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MECHANISMS OF REACTIONS BETWEEN ARYL HALIDES AND ORGANO-LITHIUM COMPOUNDS

Penelope Ann Waddle

A thesis submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg for the degree of Doctor of Philosophy.

Johannesburg 1978.

To Ken, Mom and Dad

DECLARATION

I hereby declare that the work presented in this thesis was carried out exclusively by myself, under the supervision of Prof. G.W. Ferold.

This thesis has never been submitted for a degree in any other university.

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ABSTRACT

Convertional methods for the synthesis of biaryl compounds involve free radicals as intermediates and, in the case where unsymmetrical biaryls are desired, give rise to mixtures of products. A more elegant, and certainly more specific, approach would be to define the site of substitution on the aryl substrate by suitably positioned electron-withdrawing substituents for attack by an aryl anion. Generation of the latter by using aryllithium compounds, and their use as partners in coupling reactions with aryl halides formed the basis of this study.

As the literature on organolithium chemistry is highly controversial and confusing, the present study initially involved a thorough investigation of the reaccions of aryl halides with various organolithium reagents. It was found that the aryl halides could couple with themselves after metal - halogen exchange to give rise to biaryl and triaryl products. The reaction explored most fully was that between 2,4,6-tribromophenol and methyllithium.

The effects of varying the nature of the substituents and their position on the aromatic ring were also investigated. When the para substituents on a series of brominated phenol derivatives were varied through -F, -Cl, -Br, -H, and $-CH_3$, it was found that as the substituent became more electron-withdrawing the yield of biaryl product from the reaction increased. In a parallel series of reactions, the hydroxyl group of the substrate was replaced by $-OCH_3$, $-CH_3$, -H and -Br. Biaryl products were then obtained only from those brominated aromatic compounds containing substituents capable of metal - hydrogen exchange.

These results led to more specific reactions to clarify various points of mechanism and to the proposal that the aryllithium species resulting from metal - halogen exchange may exist as dimers in solution. Two types of dimers are postulated to occur, one type which collapses via an ionic pathway with elimination of lithium halide to form a biaryl product, and a second type of dimer which yields a biaryl product via a

radical pathway with the concomitant and transient production of lithium metal. Evidence for the existence of both pathways is presented.

Finally, applications of the results of this research were studied. Several avenues to the synthesis of a cannabinol analogue related to the constituents of Cannabis sativa were pursued but this target remained elusive. Other unsymmetrical biaryl compounds were however prepared in yields comparable to those quoted in the literature (usually by different methods) and a successful instance of "ionic " steering of an "ionic" pathway for such a reaction was realized.

"The first attempt at generalization seldom succeeds; speculation anticipates experience, for the results of observation accumulate slowly."

J.J. Berzelius (1830)

CHAPTER 1

THE ORIGIN OF THE ENQUIRY.

A control on the synthesis of unsymmetrical biaryl compounds through the strategy of defining the sites of substitution on the aryl substrates by suitably positioned electronegative substituents and then attack by an aryl anion was desired. The possibility of using organolithium compounds for this purpose initiated this study

INTRODUCTION.

Organometallic chemistry had its beginnings over one hundred years ago when Frankland unintentionally prepared ethylzinc in 1849[1] when he reacted ethyl iodide with zinc in an attempt to prepare ethyl radicals. It was some sixty years later that the first pure organolithium compound was prepared by Schlenk.[2] Only after Gilman[3] and Wittig[4] independently in 19 8 discovered that the treatment of an organohalide with an organolithium compound resulted in halogen-metal interconversion, were further significant contributions made to this field of chemistry.

Some forty years have passed since their discovery and a wealth of literature has been published on organolithium compounds and the reactions they have been found to undergo. Yet many fundamental questions remain unanswered or are in dispute. This, amongst other factors, prompted our studies into the reactions of organolithium compounds with aromatic halides.

A survey of the literature on organolithium chemistry leaves one with a confused picture with regard to many aspects of this area.

1.1 The Carbon-Lithium Bond

No consistent satisfactory description of the C-Li bond has as yet

emerged.

In 1944 Morton[5] reviewed the salt-like character of organoalkali compounds and found that alkyllithium compounds were non-electrolytes which conducted poorly and whose ionic character was doubtful.

Further evidence for covalent bonding came from comparing ^{13}C chemical shifts and ^{13}C-^{1}H coupling constants for the α-carbon atoms in alkyllithium compounds and their corresponding hydrocarbons[6]. These showed relatively small differences and suggested that the α-carbon atoms are essentially sp^3 hybridised and carry only a fractional negative charge.

The fact that some configurationally stable optically active organolithium compounds have been prepared (where the α-carbon atom is the asymmetrical centre) adds further weight to the argument that the carbon-lithium bond may in these instances be largely covalent as a carbanion could be expected to undergo rapid inversion.[7]

Recent Self-Consistent-Field (SCF) calculations on methyllithium by Ghost[8] and Baird[9] show that the C-Li bond has predominantly covalent character. Palmieri[10] suggests that it is this 'tendency of lithium atoms to form covalent bonds where the vacant p orbitals are also involved' that would explain the formation of the molecular aggregates of alkyllithium compounds both in solution and in the gas phase.

On the other hand, a high degree of ionic character is predicted from a comparison of the electronegativities of carbon and lithium. Also, in contrast to Ghost's results, Streitwieser[11] has shown that *ab initio* SCF-molecular orbital calculations describe methyllithium in terms of largely ionic bonding with about 0.8e transferred from lithium to the methyl group.

In the presence of electron-donor solvents, for example, diethyl ether or tetrahydrofuran(THF), where the solvent may co-ordinate to the lithium atom one could anticipate greater ionic character of the C-Li bond. Also, when stabilisation of a carbanion is possible as in the case of benzyl-, allyl-, and aryllithium compounds, one might expect a more ionic C-Li bond.[12] This is substantiated by the fact that the nuclear magnetic

resonance (NMR) spectra of phenylmagnesium bromide, phenyllithium and pyridine are quite similar. As the phenyl anion is isoelectronic with pyridine, the NMR results have been interpreted by formulating the aryllithium compounds as salts of anions.[13,14]

It is likely that the C-Li bond is more ionic in aryllithium compounds than in alkyllithium compounds. Wakefield suggests[15] that a far more complex type of bonding than either simply covalent or ionic may be involved.

1.2 The Structure of Organolithium Compounds.

From colligative property measurements alkyllithium compounds are known to exist as polymeric aggregates, generally hexamers or tetramers, in solution. The bonding within these aggregates is approximated to a localized multicentre bond involving one alkyl group and three lithium atoms - the carbon of the organic group and each lithium atom contributes one orbital towards the bond but only one pair of electrons is found within the grouping.[16,17] While the hexamers and tetramers are of similar energy, a dimeric species involving only a three-centred bond (i.e. an alkyl group bridging two lithium atoms) is significantly less stable than either the hexamer or the tetramer.[17] Relatively electron-withdrawing groups such as phenyl or benzyl give rise to dimeric $(RLi)_2$ species.

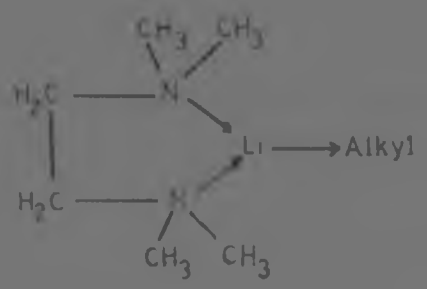
NMR gives no evidence of Li-Li bonding[18] (i.e. no ^6Li-^7Li coupling) within the aggregate but Matteson[19] believes that the small coupling constant for the Li-Li bond in the methyllithium tetramer ($J < 0,3Hz$) may be due to the chance cancellation of two terms of opposite sign. Ward[20], on the other hand, is of the opinion that the lack of ^6Li-^7Li splitting merely suggests electron deficiency in the Li-Li bonding structure. X-ray analysis of the structure of solid $(CH_3Li)_4$ by Weiss[21] gives the Li-Li distance as 2,6Å which does allow for overlap between the orbitals of the two atoms.

n-Butyllithium exists as a hexamer and methyllithium as a tetramer in benzene and cyclohexane.[22] The degree of association is found to be constant over wide ranges of concentration with no evidence of dissocia-

tion in dilute solutions.[15] Aryllithium compounds are dimers in hydrocarbon solvents and recently phenyllithium has been shown to be a dimer in diethyl ether[23] and THF[24] as well.

Alkyllithium compounds were found to be more reactive in the presence of electron-donor solvents (Lewis bases) such as THF and diethyl ether than in hydrocarbon solvents. It was therefore thought[25] that these solvents in some way caused the alkyllithium aggregates to dissociate to dimers. Recent studies by Quirck[27] have shown that, without exception, no dissociation of the hexamers and tetramers to smaller aggregates occurs in hydrocarbon solvents to which small amounts of Lewis bases were added. In pure THF or diethyl ether, however, hexamers no longer exist but the tetramers do still occur.[26] It is generally accepted that some kind of complex is formed between the electron-donor solvent and the organolithium aggregate which increases the reactivity of the latter[7] by increasing the polarization of the C-Li bonds on co-ordination of the solvent to the lithium atoms or, if a one-electron transfer process is operative, by solvating the electron.[27]

In the presence of chelating agents such as N,N,N',N'-tetramethylethylenediamine (TMEDA), alkyllithium compounds are most reactive. The alkyllithium-TMEDA chelate is regarded as monomeric with the C-Li bond of the organolithium molecule strongly polarized.[28] The complex is depicted as in (1).



(1)

[TMEDA should be used with caution in metal-halogen exchange reactions as it has been found to accelerate metallation (metal-hydrogen exchange) more than the former reaction.[29]]

1.3 The Metal - Halogen Exchange Reaction.

The work of Gilman and of Wittig has shed much light on the metal -halogen exchange reaction between an organolithium compound (RLi) and an alkyl or aryl halide (R'X).

When the halogen (X) is iodine or bromine, the reaction is reversible and may be written as

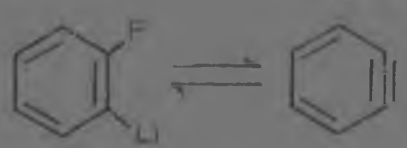
$$RLi + R'X \rightleftharpoons R'Li + RX \quad (1)$$

The lithium atom becomes attached to the R group most capable of sustaining the negative charge. If there is little difference between the electronegativities of R and R', an equilibrium mixture containing the four species above in comparable amounts will be formed. Applequist[31] has suggested that the equilibrium constants for reaction (1) may serve as a semi-quantitative measure of carbanion stability. In the case of an aryl halide and an alkyllithium compound, the equilibrium is displaced far to the right.

If the halogen is fluorine, metal-halogen exchange does not occur. Instead the fluorine, owing to its strong inductive effect, labilizes the hydrogen ortho to it on the ring and metallation occurs.[32] Reprotonation of the anion so formed competes with the loss of LiF from the ring to form a benzyne intermediate.[33]



(2)



(3)

It may be assumed that reaction (3) is reversible as Wittig[32] obtained 3 - 4% of chlorobenzene from the reaction of 2-fluorobromobenzene with magnesium in the presence of lithium chloride.

Aryl chlorides may react via either metal-halogen exchange or metallation ortho to the chlorine.

The ease of replacement of the halogen by lithium is proportional

to the degree of polarization of the halogen atom i.e. I > Br > Cl > F[34] thus showing that a positive halogen is replaced by the lithium atom.

Optimium yields of lithiated product R'Li (reaction (1)) are normally obtained in less than half a minute at room temperature.[35] If the reaction is left for longer then the R'Li is consumed in one of several side reactions (to be discussed later). If the temperature is lowered to -80° C, the rate of interconversion decreases and the yield drops.[35] However, in the case of replacement of halogen by lithium in compounds containing reactive functional groups such as carbonyl or nitro, it is essential to lower the temperature to -75° C to get the desired metal-halogen exchange reaction.[36]

As mentioned earlier, electron-donor solvents tend to increase the reactivity of organolithium compounds. The metal-halogen exchange reaction is fastest in di-n-butyl ether > diethyl ether > dimethylaniline > benzene > cyclohexane and petroleum ether. THF is also effective for the exchange reaction but it has been found to speed up one of the competing side reactions viz. coupling between R and R' more than the metal -halogen exchange reaction[37] Thus, diethyl ether is usually the solvent of choice for the reaction.

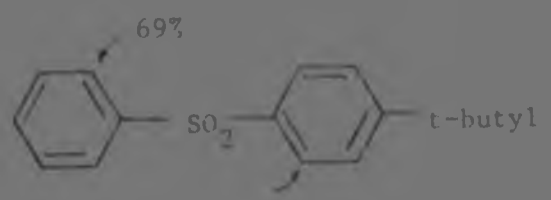
n-Butyllithium is the organolithium compound most extensively used in the interconversion reactions because it generally gives the highest yields of desired R'Li (reaction (1)) and because of its greater stability. Gilman found that methyllithium was of no value for the interconversion reaction.[34]

In most instances, reactions were carried out by adding the organolithium reagent to an anhydrous ethereal solution of the alkyl or aryl halide in a nitrogen atmosphere at a given temperature. After some specified time, the reaction was quenched by being poured onto solid carbon dioxide. The mixture was extracted with aqueous base and acidified and only the carboxylic acids so obtained from the reaction were examined. Up to 75% of a tar could be obtained from the reaction which was not examined further. Thus, while the results of these reactions are indicative of the way to obtain the maximum yield of a desired organolithium compound, they unfortunately do not give much insight into the extent and nature of the competing side reactions and hence, the

mechanism of the reaction. In Wakefield's words[38] 'no systematic study of the relative proportions of metallation and alkylation under different conditions has been published. Such a study would be highly significant in view of the suggestion[39] that both reactions may involve a common intermediate.'

Other features of organolithium reactions with aryl compounds that have become apparent over the years are as follows. (Here metallation is used loosely for exchange of either a halogen or a hydrogen atom).

(i) Electron-withdrawing substituents facilitate metallation of the aromatic ring while electron-donating substituents hinder it.[40] The presence of several halogen atoms on an aromatic ring not only facilitates metallation but also stabilizes the organolithium intermediate.[41] Shirley[42] demonstrated the deactivating influence of alkyl groups towards metallation through their inductive effect by treatment of 4-t-butyldiphenylsulphone (2) with n-butyllithium. He obtained the introduction of 69% of the lithium into the unsubstituted ring and only 31%



(2)

into the ring containing the t-butyl group.

(ii) If a substituent containing lone pairs of electrons is present in the aromatic ring being lithiated, a high proportion of metallation ortho to that substituent occurs. This is attributed to coordination of the lithium cation from the RLi compound to the lone pair of electrons on the substituent.[43] An intermediate (3) is postulated



(3) (X=H,halogen) (4)

leading to the transition state (4).

