28.8[a]	0.39[a]	0.92[a]	1.1[a]	179
i-Pr	0.64	31.0	42.0	27.0	0.60	0.81	1.0	172
Ph	2.94	48.5	23.0	28.5	2.1	1.0	2.5	172
CO_2Me	1.77	57.0	17.5	25.5	3.0	0.93	2.7	174
	1.89	48.1	19.8	32.1	2.7	1.1	3.6	178
	2.03[b]	53.6[b]	16.5[b]	29.9[b]	3.3[b]	1.0[b]	3.6[b]	178
p-diCl	1.65							178
	1.98[b]							178
1,3,5-triCl	4.99							178
	4.86[b]							178
COPh	4.39	40.1	21.1	38.8	2.65	1.4	5.1	178
	3.97[b]	47.8[b]	18.6[b]	33.6[b]	2.85[b]	1.1[b]	4.0[b]	178

a) Added oxygen.

b) Added iron (III) benzoate (0.5g/g of benzoyl peroxide in 50 ml arene substrate.

c) Added copper (II) benzoate (0.06g/g of benzoyl peroxide in 50 ml arene substrate.

* = m + p

The following observations can be made from the data in Table 2:

a) in the absence of steric factors, all substituents activate the nucleus towards phenyl radical attack independently of their polar character, with the o- and p- positions invariably more reactive than m-;

b) bulky groups e.g. the isopropyl and t-butyl, exert a pronounced steric effect on reactions at the o- positions;

c) the highest rate of reaction ratios are obtained where substituents in the substrate capable of stabilising the odd electron by delocalisation (-M) are present, e.g. Ph, NO_2, CN, COPh.

d) even though in most cases the isomer percentages obtained in the presence and absence of oxidants are different, the variations are not as much as to cast serious doubts on such measurements made in residue-forming peroxy reactions; and

e) the relative yield of the o- isomer is slightly, but consistently, lower in the uncatalysed reaction.

In the catalysed reactions nearly theoretical yields of biaryl and aroic acid were reported (maximum of 1.036 moles of biaryl per mole of peroxide)[178] whereas without additives lower biaryl yields (maximum yield 0.884 moles of biaryl per mole of peroxide)[178] were reported, together with residues.

B. Comparison between Various Aryl Radical Sources

(See Table 3)

Table 3

Biaryl Isomer Distribution, and Partial Rate Factors for the Phenylation of C_6H_5R, using Various Sources of Ph·:

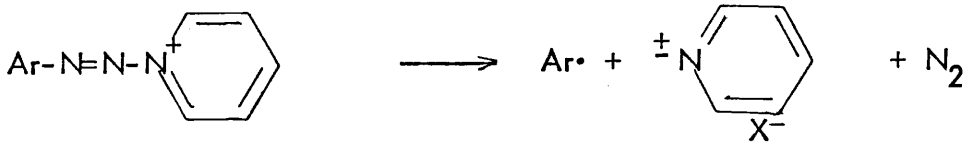
R in C_6H_5R	Benzoyl Peroxide (80° C, 72h)						Ref.	N-Nitrosoacetanilide (20°C)						Ref.	Diazonium Tetrafluoroborate-Pyridine (75°C)						Ref.
	Isomer Distribution			Partial Rate Factors				Isomer Distribution			Partial Rate Factors				Isomer Distribution			Partial Rate Factors			
	o-	m-	p-	Fo	Fm	Fp		o-	m-	p-	Fo	Fm	Fp		o-	m-	p-	Fo	Fm	Fp	
Me	66.5	19.3	14.2	2.5	0.71	1.0	172	65.5	21.6	12.6	3.3	1.09	1.27	198	61.8	21.2	15.0	2.22	0.76	1.08	118
	62.6	24.0	13.4	3.4	1.3	1.5	178														
	60.9(b)	21.6(b)	17.5(b)	3.0 (b)	1.1 (b)	1.7 (b)	178														
MeO	69.8	14.7	15.6	4.2	0.88	1.9	179	69.4	18.1	12.6	3.56	0.93	1.29	198	61.5	16.5	21.9	2.76	0.74	1.97	118
	69.8(a)	14.5(a)	15.8(a)	4.2 (a)	0.87(a)	1.9 (a)	179														
	75.8	11.0	13.2	7.2	1.05	2.5	178														
	70.1(b)	16.6(b)	13.3(b)	3.7 (b)	0.9 (b)	1.3 (b)	178														
	68.8(c)	20.1(c)	11.1(c)	4.3 (c)	1.3 (c)	1.4 (c)	178														
NO_2	62.5	9.8	27.7	5.5	0.86	4.9	172	62.3	7.7	30.0	9.38	1.16	9.05	198	52.6	14.2	33.2	4.3	1.16	5.42	118
	63.2	9.7	27.1	5.6	0.86	4.8	179														
	62.8(a)	9.7(a)	25.7(a)	5.4 (a)	0.83(a)	4.4 (a)	179														

(a) Added oxygen.

(b) Added iron (III) benzoate (0.5g/g of benzoyl peroxide in 50 ml arene substrate).

(c) Added copper (II) benzoate (0.06g/g of benzoyl peroxide in 50 ml arene substrate).

Probably one of the most accurate set of results on phenylation of monosubstituted benzenes measured under comparable conditions is that of Ito et al[194-8]. These were obtained by isotope dilution analysis of the thermolysis of N-nitrosoacetanalide in mixtures of benzene and its derivatives (Table 3). In the dilute solutions employed, high yields of phenylated products were normally obtained, and therefore possible complications arising from selective removal of some cyclohexadienyl radicals in side reactions did not arise. In turn, the general similarity between these results and those of the two other given sources (Table 3) especially of the catalysed peroxide reactions seems to confirm the similarity of all three reactions as sources of aryl radicals. Any differences, most pronounced in the case of nitrobenzene, are attributed[118,194] to the differences in reaction temperatures. In phenylation reactions using benzenediazonium tetrafluoroborate and pyridine the amount of o-isomer products formed in all cases are somewhat smaller than when using the other two radical sources. A steric effect due to the phenyl radical and pyridinium radical cation (12) not diffusing appreciably apart before attack on the aromatic substrate by the phenyl radical (see page 26), is thought[118] to be responsible for the observed trend.



(12)

C. Polarity in Aryl Radicals

The small but net nucleophilic character of the phenyl radical was mentioned in section 2.1.

The suggestion that substituted phenyl radicals can show a measure of electrophilic or nucleophilic character was made by Dannley and Steinfeld[199]. They observed a substantial increase in the m-isomer from substitution with p-chlorophenyl and p-nitrophenyl radicals. Subsequently, extensive data on arylation of nitrobenzene by substituted phenyl radicals derived from diaroyl peroxides was compiled by Hey, Williams and their colleagues (Table 5)[200-206] to support the above suggestion.

Table 5 (Reproduced from Ref. 12)

Relative Rates, Isomer Ratios and Partial Rate Factors for the Arylation of Nitrobenzene using Substituted Diaroyl Peroxide Sources at 80°

Radical	$PhNO_2$ / PhH K	Composition %			Partial Rate Factors			Ref.
		o-	m-	p-	Fo	Fm	Fp	
o-$NO_2C_6H_4$·	0.26	55.0	18.0	27.0	0.42	0.14	0.42	200
m-$NO_2C_6H_4$·	0.43	52.9	18.0	29.1	0.68	0.73	0.75	201
p-$NO_2C_6H_4$·	0.94	58.0	15.0	27.0	1.64	0.43	1.6	206
o-ClC_6H_4·	0.82	35.8	24.2	40.0	0.88	0.60	2.0	201
m-ClC_6H_4·	1.3	56.7	15.1	28.2	2.2	0.58	2.2	201
p-ClC_6H_4·	1.5	59.0	13.8	27.2	2.7	0.63	2.5	203 204a
o-BrC_6H_4·	0.79	35.0	25.0	40.0	0.83	0.59	1.90	200
p-BrC_6H_4·	1.76	57.7	13.2	29.1	3.1	0.7	2.9	204b
C_6H_5·	2.9	62.5	9.8	27.7	5.5	0.86	4.9	172
o-MeC_6H_4·	2.2	41.2	18.7	40.1	2.7	1.2	5.2	205
m-MeC_6H_4·	3.0	60.7	13.2	26.1	5.5	1.2	4.7	201
p-MeC_6H_4·	3.4	59.5	11.9	28.6	6.1	1.2	5.8	202

The results in the table do substantiate the hypothesis that various substituents contribute predictable polar influences to the attacking radical, with due allowances for steric effects. The inductive effect appears to be the predominant influence.

The hypothesis was further supported by quantitative data from p-chlorophenylation, p-nitrophenylation, p-methylphenylation and p-methoxyphenylation of monosubstituted benzene derivatives with radicals derived from appropriately substituted nitrosoacetanilides[194-8] (see Table 6).

Table 6

Relative Rates, Partial Rate Factors (P.r.f) and Isomer Distributions, for Arylation Reactions using Substituted Nitrosoacetanilides[194-8] at 20°C

Substrate	P.r.f. (I.D.) & Rate Ratios	Attacking Radical							
		p-$NO_2C_6H_4$·		p-ClC_6H_4·		p-MeC_6H_4·		p-$MeOC_6H_4$·	
$PhNO_2$	Fo (o-)	0.93	(45.6%)	4.35*	(53.9%)	10.73	(65.0%)	6.45	(54.6%)
	Fm (m-)	0.35	(17.2%)	0.61*	(7.6%)	1.07	(6.5%)	1.19	(10.1%)
	Fp (p-)	1.53	(37.5%)	6.18*	(38.3%)	8.93	(27.1%)	8.36	(35.4%)
	Rate Ratio	0.68		2.69*		5.50		3.94	
PhCl	Fo (o-)	1.53	(57.3%)	2.70	(63.8%)	3.10	(65.8%)	3.08	(53.5%)
	Fm (m-)	0.65	(24.3%)	0.87	(20.6%)	1.04	(22.1%)	1.82	(31.6%)
	Fp (p-)	1.01	(18.9%)	1.33	(15.7%)	1.16	(12.3%)	1.74	(15.1%)
	Rate Ratio	0.89		1.41		1.57		1.92	

*at 18.0°C

ID = Isomer Distribution

Table 6 (continued)

Substrate	P.r.f. (I.D.) & Rate Ratios	Attacking Radical			
		p-$NO_2C_6H_4$·	p-ClC_6H_4·	p-MeC_6H_4·	p-$MeOC_6H_4$·
PhOMe	Fo (o-)	5.17 (72.1%)	3.93* (69.7%)	3.69 (66.5%)	3.68 (68.5%)
	Fm (m-)	0.84 (11.7%)	0.94* (16.7%)	1.09 (19.6%)	1.03 (19.2%)
	Fp (p-)	2.30 (16.0%)	1.54* (13.7%)	1.52 (13.7%)	1.31 (12.2%)
	Rate Ratio	2.39	1.88*	1.85	1.79
PhMe	Fo (o-)	3.28 (60.7%)	2.97 (63.5%)	3.27 (66.1%)	3.09 (66.0%)
	Fm (m-)	1.36 (25.2%)	1.07 (22.9%)	1.00 (20.2%)	1.00 (21.4%)
	Fp (p-)	1.51 (14.0%)	1.32 (14.1%)	1.33 (13.4%)	1.18 (12.6%)
	Rate Ratio	1.80	1.56	1.65	1.56

*at 18.0°C

ID = Isomer Distribution

The expected polar effects are observed. Both the p-chlorophenyl and p-nitrophenyl radicals exhibit electrophilic character in agreement with the results obtained from experiments using diaroyl peroxy sources. On the other hand, the results obtained with the p-methylphenyl and p-methoxyphenyl radicals indicate little, if any, polar character. These conclusions are confirmed by plotting the logarithms of the partial rate factors for the m- positions, where the conjugation effects are at a minimum, against the Hammett's substituent constant. Straight line slopes of gradients -0.81 for p-nitrophenylation and -0.27 for p-chlorophenylation are obtained; while for phenylation, p-methylphenylation and p-methoxyphenylation slopes of 0.05, 0.03 and 0.09 respectively are obtained. This implies that the inductive effect is the dominant substituent effect in these reactions.

Polar effects also play an important part in reactions involving electron transfer processes as in equations (64) and (65).

$$ArH \xrightarrow{-e^-} ArH^{\overset{\bullet}{+}} \qquad (64)$$

$$ArH + e^- \longrightarrow ArH^{\overset{\bullet}{-}} \qquad (65)$$

The electron transfer can be caused by radical or ionic electrophilic and nucleophilic species, as well as electrochemical oxidation and reduction. Such transfers may occur onto neutral aromatic species as in equations (64) and (65); or onto charged aromatic species, equations (66) and (67).

$$ArH_2^+ + R\bullet \longrightarrow ArH_2R^{\overset{\bullet}{+}} \qquad (66)$$

$$ArH_2^+ + e^- \longrightarrow ArH_2^{\overset{+}{\bullet}} \qquad (67)$$

Equations (66) and (67) apply mainly in heteroaromatic reactions, e.g.

reactions in pyridine, since they are more easily protonated. Increased polarity results in general synthetic advantages, e.g. an increased positional (and substrate) selectivity in the arylation of pyridine as already discussed in section 2.3. Examples of such reactions include formation of radical cations by oxidation with (a) peroxydisulphate (equation 68), (b) metal salts (equation 69), (c) hydrogen peroxide and (d) the electrochemical process, e.g. the Kolbe synthesis, etc.

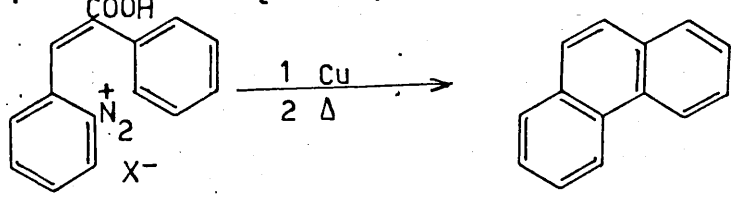
$$ArH + SO_4^{\bullet -} \longrightarrow ArH^{\bullet +} + SO_4^{2-} \qquad (68)$$

$$ArH + M^{n+} \longrightarrow ArH^{\bullet +} + M^{(n-1)+} \qquad (69)$$

The reactions have been investigated extensively and reviewed comprehensively by Minisci.[22,23,207] The cyclohexadienyl radical discussed in previous sections remains the most important intermediate in the interaction of the free radicals with aromatic compounds; it is the radical equivalent of the intermediate $(ArHE)^+$ and $(ArHN)^-$ in heterolytic aromatic substitutions.[207]

2.5.1 Intramolecular Reactions

By far the best known and studied intramolecular arylation is the Pschorr reaction (which includes various allied reactions). In the original Pschorr reaction[230,231] the diazonium salt of trans-o-amino-α-phenylcinnamic acid (45) decomposed in acid solution in the presence of a copper catalyst to give phenanthrene-9-carboxylic acid which was subsequently decarboxylated to give phenanthrene (22), see equation (71).



(21) (22) (71)

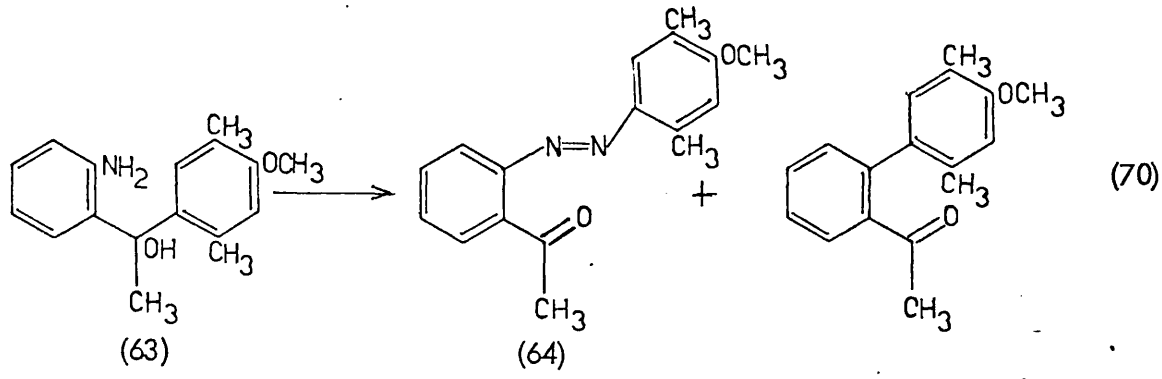
This synthesis was not the first known intramolecular reaction. Fischer and Schmidt[209] had earlier reported the preparation of fluorene by ring-closure of 2-benzylbenzenediazonium chloride in aqueous solution, Graebe and Ullmann[210] similarly prepared fluorenone from 2-benzoylbenzenediazonium chloride (equation 70) and Staedel[211] produced both fluorenone and 1-hydroxyfluorenone from treating 2,2'-diaminobenzophenone with nitrous acid. But it was Pschorr who systematized the intramolecular arylation reaction for the preparation of, and determination of structures of phenanthrene derivatives which he reported in a series of papers.[212-229] The Pschorr reaction has been comprehensively reviewed.[208,230-2]

Many intramolecular arylations have been carried out using azo- and diazonium compounds as sources. The high reactivity of these sources leads to extensive side reactions including the following:

(a) phenol formation which is always a potential competitor to the arylation process. Even in reactions in non-aqueous solvents the adventitious intrusion of water does lead to formation of some phenolic products;

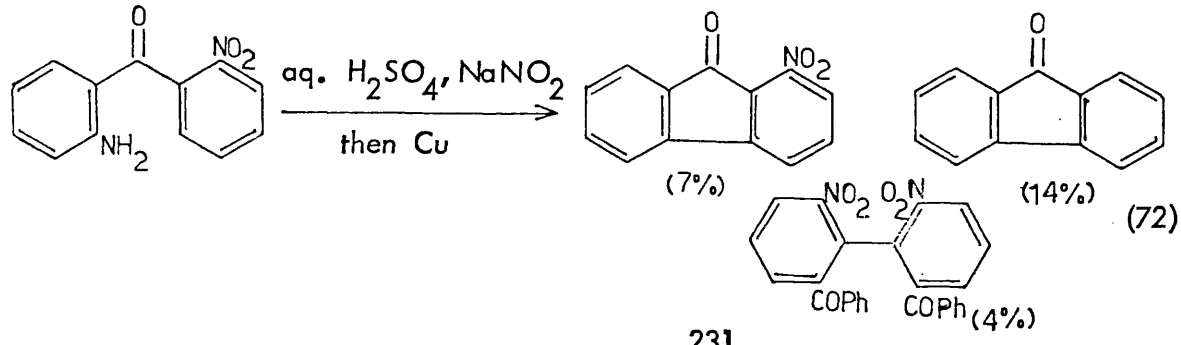
(b) deamination, whereby the diazonium group is replaced by hydrogen, e.g. the formation of benzophenone (92%)[233] when the decomposition of the diazonium tetrafluoroborate salt of o-aminobenzophenone is carried out in acetone using a copper catalyst;

(c) dimerisation (or coupling) resulting in the union of two molecules at the position(s) originally occupied by the diazonium group (equation 72); azo-coupling occurs in an analogous manner, e.g. the formation of the azo ketone (64) in 18% yield when the amino alcohol (63) was treated with nitrous acid, this being an example of an intramolecular diazo coupling and cleavage (equation 70).[316]



(70)

(d) displacement of a substituent from the aryl group attacked, e.g. the formation of fluorenone in equation (72).[46(b),231]



(72)

2'-Carboxyl groups undergo similar elimination.[231] An early observation of the elimination phenomenon was made by Loebl, Stein and Weiss[236] who reported the denitration of nitrobenzene by hydroxy radicals. Subsequently many other elimination reactions have been reported, e.g. the replacement of the halogen of the substrate by pentafluorophenyl radical (equation 83)[317,318]

$$C_6F_5.CO.O^{\bullet} + PhX \xrightarrow{-X^{\bullet}} C_6F_5.CO.OPh \qquad (83)$$

(e) the replacement of the diazonium group by halogen, which process competes with the arylation reaction where an excess of halide ions are present in the reaction.

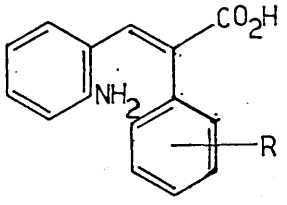
The original Pschorr phenanthrene synthesis (equation 71) was carried out at room temperature and atmospheric pressure and went in good yields (93%).[230,237] Attempts at extending both the conditions and the scope of the Pschorr synthesis met with limited success. Hey and Osbond[237] carried out the synthesis of phenanthrene-9-carboxylic acid by a number of modifications of the original Pschorr procedure and obtained yields as tabulated below.

Table 7

Yields of Phenanthrene-9-carboxylic acid under varying conditions[237]

(Starting compound: trans-o-amino-α-phenylcinnamic acid derivatives)

	Reaction Medium and a Brief Description of Conditions	% Yield
1.	Aqueous; using a copper-bronze catalyst	40
2.	Aqueous/Acidic; using Gatterman's[238] copper powder (original Pschorr conditions)	93
3.	Neutral (in acetone), using a copper catalyst	81
4.	Alkaline (in NaOH), at 0°C (Gomberg conditions)	75
5.	Alkaline (in NaOH), at room temperature	56
6.	Neutral (in benzene), o-Nitrosoacetamido-α-phenylcinnamic acid (25) heated	43
7.	Acidic, Dry HCl passed into the boiling triazen (26)	58



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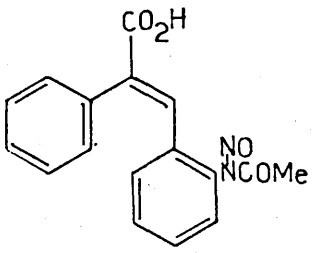

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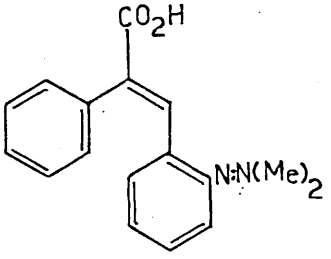


(26)

The examples given above are only a few of very many reported modifications to the Pschorr process. In fact in later[227,239] Pschorr reactions the addition of copper powder was often omitted and the diazonium salt was decomposed by warming its aqueous solution. Indeed, the efficacy of copper catalysts was an early source of controversy.[240,241] Table 7 shows the original Pschorr conditions were best for the synthesis of phenanthrene-9-carboxylic acid. However, in a variety of allied syntheses, e.g. in cyclisations of more complex molecules ring closure is superseded by side reactions, especially the formation of phenols. For this reason, modification of the Pschorr process is sometimes imperative in a synthesis.

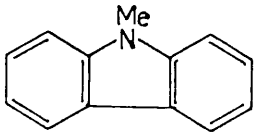
Hey and Mulley,[235] who synthesised fluorene, fluorenone and N-methyl carbozole (27) using diazonium salts of 2-aminodiphenylmethane, 2-amino-benzophenone and 2-amino-N-methyldiphenylamine respectively, observed that in none of these reactions were the high yields reported in the original phenanthrene synthesis reached. By constructing atomic models[242,243] they saw that the distances between the positions which must be linked in the unstrained molecules are large compared with those in systems like trans-o-amino-α-phenylcinnamic acid (45), which are highly favourable to cyclisation. Their approximate calculations are given in Table 8.

Table 8

Distances between Positions linked in Internuclear Cyclisations[232,235]

Parent Amine	Distance (Å)
Trans-o-Amino-α-phenylcinnamic acid	1.5
2-Aminodiphenylamine	2.0
2-Aminodiphenylmethane	2.2
2-Aminobenzophenone	2.4

suggesting the ease of formation (27) > fluorene > fluorenone



(27)

Hey and Mulley[235] observed the order (27) > fluorenone > fluorene (see Table 9).

Table 9

Pschorr Type Cyclisations (from Ref. 235)

Starting Compounds	Method of Reaction	Product Yields %		
		Cyclisation Product	Deamination Product	Phenolic Product
2-Aminodiphenylmethane	B i	-	43.5	5
	A i	13	-	56
	D in Et_2O	-	91	-
	C	-	35	22
2-Aminobenzophenone	A i	58.5	-	26.5
	D in Me_2CO	-	92	-
	B ii	52.5	-	8
	C	-	45.5	-
	E	-	95.5	-
	F	19.5	-	-
2-Amino-N-methyldiphenylamine	A ii	60	-	-
	B ii	66.5	-	-
	C	42.5	23.5	-

METHODS

A. Action of heat on aqueous diazonium salt (i, chloride; ii, sulphate).

B. Action of copper powder on an aqueous diazonium salt (i, chloride; ii, sulphate).

C. Action of copper powder on diazonium fluoroborate in acetone.

D. Action of copper powder on solid diazonium chloride on an organic solvent.

E. Action of hypophosphorous acid on the aqueous diazonium chloride.

F. Action of aqueous sodium hydroxide on the aqueous diazonium sulphate.

2.5.2 The Pschorr and Related Cyclisation Reactions; Suggested Mechanisms

Quite a few problems have beset mechanistic studies of intramolecular cyclisations. First was the doubt whether mechanisms put forward for the intermolecular reactions were equally applicable to the intramolecular counterparts. In many instances it was observed[208,235] that the best experimental conditions for a high yield in the intramolecular reaction are those which lead to a poor or negligible yield in the intermolecular reactions. Second was the difficulty encountered in following the kinetics of the intramolecular reactions. The method used in one case[246] involving measurement of the rate of evolution of nitrogen is erroneous, because as Abramovitch[208,248,249] correctly pointed out, the rate-determining, nitrogen-releasing step precedes the cyclisation step and thus does not throw any light upon the effect of substituents, or upon the magnitudes of ΔH and ΔS for the substitution. A knowledge of the two functions would permit deductions to be made as to the nature of the reactive intermediate.

In studies of the effects of substituents the yields of cyclised products have often been taken as roughly proportional to the rate of cyclisation[232]. This has been questioned[208] since such reactions are allowed to go to completion. Probably much more meaningful are the relative yields of cyclised products and by-products which provide a comparison of the ease with which the substituted nucleus competes with other substrates for the reactive intermediate. This approach is adopted in the present investigation.

2.5.2.1 The Copper-Catalysed Decompositions

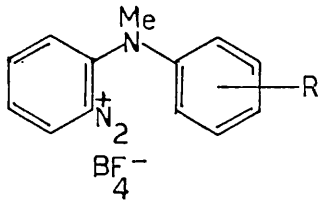
General catalysis of diazonium ion decomposition by metals of low oxidation potentials was discussed in section 2.2.2, wherein the suggested

redox reaction is given. Copper [$Cu \longrightarrow Cu^{+}_{1}$ $E_0 = -0.13v$; $Cu^{+} \longrightarrow Cu^{2+}$, $E_0 = +0.2v$]^{70} is a particularly useful catalyst. Of the many copper catalysed studies carried out, quite a few were mechanistic.

Opinion on the copper-catalysed reaction has changed from favouring a homolytic[70,250-3] process to preferring a range of mechanisms,[254,255] depending upon the actual reaction conditions used.[231,232]

A. Decompositions of Dry Diazonium Salts in Acetone

DeTar[231,246] and Hey[235,237,245] and their coworkers independently studied such reactions using a wide range of diazonium salts. Tabulated below are the results of Hey and his coworkers[235,237,245] from studies of the effects of substituents in the nucleus undergoing attack upon the yields of cyclised products.



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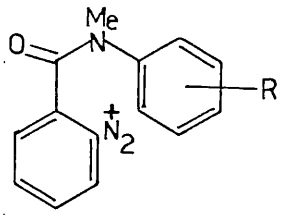


(29)

Table 10

Substituent Effects in Copper-Catalysed Internuclear Cyclisation Products in Dry Acetone

Compound	Substituent	% Yield of cyclised product	Ref.
Diazonium Chlorides of trans-amino-α-phenylcinnamic acid (21) X = Cl	H	81	237
	o-NO_2	57	237
Diazonium tetrafluoroborates of 2-Amino-N-methyldiphenylamines (28)	H	42.5[a]	235
	o-NO_2	24[b]	235
Diazonium tetrafluoroborates of o-Amino-N-methylbenzanilide (29)	H	50[c]	244
	p-CH_3	49[d]	244
	o-CH_3	22	244
	p-Br	33[d]	244
	p-Cl	44[d]	244
	p-NO_2	28.5[d]	245
	o-NO_2	21.4	245
	3,5-di-NO_2	34.5	245

(a) Together with a 23% yield of deaminated product, usually associated with hydrogen abstraction by an aryl radical from the solvent.

(b) A 40% yield of N-methylcarbazole was also obtained together with a trace of N-methyl-3-nitrocarbazole and some deaminated product (15%).

(c) Some dimer was obtained as a by-product. When the solid diazonium sulphate was used a 50% yield of N-methylphenanthridone was obtained together with a small amount of o-hydroxy-N-methylbenzanilide (3%), presumably via the sulphate.

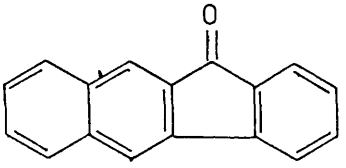
(d) Unidentified crystalline products were also formed in appreciable quantities.

Despite the differences that exist between inter- and intramolecular reactions and their mechanisms, arguments based upon the mechanism of the former process are still used in the elucidation of the latter reaction, since the former has been documented much more extensively and its mechanism is relatively better known.

The results in Table 10 suggest that under the stated conditions the polar nature of the substituents has only a minor effect upon the ease of cyclisation, with no discernible systematic trend. A nitro-group appears not to deactivate the nucleus appreciably and two nitro-groups, which are known to cause a very large decrease in ease of attack in electrophilic aromatic substitution, do not do so here. However, it must be said that the heterogenous reaction taking place at the surface of the metal catalyst introduces steric requirements the magnitude of which is not known. The loss of the o-nitro-substituent upon decomposing compound (28) together with the fact that when the N-methylcarbazole so formed is taken into account the yield of cyclised product is quite high, inclined Hey[235,244,245] to accept a homolytic mechanism for the reactions (c.f. Loebl, Stein and Weiss[236]).

Huisgen and Zahler[254,255] adopted another approach which led them to a different conclusion. Using the diazonium tetrafluoroborate of 2-(2-amino-benzoyl)-naphthalene (42) they studied the ratio of angular to linear cyclised products in the decomposition of the given salt under the above stated conditions. The ratio of angular (30) to linear (31) products was found to be 4.6:1 and dimer was formed in 22% yield. This ratio was appreciably lower than that obtained (9.5) from the decomposition of the corresponding acylarylnitrosamine in benzene, and higher than that obtained (2.4) by the uncatalysed thermal decomposition of the diazonium salt in aqueous acid

solution. Taking the ratio obtained from the uncatalysed thermal decomposition as reflecting attack by the aryl cation, and that from the acylarylnitrosamine reaction as characteristic of free radical attack, it was proposed that the copper-catalysed decomposition involved a mixture of mechanisms (Scheme XVI).[254,255]



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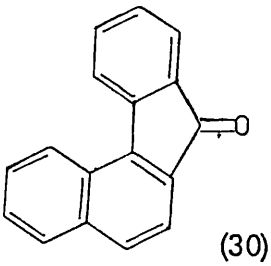

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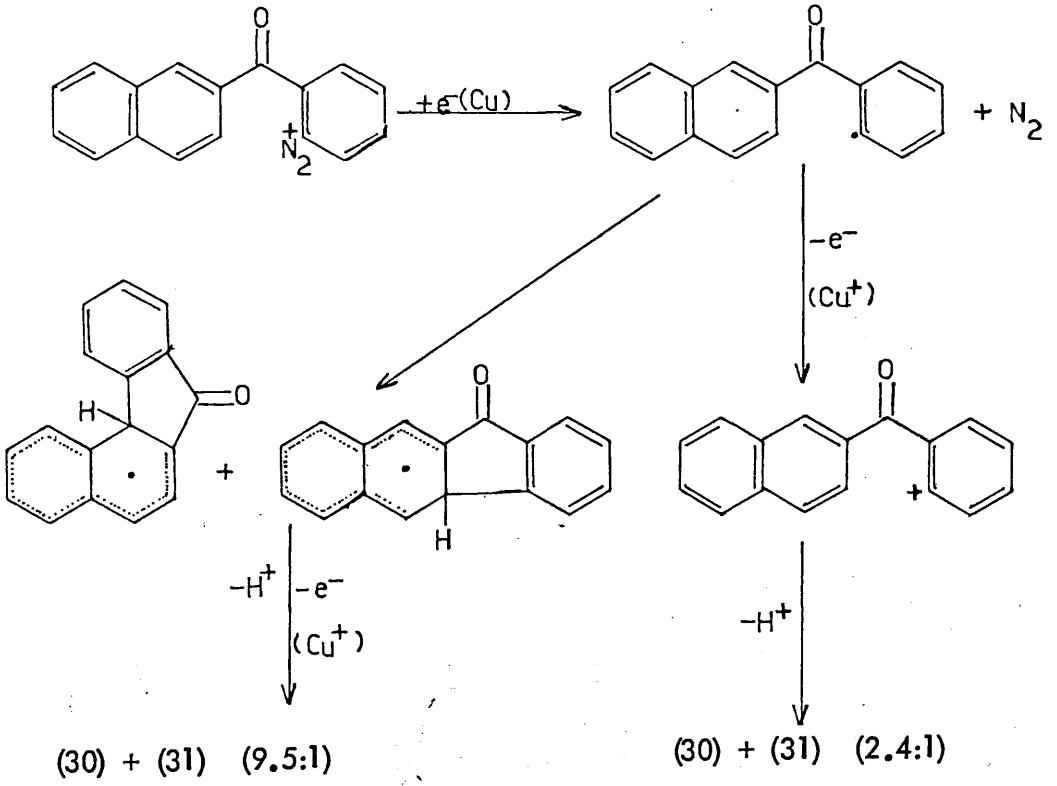
SCHEME XVI[254,255]



When the reaction was carried out under Gomberg reaction conditions (see page 11) a ratio of compound (30) to (31) of 4.4 was found;[254] and a similar ratio of 4.4[118,319] was obtained in the diazonium tetrafluoroborate-pyridine reaction (see page 26). These two reactions are unlikely to proceed by way of a carbonium ion and are most probably homolytic. However, the mechanism of the copper-catalysed decomposition reactions in dry acetone is still not resolved.

B. Decompositions in Aqueous Acid Medium

The independence of the cyclisation reaction upon the polar requirements of substituents in the aromatic ring attacked is again observable here. A selection of very many results available is tabulated below (Table 11) to indicate this fact.

Table 11 (Adopted from ref. 208)

Effects of Substituents upon the Copper-catalysed decomposition of Diazonium Salts in Aqueous Acid Solution (original Pschorr conditions)

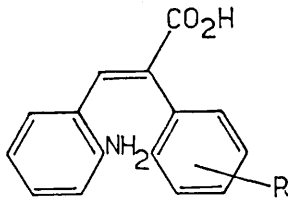
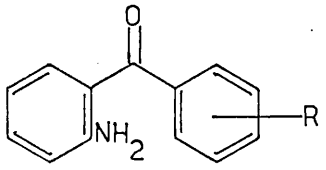
Parent Compound	R	% Yield of Cyclised Product	By-Products	Ref.
 (45)	H	86	-	235
	o-NO_2 [a]	24	Phenol (11.4%)	237
	p-CN	58	-	237
	p-CO_2H	48	-	237
	o-CO_2H	40-45	-	237
	o-OCH_3	55	-	213
	p-OCH_3	50	-	213
	o-CH_3	60-70	-	223
 (32)	H	52.5	Phenol (8.0%)	235
	o-NO_2	6.5	Fluorenone (13.5%)	235
			Phenol (21.0%)	
			o-Nitrobenzophenone (trace)	
			Dimeride* (4.0%)	
	m-NO_2	90 [b]	-	45
	p-CH_3	45	Phenol (31.0%)	45
			Deaminated (12.0%)	

Table 11 (continued)

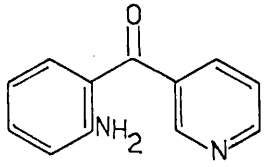
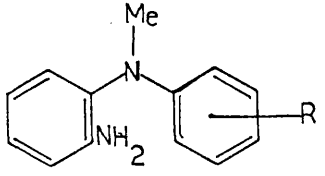
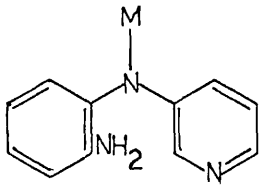
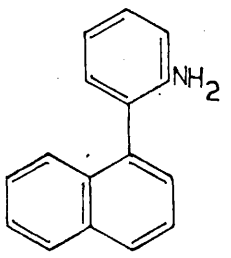
Parent Compound	R	% Yield of Cyclised Product	By-Products	Ref.
 (33)	-	49.8[c]	Phenol (10.0%) 3-Benzoylpyridine (13.0%)	256
 (34)	H o-NO_2	66.5 8	- N-methylcarbazole (56.0%) N-methyl-o-nitrodiphenylamine (8.5%) 2,4-dinitrophenylamine (trace)	235 235

Table 11 (continued)

Parent Compound	R	% Yield of Cyclised Product	By-Products	Ref.
 (35)	-	72(d)	-	257
 (36)	-	78	-	233

* Dimeride = 2,2'-Di-o-nitrobenzoyl diphenyl (see equation 72)

(a) Aqueous solution heated with copper powder.

(b) Mixture of 2- and 4-nitrofluorenones.

(c) Mixture of 2- and 4-azafluorenones.

(d) Mixture of ind-N-methyl- δ - and β-carbolines.

Different yields in some of the cyclisation reactions in Table 11 were claimed by various other workers.

The yields given in Table 11 do not point towards any one particular mechanism of ring closure. For an example, it is known that pyridine is highly deactivated towards electrophilic attack, and the pyridinium nucleus (which is the likely species under these conditions) is even more so. These systems, on the other hand, undergo homolytic arylation readily. The high yield (72%) in the cyclisation of compound (35) would suggest that the pyridine ring is not deactivated towards nuclear attack and hence that the attacking species is a radical. One possible alternative to a radical mechanism for the cyclisation of (35) was that the pyridine nucleus might have been activated towards electrophilic attack by the presence of the 3-amino-substituent. Such an argument is weakened by the fact that a positively charged aryl residue (produced in an S_N1 decomposition) attached to the 3-amino group would reduce considerably the latter's electron-donating capacity to the pyridine ring. In addition, in the acid medium used, the pyridine ring would undoubtedly be protonated and be even less susceptible to electrophilic attack. To eliminate such argument decompositions of diazonium salts of 3-(2-aminobenzoyl)pyridine (33) were carried out.[249] Here an electrophilic carbonyl group at C_3 renders pyridine even less susceptible than before to electrophilic attack. It would be hard to ascribe a yield of cyclised product of 49.8% obtained,[249] solely to electrophilic attack in such a system. In addition, 3-benzoyl pyridine (13%) and 3-(2-hydroxybenzoyl)pyridine (10%) were formed.[249] The formation of 10 per cent phenol may be a measure of the extent to which

the reaction goes by way of an aryl cationic intermediate.