The $\backslash\overset{|}{O}$----Li^+ bond will weaken the attraction between the lithium and R^- making the latter more available for attack on the ortho halogen or hydrogen. This is substantiated by the fact that compounds lacking a donor atom are metallated slowly, if at all, by n-butyllithium.[44] Co-ordination of the metal atom to the donor oxygen will increase the electron-withdrawing inductive effect of that substituent. This will be felt most strongly in the ortho position and will increase the polarity of the C - X bond thereby aiding the removal of X^- by the incipient carbanion of the RLi compound.[39]

Metal-halogen exchange and metal-hydrogen exchange (metallation) are viewed as analogous reactions involving a similar type of mechanism. Metal-halogen exchange is generally the more facile reaction owing to the higher polarizability of halogen atoms as compared with hydrogen atoms.[43] This was demonstrated by the treatment of 2-bromoanisole with n-butyllithium.[3] After work-up only 2-methoxybenzoic acid was obtained and no further metallation of the starting material had occurred. However, we found that treatment of 4-bromophenol with methyllithium followed by quenching with heavy water (D_2O), gave only 2-deutero-4-bromophenol[45] as product, i.e. metallation ortho to the methoxy group had occurred in preference to replacement of the para bromine showing that the position of the halogen is important. This reinforces the argument that co-ordination of the lithium atom to a lone pair donor atom is important (as before).

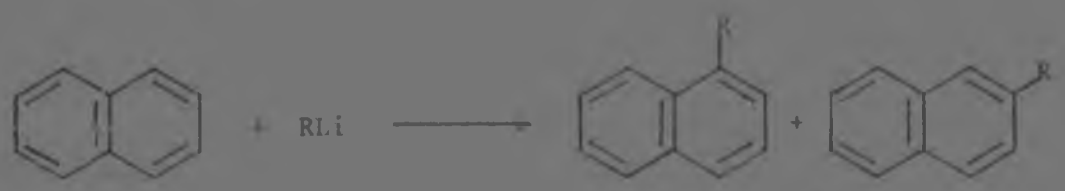
(iii) Both the metal-halogen and metallation reactions have a very low steric requirement. For example, when phenyl-t-butyl ether was metallated with t-butyllithium,[39] ortho lithiation occurred in more than 99% yield despite the bulkiness of both reagents.

1.4 Alkylation of the Substrate R'X - The Coupling Reaction

As was explained earlier, in the intensive study of metallation and metal-halogen exchange reactions after their discovery by Gilman and Wittig, usually only the major acidic carboxylation products of the

reaction were isolated and identified. Thus, some time had elapsed before it was found that products of the nature R-R' were also often present in the reaction mixture. Gilman had alluded[34] to these 'secondary coupling reactions' in 1951 stating that they may take place 'in many if not all halogen-metal interconversion systems'. However, 'prior to 1963, regardless of the choice of alkyl group in the reactions of alkyllithium,-sodium and-potassium compounds with aromatic hydrocarbons, alkylation had never been reported as a significant reaction course.'[46]

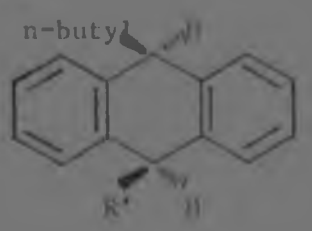
One of the earliest discoverers of this phenomenon was Dixon[47] who in 1963 found that the treatment of an aromatic hydrocarbon with an alkyllithium (RLi) reagent resulted in addition of the RLi to the aromatic substrate followed by the loss of lithium hydride. For example,



(4)

Hot on his heels, in 1964 Ziegler[48] was surprised to find that metallation of perylene with n-butyllithium at room temperature gave both 1- and 3-n-butylperylene.

Other researchers soon adopted this technique to accomplish desired alkylations and in 1969 Harvey[49] stereospecifically alkylated anthracene by treatment with n-butyllithium followed by the addition of excess alkyl halide (R'X) to give (5).

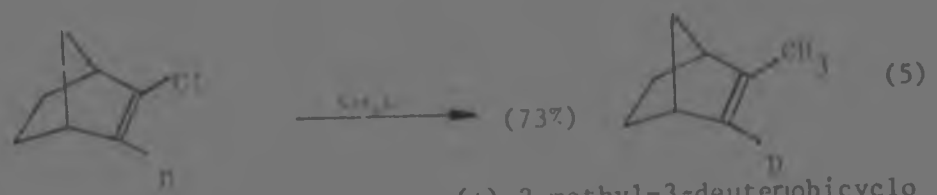


(5)

(i.e. addition of n-butyllithium followed by Li-R' exchange such that both the n-butyl and R' groups are above the plane in which the aryl rings lie.)

The most interesting results in this field come from the work of

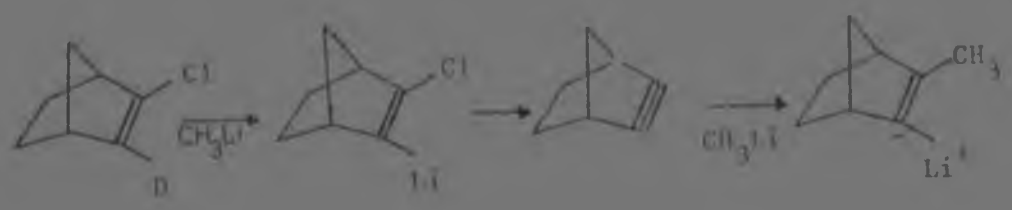
Cassman and Atkins[50] who recently studied the following reaction



(5)

(+)-2-methyl-3-deuteriobicyclo [2.2.1] heptene-2

Neither replacement of deuterium nor inversion of configuration occurred. It was thus felt that this coupling reaction did not proceed via either a cycloalkyne (route 6) nor an addition - elimination process (route 7) but that a direct coupling occurred. Unfortunately, no suggestion for the mechanism was offered.



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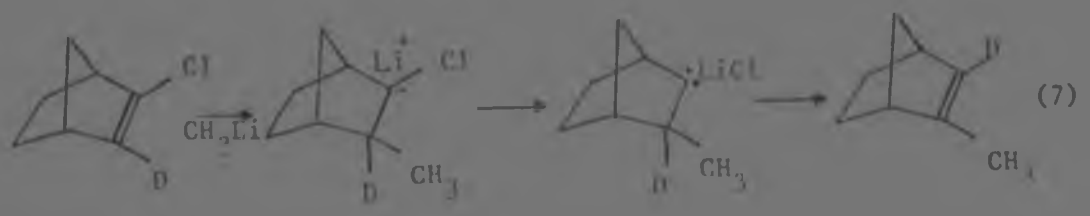


(7)

It was found[47] that for aromatic substrates electron-withdrawing groups on the ring accelerated the coupling reaction as did the more stable alkyllithium reagents (viz. t-butyl- 〉 s-butyl- 〉 n-butyllithium) Thus, this relatively facile reaction was interpreted as a nucleophilic attack (sic!) of the carbanion on the aromatic ring.

Wakefield[51] also "formalized" the reaction as nucleophilic substitution where the carbanionic part of the organolithium reagent displaced a suitable leaving group.

The reaction of aryl halides (ArX) with organolithium compounds (RLi) was also found to give products of the type Ar-R. As haiogens attached to aromatic rings are not, in general, readily displaced by

nucleophiles it has been suggested that these coupled products arise via metal-halogen exchange followed by interaction of the aryllithium with the alkyl halide so formed in the reaction[51]

$$\underline{i.e.} \quad ArX + RLi \longrightarrow ArLi + RX \qquad (8)$$

$$ArLi + RX \longrightarrow ArR + LiX \qquad (9)$$

or by an elimination-addition reaction involving an aryne-intermediate.[51,52]

It has been shown[53] that the rate of the coupling reaction is enhanced in the presence of electron-donor solvents. (e.g. amines such as piperidine and pyrrolidine[54]) and especially in THF. For example[54]

$$ArCl + Ar'Li \longrightarrow 17\%\ Ar - Ar' \text{ without amine} \qquad (10)$$

$$\longrightarrow 61\%\ Ar - Ar' \text{ with amine} \qquad (11)$$

In contrast, Korte[55] found that if the coupling reactions of resonance-stabilized organolithium reagents such as benzyl- and allyllithium with cycloalkylhalides were carried out in THF, elimination became an important side reaction. His solvent of choice for these systems is diethyl ether.

Several kinetic studies have been carried out on the coupling reaction but ' the usefulness of much of these studies is lessened by the fact that simultaneous reactions may have been involved but the product analyses were not always carried out.[51]

1.5 The Mechanism of the Exchange and Coupling Reactions.

The most contentious point about the mechanism of the exchange and coupling reactions is whether an ionic or a (free) radical pathway or a mixture of both is operative. A wealth of conflicting evidence in favour of both mechanisms is now available. We shall present the results of workers and their interpretations followed by any support or opposing opinions and finally attempt to summarize all the results.

Initially, the best evidence pointing towards free radical intermediates came from the work of Russell and Lamson.[56] They showed that

free radicals were easily detectable by electron spin resonance (esr) spectroscopy in the reactions of organolithium reagents (R^-M^+) with alkyl halides (R'X). These free radicals were detected before an appreciable amount of metal - halogen exchange had occurred. They put forward the following one-electron transfer mechanism,

$$R^-Li^+ + R'X \longrightarrow R^{\cdot} + R'^{\cdot} + LiX \qquad (12)$$

$$R^{\cdot} + R'X \longrightarrow RX + R'^{\cdot} \qquad (13)$$

$$R'^{\cdot} + RLi \longrightarrow R'Li + R^{\cdot} \qquad (14)$$

$$R^{\cdot} + R'^{\cdot} \longrightarrow \text{alkane} + \text{alkene} \qquad (15)$$

They suggested that a base like TMEDA would increase the rate of reaction (12) and the steady state concentration of radicals. This hypothesis was substantiated by the work of Panek[57] who showed that a base like hexamethylphosphoramide (HMPA) facilitated one-electron transfers from organometallic compounds to an organic substrate. Ward and Lawler[21] believe that the concept of lithium atom transfer (eq. (14)) is not necessary and that R'Li will only be formed if halogen - metal exchange is exothermic.

The disproportionation reaction (15) is supported by the work of Nugent[58] involving a thorough materials balance of a reaction between peroxides and organolithium reagents to give a product distribution which could be quantitatively related to known values for the relative rates of combination and disproportionation of the intermediate radicals. Nugent's work is not conclusive evidence for a free radical mechanism being operative generally in reactions of organolithium reagents with organic substrates as peroxides (ROOR) are well known for their ease of homolysis into two RO' groups. Also, Krusic and Kochi[59] showed that photolytically generated t-butoxy radicals attack organometallic compounds (e.g. $(CH_3)B$, $(Ethyl)_3Ga$, $(t\text{-butyl})_3Al$, $(n\text{-butyl})_2Hg$ and n-butyllithium) to produce an easily detectable steady state concentration of alkyl radicals; but in the absence of the t-butoxy radicals only a very weak spectrum of the alkyl radicals was recorded which disappeared when the radiation source was removed.

Studies of enhanced emission or absorption (chemically induced dynamic nuclear polarization - CIDNP) in the NMR spectra recorded during the reactions of alkyllithium and Grignard reagents with alkyl hal-

ides furnish strong evidence for a homolytic component[20,60,61,62] arising from both geminate and diffusive encounters. However, positive CIDNP results have only been obtained from reactions under conditions where coupling and exchange occur simultaneously.[20] This suggests that exchange does not involve a radical pair mechanism but rather a four-centre mechanism. As yet, the relationship between the concentration of radicals and the degree of enhancement of the NMR signals has not yet been calculated. Ward[63] himself admits that the polarization may arise from a chemically insignificant radical pathway while the majority of the product is formed in some other manner.

Virtually all the systems studied which gave positive CIDNP results have been composed of ALKYL halides and an ALKYLlithium reagent or a peroxide.[64,65,66,67] Likewise, the esr spectra recorded,[50,68] the reaction studied by Bryce-Smith,[69] and the systems in which radicals were trapped by α-methylstyrene[20] all involved ALKYL species only.

When Shirley[70] examined six AROMATIC substrates undergoing metallation in hydrocarbon and ether solvents, no CIDNP results were obtained. Ward[20] has suggested (vide supra) that CIDNP is effective only under conditions where coupling and exchange occur simultaneously. Thus, Shirley's results could be due to either the fact that only exchange was occurring in the systems he studied or that ARYL species do not react via a free radical pathway under normal conditions (i.e. no peroxides nor irradiation). We favour the former reason as the substrates chosen by Shirley were metallated only (and rather slowly at that) by n-butyllithium - TMEDA.

Further evidence for free radicals being involved in the mechanism came from the elegant research of Screttas[71] on the metallation of thiophene in the 2-position by lithium and lithiumhydroarylides (aryl = naphthalene or biphenylene). Product yields and magnetic titrations indicated that the transformation was a two electron process which might become one-electron in the presence of a substance that could dimerize under the reaction conditions (e.g. styrene). Paramagnetic decay in solutions of thiophene and the dihydroarylides was of the first order

and the rate constant correlated with the π-energy change[a] for the reaction

$$ArH^{-} \longrightarrow ArH + e^{-} \qquad (16)$$

A mechanism involving an unstable thiophene radical was suggested The initial electron transfer was found to be the rate-determining step followed by the relatively fast fission or dissociation of the radical anion to a carbanion.[71] There is ample experimental evidence[72,73] that certain organolithium compounds can function as single electron donors and thus generate a radical anion from an aromatic substrate.

Work by Roberts[76] on the reactivity of mono- and tetra-1-adamantyl derivatives of silicon, germanium, tin and lithium indicated that the closely related Wurtz coupling reaction[b] involved in the production of these compounds from organometallic compounds and 1-haloadamantane also, in part, involved a one-electron transfer process. In contrast, studies by Le Goff[7] on the absolute configuration of three compounds prepared by the Wurtz reaction, showed that the reaction was definitely of the S_N2 type.

The results of these one-electron transfers cannot be extended to reactions of all aromatic and aliphatic halides with organolithium compounds. The requirement for electron transfer to occur is that the substrate should possess a vacant orbital of lower energy than the odd electron of the alkali metal ion.[76] This requirement is met by many aromatic compounds with extended conjugated systems like naphthalene, biphenyl and other condensed aromatic hydrocarbons which have a fairly

---

a) The π-energy change, ΔE for the reaction (16) is equivalent to $-m_{m+1}$ where m_{m+1} is the Hückel value of the coefficient of the molecular orbital resonance integral in the expression for the energy of the lowest unoccupied orbital i.e. the electron lost from ArH^{-} in reaction (16) must have occupied a π orbital of the aromatic ring.

b) The Wurtz - Fittig reaction;

$$2M + RX \longrightarrow RM + MX$$
$$RM + RX \longrightarrow R\text{-}R + MX$$

high electron affinity, but the simple aromatic hydrocarbons are much poorer electron acceptors.[77] In fact, all the research which has led to the prediction of an electron-transfer process has involved only those species that would readily accept an electron[78] viz. anthracene,[57,77] naphthalene,[79] biphenyl[57] and thiophene.[71] Also, the most recent studies on reactions via the $S_{RN}1$ mechanism[80] involving aromatic radical anions has shown that the order of reactivity of the aromatic moiety is naphthalene $\rangle$ biphenyl $\rangle$ benzene — the order of ease of reduction of the arene.[81]

In general, the reactions of RLi compounds with unsaturated organic compounds to give radical anions,

$$RLi + ArH \longrightarrow (ArH^{\cdot}, Li^{+}) + R^{\cdot}, \qquad (17)$$

appear to be slow with the yield of $ArH^{\cdot}$ usually not high[82]

In the case of an aryl halide, if the one-electron transfer were to occur to produce $ArX^{\cdot}$, (reaction (18)) this species readily loses the halide ion to produce the aryl radical[82]

$$\text{i.e.} \quad RLi + ArX \longrightarrow ArX^{\cdot} + Li^{+} + R^{\cdot} \qquad (18)$$

$$ArX^{\cdot} \longrightarrow Ar^{\cdot} + X^{-} \qquad (19)$$

and the overall reaction reduces to that proposed by Russell and Lamson[56] and Fisher[68]

$$\text{viz.} \quad RLi + ArX \longrightarrow Ar^{\cdot} + LiX + R^{\cdot} \qquad (12)$$

Thus, until proved otherwise, any pathway involving a radical anion, if operative, can only be of minor importance in reactions between simple aromatic or aliphatic species and organolithium reagents.

In favour of an ionic mechanism, Winkler,[83] in studying the following reaction

$$ArLi + Ar'Br \rightleftharpoons ArBr + Ar'Li, \qquad (20)$$

found that it adhered to a second-order rate law. The same results were obtained for salt-free and salt-containing (e.g. lithium bromide) aryllithium reagents. He concluded that the equilibrium constant for

reaction (20) was dependent on carbanion stability. The reaction followed the Hammett $\rho\sigma$ relationship which he took to imply that an ionic mechanism was operative. A value of ρ = +4,0 for the reaction constant was obtained suggesting a build-up of negative charge in the transition state which would be in accordance with acceleration of the exchange reaction in better ion-solvating solvents.

Ironically, Batalov[84] obtained a similar value of ρ = +3,66 for the exchange reaction of phenyl radicals (sic!) between phenyllithium and substituted bromobenzene in diethyl ether. Batalov explained the results by invoking a polar four-centre transition state in the reaction.

The most compelling evidence in favour of an ionic mechanism is an example of a coupling reaction (21) which proceeds with 100% inversion of configuration.[85]

$$\underset{\text{optically active}}{C_6H_5\text{-}\overset{\overset{CH_3}{|}}{\underset{\underset{H}{|}}{C}}\text{-}Cl} + (C_6H_5)_2CHLi \longrightarrow \underset{\text{optically active}}{C_6H_5\text{-}\overset{\overset{CH_3}{|}}{\underset{\underset{H}{|}}{C}}\text{-}CH(C_6H_5)_2} + LiCl \quad (21)$$

The fact that stereoselective coupling reactions have been found to occur between allyl- and benzyllithium reagents and sec-octyl halide[85] strongly favours a conventional S_N2 mechanism and is not compatible with a free radical pathway.

(Stereoselectivy does not always imply an IONIC mechanism. Koenig has pointed out[86] that geminate combinations of radical pairs are involved in some of the fastest of all chemical reactions and they may therefore be highly stereoselective giving products with essentially complete retention of configuration.)

Simple alkyllithium compounds give largely racemized products from their coupling reactions with optically active organic halides. For example, when Zook[87] reacted (+)-2-bromobutane with n-butyllithium he obtained 37% (-)-3-methylheptane. An inversion of configuration is indicated in the coupling process as the configuration of the two compounds can be related. From the maximum value of the rotations of the compounds, racemization to the extent of 98% was calculated.

Interestingly, if silicon is the metal used in coupling reactions of organometallics with organofluorides and -chlorides then a stereoselective reaction occurs in some cases with 100% inversion and in other cases 100% retention of configuration.[88] No mechanism to explain this phenomenon was put forward.

Thus we see that most information on the mechanism of the coupling and exchange reactions can be explained in terms of either a radical or an ionic mechanism and no clear and conclusive explanation has yet been proposed.

To further complicate the issue, it has been suggested[82,89] that the solvent may play a role in diverting a reaction from homolytic to heterolytic and vice versa. It is known[84] that hydrocarbon solvents favour a radical pathway while electron-donating solvents, which can bett. olvate an ionic species and increase the charge separation in the transition state, would enhance a heterolytic pathway. The activating effects of some solvents on reactions of lithium alkyls are similar to those generally observed for bimolecular organic reactions involving anionic nucleophiles.[82]

Hine[90] suggests that a radical mechanism may be operative for reactions between organoalkalis and organohalides in the vapour phase at elevated temperatures but reactions as ordinarily carried out in solution may be satisfactorily explained on the basis of an ionic mechanism.

Wakefield[60] has summed up the state of knowledge on the exchange reactions as it 'may involve some degree of homolytic fission given by

$$R'X + RLi \rightleftharpoons [R^{\cdot}, Li, X, R'^{\cdot}] \rightleftharpoons R'Li + RX \qquad (22)$$

The symbol in brackets represents some kind of intermediate involving unpaired electrons which gives rise to the magnetic resonance phenomena and also to the coupling and disproportionation products.'

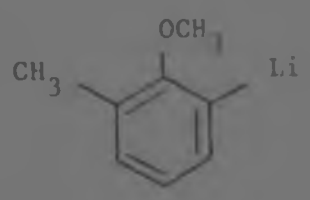
In summary;

Metallation and metal-halogen exchange may be purely ionic with the coupling reaction alone involving radicals.[60] The extent to which radical intermediates are present may be greatest in hydrocarbon sol-

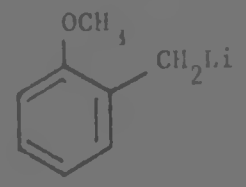
vents and in reactions involving alkyl species poorly able to accomodate the carbanionic state whilst allyl, benzyl and phenyl compounds in polar solvents will react predominantly via an ionic pathway; but the possibility of radical species in these reactions as well cannot be [illegible]ly eliminated.

[illegible] general points on the mechanism of the reaction should be mentioned.

n-Butyllithium in the presence of an equimolar amount of TMEDA rapidly metallates 2-methylanisole to give 75% of (6) and 25% of (7)



(6)



(7)

The n-butyllithium-TMEDA complex is monomeric[28] with the lithium atom chelated to the nitrogen atoms of the TMEDA and unavailable for complexation to the oxygen of the anisole group. Thus, prior complexation of the organolithium reagent to the substrate cannot be a prerequisite for the exchange reaction.[91,92]

In 1968, Shirley[39] proposed a detailed mechanism for the reaction in which the first step was given as

$$(RLi)_n \underset{\text{dependent}}{\overset{\text{Solvent}}{\rightleftharpoons}} (RLi)_2 \underset{\text{dependent}}{\overset{\text{solvent}}{\rightleftharpoons}} RLi \underset{\text{dependent}}{\overset{\text{solvent}}{\rightleftharpoons}} R:^- + Li^+ \qquad (23)$$

He believed this step (23) would be favoured by the presence of amines, particularly those capable of chelation, which would cause dissociation of the organolithium aggregates to more reactive monomers. This was supported by studies[94] of reactions of organolithium compounds in hydrocarbon solvents which had shown that the reaction was 6th order in alkyl-lithium reagent and first order in organic substrate

$$\text{i.e. Rate} = k[RLi]^6[R'X]$$

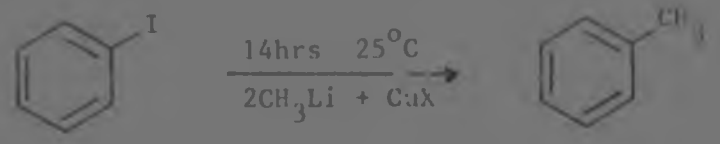
However, it is now generally accepted[20,93] that direct reaction between the most stable intact oligomer and the substrate occurs in most systems.

A cross-association between the initially formed metallated product on the surface of the intact aggregate is proposed.[70]

1.6 The Use of Copper in the Coupling Reaction.

In 1940 Gilman[93] noted the catalytic effect of some finely divided metals on the metal-halogen interconversion reaction. He found that it increased the rate of the exchange reaction but reduced the yield 'possibly by accelerating the coupling reaction' but he did not pursue this observation further. His students had prepared methylcopper in 1936 and $Li(CH_3)Cu(I)$ in 1952[94] but it was not until Corey[95] in 1967 discovered an efficient method for coupling an allylic group to an alkyl, vinyl or aryl unit using allyl nickel reagents and extended his investigation to other organotransition metal compounds that the use of copper for the coupling reaction was fully realized.[96]

One could now, for example, effect the following reaction in 90% yield[96]



(24)

Methyllithium alone was found to be a totally unsatisfactory reagent for the above transformation.

Since 1967 much research has been done in this sphere and two excellent articles reviewing the entire field have been published by Posner[97,98] who pioneered the initial research with Corey. A review by Jukes[99] has also appeared.

Some general comments about the use of copper in the Corey-Posner reaction (as it is now known).

(i) Optimum yields are obtained in the temperature range -95°C to 0°C.[96]

(ii) Secondary halides are much less suited to the coupling reaction with lithiumdialkylcuprates than primary halides[96] Tertiary alkyl

halides show virtually no reactivity with organocopper reagents.[98]

(iii) The reactions are generally executed in diethyl ether. THF can also be used.

(iv) Oxidation of the resulting mixture with nitrobenzene or oxygen prior to work-up markedly increases the yield.[100]

(v) Stereospecific couplings have been accomplished with predominantly, inversion of configuration.[96]

(vi) Replacement of iodine by R usually proceeds in high yield, bromine is satisfactorily replaced although more slowly and chlorine is sluggish in reaction but can be replaced in reasonable yields at high temperatures.[9] Tosylate as a leaving group dramatically increases the rate and the yield of the coupling reaction.[101]

(vii) Strong electron-attracting groups ortho to the halogen increase the coupling rate significantly.[102]

(viii) A complex free radical mechanism for the reaction was advanced initially.[10] Recent research by Pearson[104] mitigates against a radical mechanism and favours the sequential oxidative addition — reductive elimination process suggested earlier by Whitesides[100] and Johnson.[101] Other metals have been tried for the coupling reaction but copper is unique in this role - this has been attributed to the relatively low ionic character of the copper-carbon bond.[98]

Briefly, other metals that have been employed to give good yields of biaryls, and the limitations of these techniques, are outlined in Table I.

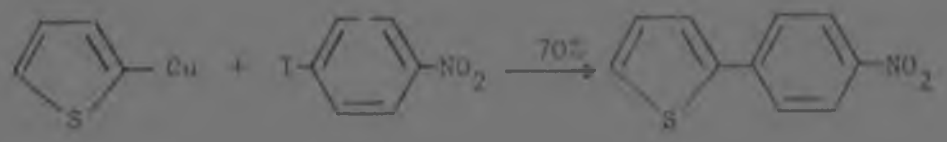
One of the original methods for preparing biaryls viz. the Ullmann biaryl synthesis reaction has not yet been discussed. This reaction involves the condensation of two molecules of aromatic halides in the presence of copper to form a new aryl-aryl bond with the elimination of copper(I) halide. Initially, it was thought that radicals were intermediates in the reaction. However, as early as 1964, Fanta[105] in his second review of the Ullmann reaction, suggested that a σ-organocopper intermediate might be involved in the reaction i.e. that the halogen in one of the aryl compounds was replaced by a copper atom and it was this species that reacted further with a second aryl halide to form the aryl-aryl compound with the elimination of copper halide. In 1970, Nilsson[106] showed conclusively that the above postulate was true by reacting crude

TABLE I

METAL	COMPLEX	PRODUCT	YIELD	REF.	LIMITATIONS
Tellurium	Bis(aryl)tellurium chloride	Symmetrical biaryl	up to 90%	107	Aryl group must bear an activating substituent (e.g. RO-, R_2N-, RS-).
Lead	Aryllead(IV)tricarboxylates	Asymmetrical biaryl	88%	108	Preferable to use highly methylated aromatic rings.
Silver	Alkylsilver	R-1,3,5-trinitrobenzene	55%	109	Organosilver compounds have low thermal stability
Copper	Arylcopper + Cu(I) [illegible]sulphonate.	Symmetrical biaryl	100%	110	———
Thallium	a)ArMgBr + Tl(I)Br	Symmetrical biaryl	high	111	Aromatic substrate must be unsubstituted in the ortho position.
		Asymmetrical biaryl	50%		
	b)Tl(II)trifluoroacetate	Symmetrical biaryl	80%	112	Substrates with powerful electron-withdrawing groups (-COOR,-CN,-NO_2) do not couple.
				113	
Mercury	Ar_2Hg(II) salts + Cu + catalytic amt. of $PdCl_2$	Symmetrical biaryl	up to 95%	114	Acidic functional groups (e.g. -OH,-COOH) inhibit coupling. Bulky ortho substituents cause yields to drop below 50%.
Nickel	Aryl halide + Ni(0) complex	Symmetrical biaryl	70-90%	115	Acidic functional groups and ortho substituents disfavour coupling.
				116	

(70% pure) 2-thienylcopper with 4-iodonitrobenzene to give 70% of coupled product (8)

i.e.



(25)

(8)

Thus, the Corey- Posner reaction was in effect an extension of the Ullmann reaction.

From this brief review of the literature one finds that research into the field is far from complete and much could be gained from studying such reactions more fully.

CHAPTER 2

2.1 Total Product Analysis of the Reaction.

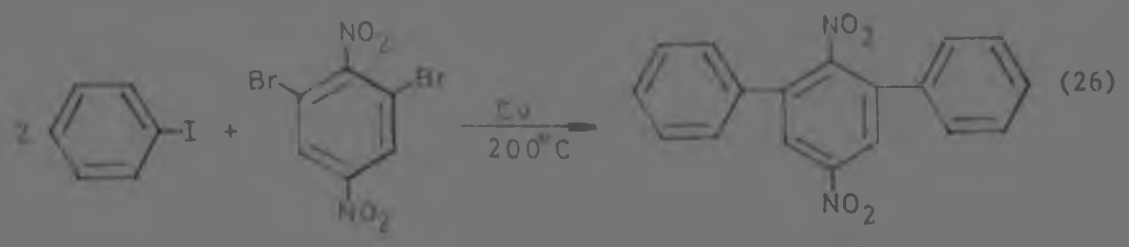
When one delves into the literature on organolithium reactions, one soon becomes aware of the fact that all the products of a reaction were seldom examined. Each researcher did a reaction with some objective in mind — normally, to determine the degree and position of metallation or, less often, the amount of alkylation that had occurred, and only those products from the reaction were studied. If, by chance, some by-product were identified, mention was made of it in passing. Generally, though, up to fifty percent of reaction products could be left unidentified. Nugent[58] and co-workers were one of the few groups to undertake a thorough materials balance of a reaction and that, as mentioned previously, was of a reaction involving peroxides and so the results are not generally applicable to organolithium reactions.