Other results in Table 11 can be similarly examined. The high yield (90%) of 2- and 4-nitrofluorenones in the decomposition of compound (32) is noteworthy. An electrophilic attack solely by a positively charged aryl residue leading to cyclic products would be unexpected to result in such high yield given the polar requirements of the $-NO_2$ group.

2.5.2.2 The Uncatalysed Thermal Decomposition in Acidic Solution

Opinion[208,231,246,258] appears to favour a unimolecular heterolytic (S_N1) mechanism for this reaction. However, some contribution by a Gomberg type process, even though unlikely under the acidic reaction conditions, has occasionally been postulated[208]. DeTar[68] supported a heterolytic mechanism by pointing out the prohibitively high energies that would be required to form aryl radicals from diazonium salts (see section 2.2.2[a]). Other important evidence comes from kinetic studies which indicated that the first-order rate constant is independent of anions present[259] and of acidity over a wide range[260] and has a very low solvent selectivity.[261] The formation of -onium salts, such as the diphenylbromonium ion from bromobenzene, can also be understood as a reaction of the aryl cation with the lone pair of electrons on bromine.[262] DeTar and Relyea[246] tentatively estimated that these reactions are 95% or more heterolytic. Their estimation was based on the supposition that the uncontrolled amount of oxygen present in the reactions would have resulted in 50-100% or more variation in rates and in products of any homolytic part of the process, which variation they[246] did not observe.

The aryl cation produced in these reactions was reported[246] to be highly reactive and unselective, showing even higher reactivity than an alkyl cation.[255] Rationalisations of the highly reactive aryl cation were put forward:

a) in the alkyl cation, the positive charge is in a $2p_z$ orbital, while the aryl cation formed upon dediazoniation does not have the geometry of a normal sp^2 carbonium ion;[255]

and b) an analogy was drawn between this aryl cation and a comparison of the migration aptitudes for the pinacol rearrangement with that for the Demjanov rearrangement[263] of β, β'-diarylethylamines, $ArAr'C^{14}HCH_2NH_2$, to stilbenes, $ArC^{14}H = CHAr'$ on treatment with nitrous acid. In the pinacol rearrangement a methyl or a methoxyl substituent greatly facilitates the migration of the tolyl or anisyl ring compared with the migration of the phenyl ring, and this reaction thus constitutes an example of the type of electronic effect observed in many reactions. But in the Demjanov reaction the migration is almost statistical and thus rather insensitive to substituents. A similar insensitivity to substituents was reported by DeTar and Relyea[246] who carried out cyclisation reactions resulting in formation of fluorenone and its derivatives.

Table 12

Uncatalysed Thermal Decomposition of Diazonium Salts in Aqueous Solution[208]

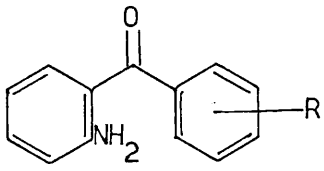
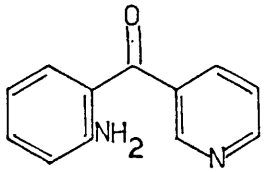
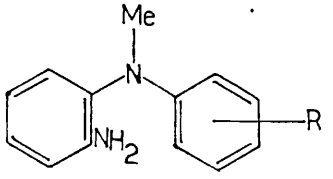
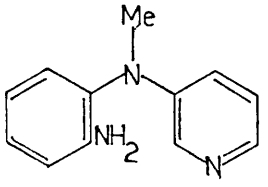
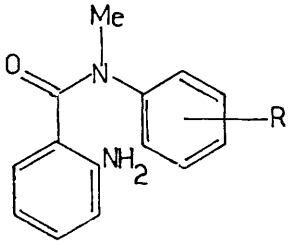
Parent Compound	R	% Cyclised Product	% Phenol	Ref.
 (32)	H	65	35	246
	o-NO_2	8.5[a]	46	235
	m-NO_2	40[b]	53	45
	m-NO_2	33[b]	67	246
	p-CH_3	61	34	246
 (33)	-	6.4[c]	67	256

Table 12 (continued)

Parent Compound	R	% Cyclised Product	% Phenol	Ref.
 (34)	H	60	-	235
	o-NO_2	37.5[d]	-	235
 (35)	-	47.2[e]	-	257
 (37)	H	50	40	244
	p-CH_3	50	20	244
	p-CO_2CH_3	26	-	265
	m-CO_2H	19	-	265

a) A 1.5% yield of fluorenone was also obtained.

b) Mixture of 2- and 4-nitrofluorenone.

c) Mixture of 4- and 2- azafluorenone in the ration 1.2:1.

d) Together with N-methylcarbazole (6.5%), N-methyl-3-nitrocarbazole (13%) the deaminated product (12%) and 2,4'-dinitrodiphenylamine (7%).

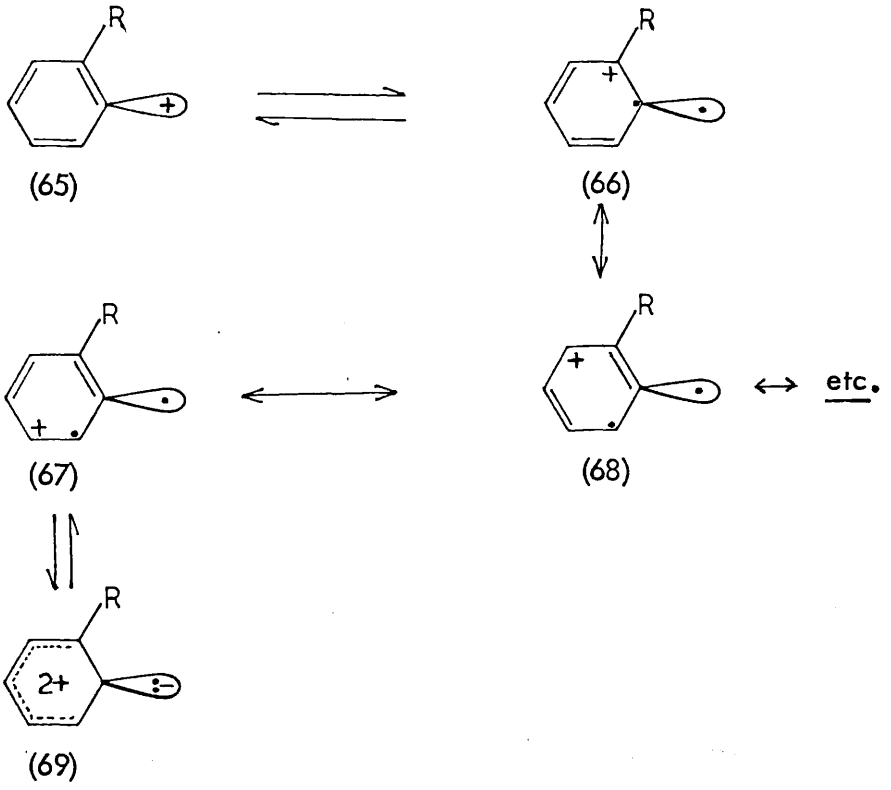
e) ind-N- δ-carboline and ind-N-methyl- β-carboline in the ratio 2.34:1. A small amount of deaminated product was also formed.

The quantitative results summarised in Table 12 were compiled with the view to studying substituent effects in uncatalysed thermal decompositions of diazonium salts in aqueous acid solutions. Overall, the observed substituent effects appear to support the concept of cationic attack. Thus, the yield of cyclised products from 2-amino-3'-nitrobenzophenone (32) was 33%, whereas those for unsubstituted and 4'-methyl substituted amines were over 60%. More important was the ratio of fluorenone to phenol, which dropped from 1.85 for the unsubstituted compound (32) to 0.5 for the 3'-nitro compound. This decrease in the fluorenone:phenol ratio is, qualitatively, in the direction expected for a heterolytic process, since the aromatic nucleus and water would compete for the aryl cation, and the presence of a nitro-group, which decreases, considerably, the nucleophilicity of the aromatic nucleus, should lead to a large increase in phenol formation relative to cyclisation.

The driving force of intramolecular, as compared with intermolecular, reactions is known to be large, the factors favouring ring closure of 5- or 6-membered rings being estimated to be in the range 20-50,000.[233,325] Even then, one would not expect appreciable amounts of heterolytic attack upon a pyridine or pyridinium nucleus, when the much more nucleophilic water molecule is readily available. In both compounds (33) and (35) in Table 12, negligible amounts of cyclisation onto the pyridine nucleus would have been expected.

Abramovitch et al[118,249,256,320] put forward what seems to be the most reasonable rationalisation of the results of reported uncatalysed thermal decompositions of diazonium salts in aqueous acid so far. Expanding a proposal originally made by Taft[321] concerning the stabilisation of the

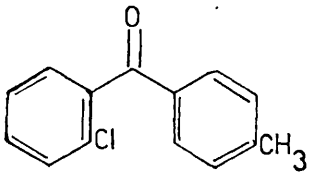
m-methoxyphenyl cation, they suggested that the aryl cation (65) initially formed in these reactions may isomerise to a diradical cation (66) with concerted uncoupling of a pair of π-electrons, one of which falls into the vacant sp^2 σ-orbital. The resulting species would be expected to behave like a highly electrophilic free radical in aromatic substitution reactions. Canonical structure (66) would give the species some of the properties of a triplet carbene. If a second π-electron fell into the σ-orbital the species (69) might behave as a singlet carbene. These species could well take part in the different observed reactions of diazonium compound decompositions.



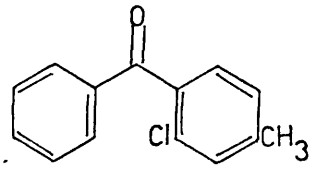
Direct evidence for the formation of radicals in these reactions in aromatic solvents has been obtained from E.S.R. spectroscopic measurements.[230] The use of the uncatalysed diazonium decomposition reaction in radical polymerisation of substrates[322,323] like acrylonitrile, styrene, methyl methacrylate and methyl acrylate provides further evidence. Thus the reactivity, albeit with slight deactivation, of nitroaryl-groups and of the pyridine nucleus towards nuclear attack by the aryl cation in the Pschorr-type cyclisations can be accounted for on the basis of an attack by a highly electrophilic diradical cation[208].

2.5.2.3 Decompositions under Gomberg Reaction Conditions

Very little quantitative data is available on this cyclisation process. The reaction is characterised by low yields of cyclised products, invariably accompanied by tarry by-products. DeTar and Relyea[246] reported yields of cyclised products of between 5% and 28% depending on the pH of the reaction mixture, in the decomposition of 2-benzoylbenzenediazonium tetrafluoroborate. At pH 8.6, yields of fluorenone of 22% and 24% were obtained, whereas at pH 12.3 the yields were about 28%[246].
Hey and Mulley[235] obtained a yield of 19.5% of fluorenone by the action of aqueous sodium hydroxide on the aqueous diazonium sulphate. No identifiable by-products were isolated. The decomposition of 2-benzoylbenzenediazonium tetrafluoroborate in the presence of carbon tetrachloride gave, in addition to 3-methylfluorenone (16%), the two 2-chlorobenzophenones, (38) and (39) in yields of 7% and 3% respectively.[246] This result suggests the intervention of radical chain-transfer and hence that radicals are formed in the reaction.

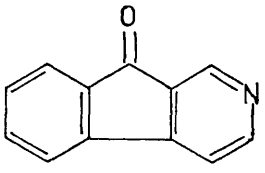


(38)

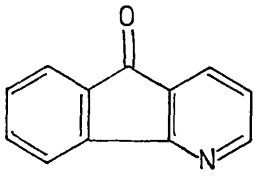


(39)

Ring-closure onto a pyridine ring was also reported. The thermal decomposition of diazotised 3-(2'-aminobenzoyl)pyridine (33) with aqueous sodium hydroxide solution gave (40) in 4% and (41) in 9.4% yields together with 3-benzoylpyridine (3.2%), but no phenolic products were obtained.[256]

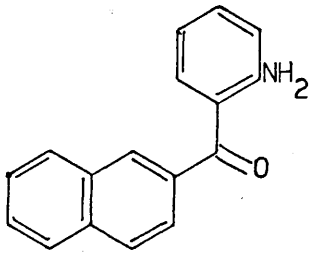


(40)



(41)

A trace of phenol together with 12% cyclised product were, however, obtained[256] upon the decomposition of 2-o-aminobenzoylnaphthalene (42) with sodium hydroxide at pH 12, temperature 100°C. The ratio of angular (30) to linear (31) product was 4.4, which was the same as that obtained from the copper-catalysed decomposition in aqueous solution[254,255] and from the pyridine-catalysed decomposition of dry diazonium tetrafluoroborate in acetone[208] (see section 2.5.2.1.A).



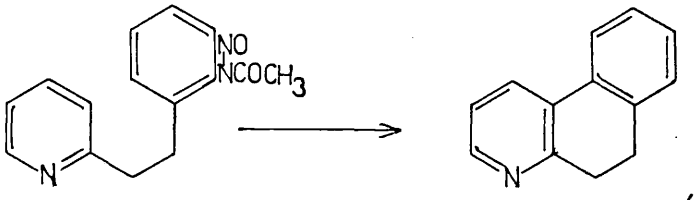
(42)

The Gomberg intramolecular arylation appears to be sensitive to benzene, which competes effectively with the cyclisation process for the reactive intermediate. For example, a 15% yield of 2-benzoylbiphenyl and a small amount of fluorenone was obtained[266] when diazotised 2-aminobenzophenone was decomposed under Gomberg reaction conditions (pH 9) in the presence of benzene).

Only limited attempts at advancing a comprehensible mechanism for the intramolecular arylation have been reported. Huisgen and Zahler[254] proposed that the decomposition, in the absence of benzene, occurred by concurrent heterolytic and free-radical processes and that the ratio of 4.4 for (30):(31) upon the decomposition of (42) was indicative of this. While a duality of mechanism is a possibility, the now generally accepted scheme put forward by Rüchardt and Merz[71] (and analogous pathways by Chalfont and Perkins[84] and by Cadogan[88,95]) point very strongly towards a homolytic mechanism, especially for intermolecular Gomberg arylations (section 2.2.2[b]). A possible explanation for the preference of intermolecular, rather than intramolecular, arylation in the presence of benzene may lie in the large bulk of the diazoanhydride grouping, which would tend to orient the aryl residue to which it was attached in such a confirmation as to render intramolecular attack sterically unlikely. The high ratio of (30):(31) upon the decomposition of (42) could be similarly explained. Considerable steric hindrance to the formation of the σ-complex with benzene, on the α-side but not on the β-side of the naphthalene nucleus would be expected. This could lead to the cyclisation of one conformation at the α-position of the naphthalene ring while the other could either cyclise at the β-position (or react with benzene, if present, to give phenylated product).[208]

2.5.2.4 Cyclisations with Acylarylnitrosamines and Triazens

Very few studies aimed at providing quantitative data on the effects of intramolecular cyclisations starting with these compounds have been carried out. Phenanthrene-9-carboxylic acid was obtained (43%)[237] when the N-nitrosoacetyl derivative of compound (45 p.59, R=H) decomposed. Ring-closure onto a pyridine ring went in good yield (41%) when (43) decomposed in benzene solution to give (44), together with a small amount of denitrosated product[237] (equation 73).



(73)

(plus small amount of denitrosated product)

(43) (44)

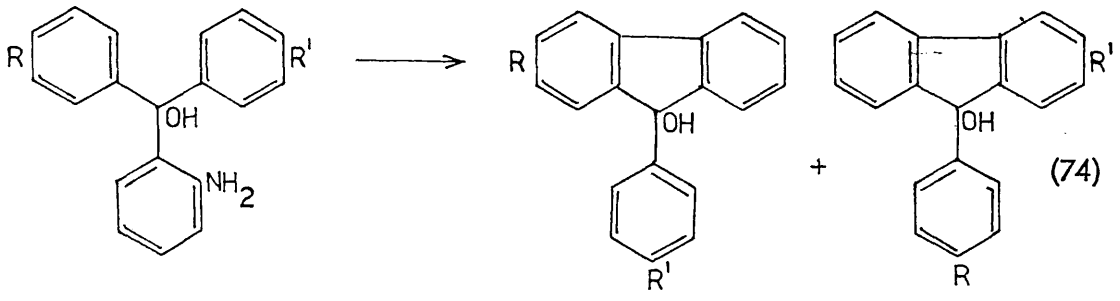
The N-nitrosoacetyl derivative of 2-aminobenzoylnaphthalene (42) decomposed in benzene to give (30) and (31) in 15% yield and a ratio of 9.4, together with phenylated product (4%).[254]

Phenanthrene-9-carboxylic acid was obtained (58%), together with a small amount of o-chloro- α-phenyl-cinnamic acid when dry hydrogen chloride was bubbled through a boiling solution of the dimethyltriazen derivative of (45).[237]

3. Some Aspects of the Homolytic Pschorr Reaction

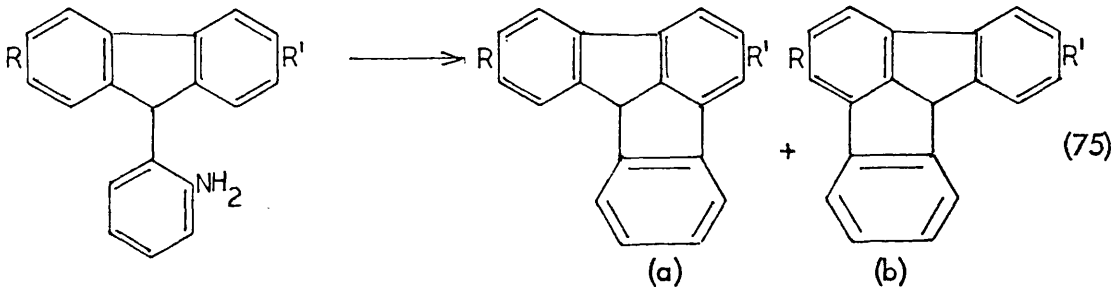
The case for further mechanistic studies on the Pschorr and allied reactions has been made in the aforegoing section. As DeTar[231] observed, the most troublesome aspect of these investigations is the preparation of the amine having the desired structure. An attempt at using compound (49) as

starting amine (equation 75) was unsuccessful. More success was achieved in investigating compound (46) (equation 74).



(74)

(46) (47) (48)



(75)

(a) (b)

(49) (50, R=R'=H, yield 23%)[267]

4. EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer 197 Spectrometer, u.v. measurements were made using a Perkin-Elmer 124 Double Beam Spectrometer with a Perkin-Elmer 165 Recorder. All m.p.'s were uncorrected.

Reagents

The following materials were available commercially (Aldrich Chemical Co. Ltd.): 2-aminobenzophenone (98%), toluene-4-sulphonyl chloride (98%), p-bromoanisole (99%), 3,5-dichloroaniline (98%), 3,5-dimethylaniline (98%), 4 bromochlorobenzene (99%), 2-bromotoluene (97%), 4-bromotoluene (98%). The bracketed percentages refer to percentage purity.

Receipt of 9-(4-chlorophenyl)fluoren-9-ol from Dr. R. Bolton is gratefully acknowledged.

4.1 Attempted Syntheses of 9-(2-Aminophenyl)fluorene (49)

4.1.1 Fluorenone, m.p. 82-3° (lit.,[271] 83-83.5°) was prepared by the oxidation of fluorene (0.60 mol.) using sodium dichromate (1 mol.) by the method devised by Huntress, Hershberg and Cliff[270,271] and as described in the "Preparation of Organic Intermediates".

4.1.2 o-Bromochlorobenzene b.p. 144°/160mm (lit.,[272] 199-201°/742mm) was prepared from o-chloroaniline (1 mol.) by the Sandmeyer process[272].