Thus it was realized that a full analysis of all the products of the reactions was essential.

The first reaction studied in depth was between 2,4,6-tribromophenol and two equivalents of methyllithium for twenty-two hours in refluxing diethyl ether. The reaction mixture was then cooled in ice and quenched with aqueous acid. 2,4,6-Tribromophenol and methyllithium were chosen as the reagents so that the products of the reaction would then be easily identifiable and characterized. The results are given in Table II.

These results were indeed interesting. Not only could a halogen be replaced by the alkyl group in the overall reaction but also by an aryl group and the latter reaction seemed as facile as the former. Biaryl products had been reported from organolithium reactions before.[117,52] The triaryl species are not entirely new either. A triaryl species (11) had been obtained from an Ullmann biaryl synthesis when a species involving TWO reactive halogens had been employed[118] (although the na-

ture of the substituents here was very different.)



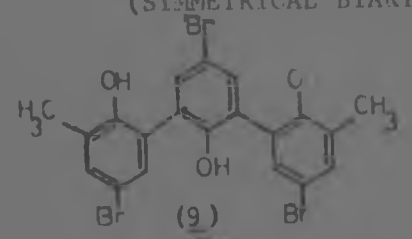
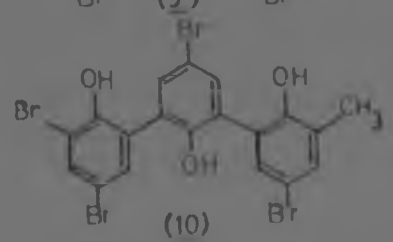
(26)

(11)

We then studied a series of reactions between 2,4,6-tribromophenol and methyllithium. The temperature, reaction times and mole ratios of

TABLE II

Products from the reaction between methyllithium and tribromophenol.

COMPOUND	% YIELD[a]
2,4-dibromophenol (DBP)	4,7
2,4-dibromo-6-methylphenol (DBMP)	0,5
4-bromo-2,6-dimethylphenol (BDMP)	4,5
5,5'-dibromo-3,3'-dimethyl-2,2'-dihydroxybiphenyl (SYMMETRICAL BIARYL)  (9)	29,0
(SYMMETRICAL TRIARYL)	29,5
 (10) (UNSYMMETRICAL TRIARYL)	20,0
TOTAL	88,2
PERCENTAGE METHYLATION	65,0
PERCENTAGE ARYLATION	48,0

(a. Percentages are based on the amount of starting material consumed. i.e. 30% biaryl implies 30% starting material consumed in production of that compound although only 1[illegible] coupling occurred.)

the two reactants were varied to determine the effects these factors had on the product distribution. Table III gives a summary of these findings.

Certain trends can be seen.

(i) In accordance with Gilman's findings,[3] optimum yields of the monomers are obtained at low temperatures and very short reaction times. As the reaction time is extended these monomers (with the exception of 4-bromo-2,6-dimethylphenol) are consumed in the production of biaryl and triaryl compounds which then become the major products of the reaction.

(ii) Although the percentages of biaryl and triaryl products outweigh those of the monomers, alkylation always predominates over arylation.

(iii) As found by Gilman,[34] methyllithium is of no value in the lithiation reactions as no conditions produce greater than 25% of 2,4-dibromophenol, the product from quenching 2,4-dibromo-6-lithiolithiumphenolate with aqueous acid. Most of the dibromophenol is consumed in the numerous side reactions.

The incorporation of the alkyl group into the products is not peculiar to methyllithium alone.

When 2,4,6-tribromophenol was added to 2 moles of phenyllithium and refluxed at 37°C for 21 hours, 25% of 2,4-dibromophenol was obtained.[119] However, when the reaction time was extended to 71 hours and 3 moles of phenyllithium were employed, the major product of the reaction (35%) was 4-bromo-2-hydroxybiphenyl.[119] When the reaction was repeated with 4 equivalents of phenyllithium and the reaction time extended to 95 hours, the major product (31%) was again 4-bromo-2-hydroxybiphenyl i.e. exchange of the para bromine by lithium did not occur.

When 5 equivalents of n-butyllithium were refluxed with 1 equivalent of 2,4,6-tribromophenol in diethyl ether for 40 hours, 27% of 2-butylphenol was obtained. It is significant that in this case the bromine para to the hydroxyl group was also exchanged. The ortho bromine atoms are generally far more reactive in these cases than those para to

TABLE III

MOLES CH_3Li	TIME (hrs)	TEMP. (^oC)	TBP	DBP	DBMP	BMP	BDMP	SYM. BIARYL	UNSYM BIARYL	SYM. TRIARYL	UNSYM. TRIARYL	% METHYLATION	% ARYLATION
1	7	25	100[a]	0	0	0	0	0	0	0	0		
1	7	25	95[b]	5	0	0	0	0	0	0	0		
1	7	25	50[c]	50	0	0	0	( )	( )	( )	( )		
2	1/6	0	80	10	0	0	0	( )	( )	0	0		
2	1	0	4	2[illegible]	7	0	0	14	50	( )	( )		
2	2	0		25	6	0	0	(✓)	(✓)	( )[e]	( )		
2	5	25	0	21	15	10	0	(✓)	(✓)	( )	( )		
2	5	37	0	7	2	1	4	30	9	15	11	60	36
2	22	37	0	5	1	0	5	29	0	30	20	65	48
3	5	37	0	0	2	20	6	31	5	14	2	7[illegible]	28
3	18	37	0	3	6	13	10	31	0	22	0	72	30
3	23	37	0	0	0	7	10	22	0	30	0	68	30

P.T.O. for explanation of table.

Explanation of Table III

a) TBP solution added to methyllithium within 10 seconds.

b) TBP solution added to methyllithium over 5 minutes.

c) TBP solution added gradually drop by drop over 25 minutes to the methyllithium.

d) (✓) implies that the compound was present but the exact amount was never determined.

e) ( ) implies that this product was not investigated.

TBP = 2,4,6-tribromophenol

DBP = 2,4-dibromophenol

DBMP = 2,4-dibromo-6-methylphenol

BMP = 4-bromo-2-methylphenol

BDMP = 4-bromo-2,6-dimethylphenol.

SYMMETRICAL BIARYL = 5,5'-dibromo-3,3'-dimethyl-2,2'-dihydroxybiphenyl

UNSYMMETRICAL BIARYL = 2,2'-dihydroxy-3-methyl-3',5,5'-tribromobiphenyl

SYMMETRICAL TRIARYL = 3,3"-dimethyl-5,5',5"-tribromo-2,2',2"-trihydroxy-m-terphenyl.

UNSYMMETRICAL TRIARYL = 3"-methyl-2,2',2"-trihydroxy-3,5,5',5"-tetra-bromo-m-terphenyl.

the hydroxyl group. However, the fact that alkylation occurs ortho to the hydroxyl group only suggests some kind of assist from the hydroxyl group during the reaction as the ortho position is more sterically hindered than the para position.

This type of alkylation has been found before. Porzi and Concilio[120] found that when 2,7-dibromonaphthalene was reacted in THF at -35°C with one equivalent of n-butyllithium, 2-bromo-7-butylnaphthalene was obtained quite rapidly and 2,7-dibutylnaphthalene appeared after 15 minutes. (The yields were not quoted.) However, when the reaction was repeated in refluxing diethyl ether only 2-bromonaphthalene (91%) and naphthalene (3%) were obtained. This favouring of alkylation in THF is well known.[121]

We later showed that n-butyllithium could replace a bromine para to hydroxyl group even when there were ortho halogens present. The reaction between 2,4,6-tribromophenol and 2 equivalents of n-butyllithium at 25°C for one hour followed by 5 hours at reflux temperature gave 18% of 2,4-dibromophenol and 4% of 2,6-dibromophenol as well as small amounts of both 2- and 4-bromophenol as products.

These results are in contrast to those of Gilman[122] who found that when 2,4,6-tribromoanisole was treated with excess n-butyllithium only the two ortho bromine atoms were replaced.

2.2 The Effect of the Position of the Halogen on the Course of the Reaction.

While metal-halogen exchange is generally far more facile than metal-hydrogen exchange, the latter reaction will occur if no halogen is suitably placed ortho to a substituent bearing a lone pair of electrons.

For example, when 2-bromophenol was reacted with 2 equivalents of methyllithium in refluxing diethyl ether, 80% phenol, 16% of 2-methylphenol, some starting material and a small amount of 2,2'-dihydroxybiphenyl were obtained. An identical reaction with 4-bromophenol seemed unsuccessful even when left for 72 hours. However, when the

reaction was repeated and quenched with deuterium oxide at least 19% of the total reaction product was 2-deutero-4-bromophenol i.e. metal-hydrogen exchange ortho to the hydroxyl group had occurred in preference to metal-halogen exchange in the para position. Gilman obtained similar results with 3- and 4-bromoanisole.[123]

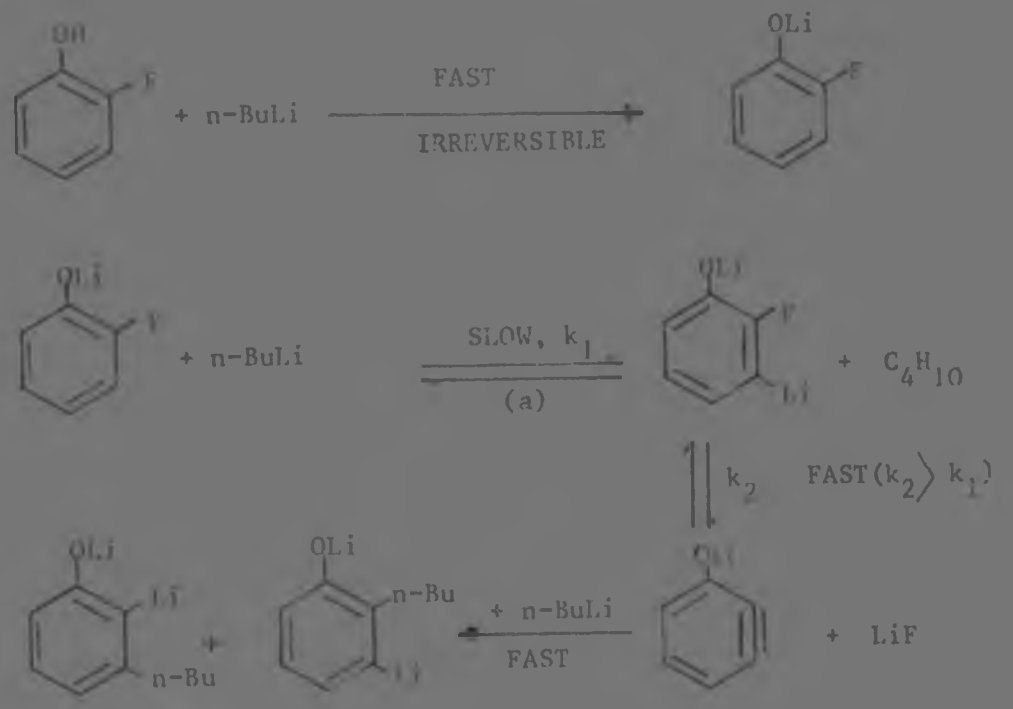
If the positions ortho to the hydroxyl group were blocked as, for example, in the case of 4-bromo-2,6-dimethylphenol, refluxing for 48 hours in diethyl ether with 3 equivalents of methyllithium yielded only a minute amount of 2,6-dimethylphenol. Treatment of the same starting material with only 2 equivalents of n-butyllithium for 5 hours caused 50% of the para bromine atom to be replaced. Thus, n-butyllithium is a strong enough base to remove a bromine atom without the assistance of an ortho substituent bearing lone pairs of electrons for co-ordination to the lithium atom, but methyllithium is not. (The two methyl groups already present in the substrate significantly deactivate the aromatic ring towards metal-halogen exchange.[42])

2.3 The Effect of the Type of Halogen on the Course of the Reaction.

After studying the reactions of various bromophenols with n-butyl-, phenyl- and methyllithium, we turned our attention to the other halogenophenols to determine the effect of the type of halogen on the course of the reaction.

The first reaction undertaken was that between 2-fluorophenol and n-butyllithium. As mentioned previously, the fluorine atom does not undergo metal-halogen exchange.[124,125] In fact, the fluorine cation is not thought to exist.[126] Instead the fluorine, by its particularly strong inductive effect, labilizes the C-H bond ortho to itself and metallation occurs.[32] This proton abstraction is thought to be the rate-determining step for the aryne formation process.[127] (See Scheme I) This is generally followed by the loss of lithium fluoride from the aromatic nucleus to form an aryne intermediate. Only at temperatures below $-70^{o}C$ can loss of LiF be prevented.[128]

SCHEME I



a) Only when the halogen is fluorine is this equilibrium established. With the other halogens elimination of LiX is faster than the metallation step.[129]

We reacted 2-fluorophenol with 3 equivalents of n-butyllithium for 24 hours at 40°C and obtained 48% of 2-butylphenol and 11% of 3-butylphenol. When only 2 equivalents of n-butyllithium were used, some starting material (26%) was recovered from the reaction. Thus, it is apparent that the subsequent addition of n-butyllithium to the benzyne intermediate must be faster than the initial metallation reaction.

The mixture of products from the reaction is expected. The intermediate aryne is a soft acid[130] and the nucleophilic portion (electron donor) of RLi attacks the aryne first. A substituent (Y) already present on the ring stabilizes one of two possible transition states in the nucleophilic addition.[131]



If Y is inductively electron-withdrawing it will preferentially stabilize the developing negative charge in the ortho position and so favour meta attack by the nucleophile. The conjugative effect generally does not have a marked effect on the preferred position of attack except in the case where Y is O when the powerful mesomeric effect of this substituent leads to 85 - 90% of ortho attack by the nucleophile and only 10 - 15% meta attack.[100] Our results are indicative of 18% meta and 82% ortho attack.

When 2-fluorophenol was reacted with 3 equivalents of methyllithium at 37°C for 24 hours, only starting material was recovered from the reaction. Methyllithium is obviously not a strong enough base to abstract a hydrogen cation from the aromatic nucleus.

When phenyllithium was employed in the reaction with 2-fluorophenol, 17% 2-phenylphenol and 7% 3-phenylphenol were obtained i.e. 71% ortho, 29% meta attack; 24% overall reaction.

With n-butyllithium we obtained 82% ortho, 18% meta attack 58% overall reaction. Thus the ratio of the isomers must also be dependent on the nature of the attacking nucleophile since the aryne intermediates in the above two reactions are presumably identical. It seems that the stronger the nucleophile, the less selective is the addition.[129] However, the reaction occurred to a greater extent with the stronger base, n-butyllithium (58%), than with phenyllithium (only 24%).

The effect of replacing the bromine para to the hydroxyl group in 2,4,6-tribromophenol with fluorine or chlorine will be discussed in section 2.6.1.

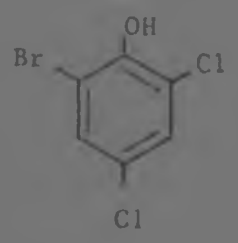
When a bromine atom ortho to the hydroxyl group in 2,4,6-tribromophenol was replaced by fluorine (as in the case of 2,4-dibromo-6-fluorophenol) and this was reacted with two equivalents of methyllithium in refluxing diethyl ether for 24 hours, the expected reaction products from bromine-lithium exchange plus 4% of 2,4-dibromo-5,6-dimethylphenol and 2% of 4-bromo-2,3,6-trimethylphenol were obtained.

It had been hoped to include 2,4-difluoro-6-bromophenol in this

series but several attempts to prepare the compound from 2,4-difluoroaniline were unsuccessful.

When two bromine atoms, one ortho and one para to the hydroxyl group, were replaced by chlorine, the products from the reaction were not very different from those obtained with 2,4,6-tribromophenol.

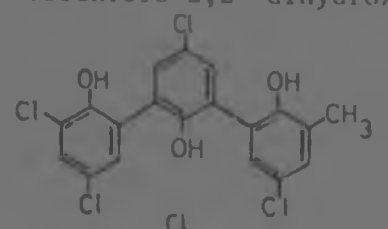
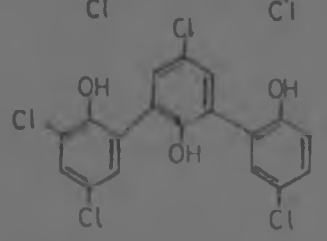
For the reaction



$$+ \; 3CH_3Li \xrightarrow[37^{\circ}C,\ 1hr.]{(CH_3CH_2)_2O} \text{PRODUCTS} \qquad (27)$$

the products obtained are detailed in Table IV.[1)]

TABLE IV

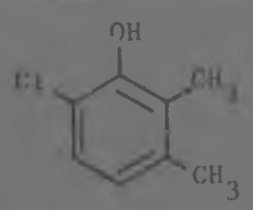
COMPOUND		% YIELD
2,4-dichlorophenol		8,0
2,4-dichloro-6-methylphenol		9,5
4-chloro-2-methylphenol		11,2
3-methyl-3',5,5'-trichloro-2,2'-dihydroxybiphenyl		31,7
3,5,5'-trichloro-2,2'-dihydroxybiphenyl		10,6
	(12)	8,3
	(13)	1,8
	TOTAL	81,1

1) A preliminary study of this reaction by P.Bert produced similar results but the triaryl species were not examined by him.[13]

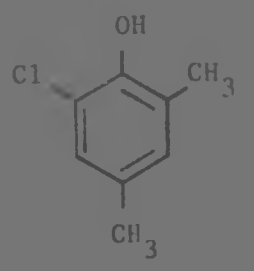
PERCENTAGE ALKYLATION	38,4
PERCENTAGE ARYLATION	28,0

These results are similar to those in Table II for the identical reaction with 2,4,6-tribromophenol for 5 hours. The decrease in the percentage of biaryl and triaryl products with the dichloro-compound is most likely due to the fact that the reaction was left for a shorter period of time. The difference in the type of dimers is expected owing to the fact that the replacement of chlorine on the ring by lithium is more difficult than the replacement of bromine. (The strength of the C-Cl bond is 340 kJ/mole, while that of the C-Br bond is 285 kJ/mole) Chlorine does not generally undergo metal-halogen exchange but, analogously to fluorine, causes metallation ortho to itself followed by aryne formation on the loss of lithium chloride from the compound. In this case where only one mole of methyllithium was available for reaction on the ring, it reacted preferentially with the bromine.

When 2,4,6-trichlorophenol was reacted with 3 equivalents of methyllithium for 18 hours at 37°C, 48,7% of the total product consisted of the two monomers (14) and (15) in the ratio 1:2,1:1.[132]



(14)



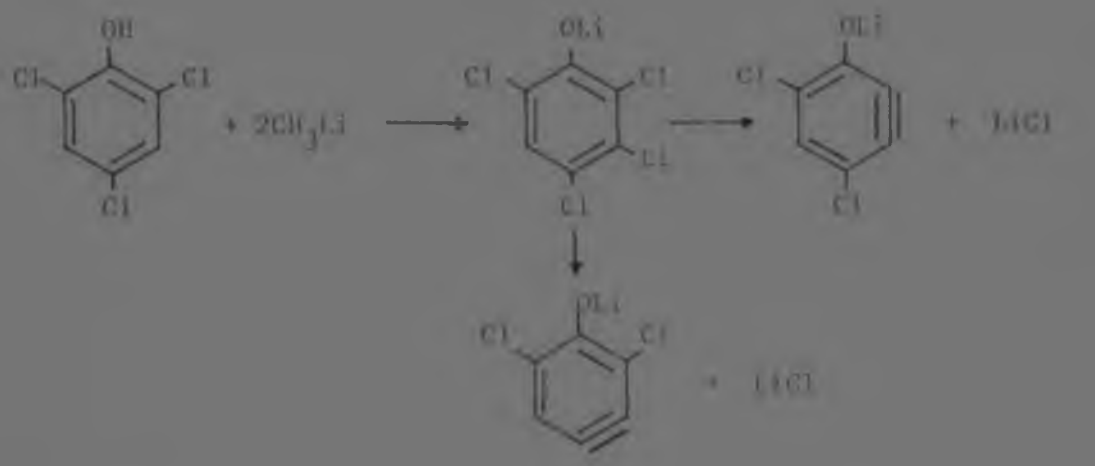
(15)

The remainder of the products were biaryl and triaryl species The monomers probably arose via the reaction sequence given in Scheme II.

Thus, one sees that the chloro- and fluoro-derivatives give the same basic type of products as the bromo-compounds viz. monomers, biaryl and triaryl species but, owing to the fact that the chloro- and fluoro-compounds can react via an aryne intermediate, a greater variety of products is possible.

A reaction between 2,4,6-triiodophenol and 2 equivalents of methyl-

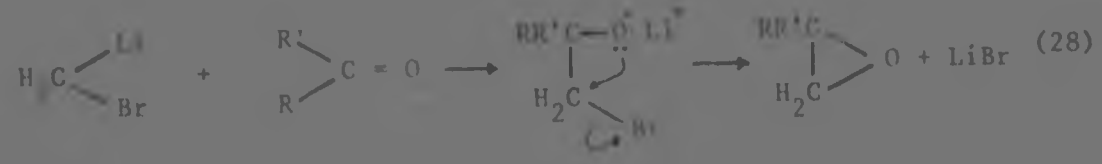
SCHEME II



lithium yielded 11% of 4-iodo-2-methylphenol, 33% of 5,5'-diiodo-3,3'-dimethyl-2,2'-dihydroxybiphenyl and 24% of 5,5'-diiodo-2,2'-dihydroxy-3-methylbiphenyl. Again, the products and yields are analogous to those from reactions between 2,4,6-tribromophenol and methyllithium.

2.4 An Epoxide as a Possible Intermediate in the Alkylation Reaction.

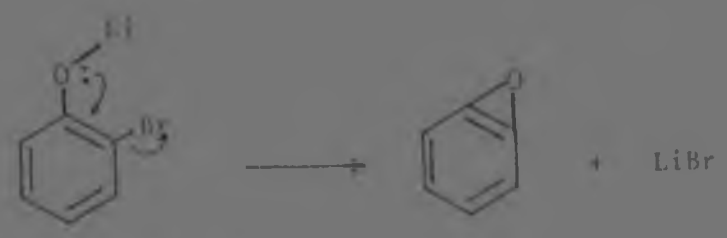
A new general method for obtaining an epoxide was advanced by Cainelli in 1969[11] and again in 1972.[13] The following mechanism was suggested:



(28)

Thus it was felt that a possible explanation for the almost exclusive ortho reactivity of aromatic species containing a substituent with lone pairs of electrons could be due to the intermediacy of an aryne-oxide derivative or its electronic equivalent.

i.e.

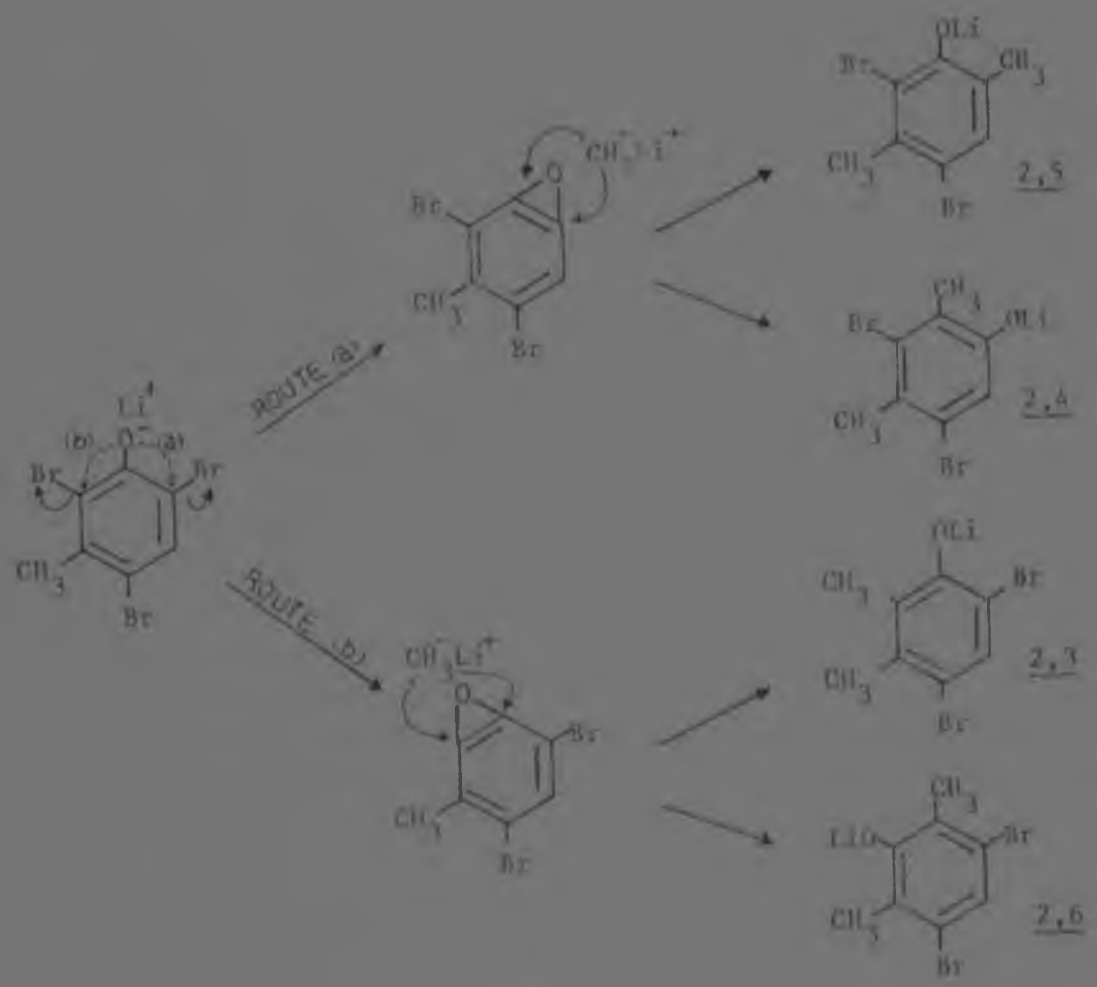


Further attack by R----Li to open the epoxide would give the alkylated products obtained in the reactions of aryl halides with alkyllithium compounds.

To determine whether an epoxide was involved in the reaction sequence between aryl halides and organolithium compounds the following reaction was undertaken:
2,4,6-Tribromo-3-methylphenol was refluxed with 2 equivalents of methyllithium in diethyl ether for 2 hours before quenching with aqueous acid. The reagents were so chosen that, again, any alkylated products would be known and identifiable compounds (xylenols). The methyl group in the 2,4,6-tribromo-3-methylphenol would act as a marker to indicate whether any migration of the hydroxyl group (leading to ciné substitution) had occurred since the epoxide, once formed, may be opened from either side when attacked by MeLi (See Scheme III). The possible products from the reaction would be brominated 2,3- and 2,5-dimethylphenol from direct substitution and brominated 2,4- and 2,6-dimethylphenol from ciné substitution.

The products from the reaction were dehalogenated over palladium hydroxide on calcium carbonate[135] and analysed by gas chromatography.

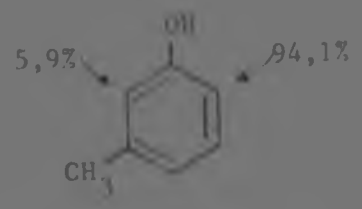
SCHEME III



However, no operating conditions could be found under which 2,4- and 2,5-dimethylphenol could be separated. Various techniques, namely silylation,[136] acetylation, nitration[137] and benzoylation of the dimethylphenols proved unsuccessful with the 2,4- and 2,5- derivatives always appearing as single peaks on all the gas chromatographic traces. It was thus decided to re-brominate the dehalogenated product as 2,5-dimethylphenol would yield a dibrominated product whereas 2,4-dimethylphenol would be monobrominated. The two brominated compounds were readily separated on the gas chromatography column.

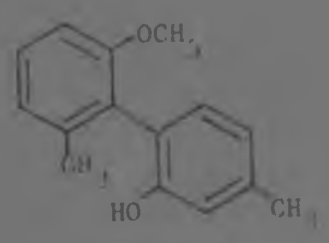
Co-injection of the brominated authentic dimethylphenols with the re-halogenated reaction material showed that the major monomeric product of the reaction was 2,5-dimethylphenol with a small amount of the 2,3-isomer formed. Neither 2,4- nor 2,6-dimethylphenol was obtained al-

though amounts as small as 1/1000th per cent of the reaction products were detectable under the conditions employed. The reaction was repeated with the authentic dimethylphenols and the dehalogenated product of the reaction being chlorinated by a novel simple method (see experimental section.) These results confirmed the above findings. Of the two dimethylphenols obtained from the reaction (about 40% of the total reaction product) the distribution was as shown

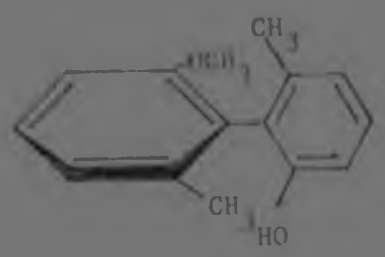


by measurement of the relative areas under the peaks on the gas chromatography trace (assuming equal flame ionization detection (FID) responses for the two dimethylphenols)

A similar distribution of isomers was obtained when 2-lithio-3-methylanisole was refluxed in diethyl ether for 15 hours with 2,4,6-tribromo-3-methylphenol. Thirty-three per cent of (16) and 3% of the highly hindered species (17) in which the two aromatic rings are perpendicular to each other were obtained after dehalogenation.[119]

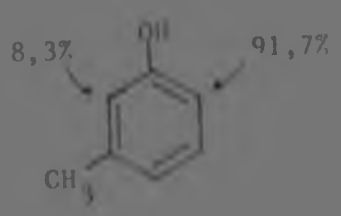


(16)



(17)

i.e.