4.1.3 The reported[274] preparation gave 9-(2-chlorophenyl)fluoren-9-ol (57%) m.p. 139-41° (lit.,[274] 140-1°) from fluorenone (0.17 mol.) and the Grignard reagent from o-bromochlorobenzene (0.51 mol.) The subsequent reduction of 9-(2-chlorophenyl)fluoren-9-ol to 9-(2-chlorophenyl)-fluorene (51%) m.p. 73-5° (lit.,[274] 76-7°) proceeded also as described[274].

4.1.4 Attempts were made to synthesize 9-(2-carboxyphenyl)fluorene from 9-(2-chlorophenyl)fluorene (on a 0.070 molar scale) by a two-stage process, viz., the Rosenmund-von-Braun nitrile synthesis[275,277] followed by the hydrolysis of the nitrile, *in situ*, to the required product. The reaction, described by Rapoport and Smolinsky[269], went in maximum yields of approximately 2% (cf. lit.,[269] 59%) m.p. 238-242° (lit., 240-2°[269] and also 241-2°[276]).

4.1.5 9-(2-Tolyl)fluoren-9-ol was prepared from fluorenone (0.12 mol.) and the Grignard reagent from o-bromotoluene (0.36 mol.) following the procedure as described by Campbell and Marks[274]. It was recrystallised (methanol) as yellow plates (60%) m.p. 121-2° (lit., 121-1.5°[292]; 121-3°[307]); ν_{max} (nujol) 3605 (OH) cm^{-1}.

4.1.6 An attempted oxidation of 9-(2-tolyl)fluoren-9-ol (0.06 mol.) using sodium dichromate (0.09 mol.) to give 9-(2-carboxyphenyl)fluoren-9-ol, and following a procedure[278] for the preparation of 2,3-naphthalenedicarboxylic acid, gave an intractable black tar as similar to that observed earlier by Stubbs and Tucker[279].

4.1.7 o-Diphenylenephthalide was prepared (61%) from the oxidation of 9-(2-tolyl)fluoren-9-ol (0.04 mol.) with manganese dioxide and concentrated nitric acid[279], m.p. 218-221° (lit.,[279] 226°). A subsequent attempt at reducing this compound to 9-(2-carboxyphenyl)fluorene using the conditions described for the reduction of 9-(2-chlorophenyl)fluoren-9-ol[274] was unsuccessful though reaction time was increased tenfold.

4.1.8 An unsuccessful attempt was also made to prepare 9-(2-aminophenyl)fluorene by the direct reaction between nitrobenzene (0.01 mol.) and 9-fluorenyllithium (0.05 mol.) followed by reduction, *in situ*, of the product using copper (I) iodide. The reaction was based on reports of similar preparations involving conjugate additions of alkyl Grignard (or alkyllithium) compounds to nitroarenic systems in tetrahydrofuran (T.H.F.) to give *o*- or *p*- nitronate products carried out by Bartoli and co-workers[280-4]. 9-Fluorenyllithium was prepared from fluorene (0.07 mol.) in dry ether and phenyllithium (0.105 mol.) also in dry ether according to the method as described by Bavin[308]. To this fluorenyllithium solution was added, dropwise at -40° a solution of nitrobenzene (0.01 mol.) in T.H.F., the reaction being stirred and kept under nitrogen. Copper (I) iodide (0.0015 mol.) was also added. The reaction was stirred for 8h. with the temperature allowed to rise gradually to room temperature. Aqueous

hydrochloric acid (5 ml) was added followed by ammonium hydroxide (20 ml of bench solution). The resulting mixture was extracted with dichloromethane; the organic layer was washed several times with water, dried ($MgSO_4$) and the solvent removed (rotary evaporator). The crude product was taken up in benzene and passed down a column of silica gel using a benzene/ethyl acetate (8:2) solvent mixture. Only fluorene (50% of starting material) could be isolated from the products thus eluted.

4.2 2-Aminotriphenylmethanol and Derivatives

4.2.1 Substituted 2-Aminobenzophenones

A. p-Toluenesulphonylanthranilic acid (51) m.p. 229-30° (lit.,[285] 229-30°), neutral equivalent 295 (lit.,[285] 295) was prepared (92%) from anthranilic acid (0.5 mol.) and p-toluenesulphonyl chloride (0.6 mol.) according to the procedure described by Scheifele and DeTar[285]. p-Toluenesulphonylanthranilic acid chloride (52) prepared from p-toluenesulphonylanthranilic acid as described[285], was used in the Friedel Crafts acylation of appropriately substituted benzene derivatives to give the following substituted 2-aminobenzophenones:

(a) 2-Amino-4'-methylbenzophenone (72%) m.p. 92-3° (lit.,[285] 92-3°) was made by treating (52) (0.05 mol.) with toluene (150 ml) according to the route described by Scheifele and DeTar[285].

(b) 2-Amino-4'-chlorobenzophenone (34%) m.p. 101-2° (lit., 120°[299]; 102°[298]) was obtained analogously using chlorobenzene (190 ml); and

(c) 2-Amino-4'-methoxybenzophenone (40%) m.p. 78-9° (lit.,[286] 78-80°) was made using (52) (0.05 mol.) and methoxybenzene (195 ml).

B.

(a) 2-Amino-3',5'-dimethylbenzophenone (8%) m.p. 68-70° (lit.,[301] 68-70°); υ_{max} (nujol) 3450, 3350 (NH_2); 1620 (CO)cm^{-1}. (Found: C, 79.9; H, 6.7; N, 6.3; Calc. for $C_{15}H_{15}NO$: C, 80.0; H, 6.7; N, 6.2%) was prepared by the inverse addition of the Grignard reagent derived from 3,5-dimethylbromobenzene (0.072 mol.) to 2-methyl-3,1,4-benzoxaz-4-one (0.072 mol.) according to the method of Lothrop and Goodwin[287].

3,5-Dimethylbromobenzene (38%) b.p. 109-110°/3.6mm was prepared from 3,5-dimethylaniline (0.5 mol.) by the Sandmeyer process (section 4.1.2).

2-Methyl-3,1,4-benzoxaz-4-one was prepared (62%) from anthranilic acid (0.15 mol.) and acetic anhydride (0.45 mol.)[297].

(b) 2-Amino-3,5-dichlorobenzophenone was prepared by addition of sulphuryl chloride (0.204 mol.) to a solution of 2-aminobenzophenone (0.051 mol.) in nitromethane (100 ml). The warm reaction mixture was shaken for a few minutes, water was added and the mixture was neutralised with ammonium hydroxide (2M). The product was extracted with ether and the solvent was removed (rotary evaporator). The product was crystallised from the resulting viscous oil (methanol) (24%), m.p. 85-8° (lit.,[310] 93-4°). υ_{max} (nujol) 3400, 3300 (NH_2), 1640 (CO) cm^{-1}. (Found: C, 58.0; H, 3.4; N, 5.2; Calc. for $C_{13}H_9Cl_2NO$: C, 58.65; H, 3.4; N, 5.3%).

4.2.2 Substituted Fluorenones

The general cyclisation procedure described by DeTar and Whiteley[45], starting with the appropriate 2-aminobenzophenone derivative, was followed in the preparation of the substituted fluorenones. Briefly, the method involves the preparation of the diazonium sulphate from the appropriate 2-aminobenzophenone followed by the thermal decomposition (80°) of the diazonium salt in a 21N strength sulphuric acid. The following fluorenones were thus prepared:

(a) 3-methylfluorenone (72%), m.p. 67° (lit.,[45] 66.0-66.5°[b]) υ_{max} (nujol) 1705 (CO) cm^{-1} starting with 2-amino-4'methylbenzophenone (0.007 mol.).

(b) 3-chlorofluorenone (75%) m.p. 160° (lit., 159°[298], also 157°[302] and 156-157°[303]); υ_{max} (nujol) 1710 (CO) cm^{-1}. (Found: C, 72.5; H, 3.2; Calc. for $C_{13}H_7ClO$: C, 72.6; H, 3.3%) starting with 2-amino-4'-chlorobenzophenone (0.0095 mol.).

(c) 3-methoxyfluorenone (77%) m.p. 99° (lit., 92-4°[288], 99.5-100°[303]; 100°[304]); υ_{max} (nujol) 1700 (CO) cm^{-1} from 2-amino-4'-methoxybenzophenone (0.0031 mol.).

(d) 2,4-dimethylfluorenone (82%) m.p. 149° (lit., 149-150°)[300] υ_{max} (nujol) 1710 (CO) cm^{-1}. (Found: C, 86.0; H, 5.9; Calc. for $C_{15}H_{12}O$: C, 86.1; H, 6.2%) starting with 2-amino-3',5'-dimethylbenzophenone (0.0024 mol.).

(e) 2,4-dichlorofluorenone (20%) m.p. 144-6° υ_{max} (nujol) 1720 (CO) cm^{-1}. (Found: C, 62.7; H, 2.5. Calc. for $C_{13}H_6Cl_2O$: C, 62.7; H, 2.4%) starting with 2-amino-3,5-dichlorobenzophenone (0.0056 mol.).

4.2.3 Nuclear and Phenyl-Substituted 9-Phenylfluoren-9-ols

The following two general procedures were followed in the preparation of the 9-phenylfluoren-9-ols.

A. An ethereal solution of a Grignard reagent using magnesium and aryl halide (approx. 2.5 molecular equivalents each, based on the fluorenone used) was added slowly and with stirring, through a plug of glass wool, to an ice-cold solution of the appropriate fluorenone in 5% benzene in ether solution. After complete addition of Grignard reagent the mixture was allowed to warm gradually to room temperature and then was boiled for a further half-hour. Hydrolysis of the adduct was achieved by pouring the reaction mixture onto acidified (dil. HCl) ice-water.

The organic layer was separated, dried (Na_2SO_4) and the solvent was removed in a rotary evaporator. The resulting oil was dissolved in a minimum amount of benzene and passed down an alumina column using petroleum ether (b.p. 40-60°) as eluent. The major by-product in this reaction, viz., biaryl, came out as the first fraction and elution was repeated (at least twice) until biaryl could not be detected. The 9-phenylfluoren-9-ol was finally crystallised from petroleum ether (b.p. 40-60°). Crystallisations were very slow, in some cases requiring several weeks.

The following alcohols were thus prepared:

(a) 9-phenylfluoren-9-ol (86%) m.p. 84-6° (lit., 85-8°[291], also 85°[292] and 109°[293,295]), υ_{max} (nujol) 3450-3220 (OH) cm^{-1}, starting with fluorenone (0.045 mol.) and the Grignard derivative of bromobenzene (0.14 mol.).

(b) 9-(4-tolyl)fluoren-9-ol (81%) m.p. 84-6° (lit.,86-7°[292] and 85.5-86.5°[293]).

(Found: C, 88.1; H, 5.9; Calc. for $C_{20}H_{16}O$: C, 88.0; H, 5.9%) with fluorenone (0.056 mol.) and 4-bromotoluene (0.139 mol.) as starting compounds.

(c) 9-(4-methoxyphenyl)fluoren-9-ol (70%) m.p. 86-8° (lit., oil[292], but also 130-132°[293] and 87-8°[294]).

υ_{max} (nujol) 3540, 3440 (OH) cm^{-1}.

(Found: C, 83.2; H, 5.6; Calc. for $C_{20}H_{16}O_2$: C, 83.3; H, 5.5%) starting with fluorenone (0.028 mol.) and 4-bromoanisole (0.083 mol.).

(d) 3-methyl-9-phenylfluoren-9-ol (71%) m.p. 87°

υ_{max} (nujol) 3600, 3350 (OH) cm^{-1}.

(Found: C, 87.8; H, 5.9; Calc. for $C_{20}H_{16}O$: C, 88.0; H, 5.9%) starting with 3-methylfluorenone (0.0051 mol.) and the Grignard derivative of bromobenzene (0.0153 mol.).

(e) 3-chloro-9-phenylfluoren-9-ol (70%) m.p. 87-9°

υ_{max} (nujol) 3350 (OH) cm^{-1}.

(Found: C, 77.6; H, 4.7; Calc. for $C_{19}H_{13}ClO$: C, 78.0; H, 4.4%) using 3-chlorofluorenone (0.0047 mol.) and bromobenzene (0.0111 mol.) as reagents.

(f) 3-methoxy-9-phenylfluoren-9-ol (65%) m.p. 124-6°

υ_{max} (nujol) 3450 (OH) cm^{-1}.

(Found: C, 83.0; H, 5.6; Calc. for $C_{20}H_{16}O_2$: C, 83.3; H, 5.5%) using 3-methoxyfluorenone (0.0024 mol.) and bromobenzene (0.006 mol.), as starting compounds.

(g) 3-chloro-9-(4-tolyl)fluoren-9-ol (40%) m.p. 64-66°

υ_{max} (nujol) 3580, 3350 (OH) cm^{-1}.

(Found: C, 78.7; H, 5.3; Calc. for $C_{20}H_{15}ClO$: C, 78.3; H, 4.9%) by using 3-chlorofluorenone (0.0033 mol.) and the Grignard derivative of 4-bromotoluene (0.0098 mol.)

(h) 3-methyl-9-(4-chlorophenyl)fluoren-9-ol (31%) m.p. 69-70°

υ_{max} (nujol) 3450 (OH) cm^{-1}.

(Found: C, 78.2; H, 5.1; Calc. for $C_{20}H_{15}ClO$: C, 78.3; H, 4.9%) using 3-methylfluorenone (0.0033 mol.) and 4-bromochlorobenzene (0.0099 mol.) as starting compounds.

(i) 9-(3,5-dichlorophenyl)fluoren-9-ol (23%) m.p. 107-110°

υ_{max} (nujol) 3550, 3440 (OH) cm^{-1}.

(Found: C, 69.2; H, 4.1; Calc. for $C_{19}H_{12}Cl_2O$: C, 69.6; H, 3.8%) and in the reaction, fluorenone (0.0083 mol.) and 3,5-dichlorobromobenzene (0.021 mol.) were used as starting reagents.

3,5-Dichlorobromobenzene was prepared from 3,5-dichloroaniline (0.5 mol.) by the Sandmeyer process as described by Hartwell[272] and crystallised as yellow needles from methanol (63%) m.p. 74° (lit., 74[309]). (Found: C, 31.7; H, 1.2; Calc. for $C_6H_3BrCl_2$: C, 31.9; H, 1.3%).

(j) 2,4-dichloro-9-phenylfluoren-9-ol (19%) m.p. 89-91°

υ_{max} (as an oil), 3540, 3390 (OH).

(Found: C, 69.4; H, 4.1; Calc. for $C_{19}H_{12}Cl_2O$: C, 69.6; H. 3.8%) using 2,4-dichlorofluorenone (0.0004 mol.) and bromobenzene (0.001 mol.) as starting compounds.

B. The aryllithium, prepared from the aryl halide according to the general procedure as described by Gilman and Woods[290], was added slowly with stirring to a cold (ice-bath) solution of fluorenone in benzene/ether (1:19), under a nitrogen atmosphere, as described[290]. The reaction mixture was allowed to warm gradually to room temperature and left to stand at room temperature for a further half-hour.

The adduct was hydrolysed by pouring onto acidified (dil. HCl) crushed ice. Separation of the organic layer and product purification was carried out as described in A.

The following alcohols were thus prepared:

(a) 9-(3,5-dimethylphenyl)fluoren-9-ol (69%) m.p. 117-9°

υ_{max} (nujol) 3550 (OH) cm^{-1}.

(Found: C, 88.0; H, 6.5; Calc. for $C_{21}H_{18}O$: C, 88.1; H, 6.3%) from the reaction between fluorenone (0.011 mol.) and the aryllithium reagent from 3,5-dimethylbromobenzene (0.022 mol.) and n-butyllithium (0.022 mol.) as its solution in n-hexane (1.55M).

(b) 2,4-dimethyl-9-phenylfluoren-9-ol (64%) m.p. 100.5°

υ_{max} (nujol) 3600, 3450 (OH) cm^{-1}.

(Found: C, 88.4; H, 6.3; Calc. for $C_{21}H_{18}O$: C, 88.1; H, 6.3%) by using 2,4-dimethylfluorenone (0.00197 mol.) bromobenzene (0.00394 mol.) and n-butyllithium (0.00394 mol. 1.55M solution in n-hexane).

4.2.4 2-Aminotriphenylmethanols

(a) The unsubstituted 2-aminotriphenylmethanol was prepared from methyl anthranilate (0.24 mol.) and phenylmagnesium bromide (0.78 mol.) according to the procedure described by Baeyer and Villiger[296] (31%) m.p. 121°

(lit.,[296] 121.5°).

(b) 2-Aminotriphenylmethanols containing substituents in another phenyl group were prepared by the following general procedure:

An ethereal solution of the appropriate arylmagnesium bromide (3 molar equivalents based on the aminobenzophenone used) was added slowly through a plug of glass wool, to a well stirred, ice-cold solution of o-aminobenzophenone in benzene/ether (1:19). After complete addition of the Grignard reagent the temperature of the reaction mixture was allowed to rise gradually to ambient temperature. The reaction mixture was boiled for 1h., the organic layer was separated and concentrated on the rotary evaporator.

The thick residue was digested with bench (3M) HCl*, and where an insoluble amine hydrochloride resulted, the mixture was filtered, and the residue thoroughly leached with benzene. The benzene layer was concentrated (rotary evaporator) and the digestion and filtration processes repeated until no more amine hydrochloride could be isolated from the filtrates. The combined amine hydrochloride products were made alkaline with ammonium hydroxide, the resulting amine was dissolved in benzene, and the benzene layer was washed with water, dried (Na_2SO_4) and concentrated (rotary evaporator). Many crystallisations from benzene were required, in each case, before a product of constant, sharp melting point could be obtained.

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*The method of bubbling gaseous HCl through a benzene solution of the residue was also used.

In a few cases where the amine hydrochloride was not precipitated from the aqueous acid solution, the solution was washed with benzene. The separated benzene layer was extracted twice with bench HCl (3M), the aqueous acidic extracts combined, neutralised with a solution of ammonium hydroxide (33% w/w in water) and subsequently treated as described above. Below are the compounds thus prepared:

(a) 2-amino-4'methyltriphenylmethanol (25%) m.p. 88-9°

υ_{max} (nujol) 3390, 3290 (NH_2); 3160 (OH) cm^{-1}.

(Found: C, 83.0; H, 6.6; N, 4.8; Calc. for $C_{20}H_{19}NO$: C, 83.0; H, 6.6; N, 4.9%) with 2-aminobenzophenone (0.10 mol.) and 4-bromotoluene (0.30 mol.) as starting compounds.

(b) 2-amino-4'-chlorotriphenylmethanol (22%) m.p. 94-6°.

υ_{max} (nujol) 3370, 3280 (NH_2); 3150 (OH) cm^{-1}.

(Found: C, 74.0; H, 5.5; N, 4.4. Calc. for $C_{19}H_{16}ClNO$: C, 73.7; H, 5.2; N, 4.5%).

from the reaction between 2-aminobenzophenone (0.050 mol.) and the Grignard reagent derived from 4-bromochlorobenzene (0.15 mol.).

(c) 2-amino-4'-chloro-4''-methyltriphenylmethanol (13%) m.p. 90-2°

υ_{max} (nujol) 3600 (OH); 3400, 3350 (NH_2) cm^{-1}

(Found: C, 73.8; H, 5.9; N, 4.1; Calc. for $C_{20}H_{18}ClNO$: C, 74.2; H, 5.6; N, 4.3%); the reagents used in this preparation being 2-amino-4'-methylbenzophenone (0.016 mol.) and p-bromochlorobenzene (0.048 mol.).