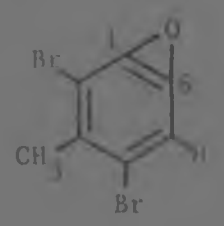
From the results, then, it seems unlikely that epoxide formation occurs during the reaction sequence unless the epoxide opens only from that side from which it was formed. Johnson[138] found that saturated epoxides were opened in good yield by lithiumdimethylcuprate in such a way that the methyl group was introduced at the least hindered carbon of the epoxide.



$$+ (CH_3)_2CuLi \longrightarrow \longrightarrow CH_3CH_2\underset{\underset{OH}{|}}{C}HCH_2CH_3 \qquad (88\%)$$

(No mention of the alternate-attack product is made)

In (18), an unsaturated epoxide, one could argue that C-1 is more hindered than C-6, leading to exclusive attack at C-6 by CH_3.



(18)

2.5 Verification of the Route of Alkylation.

An alternate mechanism for the alkylation reaction could be that proposed by Wakefield[51]

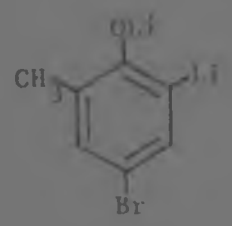
$$RLi + ArX \rightleftharpoons ArLi + RX \qquad (8)$$

$$RX + ArLi \longrightarrow ArR + LiX \qquad (9)$$

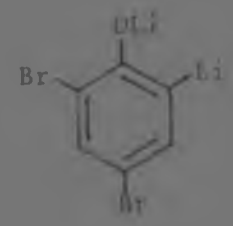
i.e. metal-halogen exchange followed by replacement of the lithium by the alkyl group in an electrophilic aromatic substitution reaction.

Treatment of 2,4,6-tribromophenol with 3 equivalents of methyllithium yielded as one of the products of the reaction (after quenching with water) 4-bromo-2-methylphenol. When the reaction was repeated and quenched with D_2O, incorporation of the deuterium atom ortho to

the hydroxyl group occurred indicating that (19) is an intermediate in the reaction.



(19)



(20)

Furthermore, when species (20) was generated from 2,4,6-tribromophenol by treatment with 2 equivalents of n-butyllithium (a good lithiating reagent but known to be sluggish in the alkylation reaction[34]) and then treated with increasing amounts of methyl iodide (the methyl group now a carbocation source) increasing amounts of methylated product, (viz. 2,4-dibromo-6-methylphenol) were obtained. See Table V.

TABLE V

MOLES TBP	MOLES n-BuLi	MOLES CH_3I	%DBP[a]	%DBMP	MOLAR RATIO DBP : DBMP
1	2	1	85	15	1 : 0,168
1	2	7	47	53	1 : 1,07
1	2	19	14	86[b]	1 : 5,88

(TBP = 2,4,6-tribromophenol; DBP = 2,4-dibromophenol; DBMP = 2,4-dibromo-6-methylphenol)

a) The percentages are calculated in terms of the area under the peak of the g.c. trace due to that compound relative to the area under both peaks. The molar ratios are calculated taking into account the relative FID responses of the two compounds.

b) Reaction products were separated and purified to give 6% of 2,4-dibromophenol and 22% of 2,4-dibromo-6-methylphenol in terms of recovered pure products.

These results strongly indicate that the reaction is, indeed, a two-step process in which metal-halogen exchange precedes replacement

of the lithium in the aryllithium intermediate by a positively charged alkyl group.

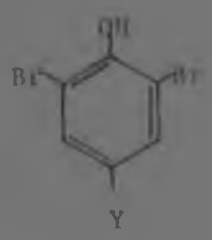
2.6 The Effect of Varying the Substituent on the Ring.

A question we came to ask ourselves was whether the formation of the biaryls and triaryls was peculiar to phenols or whether other species reacted in like fashion. Scant mention of biaryls from reaction of an aryl halide with an organolithium compound appears in the literature. Heaney[117] had found that treatment of 1,2-diiodobenzene with n-butyllithium gave 2,2'-diiodobiphenyl and Gilman[32] had reported that treatment of 1,2-dibromobenzene with n-butyllithium in THF gave up to 74% of the 2,2'-dibromobiphenyl but that 'there was a strong inference that the solvent may play an important role in the reaction' as no coupled products were isolated in diethyl ether. Other examples of production of biaryls[120] were shown to proceed via a benzyne intermediate which was captured by furan to give a Diels-Alder adduct. We also wished to know whether the yield of biaryl product could be increased by altering the substituents on the aromatic ring.

Two series of reactions were undertaken.

2.6.1 The Effect of Varying Y in 2,6-dibromo-4-Y-phenol.

First Y in (21) was varied in a series of reactions to determine the effect this had on the product distribution. Table VI summarizes the results of reaction (29) for Y = CH_3,H,Br,Cl,F.



+ 3 CH_3Li $\xrightarrow[37^{\circ}C,\ 5hrs.]{(Et)_2O}$ PRODUCTS (29)

(21)

TABLE VI

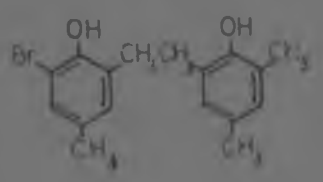
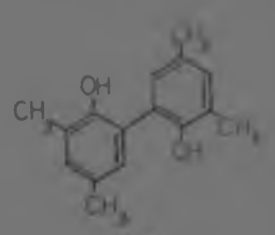
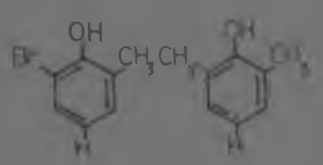
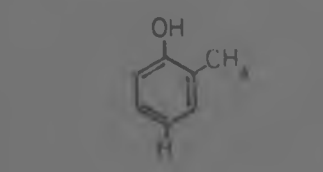
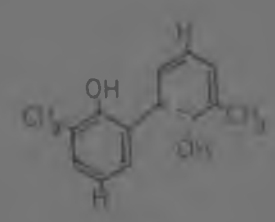
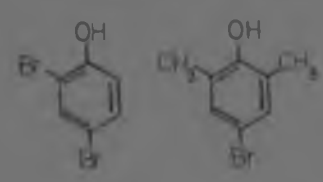
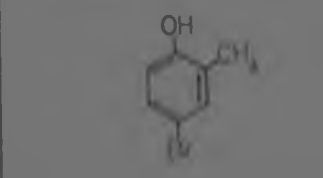
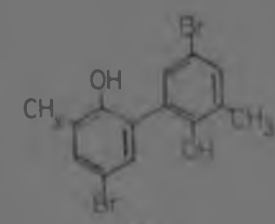
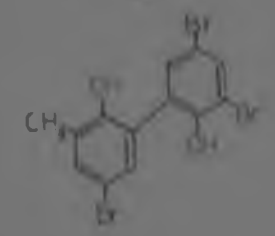
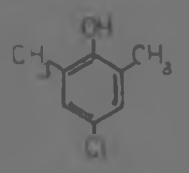
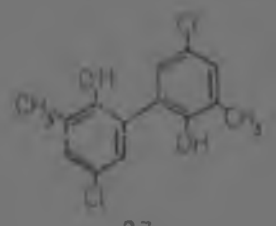
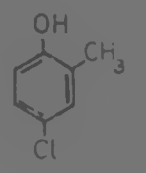
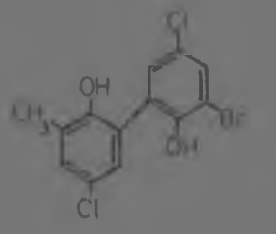
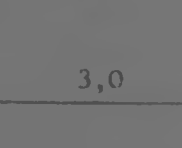
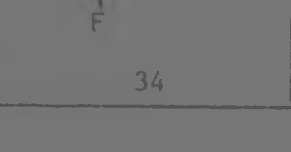
X	MONOARYL PRODUCTS %	BIARYL PRODUCTS %	HIGHER MW prods %	%Li-CH_3 exchange.	%Li-Ar
CH_3	 11,7 8,6 14,5	 42 13	< 10	~95	~30
H	 8,5 5,1  7,4	 44	~35	~90	~45
Br	 1,0 7,0  10,0	 30  10	~42	~80	~50

TABLE VI cont.

Y	MONOARYL PRODUCTS %	BIARYL PRODUCTS %	HIGHER MW Prods %	%Li-CH_3 exchange.	%Li-Ar exchange.
Cl	 5,2	 27	~45	~78	~55
	 12,1	 10			
F	 3,0	 34	~60	~70	~60

(All reactions were duplicated and the percentages quoted are the average of the two results which differed by no more than ±2%. The percentage of triaryl product was estimated as the symmetrical and unsymmetrical species could not always be fully separated.)

From a study of Table VI it appears that as the electron-donating ability of Y increases so the percentage of lithium-methyl exchange increases, and the percentage of lithium -aryl exchange decreases and more monomeric material is obtain d. It seems strange, though, that the product distributions for Y = chlorine or bromine are fairly similar while that for Y = fluorine is so markedly different with virtually no monomeric products being formed.

The Hammett σ values[139] and electronegativities for the halogens are given in Table VII.

TABLE VII

HALOGEN	$\sigma_m(\sigma_I)$	σ_p	$\sigma_p-\sigma_m(\sigma_R)$	ELECTRONEGATIVITY.
F	0,34	0,06	-0,28	4,10[140] (3,98)[141]
Cl	0,37	0,23	-0,14	2,83 (3,16)
Br	0,39	0,23	-0,16	2,74 (2,96)
(I)	0,35	0,28	-0,07	2,21 (2,66)

The resonance effect (R) of a substituent involves the interaction of the orbitals of the substituent which are in the same plane as the electron orbitals of the ring. This interaction affects alternative positions around the ring relative to the point of attachment of the substituent giving rise to it. i.e. ortho and para positions only. Thus σ_m is taken to be an approximate measure of the inductive effect (I) only of a substituent and σ_p is the sum of both the resonance and inductive effects.

$$\underline{i.e.}\ \sigma_p = \sigma_I + \sigma_R$$

$$= \sigma_m + \sigma_R \quad \text{since } \sigma_m \approx \sigma_I$$

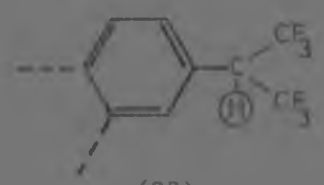
$$\therefore \sigma_R = \sigma_p - \sigma_m$$ [139]

A study of the σ_m values in Table VII shows that they are not significantly different for the three halogens under discussion. This is rather surprising when one considers that the inductive effect originates in the polarization of the electrons of the σ bond due to the effective electron attracting ability of the substituent and should in this case be proportional to the electronegativities of the halogens. Thus, induction alone could not be responsible for the vastly different results obtained even though a kinetic study of the rate of metallation of aryl compounds with n-butyllithium by Shirley[91] suggested that the reaction was controlled by the inductive effect of the ring substituents.

The resonance values, σ_p, of the halogens are significantly different with that of fluorine far greater than any other halogen. In fact, the σ_p value of fluorine is fairly close to that of hydrogen (taken to be zero) showing that for fluorine the inductive and resonance effects al-

most cancel each other. Thus, 2,6-dibromophenol (Y=H) was included in the series. One would expect to obtain similar proportions of monomer and biaryl products for Y=H and Y=F. As can be seen from Table VI, the results were very different.

A search through the literature revealed that when Klabunde[142] studied the relative rate of ionization of some meta and para substituted 2-phenyl-1,3-hexafluoropropanes (22) to form the carbanions, he obtained the following results:-



(22)

TABLE VIII

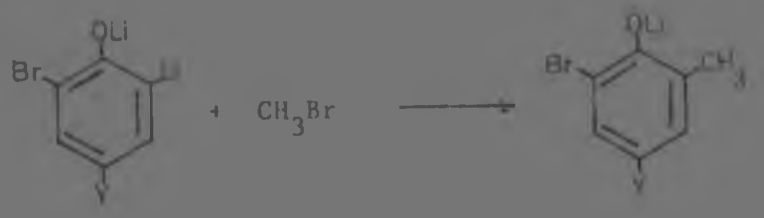
SUBSTITUENT	RELATIVE RATE	
	meta	para
H	1,0	1,0
F	18,5	1,57
Cl	27,9	10,9
Br	47,1	16,2
I	33,7	19,1

The relative rates in the meta position are as expected for the inductive effect of the four halogens but the rate for fluorine in the para position is markedly different from those for bromine and chlorine and is, again, close to that for hydrogen.

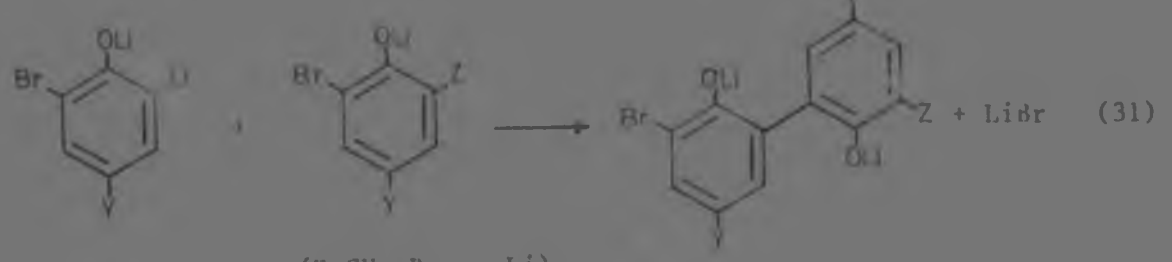
Klabunde suggested that the destabilizing mesomeric back donation of the electron density from the substituent was important in the para series as this would explain the relative rates of ionization of the para substituted compounds and the large differences between the meta and para series.

Accepting that the inductive stabilization is more effective in the meta position than in the para, their results showed that the inductive effect was the overriding factor in the stabilization of the carbanions.[143]

The two competing reactions for the formation of the monomer and the biaryl product are (30) and (31).