(d) 2-amino-3',5'-dimethyltriphenylmethanol (27%) m.p. 130-2°

υ_{max} (nujol) 3400, 3300 (NH_2), 3175 (OH) cm^{-1}.

(Found: C, 83.3; H, 7.1; N, 4.4; Calc. for $C_{21}H_{21}NO$: C, 83.2; H, 6.9; N, 4.6%) from the reaction between fluorenone (0.025 mol.) and

the Grignard derivative of 3,5-dimethylbromobenzene (0.075 mol.).

(e) 2-Amino-3'5'-dichlorotriphenylmethanol (43%) m.p. 125-6°

ν_{max} (nujol) 3380, 3300 (NH_2), 3180 (OH) cm^{-1}.

(Found: C, 66.1; H, 4.4; N, 4.1; Calc. for $C_{19}H_{15}Cl_2NO$: C, 66.3; H, 4.4; N, 4.1%) from the reaction between fluorenone (0.0083 mol.) and the Grignard reagent from 3,5-dichlorobromobenzene (0.025 mol.) and magnesium (0.025 mol.).

(f) 2-amino-4'-methoxytriphenylmethanol (9%) m.p. 116-8°

ν_{max} (nujol) 3400, 3310 (NH_2), 3150 (OH) cm^{-1}.

(Found: C, 78.7; H, 6.3; N, 4.6; Calc. for $C_{20}H_{19}NO_2$: C, 78.7; H, 6.2; N, 4.6%) from the reaction between 2-amino-4'-methoxybenzophenone (0.0097 mol.) and the Grignard reagent from bromobenzene (0.0291 mol.) and magnesium (0.0291 mol.).

4.2.5 Deamination Reactions of the 2-Aminotriphenylmethanols

Three general deamination procedures followed are described below.

A. Thermal Decompositions in Aqueous-Acidic Solutions

The amino alcohol was diazotised in aqueous sulphuric acid (10% weight for weight acid in water solution) at 0-5° with slightly more than an equivalent quantity of sodium nitrite.

The amino alcohol was dissolved in the aqueous acid (approximately 25 ml of acid solution per millimole of amino alcohol) and the solution of sodium nitrite, in water added over a period of 15 minutes. The reaction was left at 0-10° for at least 30 minutes before warming to room temperature. After 4h. the reaction mixture, from which an oily layer had separated, was warmed to 50° for a few minutes. The mixture was extracted three times with ether, and the ether extracts combined. Phenolic products were extracted (5% sodium hydroxide solution) and precipitated from the basic solution using bench HCl. The precipitate was extracted with ether, the ether layer dried (Na_2SO_4) and the solvent removed (rotary evaporator). The phenolic products were weighed but not characterised further.

The neutral layer left behind after phenolic products extraction was washed with water, dried (Na_2SO_4) and the solvent removed. The residue was analysed as described in section 4.2.6. The following amino alcohols were thus deaminated (Table 13).

Table 13: Thermal Decompositions of o-Aminotriphenylmethanols in Aqueous-Acidic Solutions

Amino Alcohol	Amounts of Amino Alcohol g	mmol	Amounts of $NaNO_2$ g	mmol	Amount of 10% H_2SO_4 used as decomposition medium (ml)
a) o-Aminotriphenylmethanol	1.5	6.0	0.5	7.2	150.0
b) 2-Amino-4'-chlorotriphenylmethanol	0.21	0.60	0.06	0.90	15.0
c) 2-Amino-4'-methyltriphenylmethanol	0.47	1.60	0.15	2.20	40.0
d) 2-Amino-3',5'-dimethyltriphenylmethanol	0.15	0.50	0.05	0.73	12.5
e) 2-Amino-3',5'-dichlorotriphenylmethanol	0.20	0.60	0.06	0.87	15.5
f) 2-Amino-4'-chloro-4"-methyltriphenylmethanol	0.09	0.30	0.03	0.44	8.0
g) 2-Amino-4'-methoxytriphenylmethanol	0.03	0.099	0.007	0.48	3.0

Table 14: Product Yields in the Thermal Decomposition of 2-Aminotriphenylmethanols in Aqueous Acidic Solutions

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Average	Yield of Phenolic By-products (% w/w of amine)
2-Aminotriphenylmethanol	a) 9-Phenylfluoren-9-ol	(i) 86.3 ±2.0 (ii) 71.7 ±1.3	79.0 ±1.7 (41 isolated)	18
	b) *see below			
2-Amino-4'-chloro-triphenylmethanol	a) 9-(4-Chlorophenyl)fluoren-9-ol	(i) 38.2 ±5.3 (ii) 40.0 ±7.3 (iii) 37.3 ±5.4	38.5 ±6.0	19
	b) 3-Chloro-9-phenylfluoren-9-ol	(i) 33.1 ±5.3 (ii) 39.6 ±7.3 (iii) 31.7 ±5.4	34.8 ±6.0	
2-Amino-4'-methyl-triphenylmethanol	a) 9-(4-Tolyl)fluoren-9-ol	(i) 50.2 ±4.7 (ii) 46.3 ±4.5 (iii) 45.4 ±3.7	47.4 ±4.3	14
	b) 3-Methyl-9-phenylfluoren-9-ol	(i) 40.3 ±4.7 (ii) 35.3 ±4.5 (iii) 39.6 ±3.7	38.4 ±4.3	

b) * Triphenylmethanol (3%) also produced in the reaction

Table 14 (continued)

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Average	Yields of Phenolic By-products (% w/w of amine)
2-Amino-3',5'-dimethyl-triphenylmethanol	a) 9-(3,5-Dimethylphenyl)fluoren-9-ol	(i) 46.2 ±2.9 (ii) 53.6 ±4.7 (iii) 44.2 ±4.1	48.0 ±3.9	8
	b) 2,4-Dimethyl-9-phenylfluoren-9-ol	(i) 49.1 ±2.9 (ii) 42.0 ±4.7 (iii) 46.9 ±4.1	46.0 ±3.9	
2-Amino-3',5'-dichloro-triphenylmethanol	a) 9-(3,5-Dichlorophenyl)fluoren-9-ol	(i) 49.1 ±2.0 (ii) 45.0 ±2.2 (iii) 46.0 ±2.1	46.7 ±2.1	9
	b) 2,4-Dichloro-9-phenylfluoren-9-ol	(i) 45.7 ±2.0 (ii) 44.7 ±2.2 (iii) 39.8 ±2.1	43.4 ±2.1	
2-Amino-4'-chloro-4"-methyltriphenylmethanol	a) 3-Chloro-9-(4-tolyl)fluoren-9-ol	(i) 42.1 ±3.3 (ii) 38.2 ±2.6 (iii) 40.3 ±2.5	40.2 ±2.8	17
	b) 3-Methyl-9-(4-chlorophenyl)fluoren-9-ol	(i) 41.3 ±3.3 (ii) 42.0 ±2.6 (iii) 34.9 ±2.5	39.4 ±2.8	

Table 14 (continued)

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Average	Yield of Phenolic By-products (% w/w of amine)
2-Amino-4'-methoxy-triphenylmethanol	a) 9-(4-Anisyl)fluoren-9-ol	(i) 42.6 ±3.0 (ii) 46.3 ±2.3 (iii) 45.8 ±2.2	44.9 ±2.5	10
	b) 3-Methoxy-9-phenylfluoren-9-ol	(i) 47.2 ±3.0 (ii) 40.0 ±2.3 (iii) 43.0 ±2.2	43.4 ±2.5	

B. Thermal Decompositions in Benzene, the Use of Amyl Nitrite in Diazotisations Leading to Intramolecular Cyclisation

The method was an adaptation for intramolecular cyclisations of the procedure for biaryl synthesis as devised independently by Cadogan[121] and Hwang Shu[120].

The mixture of benzene, the amino alcohol and a slight excess of amyl nitrite were warmed until a perceptible evolution of gas set in. This was allowed to proceed without further heating until it had subsided. The mixture then boiled until the β-naphthoxide test proved negative (approximately 8h.). The solvent and low-boiling components were removed (rotary evaporator), the resulting residue was redissolved in benzene, and was extracted with sodium hydroxide (5% solution). Phenolic products were isolated from the aqueous-alkaline layer as previously described. The benzene layer was washed (water), dried (Na_2SO_4) and the solvent removed. The residue was examined as described in section 4.2.6. The following amino alcohols were thus deaminated (Table 15).

Table 15: Decompositions in Benzene using Amyl Nitrite as Diazotising Agent

Amino Alcohol	Amounts of				Amount of Benzene Solvent
	Amino Alcohol		Amyl Nitrite		
	g	mmol	g	mmol	ml
a) o-Aminotriphenylmethanol	2.2	8.0	1.4	12.0	200.0
b) 2-Amino-4'-chloro-triphenylmethanol	0.22	0.71	0.10	0.90	18.0
c) 2-Amino-4'-methyltriphenylmethanol	0.47	1.60	0.28	2.4	40.0
d) 2-Amino-3',5'-dimethyltriphenylmethanol	0.15	0.50	0.09	0.75	12.5
e) 2-Amino-3',5'-dichlorotriphenylmethanol	0.20	0.6	0.11	0.9	15.0
f) 2-Amino-4'-chloro-4"-methyltriphenylmethanol	0.09	0.30	0.05	0.45	7.5
g) 2-Amino-4'-methoxytriphenylmethanol	0.03	0.09	0.015	0.14	2.5

Table 16: Product Yields in the Decomposition of 2-Aminotriphenylmethanols in Benzene by Amyl Nitrite

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Average	Yield of Phenolic By-products (% w/w of amine)
2-Aminotriphenylmethanol	a) 9-Phenylfluoren-9-ol b) *see below	(i) 34.2 ±1.3 (ii) 29.8 ±0.9	32.0 ±1.1	6
2-Amino-4'-chloro-triphenylmethanol	a) 9-(4-Chlorophenyl)fluoren-9-ol	(i) 15.0 ±1.7 (ii) 12.1 ±1.6 (iii) 13.4 ±2.6	13.5 ±2.0	2
	b) 3-Chloro-9-phenylfluoren-9-ol	(i) 12.2 ±1.7 (ii) 17.0 ±1.6 (iii) 12.7 ±2.6	14.0 ±2.0	
2-Amino-4'-methyl-triphenylmethanol	a) 9-(4-Tolyl)fluoren-9-ol	(i) 20.0 ±5.1 (ii) 16.3 ±4.1 (iii) 17.5 ±4.0	18.0 ±4.4	8
	b) 3-Methyl-9-phenylfluoren-9-ol	(i) 26.2 ±5.1 (ii) 18.9 ±4.1 (iii) 22.4 ±4.0	22.5 ±4.4	

b)*Triphenylmethanol (37%) also produced in the reaction

Table 16 (continued)

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Average	Yield of Phenolic By-products (% w/w of amine)
2-Amino-3',5'-dimethyl triphenylmethanol	a) 9-(3,5-Dimethylphenyl)fluoren-9-ol	(i) 10.3 ± 5.1 (ii) 7.3 ± 4.1 (iii) 6.4 ± 4.0	8.0 ± 2.0	10
	b) 2,4-Dimethyl-9-phenylfluoren-9-ol	(i) 15.2 ± 5.1 (ii) 17.7 ± 4.1 (iii) 20.6 ± 4.0	17.9 ± 2.0	
2-Amino-3',5'-dichloro-triphenylmethanol	a) 9-(3,5-Dichlorophenyl)fluoren-9-ol	(i) 8.4 ± 6.0 (ii) 6.4 ± 4.7 (iii) 6.2 ± 4.9	7.0 ± 5.2	9
	b) 2,4-Dichloro-9-phenylfluoren-9-ol	(i) 23.3 ± 6.0 (ii) 20.1 ± 4.7 (iii) 22.6 ± 4.9	22.0 ± 5.2	
2-Amino-4'-chloro-4"-methyltriphenylmethanol	a) 3-Chloro-9-(4-tolyl)fluoren-9-ol	(i) 14.1 ± 1.0 (ii) 10.5 ± 0.8 (iii) 11.9 ± 1.1	12.2 ± 1.0	6
	b) 3-Methyl-9-(4-chlorophenyl)fluoren-9-ol	(i) 18.2 ± 1.0 (ii) 14.7 ± 0.8 (iii) 15.1 ± 1.1	16.0 ± 1.0	

Table 16 (continued)

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Average	Yield of Phenolic By-products (% w/w of amine)
2-Amino-4'-methoxy-triphenylmethanol	a) 9-(4-Anisyl)fluoren-9-ol	(i) 18.1 $\pm$ 5.0 (ii) 16.0 $\pm$ 3.1 (iii) 15.9 $\pm$ 4.2	16.7 $\pm$ 4.1	9
	b) 3-Methoxy-9-phenylfluoren-9-ol	(i) 9.9 $\pm$ 5.0 (ii) 6.2 $\pm$ 3.1 (iii) 7.2 $\pm$ 4.2	7.8 $\pm$ 4.1	

C. The Copper-Catalysed Decompositions in Aqueous Acidic Solution

These decompositions were carried out under the following conditions described for the Pschorr reaction:

To a well stirred solution of the amino alcohol in aqueous sulphuric acid (10% w/w in water) at 0° was added, dropwise a solution of sodium nitrite in water (quantities listed in Table 17). On addition of copper powder decomposition commenced and the reaction was completed by warming until a negative coupling reaction with β-naphthol was observed. The reaction mixture was extracted with ether and the ether layer filtered from any copper powder. Isolation of phenolic products and analysis of the remaining product mixture was carried out as described in section A. The amino alcohols thus decomposed are included in Table 17.

Table 17: Copper-Catalysed Decompositions in Aqueous-Acidic Solution

	Amounts of					Aqueous Sulphuric Acid ml
	Amino Alcohol		Sodium Nitrite		Copper Powder g	
	g	mmol	g	mmol		
a) 2-Aminotriphenylmethanol	0.07	0.26	0.02	0.29	0.05	2
b) 2-Amino-4'-chloro-triphenylmethanol	0.18	0.58	0.05	0.73	0.12	6
c) 2-Amino-4'-methyltriphenylmethanol	0.15	0.52	0.05	0.73	0.10	5
d) 2-Amino-3',5'-dimethyltriphenylmethanol	0.15	0.50	0.04	0.58	0.10	5
e) 2-Amino-3',5'-dichlorotriphenylmethanol	0.20	0.58	0.05	0.73	0.12	6
f) 2-Amino-4'-chloro-4"-methyltriphenylmethanol	0.02	0.06	0.005	0.07	0.01	1

Table 18: Product Yields in the Copper Catalysed Decompositions of 2-Aminotriphenylmethanols

Amino Alcohols	Cyclisation Products	Yield(Mole % per mole of amine)	Average	Yield of Phenolic By-products (% w/w of amine)
2-Aminotriphenylmethanol	9-Phenylfluoren-9-ol	(i) 88.2 ± 3.0 (ii) 83.7 ± 1.1	86.0 ± 2.1	7
2-Amino-4'-chloro-triphenylmethanol	a) 9-(4-Chlorophenyl)fluoren-9-ol	(i) 41.0 ± 7.1 (ii) 40.4 ± 2.9	40.7 ± 5.0	3
	b) 3-Chloro-9-phenylfluoren-9-ol	(i) 28.1 ± 7.1 (ii) 23.7 ± 2.9	25.9 ± 5.0	
2-Amino-4'-methyl-triphenylmethanol	a) 9-(4-Tolyl)fluoren-9-ol	(i) 56.7 ± 7.7 (ii) 57.8 ± 5.1	57.3 ± 6.4	3
	b) 3-Methyl-9-phenylfluoren-9-ol	(i) 40.3 ± 7.7 (ii) 38.9 ± 5.1	39.6 ± 6.4	
2-Amino-3',5-dimethyl-triphenylmethanol	a) 9-(3,5-Dimethylphenyl)fluoren-9-ol	(i) 36.8 ± 6.9 (ii) 42.4 ± 6.5	39.6 ± 6.7	3
	b) 2,4-Dimethyl-9-phenylfluoren-9-od	(i) 58.0 ± 6.9 (ii) 57.4 ± 6.5	57.7 ± 6.7	

Table 18 (continued)

Amino Alcohols	Cyclisation Products	Yield(Mole % per mole of amine)	Average	Yield of Phenolic By-products (% w/w of amine)
2-Amino-3',5-dichloro-triphenylmethanol	a) 9-(3,5-Dichlorophenyl)fluoren-9-ol	(i) 55.0 ± 7.9 (ii) 50.1 ± 4.0	52.6 ± 6.0	5
	b) 2,4-Dichloro-9-phenylfluoren-9-ol	(i) 21.0 ± 7.9 (ii) 16.8 ± 4.0	18.9 ± 6.0	
2-Amino-4'-chloro-4"-methyltriphenylmethanol	a) 3-Chloro-9-(4-tolyl)fluoren-9-ol	(i) 23.7 ± 3.9 (ii) 29.1 ± 2.0	26.4 ± 3.0	2
	b) 3-Methyl-9(4-chlorophenyl)fluoren-9-ol	(i) 44.0 ± 3.9 (ii) 39.4 ± 2.0	41.7 ± 3.0	

4.2.6 Quantitative Analysis of Reaction Products

The complete quantitative separation of the isomeric products of the deamination reactions described in section 4.2.5 was considered almost impossible. Therefore, the product mixtures were analysed spectrophotometrically by an extension of the Dewar and Urch method[267,268].

The actual method followed can be summarised thus: In a solution containing two substances 1 and 2, of concentrations C_1 and C_2 (in grams or moles per litre) which give rise to absorptions (measured as $\log_{10} I_0/I$), of A_1, A_2, ... etc. at various wavelengths λ_1, λ_2, ... etc., and if Beer's law is obeyed, then: at any wavelength x

$$C_1 = \frac{A_x}{\epsilon_1} - C_2 \, \epsilon_2/\epsilon_1 \qquad (76)$$

where ϵ_1 and ϵ_2 are the respective extinction coefficients of compounds 1 and 2. If the values Ax/ϵ_1 for various wavelengths are plotted against the corresponding values of ϵ_2/ϵ_1, the points should lie on a straight line of slope C_2; and the intercept on the Ax/ϵ_1 axis gives C_1. This procedure can be used to determine C_1 and C_2 in any mixture of unknown composition. Any systematic deviations from the straight line, measured by the method of least squares[314], indicate the presence of other components. When a region of the spectrum is found in which minimal deviation from the straight line occurs when plotting equation (76) this was used to obtain C_1 and C_2. Interference from other components could be minimised in this way, but only if the shape of the absorption curves of 1 and 2 were sufficiently different from each other and from those of any of the other components present. This could be confirmed, in some cases, by taking

measurements over a second range of wavelengths and comparing the two sets of concentrations obtained.