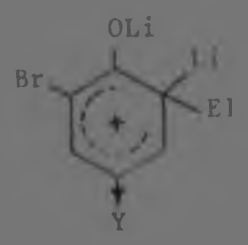
(30)



+ LiBr (31)

(Z=CH_3,Br or Li)

If one regards these two reactions as electrophilic substitution on the aromatic ring with the Li^+ as a good leaving group, then as the electron-withdrawing power of Y increases, greater stabilization of the intermediate (23) will occur



(El = electrophile)

(23)

but this will be equal in both reaction (30) and (31). It is only when one considers the reaction in terms of Pearson's Hard-Soft Acid Base Principle[144,145,146] that one finds an explanation for the results. (See Table IX).

In reactions (30) and (31) there is direct competition between CH_3^+ and Ar^+ for Ar^-. Any factor that increases the hardness of Ar^+ would favour its reaction with Ar^-. It is known[147] that replacement of a hydrogen in an organic species by a more electronegative group e.g.Br, F, makes the acid harder as it increases the relative positive charge on

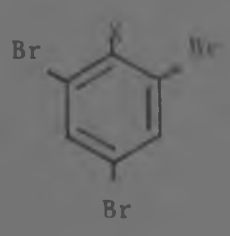
TABLE IX

ACIDS	
CH_3^+	softest organic acid
Ar^+	soft
Li^+	hard
BASES	
Br^-	borderline
Ar^-	soft, but harder than CH_3^- 1)

the carbocation. As one proceeds down Table VI from Y = CH_3 to I, Ar^+ becomes increasingly hard and thus improves its chances of reaction with Ar^-.

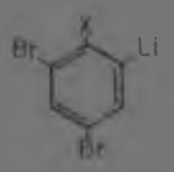
2.6.2 The Effect of Varying X in 2,4,6-tribromo-1-X-benzene.

Table X is a summary of the products from the following set of reactions (X = Br,H,CH_3,OCH_3,OH)



CH_3Li $\xrightarrow[25°C,5\ hrs.]{(Et)_2O}$ PRODUCTS. (32)

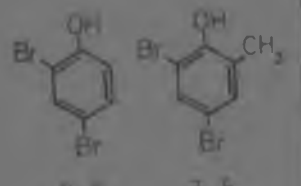
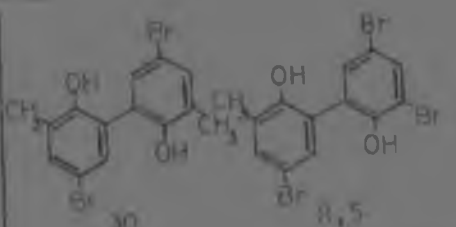
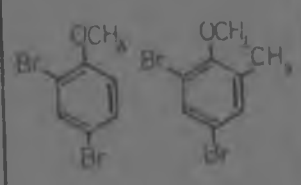
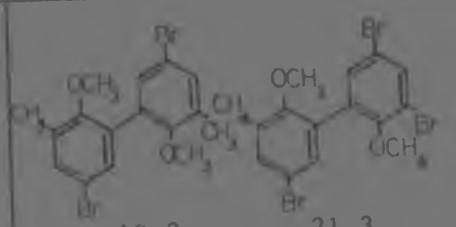
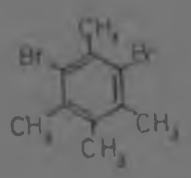
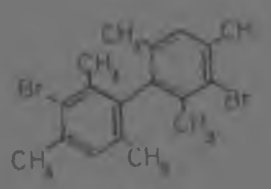
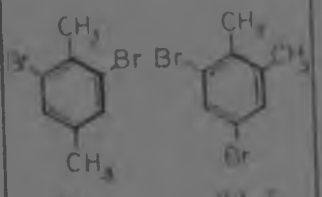
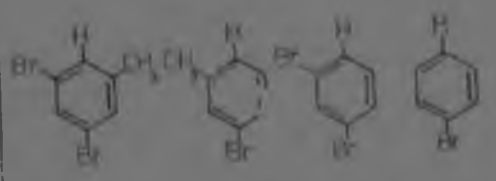
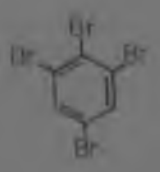
On reviewing the results initially it seemed that as the electron density on the ring increased in the order H < CH_3 < $3xCH_3$ < OCH_3 < OH, the amount of monomer decreased and the percentage of biaryl and higher molecular weight species increased i.e. as the electron density on the ring increased replacement of the lithium atom in (24) by an aryl group became more favourable than replacement by a methyl group.



(24)

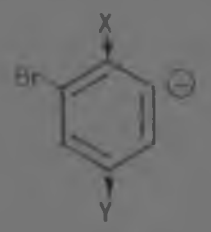
1) Since, in the reaction between CH_3Li and ArBr, the hard Li^+ rapidly replaces Br^+ to co-ordinate to Ar^- rather than to CH_3^-.

TABLE X

X	MONOMERS. %	BIARYL PRODUCTS %	HIGHER MW products
OLi	 8,5 7,5	 30 8,5	25%
OCH_3	 8,0 4,4	 10,2 21,3	37%
$1xCH_3$	 48	 15	21%
CH_3	 30 23,5	INSEPARABLE MIXTURE that glc shows to be four compounds. 5	Baseline material in pure hexane 21%
H	 52 —16— 8,0	4 compounds. <15mgs of each. 5	—
Br	 i.e. Starting material 28	Some $C_{12}H_4Br_6$, 4 other compounds, <10mgs of each. 6	Main products are high MW. Melt 300°C. e.g. 14% of MW 861! 60%

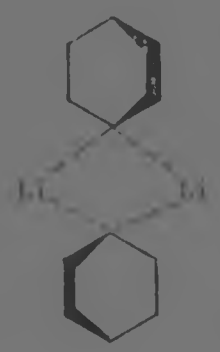
In summary then, initially it seemed that an electron-donating group ortho to the carbanionic site or an electron-withdrawing group meta to it, favoured metal-aryl exchange and enhanced biaryl and triaryl formation.

1.6.



We then turned to the literature to find the effect of substituents on other biaryl syntheses. Fanta,[105,148] on reviewing the Ullmann reaction, had found that strongly electronegative groups ortho to the halogen replaced had a powerful activating effect which was somewhat reduced in the meta and para positions. This seemed contrary to our results unless the $-OCH_3$ and -OLi groups were co-ordinated to a (further) lithium atom at the time of biaryl formation. Wakefield[40] had made the point that co-ordination of the lone pairs of electrons on a substituent would render those electrons unavailable for mesomeric back donation and leave the substituent inductively electron-withdrawing. This line of thought finally provided a clue to the mechanism of the coupling reaction.

It is well known that organolithium compounds form aggregates in solution[22] (and in the vapour phase) and that aryllithium compounds exist as dimers.[24] For example, phenyllithium exists as the dimer (25)



(25)

We now postulate that the biaryl products obtained in the reactions of aryl halides with organolithium compounds arise from dimeric reaction intermediates similar to (25). The two aryl groups, while held together in this manner, may react further if suitable atoms or groups are close enough to cause the necessary polarization of electrons leading to new

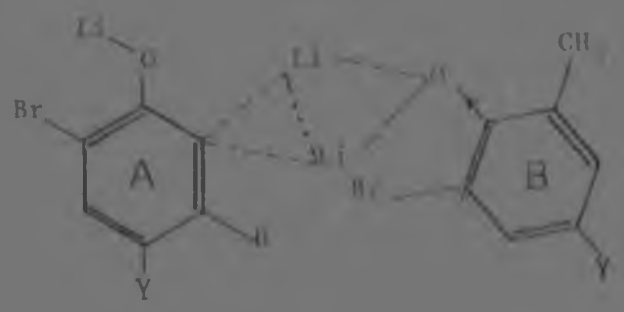
partial bond formation.

The first type of dimer we propose — called DIMER I — is one in which the lithium atoms will be bonded to a carbon atom of one aryl ring and to an atom of a substituent on the other aryl ring. This dimer is further postulated to collapse via an IONIC pathway to the biaryl product. The aryl carbanion attached to the lithium will attack a suitably placed carbocation (bonded to a halogen) on the adjacent aryl ring to form a new C-C bond with the concurrent elimination of lithium halide from the dimer. (DIMER II will be elaborated in Chapter 3.3)

The highest percentages of biaryl and triaryl products were obtained from compounds in which the substituent ortho to the bromine atom replaced possessed a lone pair of electrons or had a replaceable hydrogen.

For example, when X = OLi, dimer (26) is formulated to occur in solution where the electropositive lithium atom is attracted to the highly electronegative oxygen atom. This has a two-fold effect:-

DIMER I



(26)

(i) the mesomeric (back-donating) effect of the oxy or methoxy group on ring B is decreased and it becomes inductively electron-withdrawing[40] making C* more electropositive.

(ii) the lithium atom is brought into close enough contact with the bromine for partial Li····Br bond formation to occur. The carbon atom attached to that bromine will assume greater electrophilic character as the Br - C* bond weakens. Halogens attached to aromatic rings are not, in general, readily replaced by nucleophiles[131] and direct nucleophilic substitution of an aryl halide only occurs when a Meisenheimer-type intermediate (27) stabilized by strongly electron withdrawing groups on the

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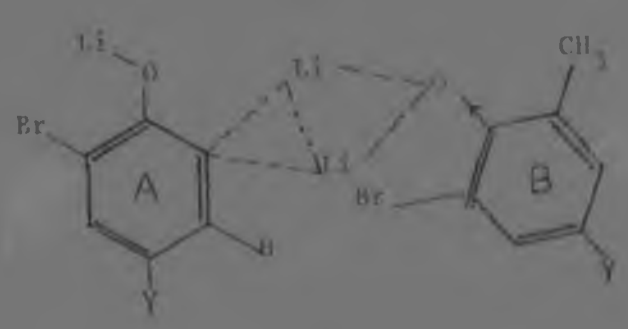

(26)

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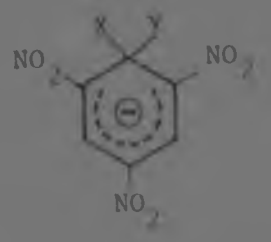
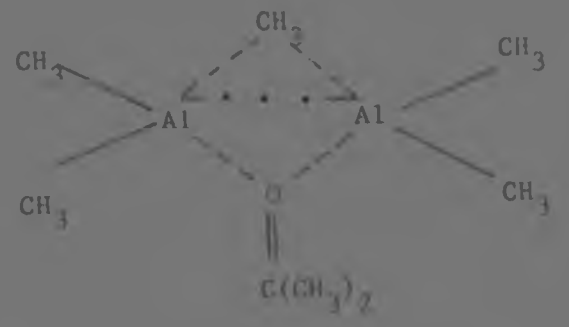


(27)

ring can be formed.[51] It is therefore highly unlikely that C^+ is still tightly bonded to the bromine when the carbanion of ring A attacks it.

This dimer is analogous to that postulated by Matteson[149] to form between $Al_2(CH_3)_6$ and acetone.



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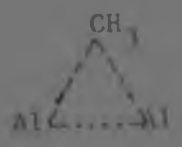


is the shorthand representation adopted by Matteson[19] for



(the) als are involved in two such bonds to carbon atoms, this is represented as



The oxygen can readily bond to two metals and the bond is quite strong[149]. Lithium has an even greater tendency to favour bridge bond-

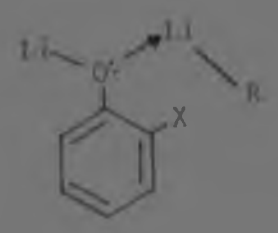
ing than aluminium or magnesium.[150] In the case of lithium, the vacant 2p orbitals will hybridise with the 2s orbitals to form four sp^3 orbitals. In the aggregates with $n \geq 4$, each lithium is always bonded to four other species.[20]

X-ray studies by Weiss[21] on the structure of metallic lithium yielded the following interatomic distances.

Li.....Li	2,3Å
Li.....C	2,6Å
C.....C	3,6Å

If a Dreiding model of (26) is constructed and the C...O distance is taken as 3,6Å (it will probably be shorter due to the O - Li bond being stronger than the C - Li bond), it is found that ring B must be out of the plane in which ring A lies as otherwise Br - H interference occurs. However, the Li - Br distance as measured is found to be 2,4Å and it becomes greater as ring B tilts further away from ring A. Thus, simple rotation around the C - O bond in ring B will bring the bromine within bonding distance of the lithium and ring B almost parallel to ring A.

The dimer (26) is different from that postulated by Gilman[41] and Shirley[39] for the initial lithiation of the aromatic ring by the organolithium compound. There the intermediate is envisaged as (3) and a mol-

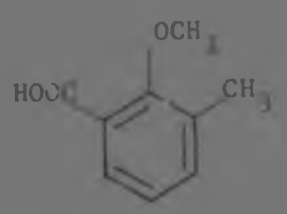


(3) (X = H,halogen)

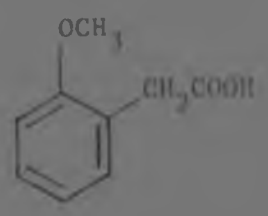
ecular model of this intermediate now shows the halogen to be closer to the carbanionic R group than the lithium so that R^- would be expected to attack the halogen and that the lithium atom could move onto the ring.

In the case of tribromomesitylene and tribromotoluene, the situation is slightly different.

Alkylaromatic compounds are metallated in the side chain (α-metallation)[91] as well as on the ring to give a mixture of products. For example, treatment of 2-methylanisole with n-butyllithium for 10 hours gave as products after carbonation 19% of (29) and 38% of (30)[91]

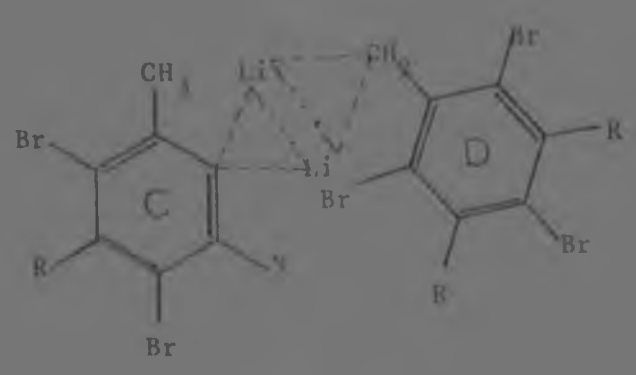


(29)



(30)

Thus, the dimer formed in the reactions of tribromomesitylene (R = CH_3) or tribromotoluene (R = H) with methyllithium is formulated as species (31)



(31) (R = H,CH_3)

In tribromomesitylene the two rings will be further apart than in dimer (26) owing to the bulkiness of the particular methyl group on the ring. In tribromomesitylene there are three methyl groups available for α-metallation relative to only one in tribromotoluene and so the probability of formation of dimer (31) is higher in the former and hence its yield of dimer is greater.