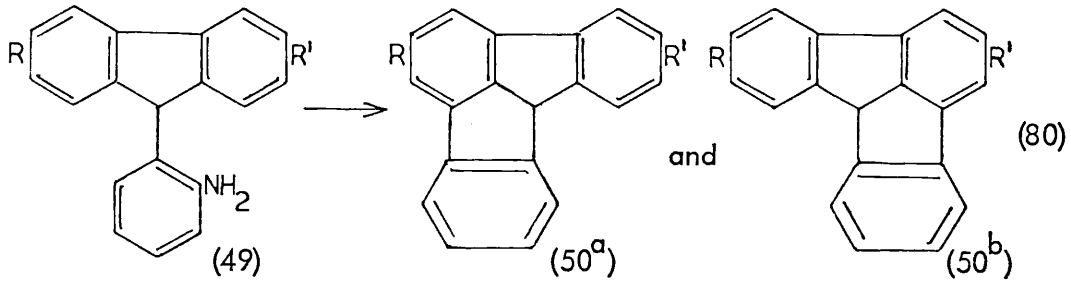
5. DISCUSSION

5.1 Synthesis of Intermediates

5.1.1 9-(2-Aminophenyl)fluorene (49)

Compound (49) appeared to be particularly suitable as an amine with the desired structure for use in mechanistic studies for the Pschorr-type reactions for the following reasons:

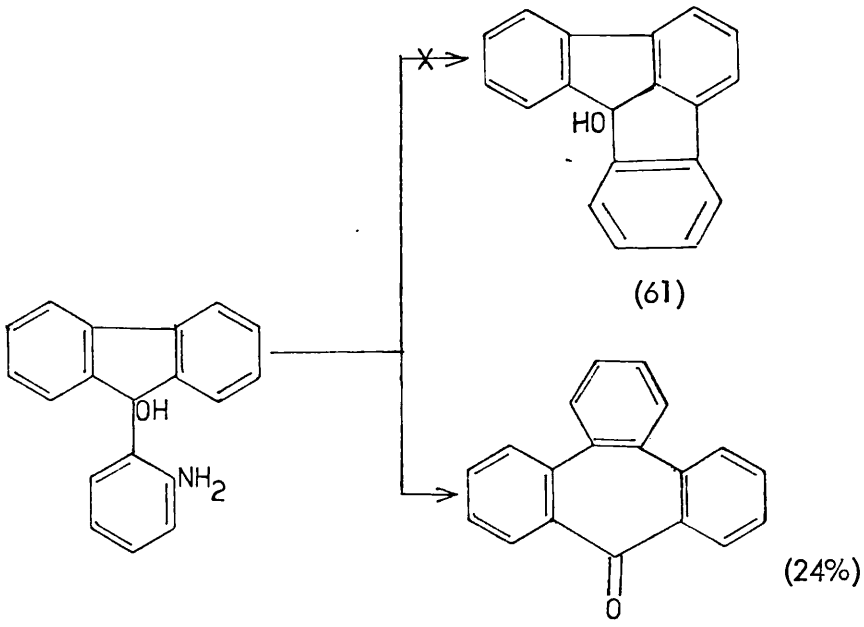
(a) When (49) was unsymmetrically substituted cyclisation could occur at either aromatic ring; the products thereby providing evidence of the effect of the substituents upon the direction of the cyclisation (equation 80).



(80)

Also, (b) the presence of a rigid unsymmetrically substituted fluorenyl nucleus would ensure an equal probability of attack upon either nuclear aromatic ring by the reactive centre created on elimination of the diazonium group.

The deamination (dediazoniation) of compound (49) had previously been reported[269] (R=R'=H) to give the expected indeno-[1,2,3-jk]-fluorene (50) in 23% yield. Compound (50) is an example of a strained cyclopentadiene ring system and it is therefore not surprising that its formation should be less favoured. The interest in the preparation of compound (50) (also called fluoradene) stemmed from a previously reported[311] isolation of tribenzotropone (60) from the deamination of 9-(2-aminophenyl)-9-fluorenol (59).



(61)

(81)

(24%)

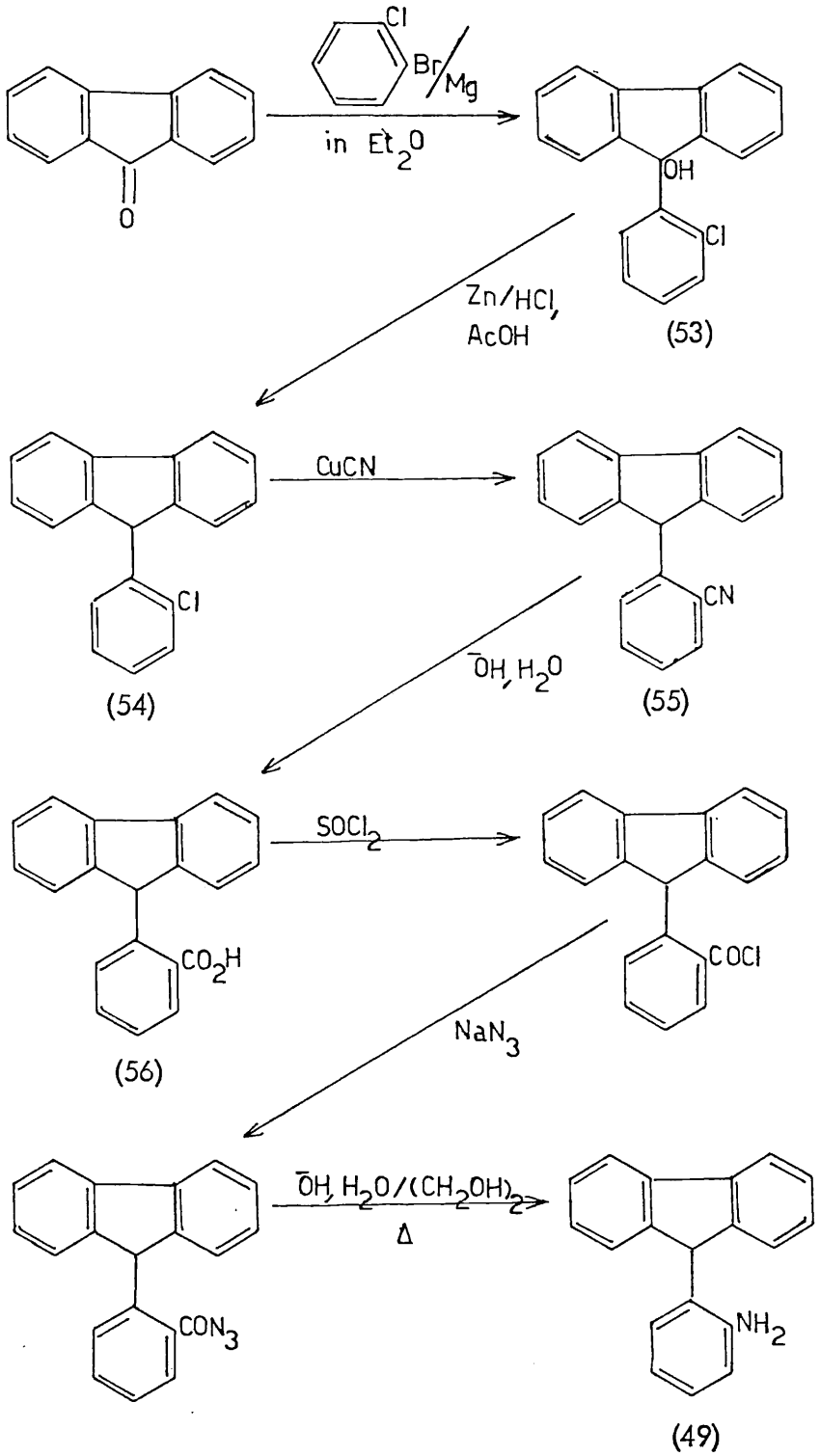
(60)

In equation (81) the expected cyclisation to form (61) was prevented by the ring strain in the resulting compound. Instead, a 1,3-shift of an aryl group to an electron-deficient carbon atom appeared to be the preferred route, resulting in the formation of (60).

The ring strain energy in fluoradene (50) may be altered by substituents in the benzene ring. This could constitute a major drawback in the application of compound (49) to the present mechanistic studies.

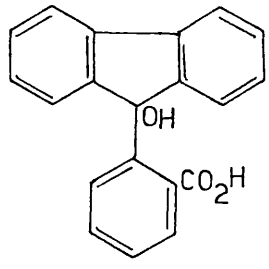
The multistage synthesis[269] of 9-(2-aminophenyl)fluorene (49) can be summarised as in Scheme XV.

SCHEME XV

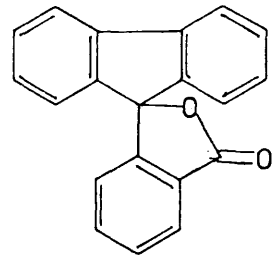

Cl
Br/Mg
in Et2O
O
OH
Cl
(53)
Zn/HCl,
AcOH
CuCN
Cl
(54)
CN
(55)
⁻OH, H2O
SOCl2
CO2H
(56)
COCl
NaN3
⁻OH, H2O/(CH2OH)2
Δ
CON3
NH2
(49)

The preparation of compound (53) and its subsequent reduction to (54) went easily and in yields similar to those reported[276]. An attempt to repeat the preparation of (55) and subsequently of (56) by alkaline hydrolysis of (55) in situ, also as reported, gave unacceptably low yields (~ 2%, c.f. 59% reported[269]) which could not be improved.

The oxidation of 9-(2-tolyl)fluoren-9-ol, followed by the reduction of either 9-(2-carboxyphenyl)fluoren-9-ol (57) or o-diphenylenephthalide (58) offered a synthesis of (56). Compound (57) was not found, but (58) was obtained in high yield (61%) from the oxidation of 9-(2-tolyl)fluoren-9-ol. The attempted reduction of (58) to (56) was unsuccessful, with the starting compound remaining unchanged.



(57)



(58)

The reports, by Bartoli and co-workers[280-2] of conjugate additions of alkyl Grignard (and alkyllithium) compounds to nitroarenic systems in THF resulting in the formation of o- and p- alkyl nitronate products appeared to be an attractive alternative route to (49). If successful, such a method would avoid the stepwise preparations (Scheme XV) and the accompanying disadvantage of low yields. The possible further reduction, in situ, of the nitro-group to the amino system using copper (I) iodide, also reported[280] presented a further synthetic advantage. The report of a reaction between

2-phenylethyl bromide and p-chloronitrobenzene which gave 4-chloro-2-(2-phenyl)-1-nitrobenzene (36%) encouraged an attempt to combine 9-fluorenyl-lithium with nitrobenzene under similar conditions. The latter reaction was however unsuccessful.

The deaminations of unsymmetrically substituted 9-(2-aminophenyl) fluorenes (50, R ≠ R') can lead to isomeric fluoradene derivatives (50^a and 50^b) as in equation (80), the complete separation of which would be difficult. Product mixtures from such reactions could, conceivably, be analysed spectrographically, e.g. by the Dewar and Urch method. The difficulty in obtaining pure reference compounds (50^a) and (50^b) plus the already stated difficult synthesis of compound (49) led to the attempt at using the latter, i.e. (49) as parent amine in the study of the Pschorr reaction to be abandoned.

5.1.2 2-Aminotriphenylmethanols and Derivatives

A procedure for the preparation of 2-aminotriphenylmethanol (46, R = R' = H) from the reaction between methyl anthranilate and phenyl magnesium bromide was reported by Baeyer and Villiger.[296] The product was isolated by many crystallisations from benzene and finally from ether, and as a consequence yields were very low (< 10%). Yields were only slightly improved by digesting the product mixture with hydrochloric acid, neutralising the acid extract with ammonia prior to crystallising the product as reported.[296]

Whereas the reaction between methyl anthranilate and the aryl-magnesium bromide is suitable for the preparation of 2-aminotriarylmethanols where the two other aryl (phenyl) rings are similar (46, R = R'), unsymmetrically substituted systems (R ≠ R') cannot be unambiguously thus prepared. In the latter case 2-aminobenzophenones (appropriately substituted where necessary)

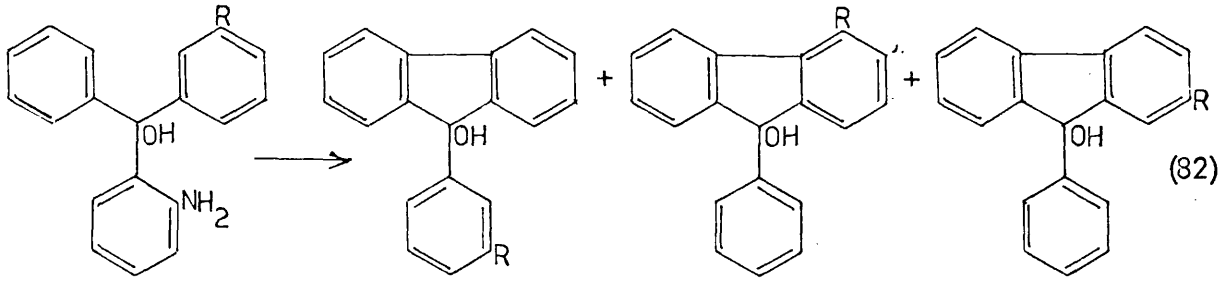
were used in the place of methyl anthranilate. The amino alcohols thus prepared were all new compounds. The substituted 2-aminobenzophenones not commercially available were prepared following procedures reviewed by Simpson et al.[286]

Compound (46) does not possess the rigid frame of 9-(2-aminophenyl)-fluorene (49). Therefore, (46) may lack the expected advantage in the latter compound (49) of an equal probability of attack by the reactive centre created during dediazoniation on either aryl ring of the fluorenyl system. However, the products of ring closure in the former, viz., (47) and (48) are free from the ring strain in the cyclopentadiene systems of (50^a) and (50^b). A comparatively higher yield of cyclised product (46%) was previously reported[291] when the diazonium salt of 2-aminotriphenylmethanol was decomposed under acidic conditions (c.f. 23% yield of fluoradene formed under similar conditions[269]). In the given diazonium decomposition[291] there was no reported formation of the product of molecular rearrangement found in many other o-aminobenzohydrol and similar reactions[291,311] (e.g. equation 81). This fact provided further evidence of the lesser ring strain in compounds (47) and (48) as compared to (50^a) and (50^b). Thus the ready formation of cyclic product presented an advantage in the use of (46) as compared to (49) as starting amine.

Only 2-aminotriphenylmethanols with substituents at the 4'- (and 4"-) and disubstituents at the 3',5'- positions were used as parent compounds in the present investigation. 2'- (and 2"-) Substituted amino alcohols were avoided for the following reasons:

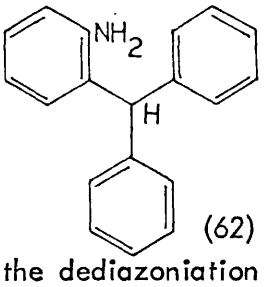
a) a position of potential ring closure is blocked by the substituent; and b) apart from the electronic contribution being investigated, a

considerable steric factor is introduced, and it would be difficult to estimate the contribution of each separate factor. 3'- (and 3"-) Substituted 2-aminotriphenylmethanols could give rise to three cyclic products (equation 82), further complicating product analyses.



(82)

Low yields (9-11% based on amine) of cyclised product were obtained when 2-aminotriphenylmethane (62) was used as starting amine. No further investigation of this route was carried out.



(62)

Analyses of the dediazoniation products were made by a modified Dewar and Urch method (section 4.2.6). The reference 9-phenylfluoren-9-ols were prepared from appropriate fluoren-9-ones and arylmagnesium bromide, following procedures similar to those previously described.[292,293,295,315] Repeated chromatographic separation and fractionation of the reaction products followed by crystallisation of the 9-phenylfluoren-9-ol fraction from petroleum ether (b.p. 40°-60°) gave the desired products. Crystallisations were very slow, in almost all cases refrigeration being necessary to obtain relatively rapid crystallisation. All the nuclear substituted 9-phenylfluoren-9-ols were new compounds.

5.2 Decomposition Reactions of Diazotised 2-Aminotriphenylmethanols

Three conditions for the decomposition of diazotised 2-aminotriphenylmethanols were used. Decompositions in dilute sulphuric acid, both a) without and b) with a copper catalyst were considered a necessary part of the studies, since these are the most commonly used cyclisation conditions. The uncatalysed reaction in dilute sulphuric acid nearly always gives some of the cyclisation product if cyclisation is structurally possible.[231] As already indicated in Section 2.5, opinion appears to favour intervention by aryl cation species in the course of such reactions. c) The decomposition of amines by pentyl nitrite in benzene is thought[120,121] to involve the formation of aryl radicals (Section 2.2.2.g) and so a study of the cyclisation of derivatives of 2-aminotriphenylmethanol under such conditions makes a useful comparison with those brought about in aqueous acid.

5.2.1 Reactions in Benzene, using Amyl Nitrite for Diazotisation

The total yields of cyclised products were low (Table 19) compared to those previously reported[120,121] for intermolecular arylation reactions under similar conditions (Section 2.2.2.g). They were also low compared to yields from cyclisations carried out in aqueous acidic conditions (Tables 21 and 25). The yields reported for intermolecular reactions referred to isolated products, and no doubt the spectrographic product analyses which were employed here would have indicated even higher yields. Low yields of isolated products were reported[235,237,246] in Pschorr-type cyclisations which were considered to involve the formation of aryl radicals. For example, the decomposition of 2-benzoylbenzenediazonium tetrafluoroborate under Gomberg conditions was reported to give fluorenone in yields varying from 5% to 28% depending upon the pH of the reaction mixture[246] (Section 2.5.2.3).

Table 19: Product Yields in the Decomposition of Diazotised 2-Aminotriphenylmethanols in Benzene using Amyl Nitrite for Diazotisation

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Total % Yield of all cyclised products	Yield of Phenols (% w/w of amine)
2-Aminotriphenylmethanol	a) 9-Phenylfluoren-9-ol*	32.0 $\pm$1.1	32.0 $\pm$1.1	6
2-Amino-4'-chloro-triphenylmethanol	a) 9-(4-Chlorophenyl)fluoren-9-ol	13.4 $\pm$2.0	27.4 $\pm$2.0	2
	b) 3-Chloro-9-phenylfluoren-9-ol	14.0 $\pm$2.0		
2-Amino-4'-methyl-triphenylmethanol	a) 9-(4-Tolyl)fluoren-9-ol	18.0 $\pm$4.4	40.5 $\pm$4.4	8
	b) 3-Methyl-9-phenylfluoren-9-ol	22.5 $\pm$4.4		
2-Amino-3',5'-dimethyl-triphenylmethanol	a) 9-(3,5-Dimethylphenyl)fluoren-9-ol	8.0 $\pm$2.0	25.9 $\pm$2.0	10
	b) 2,4-Dimethyl-9-phenylfluoren-9-ol	17.9 $\pm$2.0		
2-Amino-3',5'-Dichloro-triphenylmethanol	a) 9-(3,5-Dichlorophenyl)fluoren-9-ol	7.0 $\pm$5.2	29.0 $\pm$5.2	9
	b) 2,4-Dichloro-9-phenylfluoren-9-ol	22.0 $\pm$5.2		

*Deamination product (triphenylmethanol) also obtained in 37% yield.

Table 19: (continued)

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Total % Yield of all cyclised products	Yield of Phenols (% w/w of amine)
2-Amino-4'-chloro-4"-methyltriphenylmethanol	a) 3-Chloro-9-(4-tolyl)fluoren-9-ol	12.2 $\pm$1.0	28.2 $\pm$1.0	6
	b) 3-Methyl-9-(4-chlorophenyl)fluoren-9-ol	16.0 $\pm$1.0		
2-Amino-4'-methoxy-triphenylmethanol	a) 9-(4-Anisyl)fluoren-9-ol	16.7 $\pm$4.1	24.5 $\pm$4.1	9
	b) 3-Methoxy-9-phenylfluoren-9-ol	7.8 $\pm$4.1		

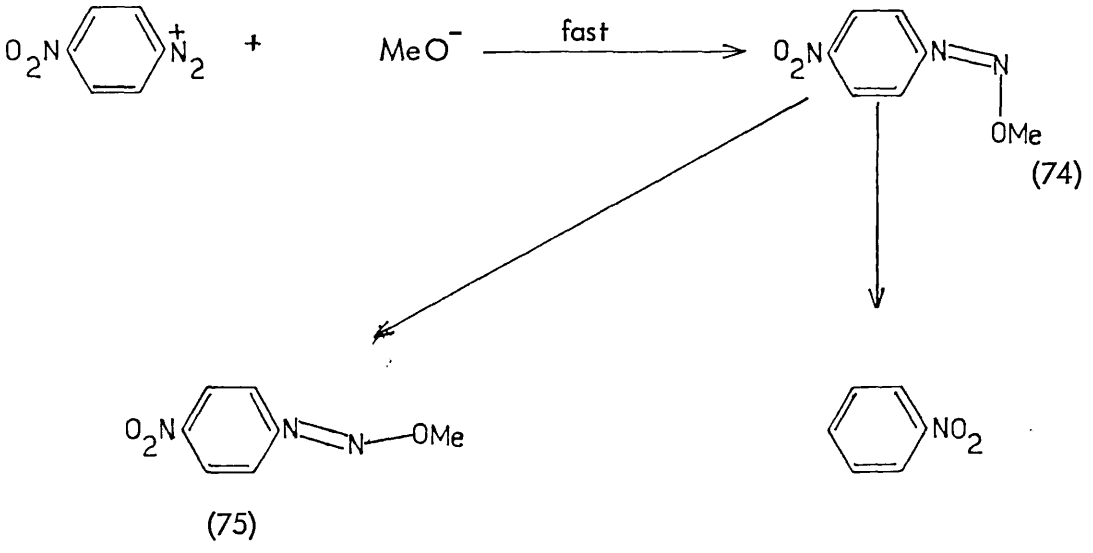
Apart from phenols, other by-products of the decomposition reactions were not identified. However, since these reactions were carried out in benzene, competition between the cyclisation reactions and the straightforward intermolecular reaction was very likely. Such a competition was previously observed in the decomposition of diazotised 2-aminobenzophenone under Gomberg reaction conditions with added benzene (Section 2.5.2.3) when the product of intermolecular arylation (2-benzoyl biphenyl) was formed in a higher yield (20%) than fluorenone ("only a little reported as found"[266,231]). The explanation given for the preference for intermolecular, rather than intramolecular, arylation under Gomberg conditions[208] could also be used to rationalise our low yields of cyclised products in the deamination of 2-aminotriphenylmethanols using amyl nitrite for diazotisation; that is, the preference for intermolecular arylation under Gomberg conditions was explained[208] by assuming an orientation around -N=N- which did not permit the easy approach of other aryl systems within the molecule at the moment of homolysis. Ring-closure was then sterically hindered. Provided that the aryl radical had a short life, and so shielding by the expelled radical fragments in the homolysis of Ar N=N-OX encumbered attack within the same molecule, intermolecular arylation was preferred. Such an explanation, first applied to diazoanhydrides[208], might be similarly applied to the intermediates formed during diazotisation by nitrite esters.

An alternative cause of the low yields of cyclised products in the Gomberg reactions might be deduced from the observation by DeTar and Relyea[246] that nitrogen yields in the thermal decomposition of 2-benzoylbenzenediazonium fluoroborates were lower at higher pH values than at lower pH, e.g. at pH = 12.3 the yields of nitrogen were in the range 13-54%

$\pm$15%, whereas at pH = 1 nitrogen yields rose to 75-102% $\pm$15%. Such an observation suggested that incomplete dediazoniation occurred in the Gomberg reaction. Conclusive evidence of this came from the later reported[333] reaction between p-nitrobenzenediazonium ions (73) and sodium methoxide in alkaline methanol which gave cis-p-nitrophenylazo methyl ether (74). Further reaction of (74) in the absence of added aromatic substrate, led to the formation of nitrobenzene and trans-azo-ether (75), in approximately equal amounts (Scheme XIX). Thus it would appear that only one conformer of the diazo-ether, the cis-conformer, was capable of decomposing to form nitrogen and the reactive phenyl intermediate (this directly contradicted the postulation by Huisgen[81] that the trans-diazo esters led to decomposition products).

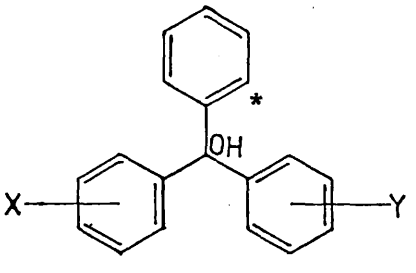
A similar argument could be used to rationalise the low yields of cyclisation products in the reaction of 2-aminotriarylmethanols with pentyl nitrite. It could be argued that only one conformer of the diazoester (from acylarylnitrosamine $\rightleftharpoons$ diazoester tautomerism) would be capable of decomposition. Cis-trans isomerisation would be difficult since the reactions were carried out in a benzene medium, which meant that formation of ions was improbable.

SCHEME XIX[333]



(75)

The results in Table 20 showed the competition between attack on the rings substituted with X and Y in (70). These relative rates might be compared with values obtained by intermolecular competitive arylations using various sources of aryl radicals, also included in Table 20.



*reactive centre

(70)

Table 20: Relative Rates of A) Intramolecular Arylations of Triarylmethanols in Benzene using Amyl Nitrite for Diazotisation of 2-Amino-triarylmethanols, and B) Intermolecular Competitive Arylations using various sources of Ph·

X	Y	k_x/k_y in intramolecular arylations[A]	k_x/k_y in intermolecular arylations[B]
i) m-Cl	H	$1.0_4 \pm 0.3$	178 0.9[b]; 172 1.0[b]; 197 1.01[a]; 178 1.1[c]
ii) m-Me	H	$1.2_5 \pm 0.6$	172 0.71[b]; 197 1.09[a]; 178 1.1[c]; 178 1.3[b]
iii) o,p-Me_2	H	$2.2_4 \pm 1.1$	197 4.19[a]; 178 5.1[b]; 178 5.1[c]; 172 2.5[b]
iv) o,p-Cl_2	H	$3.1_4 \pm 4.7$	197 4.57[a]; 178 3.75[c]; 172 1.92[b]; 178 2.28[b]
v) m-Me	m-Cl	$1.3_1 \pm 0.2$	197 1.26[a]; 178 1.44[b]; 178 1.0[c]; 172 0.71[b]
vi) m-OMe	H	$0.4_7 \pm 0.2$	197 0.93[a]; 178 1.9[c]; 179 0.88[b]; 179 0.87[e]; 178 1.05[b]; 178 1.3[d]

a) Arylation reactions with acylarylnitrosamines.

b) Uncatalysed arylation reactions with benzoyl peroxide.

c) Arylation reactions with benzoyl peroxide; added iron (III) benzoate.

d) Arylation reactions with benzoyl peroxide; added copper (II) benzoate.

e) Arylation reactions with benzoyl peroxide; added oxygen.

NOTE: The results from literature in sections iii) and iv) (of Table 20) were calculated using the additivity principle starting from reported partial rate factors for phenylation of appropriate monosubstituted benzenes.

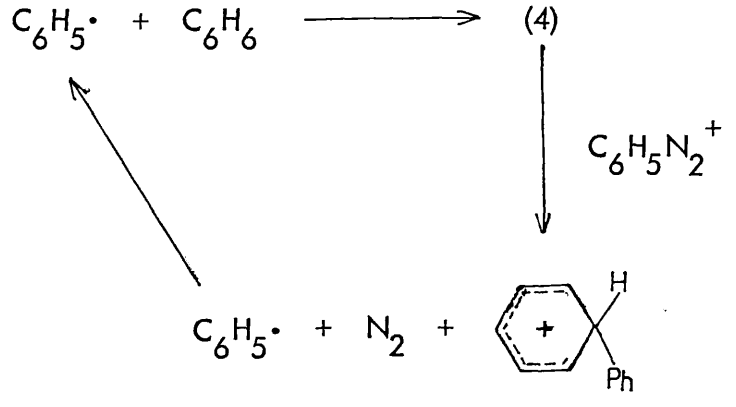
The relative rates of arylation recorded in Table 20, together with the low yields of cyclised products given in Table 19 pointed towards a homolytic mechanism in the decomposition of diazotised 2-aminotriarylmethanols in benzene. The large relative deviations in some of the arylation ratios, k_x/k_y (Table 20) and in the yields of cyclised products (Table 19) rendered some of the results unreliable. For example in the reaction of 2-amino-3',5'-dimethyltriphenylmethanol the margin of error in the ratio k_x/k_y was 50% of the observed ratio; and the error margin was as high as 150% of the observed ratio in the reaction of 2-amino-3',5'-dichlorotriphenylmethanol (Table 20, sections (iii) and (iv) respectively). High margins of error were not totally unexpected in these reactions, because the relatively high yields of by-products of the dediazoniation reaction might produce relatively large additional absorption within the u.v. range chosen for the determination of cyclised products. In certain reactions it was inevitable that the cyclisation product was only the minor product, e.g., in the reaction of 2-aminotriphenylmethanol the formation of 9-phenylfluoren-9-ol in 32% yield was accompanied by a higher yield (37%) of triphenylmethanol, the deamination product. In reactions where either of the other two phenyl rings of the amine was substituted the amounts of deamination products were not determined. Although our analyses sought to minimise absorption by the by-products in the useful region of the spectrum, the total elimination of such contributions was not possible. When relatively high yields of cyclised products were involved, the errors in the analyses of products were usually small (Tables 21 and 25). Conversely these errors became more significant when yields of cyclised products were low.

The high yields of phenols in these reactions were rather perplexing (Table 19). Water is formed from diazotisations with alkyl nitrites according to equation (34),[125] (Section 2.2.2.g); intrusion of water might also result from incompletely dry reagents.

$$ArNH_2 + RONO \longrightarrow ArN{=}N{-}OR + H_2O \qquad (34)$$

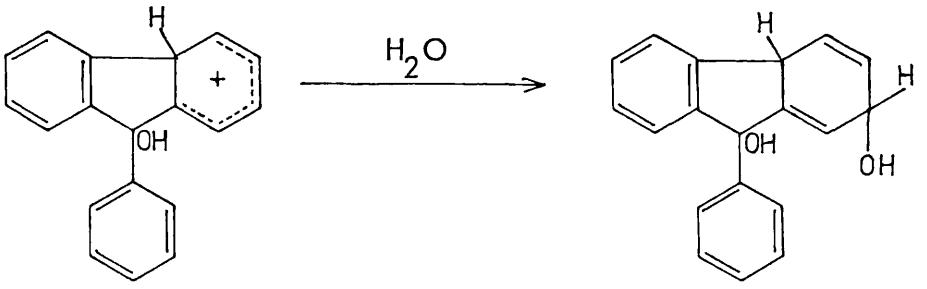
One possible rationalisation of phenol formation in a free-radical process would be by reference to Scheme IV (page 19) proposed by Cadogan et al.[89,95] The scheme proposed the formation of arylcationic species (77) as shown below:

SCHEME IV (part of) Chain Propagation



(77) (4) = $[C_6H_5C_6H_6]^{\bullet}$

The formation of compound (71) can be argued in like manner to (77). Instead of a proton loss as in Scheme IV, (71) might be attacked by the nucleophilic water molecules resulting in the formation of a dihydrophenol (72) (equation 85).



(85)

(71) (72)

5.2.2 Uncatalysed Decompositions in Aqueous Acidic Media

The yields of cyclised products in these reactions were high (Table 21) compared to those of reactions in benzene reported in the preceding section. Notably, almost all the starting amines in each reaction could be accounted for as cyclised products and phenols. A comparison between the yields in Table 21 and those of cyclisation reactions reported previously (Table 12) would be unjustified since values in the latter table referred to isolated products whereas yields in the former were obtained spectrophotometrically. For instance, a 46% yield of isolated product had previously been reported[291] in the decomposition of 2-aminotriphenylmethanol under the title conditions. A comparable yield (41%) of isolated product resulted in the present study, but spectrographic analyses of the product mixture indicated a much higher (79%) conversion to cyclised product.

Table 21: Product Yields in the Thermal Decomposition of Diazotised 2-Aminotriphenylmethanols in Aqueous Acidic Solutions

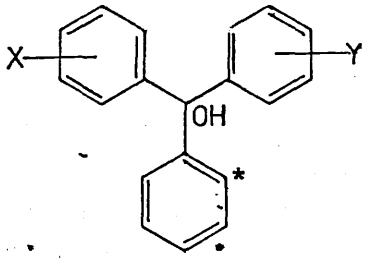
Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine	Total % Yield of all cyclised products	Yield of Phenols (% w/w of amine)
2-Aminotriphenylmethanol	9-Phenylfluoren-9-ol*	79.0 $\pm$1.7 (41 isolated)	79.0 $\pm$1.7	18
2-Amino-4'-chloro-triphenylmethanol	a) 9-(4-Chlorophenyl)fluoren-9-ol	38.5 $\pm$6.0	73.3 $\pm$6.0	19
	b) 3-Chloro-9-phenylfluoren-9-ol	34.8 $\pm$6.0		
2-Amino-4'-methyl-triphenylmethanol	a) 9-(4-Tolyl)fluoren-9-ol	47.4 $\pm$4.3	85.8 $\pm$4.3	14
	b) 3-Methyl-9-phenylfluoren-9-ol	38.4 $\pm$4.3		
2-Amino-3',5'-dimethyl-triphenylmethanol	a) 9-(3,5-Dimethylphenyl)fluoren-9-ol	48.0 $\pm$3.9	94.0 $\pm$3.9	8
	b) 2,4-Dimethyl-9-phenylfluoren-9-ol	46.0 $\pm$3.9		
2-Amino-3',5'-dichloro-triphenylmethanol	a) 9-(3,5-Dichlorophenyl)fluoren-9-ol	46.7 $\pm$2.1	90.1 $\pm$2.1	9
	b) 2,4-Dichloro-9-phenylfluoren-9-ol	43.4 $\pm$2.1		

*Deamination product (triphenylmethanol) also produced in the reaction in 3% yield.

Table 21 (continued)

Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Total % Yield of all cyclised products	Yield of Phenols (% w/w of amine)
2-Amino-4'-chloro-4"-methyltriphenylmethanol	a) 3-Chloro-9-(4-tolyl)fluoren-9-ol	40.2 $\pm$2.8	79.6 $\pm$2.8	17
	b) 3-Methyl-9-(4-chlorophenyl)fluoren-9-ol	39.4 $\pm$2.8		
2-Amino-4'-methoxy-triphenylmethanol	a) 9-(4-Anisyl)fluoren-9-ol	44.9 $\pm$2.5	88.3 $\pm$2.5	10
	b) 3-Methoxy-9-phenylfluoren-9-ol	43.4 $\pm$2.5		

Variation of the yields of cyclised products in Table 21 suggested that the polar nature of substituents in the rings undergoing attack in these systems had very little influence upon the direction of ring closure under these conditions. For example, in the decomposition of diazotised 2-amino-3',5'-dimethyltriphenylmethanol the polar requirements of the dimethyl substituents would make the sites of ring closure in the disubstituted phenyl ring highly activated towards electrophilic attack, and perhaps less so towards radical attack, compared to the corresponding sites in the unsubstituted ring. However, the relative yields of 9-(3,5-dimethylphenyl)fluoren-9-ol (48%) and 2,4-dimethyl-9-phenylfluoren-9-ol (46%) were not in agreement with such a prediction. Also, in the decomposition of diazotised 2-amino-4'-chloro-4"-methyltriphenylmethanol both the homolytic and heterolytic reaction processes would be expected to favour cyclisation onto the methyl-substituted ring and not the chloro-substituted one. However, yields of 3-chloro-9-(4-tolyl)fluoren-9-ol (40.2%) and 3-methyl-9-(4-chlorophenyl) fluoren-9-ol (39.4%) did not agree with this prediction either. Table 21, however, shows cyclisation onto either ring to be equally likely, regardless of the polar nature of the substituents. Such results give relative rates of attack upon either aryl ring of the triarylmethanol systems (70); they are summarised in Table 22.



* = reactive intermediate

(70)

Table 22

Relative Rates of Intramolecular Arylation of Triarylmethanols under Aqueous Acidic Conditions

X	Y	k_x/k_y intramolecular arylation
m-Cl	H	$0.9_0 \pm 0.3$
m-Me	H	$0.8_1 \pm 0.2$
o,p-Me_2	H	$0.8_3 \pm 0.1$
o,p-Cl_2	H	$0.9_3 \pm 0.1$
m-Me	m-Cl	$0.9_8 \pm 0.1$
m-OMe	H	$0.9_7 \pm 0.1$

The results in Table 22 pointed towards random cyclisation onto either of the two remaining phenyl rings by the reactive intermediates generated on dediazoniation of diazotised 2-aminotriphenylmethanols, almost independently of the polar nature of the substituents present. Neither the yields of cyclised product (Table 21), nor the relative extents of cyclisation onto the alternative aromatic sites supported a homolytic mechanism. The yields of cyclised products were higher and the intermediates produced in dediazoniation much more unselective compared to the results in Tables 19 and 20. The unselectivity of these arylations could be further demonstrated from the Hammett reaction constant (ρ) for the arylation. The value of $\rho = +0.098 \pm 0.063$, calculated by means of the least squares method and using data in Table 23, indicated that the polar nature of the substituents present had little effect upon the direction of ring closure.

Table 23

Polar Nature of Substituted Aryl Substrates in Intramolecular Arylation of Diazotised 2-Aminotriarylmethanols in Aqueous Acid Solutions

X, Y, in (70)		k_x/k_y	σ 327, 334 (Substituent constant)	$\log k_x/k_y$
X	Y			
m-Cl	H	$0.9_0 \pm 0.3$	+0.373	-0.0458
m-Me	H	$0.8_1 \pm 0.2$	-0.069	-0.0915
o,p-Me	H	$0.8_3 \pm 0.1$	+0.123	-0.0809
o,p-Cl_2	H	$0.9_3 \pm 0.1$	+0.487	-0.0315
m-Me	m-Cl	$0.9_8 \pm 0.1$	+0.304	-0.0088
m-OMe	H	$0.9_7 \pm 0.1$	+0.115	-0.0132

Note

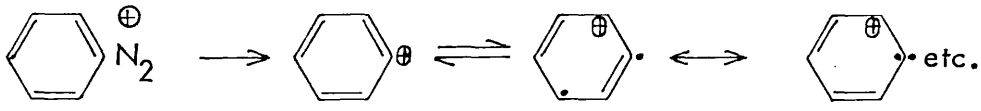
The Hammett relation is expressed as: $\log k/k_0 = \rho\sigma$ where k and k_0 are rate of reaction constants of the substituted and unsubstituted benzene; ρ and σ the Hammett reaction and the substituent constants, respectively.

The low selectivity (based upon the polar nature of the substituents) in these reactions could be emphasised by comparing the results in Table 22 with nitration data. In the latter reactions, a methyl-substituted phenyl ring was observed[327] to be approximately 3000 times more likely to be attacked at the meta- position by the electrophilic nitronium ion than a chloro-substituted ring. The greater resonance stabilisation of the nitronium ion as compared to the phenyl cation might be responsible for the greater selectivity shown by the nitronium ion.

The decomposition of diazonium salts under aqueous acidic conditions was discussed in the previous sections (page 8 and page 73) and was thought to show a unimolecular step resulting in the formation of an aryl cation which then underwent rapid reaction with nucleophiles or aromatic substrates. Evidence in support of such a mechanism came from the observed intensity of the rate of decomposition of diazonium salts towards the concentration and nature of any added halide ions.[259,261] However verifications of the unimolecular nature of the process remained limited[328] and the nature of the product composition on increasing the concentration of the diazonium salts (see below) cast some doubt on the validity of the simple kinetic interpretation. At most these decompositions could be unambiguously regarded only as pseudo-first-order processes, the role of solvent never having been truly determined.[329]

Some of the previously reported aromatic substitution reactions[320] in aqueous acid media and Pschorr cyclisations[249,256] were said to involve intermediates (generated from the diazonium ion) which were highly reactive, and at the same time, apparently highly selective. One attempt at

rationalising the high reactivity and selectivity shown by the reactive intermediates was that made by Abramovitch[208] and was summarized in Scheme XVII. In the scheme, the loss of nitrogen was envisaged as an S_N1 step which resulted in an aryl cation which existed in equilibrium with the diradical cation (66) described previously (section 2.5.2.2). The resonance in species (66) was presumed to imbue the intermediate with the stabilisation necessary for it to show a degree of selectivity (equation 84)[208] in its reactions.



(84)

(66)

Another attempt at explaining the high reactivity-cum-selectivity reported above had as its basis an objection to the extremely high energy requirements implicit in the generation of free phenyl cations.[329] Instead, a process of lower energy was suggested in which the free aryl cation in any form was bypassed, and electrophilic processes were attributed to bimolecular reactions between the diazonium ion and a nucleophile (or aromatic substrate). The nucleophile (or aromatic substrate) was postulated to begin to bond to the sp^2 carbon atom when charge developed on it as nitrogen departed.[329]

The above postulates were investigated by the kinetic study of the reaction of benzenediazonium chloride in acidic aqueous media with added sodium bromide.[329] An enhanced rate of reaction was observed on increasing the concentration of sodium bromide, which was attributed to a bimolecular reaction of bromide and diazonium ion to form aryl cation. Significantly, a description of the system solely in terms of bimolecular

processes was consistent with the rate data obtained, but was discarded in view of the popularity of the cation intermediate.[330] Subsequent results[329] pointed to competing uni- and bi-molecular mechanisms which did not fit the kinetics observed in similar systems. The suggestion of a common intermediate leading to all products was made even though its nature, although distinct from both the cation and the diazonium, ion could not be delineated on the basis of the observed data.[331]

Lewis et al[335] investigated the rates of reaction of substituted diazonium salts in aqueous media, and some added nucleophiles, Nu^-. Their observations led to their rejecting the existence of a common intermediate and to the postulation of a one-step (bimolecular) mechanism. Such a conclusion was based on the competition between solvent and added substances (Nu^-) for the reagent or the highly reactive intermediate measured using the results of such reactions. The distinguishing factor between one-step formation of the products and rate-determining formation of a highly reactive intermediate which Lewis and co-workers used, was the sensitivity, or insensitivity, of the rates towards the concentration of added substance. They[335] concluded from their investigations that the rate- and product-determining steps were identical. They proposed that reactions of diazonium salts under the stated conditions occurred as summarized below (equations 87-89) [325]

$$ArN_2^+ + H_2O \xrightarrow{k_w} ArOH \qquad (87)$$

$$ArN_2^+ + Nu^- \xrightarrow{k_{Nu^-}} ArNu \qquad (88)$$

$$ArN_2^+ \xrightarrow{k_r} ArN_2^+ \ (r) \qquad (89)$$

where k_w and k_{Nu} were the rates of reaction constants for reactions of diazonium salts with water and added nucleophiles ($N\bar{u}$) respectively. k_r was the rate constant for the rearrangement of ArN_2^+, i.e. the reversible loss of N_2 from ArN_2^+. The rearrangement had been demonstrated by showing that an aryl diazonium ion labelled in the α-position with ^{15}N did rearrange to the β-labelled diazonium ion.[336]

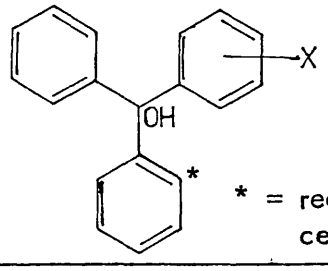
In view of the aforegoing arguments it would appear that more than one pathway could be quoted to account for the reactions of aryl diazonium ions. The free cation, the diradical cation and the bimolecular reaction of the diazonium ion with nucleophile (or aromatic substrate) could all be fitted to the experimental observations with varying degrees of success.[339]

In the absence of more rigorous kinetic evidence, it was difficult to assign a completely definitive mechanism for the reactions of diazotised 2-aminotriphenylmethanols in aqueous media. The unselectivity of direction of cyclisation in the reactions of diazotised 2-aminotriarylmethanols in which one other phenyl ring was substituted would appear to indicate the intermediacy of a very reactive intermediate, possibly a cation. It would be expected that the reactions involving the diradical cation and the bimolecular process would show selectivity in these cyclisations; the former owing to the higher resonance stabilisation of the reactive intermediate, and the latter because of the lower reactivity of the systems combined. However, Lewis et al[335] rejected use of arguments based on high reactivity-low selectivity as definite indicators of intervention of aryl cations. Their specific reasons for rejecting such evidence were not very clear, but were probably tied up with their arguments against intermediacy of the aryl cation species on the basis that its generation could "not represent an energy minimum" in the reactions they carried out.[335]

Additional evidence concerning the nature of the reactions of 2-aminotriarylmethanols in aqueous acidic media came from observing the ratios of the nuclear substituted 9-phenylfluoren-9-ols to phenols formed. These are given in Table 24. The ratios provided a measure of the competition between the substituted aromatic nucleus and water for the reactive centre created during dediazoniation. If the intermediate were a "normal" cation, electron-withdrawing groups should have rendered the aromatic nucleus less liable to attack, and thereby have led to a relative increase in phenol formation, and conversely the relative amount of phenol would be expected to fall where electron-donating groups were present.

Table 24

Ratios of attack by Substituted Aromatic Nuclei to Water Molecules in the Dediazoniation of Diazotised 2-Aminotriphenylmethanols

X in  * = reactive centre	k_x/k_{OH}
i) m-Cl	1.8 ± 0.15
ii) m-Me	2.7 ± 0.1
iii) o,p-Me_2	5.8 ± 0.05
iv) o,p-Cl_2	4.8 ± 0.05
v) m-OMe	4.3 ± 0.05

The results in sections i), ii) and iii) of Table 24 were in qualitative agreement with the predicted intermediacy of cationic species. Thus, a ratio of k_x/k_{OH} = 5.8 indicated that the disubstituted phenyl ring in 2-amino-3',5'-dimethyltriphenylmethanol was more nucleophilic than water or compared to the mono-substituted phenyl rings in i) and ii). The dichloro-substituents in section iv) were expected to deactivate the phenyl nucleus towards electrophilic attack. The unexpectedly high ratio of k_x/k_{OH} 4.8 observed in iv) might have reflected the chloro-substituents hindering attack by water molecules upon the reactive sites.

The positions of ring-closure in i), ii) and v) in Table 24 were meta- to the substituents, Cl, Me and OMe respectively and in iv) ortho-, para- to Cl_2. When compared to the corresponding positions in iii), viz. ortho-, para- to Me_2 ring closure onto the positions in i), ii), iv) and v) would be expected to be much less favourable than the relative ratios of k_x/k_{OH} in Table 24 would indicate. Thus the polar character of the substituents in the phenyl rings appeared to have only a small influence upon the direction of the competing reactions of arylation and phenol formation. Notably, however, all the ratios of k_x/k_{OH} were greater than unity indicating a greater efficacy of the rate of cyclisation as compared to phenol formation.

The low selectivity shown in the intramolecular arylations and phenol forming reactions discussed above could apparently be most satisfactorily interpreted by postulating an intermediate aryl cation in these reactions. Such species was discussed earlier (section 2.5.2.2) as lacking resonance stabilisation and consequently highly reactive and unselective. The alternative routes via the diradical cation and the bimolecular process would

be expected to show a higher degree of selectivity than observed in the reactions of diazotised 2-aminotriarylmethanols; however contribution by such processes could not be totally discounted from evidence so far available.

5.2.3 Copper-Catalysed Decompositions of Diazotised 2-Amino-triphenylmethanols in Aqueous Acidic Media

Copper catalysis had a varied effect upon yields of different cyclic products. Cyclisations onto the unsubstituted and methyl-substituted phenyl rings were enhanced by catalysis (Table 25) compared to the uncatalysed reactions (Table 21). Decreases in yields of cyclisations onto the chloro-substituted phenyl rings in these reactions relative to the corresponding uncatalysed reactions, were, on the other hand, observed. Thus, 2,4-dichloro-9-phenylfluoren-9-ol was obtained in only 18.9% in the catalysed reaction, this yield as compared to 43.4% in the uncatalysed reaction.

Table 25: Product Yields in the Copper-catalysed Decompositions of 2-Aminotriphenylmethanols in Aqueous Acidic Solutions

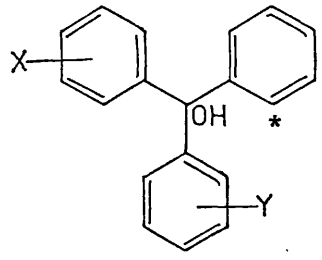
Amino Alcohols	Cyclisation Products	Yield (Mole % per mole of amine)	Total % Yield of all cyclised products	Yield of Phenols (% w/w of amine)
2-Amino-triphenylmethanol	9-Phenylfluoren-9-ol	86.0 $\pm$2.1	86.0 $\pm$2.1	7
2-Amino-4'-chloro-triphenylmethanol	a) 9-(4-Chlorophenyl)fluoren-9-ol	40.7 $\pm$5.0	66.6 $\pm$5.0	3
	b) 3-Chloro-9-phenylfluoren-9-ol	25.9 $\pm$5.0		
2-Amino-4'-methyl-triphenylmethanol	a) 9-(4-Tolyl)fluoren-9-ol	57.3 $\pm$6.4	96.9 $\pm$6.4	3
	b) 3-Methyl-9-phenylfluoren-9-ol	39.6 $\pm$6.4		
2-Amino-3',5'-dimethyl-triphenylmethanol	a) 9-(3,5-Dimethylphenyl)fluoren-9-ol	39.6 $\pm$6.7	97.3 $\pm$6.7	3
	b) 2,4-Dimethyl-9-phenylfluoren-9-ol	57.7 $\pm$6.7		
2-Amino-3',5'-dichloro-triphenylmethanol	a) 9-(3,5-Dichlorophenyl)fluoren-9-ol	52.6 $\pm$6.0	71.5 $\pm$6.0	5
	b) 2,4-Dichloro-9-phenylfluoren-9-ol	18.9 $\pm$6.0		
2-Amino-4'-chloro-4"-methyltriphenylmethanol	a) 3-Chloro-9-(4-tolyl)fluoren-9-ol	26.4 $\pm$3.0	68.1 $\pm$3.0	2
	b) 3-Methyl-9-(4-chlorophenyl)fluoren-9-ol	41.7 $\pm$3.0		

Yields in previously reported cyclisations carried out under these conditions (Table 11) referred to isolated products, and a comparison of the absolute results in Table 11 and those in Table 25 would not be valid since the results in the latter table were obtained spectrographically. However, a comparison of the influences of substituents upon the direction of ring closure between the previously reported reactions and the reactions we carried out on triarylmethanols could be useful. The results in Table 11 indicated that all the given substituents in the rings undergoing attack led to lower yields of cyclised products in the decompositions of substituted derivatives of diazotised trans-o-amino-α-phenylcinnanic acid (45) than observed in the reactions of the unsubstituted compound. More important was the observations that substantial cyclisations occurred onto rings supposedly deactivated towards electrophilic attack. For example, high yields (90%) of 2- and 4-nitrofluorenones were obtained in the decomposition of diazotised 2-amino-3'-nitrobenzophenone,[45] and moderately high yields (range of 50%-72%) were obtained where pyridine rings were attacked.[256,257] Intervention by aryl radicals in these reactions was suggested (section 2.5.2) Subsequent investigations led to conflicting theories about the mechanisms of these reactions as discussed under section 2.5.2. Perhaps the most lucid postulation was that by Huisgen[254,255] which envisaged both free radical and cationic aryl species as taking part in these reactions (Scheme XVI).

The high yields of 9-phenylfluoren-9-ols (Table 25) in the reactions we carried out on 2-amino-triarylmethanols meant that a purely homolytic mechanism for these reactions would be hard to justify (c.f. Table 19 and section 2.5.1). On the other hand the intermediacy of an aryl cation as postulated for the uncatalysed reactions (section 2.5.2) would not be totally

valid. A higher degree of selectivity, in accord with a mildly electrophilic reactive intermediate was observed for these copper-catalysed reactions than that in the uncatalysed reactions (compare data in Table 25 with that in Table 21). For example, the respective yields of 2,4-dimethyl-9-phenyl-fluoren-9-ol and 2,4-dichloro-9lphenylfluoren-9-ol in the uncatalysed and catalysed reactions were: 46.0% and 57% for the former compound, and 43.4% and 18.9% for the latter, suggesting an electrophilic attack which was less favourable in the latter compound than in the former in the catalysed reactions. The lower yield of 2,4-dichloro-9-phenylfluoren-9-ol (18.9%) in the catalysed reaction as compared to the yield (43.4%) in the uncatalysed reaction was perhaps surprising. Enhancement of some diversionary reactions by copper-catalysis, or the presence of copper, introducing stereochemical factors whose exact nature and effects were not known, might have resulted in this unexpected result.

Data in Table 26, which refers to competition between attack upon potential sites of ring closure in the phenyl rings with substituents X and Y in compound (70) was used to investigate further the effects of substituents upon intramolecular arylation reactions.



*reactive centre

(70)

Table 26

Relative Rates of Copper-Catalysed Intramolecular Arylations of Triarylmethanols (70)

X	Y	k_x/k_y
i) m-Cl	H	$0.6_5 \pm 0.2$
ii) m-Me	H	$0.6_9 \pm 0.2$
iii) o,p-Me_2	H	$1.4_6 \pm 0.5$
iv) o,p-Cl_2	H	$0.3_6 \pm 0.1$
v) m-Me	m-Cl	$1.5_8 \pm 0.3$

It was noteworthy that the results in Table 26 did not fit into the patterns set by data in either Table 20 or 22. Thus, all the ratios of k_x/k_y in Table 20 (apart from the -OMe substituted compound) were higher than unity, which meant that for reactions carried out in benzene these substituents increased reactivity over that of the unsubstituted phenyl ring. When considering only those 2-aminotriphenylmethanols where one other phenyl ring was substituted in Table 26, it was observable that a ratio of k_x/k_y greater than unity was obtained only in the decomposition of diazotised 2-amino-3',5'-dimethyltriphenylmethanol. Results in Table 26 suggested that the attacking species in the copper-catalysed reactions were mildly electrophilic, which could in turn be taken as indication that cationic species (or similar species) of slightly greater selectivity than those postulated for the uncatalysed reactions were involved. Such conclusions derive from the fact that cyclisations in i) and ii) in Table 26 occur onto positions meta- to the chloro- and methyl-substituents respectively, which positions are deactivated towards electrophilic attack. Cyclisation in iv) occurs onto positions (o-p to Cl_2) also deactivated towards electrophilic attack. The

two methyls in iii) were the only substituents predicted to enhance the possibility of attack by electrophiles at the positions of potential ring-closures.

The Hammett reaction constant $\rho = 0.467 \pm 0.50$ obtained by the least squares method and using data in Table 27, somewhat confirmed the mild electrophilicity of the reactive intermediates in these reactions. This value (-0.467) could not, however, be completely depended upon as quantitative basis for further mechanistic discussion in view of the large margin of possible error expressed.

Table 27

Polar Nature of Substituted Aryl Substrates in Copper Catalysed Intramolecular Arylation Reactions of Diazotised 2-Aminotriarylmethanols in Aqueous Acid Solutions

X, Y in (70)		k_x/k_y	$^{327}_{\sigma}$ ^{334} (Substituent constant)	log k_x/k_y
X	Y			
m-Cl	H	0.6_5	+0.373	-0.187
m-Me	H	0.6_9	-0.069	-0.161
o,p-Me_2	H	1.4_6	+0.123	0.164
o,p-Cl_2	H	0.3_6	+0.487	-0.444
m-Me	m-Cl	1.5_8	+0.304	0.199

If indeed, aryl cations were formed in the decompositions of diazotised 2-amino-triarylmethanols under the present conditions, then yields of phenols reported in Tabel 25 were unexpectedly low, varying between 2% and 7% (w/w) of starting amine (cf. Table 21). It was interesting to compare the 3% yield of phenol in the decomposition of diazotised 2-amino-4'-methyltriphenylmethanol (together with approximately 39.6% of 3-methyl-9-phenylfluoren-9-ol) with that previously reported for the reaction of 2-amino-4'-methylbenzophenone (Table 11) when phenol was formed in 31% yield (together with 45% of 3-methylbenzophenone). Such low phenolic yields appear inconsistent with a free aryl cation concept. Rather, a bimolecular reaction process where the two nuclear positions combined in arylation were held in position by the catalyst until ejection of the nitrogen molecule seemed more satisfactory. Steric factors might in this case hinder the water molecule from competing as effectively for the electrophilic centre as previously observed (Table 11).

The idea of a diazonium salt-copper complex was not new. A similar example of a complex between an aryldiazonium salt and copper (II) chloride, $(ArN_2CuCl)^+ Cl^-$, had previously been put forward in the interpretation of the Meerwein arylation reaction mechanism.[41,332] The existence of the above complex was based upon the observed polarographic and spectroscopic behaviour of diazonium solutions containing cupric chloride.[332] Such a complex was believed to undergo reaction with olefin (butadiene) by a displacement of the inner sphere chloride to give $(ArN_2CuC_4H_6)^{2+} 2Cl^-$; an internal electron shift then expelling nitrogen with the formation of the Ar-C bond within the complex. A direct

analogy between the copper-catalysed reactions of diazotised 2-amino-triarylmethanols and the Meerwein reactions just referred to might be difficult to envisage since in the former copper (0) was used and in the latter the catalyst was copper (II). However, the low redox potentials of copper which were discussed elsewhere in this thesis (section 2.5.2.1) meant that a case for analogous complexation with copper in the two reactions could be argued. The mechanism suggested agreed with both the selectivity observed in these reactions and the mild electrophilic nature of the phenyl ring from which nitrogen was ejected. Such a bimolecular reaction mechanism was fully discussed under section 5.2.2.

5.3 Conclusion

The following conclusions were drawn from the results of reactions of diazotised 2-aminotriarylmethanols carried out under the conditions stated:

a) Arylation reactions carried out in benzene using amyl nitrite for diazotisation resulted in the formation of products similar in nature to those previously obtained in reactions considered to go by way of free aryl radicals. Accordingly, a homolytic mechanism was suggested for these reactions. The relatively high yields of phenols obtained in these reactions were unexpected in the light of previous reports, and the little amount of water expected to intervene in such reactions.

b) The uncatalysed reactions in aqueous acidic media appeared to proceed by way of an intermediate with a low substrate selectivity. Thus, the rates of attack by the intermediate species upon the substituted and unsubstituted phenyl rings and water molecules were almost equal. However, the rates of attack on water molecules (to form phenols) were observed to be consistently lower than those upon phenyl rings (arylation) in the various reactions carried out. Steric and entropy factors were thought to be responsible for the observed preference for intramolecular arylation rather than phenol formation.

and c) In the copper-catalysed reactions in aqueous acidic media, there was evidence of substrate selectivity shown by the intermediates formed upon dediazoniation. Attack upon phenyl substrates containing electron-donating substituents was enhanced, and the opposite occurred where electron-withdrawing groups were present. Such results indicated the formation of an electrophilic centre at the site of nitrogen departure. The suggestion

that aryl cations were involved was discounted on the evidence of the low yields of phenols obtained in these reactions. The most probable course appeared to be by way of a diazonium ion-copper complex, which on decomposition, resulted in the formation, intramolecularly, of an Ar-C bond. This was a kind of internal bimolecular mechanism, and phenol formation could have been sterically hindered by both the presence of copper and by the outgoing nitrogen.

Additional kinetic work would no doubt help in the postulation of more definitive mechanisms in these reactions.

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