The methyl group is electron-donating and will decrease the electrophilic character of ring D in (31) relative to ring B in (26). However, a kinetic study (see experimental) of the rate of metal-halogen exchange of tribromomesitylene showed that there was an appreciable amount of starting material present after 40 minutes. This decreased but still

had not disappeared after 100 minutes (obviously, any 2,4,6-tribromo-3,5-dimethylbenzyllithium present will revert back to starting material on quenching with water.) Thus, for a significant period of time species (31) with three bromine atoms on ring D will be present in solution. These three electron-withdrawing bromine atoms on ring D must compensate for the electron-donating methyl groups to make ring D sufficiently electrophilic for 11% of biaryl product to be formed in the reaction.

It had been hoped to include 2,4,6-tribromobenzotrichloride in the series 2.6.2. Two attempts were made to prepare this compound from 2,4,6-tribromotoluene according to the method[168] for the α,α,α-trichlorination of toluene. The first attempt gave a mixture of 6 compounds in virtually equal amounts and inseparable on thin layer or by column chromatography. Repetition of the reaction using a 500W incandescent light source to aid the production of chlorine radicals gave as the main product a $C_7H_4Cl_4$ species (i.e.all the bromine atoms on the ring had been replaced by chlorine) and about 10% of the desired compound $C_7H_2Br_3Cl_3$ contaminated with some $C_7Br_3Cl_5$ (i.e.all the hydrogen atoms had been replaced by chlorine.) Furthermore, the desired compound was a crystalline solid which was insoluble in all the usual organic solvents for metallation reactions.

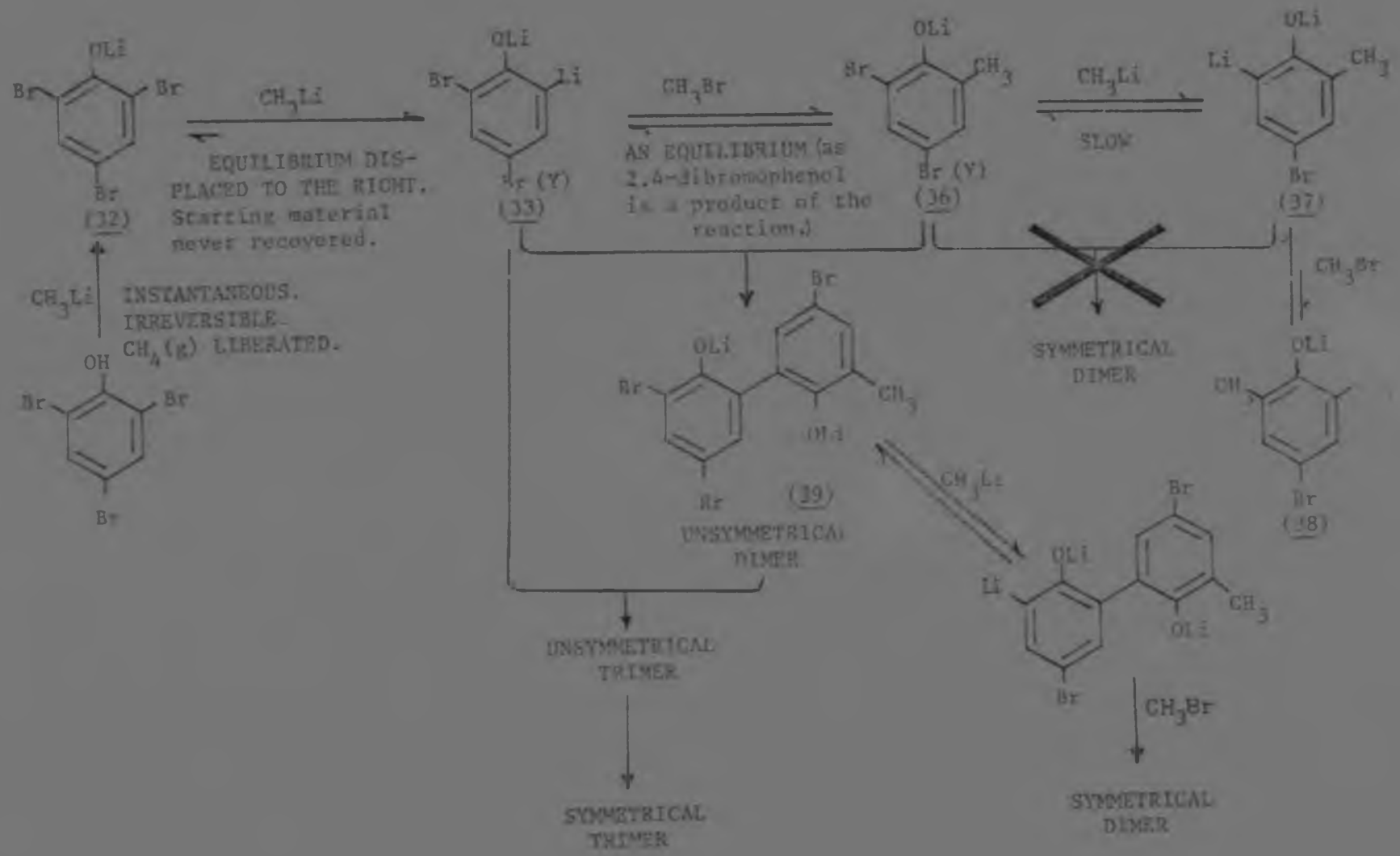
2.7 The Order of Events in a Typical Reaction.

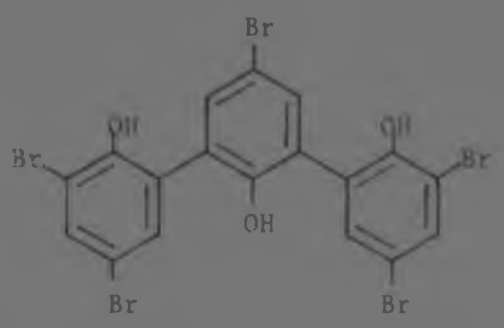
Scheme IV is a proposed reaction pathway for the sequence of events in the reaction between 2,4,6-tribromophenol and methyllithium.

To verify some of the proposals, three further reactions were undertaken.

(i) 2,4,6-Tribromophenol was reacted with 1,5 equivalents of methyllithium. The species present in the reaction mixture after 5 minutes should be equal amounts of (32),(33) and methyl bromide. Thus, there would be a direct competition between (32)and the methyl bromide for the lithiated species (33) and the ratio of monomer to biaryl product would afford an impression of the sequence of events in the reaction. Interestingly, over 50% of the product of the reaction was the triaryl species

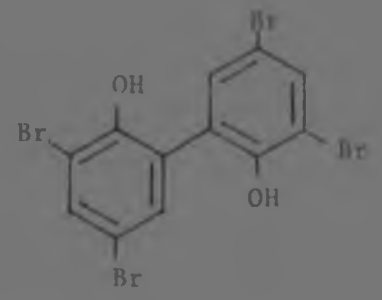
SCHEME IV


OLi
Br
Br
Br
(32)
CH3Li
EQUILIBRIUM DISPLACED TO THE RIGHT. Starting material never recovered.
OLi
Br
Li
Br (Y)
(33)
CH3Br
AN EQUILIBRIUM (as 2,4-dibromophenol is a product of the reaction.)
OLi
Br
CH3
Br (Y)
(36)
CH3Li
SLOW
OLi
Li
CH3
Br
(37)
CH3Li
INSTANTANEOUS. IRREVERSIBLE- CH4(g) LIBERATED.
OH
Br
Br
Br
SYMMETRICAL DIMER
CH3Br
Br
OLi
Br
CH3
OLi
Br
(39)
UNSYMMETRICAL DIMER
OLi
CH3
Br
(38)
CH3Li
Br
OLi
Li
CH3
OLi
Br
UNSYMMETRICAL TRIMER
CH3Br
SYMMETRICAL TRIMER
CH3Br
SYMMETRICAL DIMER



(34)

(34) with only 4% of 2,4-dibromo-6-methylphenol formed and a total of about 14% for both the symmetrical and unsymmetrical biaryl products. Conversion of (32) to (33) should be so rapid that no appreciable amount of the tribromo-species should exist at any time in the reactions as normally carried out (i.e. equimolar amounts of 2,4,6-tribromophenol and methyllithium employed). In the reaction described above, the concentration of (32) is large. The three electron-withdrawing bromine atoms considerably decrease the electron density on the ring making it extremely susceptible to nucleophilic attack by the carbanionic part of (33) thus leading to the biaryl (35), 2,2'-dihydroxy-3,3',5,5'-tetrabromobiphenyl.



(35)

This statement is verified by Gerold's results.[119] When he added less than one equivalent of phenyllithium to 2,4,6-tribromophenol in diethyl ether, the major product of the reaction (44%) was the non-phenylated symmetrical biaryl (35)

Now, a phenyl group is normally inductively electron-withdrawing[17,151] so a phenyl group containing two electron-withdrawing bromine atoms should be even more so. Thus, the biaryl (35) will also be a good electrophile and will readily be attacked by yet another carbanion at either of the carbon atoms bonded to a bromine atom ortho to a hydroxyl group to form the trimer (34) on elimination of lithium bromide.

(ii) A reaction in which 2,4-dibromo-6-methylphenol in diethyl ether was refluxed with two equivalents of methyllithium for 5 hours produced 33% of 4-bromo-2-methylphenol, 6% of 4-bromo-2,6-dimethylphenol and only 3% of the biaryl species. Forty-nine percent of the starting material was recovered unchanged from the reaction. Thus one concludes that lithiation of (36) is slow and unfavourable,as expected in view of the electron-donating properties of the methyl group. Also, as the percentage of dimethylated product is so low, the equilibrium between (37) and (38) must be displaced well towards the lithiated compound (viz.(37)). Since the amount of dimer recovered from the reaction is so small, it appears that the symmetrical biaryl product does not arise from coupling between (36) and (37) but must arise from the lithiation of the unsymmetrical biaryl product (39) followed by methyl-lithium exchange. Obviously, the symmetrical and unsymmetrical triaryl compounds can only arise from the unsymmetrical biaryl and this accounts for the low percentage of unsymmetrical biaryl relative to symmetrical biaryl recovered from the reactions.

(iii) A reaction in which equimolar amounts of 2,4,6-tribromophenol and 2,4-dibromo-6-ethylphenol were refluxed with insufficient methyl-lithium (three equivalents) for 5 hours in an attempt to determine the difference in the ease of lithiation of (32) and (36) gave back 92% of the 2,4-dibromo-6-ethylphenol. This suggests that in the normal reaction sequence most of (32) would be lithiated in preference to (36) i.e. that the amount of (33) present should far exceed (37) and that (36) $\longrightarrow$ (37) $\longrightarrow$ (38) is a minor pathway.

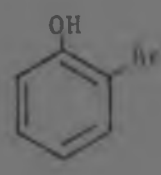
Consideration of Scheme IV shows that replacement of the para bromine in (32) by a more electron-withdrawing atom or group would enhance the speed of lithiation of that compound. Also, the stability and hence the standing concentration of (33) during the reaction would be increased. Thus one would expect an increase in the amount of biaryl and triaryl products from the reaction. This could explain the increase in the percentage of biaryl and triaryl species obtained as the electron-withdrawing power of Y increased. (See section 2.6.1)

CHAPTER 3

During the course of this research several reactions yielded most unexpected results. This chapter deals with the significance of these results and with further elaboration of the mechanism of the reaction between alkyllithium compounds and aryl halides.

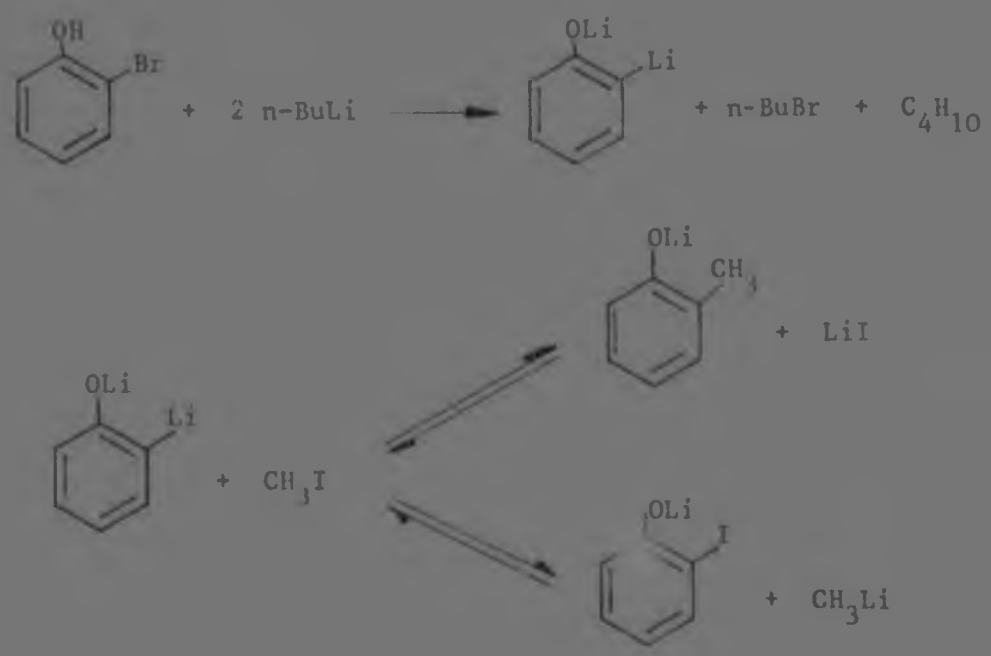
3.1 Proof of Free Radical Intermediates.

When the following reaction was undertaken



$$+ \ 2 \text{ n-BuLi} \xrightarrow[25^{\circ}C,\ 1 \text{ hr}]{\text{DEE}} + 20\ CH_3I \xrightarrow[5 \text{ hrs.}]{37^{\circ}C} \text{PRODUCTS} \qquad (33)$$

in an attempt to verify the mode of alkylation, the major product of the reaction (29% after isolation and purification) was found to be 2-iodophenol. The course of formatio of this product was initially formulated in overall terms as follows:-



as the metal - halogen exchange reaction had been shown to be reversible IF THE TWO CARBANIONS INVOLVED WERE OF SIMILAR STABILITY. However, the equilibrium in reactions of

aryl halide + alkyllithium ⟷ alkyl halide + aryllithium

are displaced far over to the right.[34] In fact, Gilman[30] had found that reactions of the above type are essentially IRREVERSIBLE.

Thus, an alternative mechanism , possibly involving free radicals, had to be considered. This was further supported by the fact that when the reaction described on page 38 was quenched with D_2O, only 73% of the product molecule had been deuterated. This implies[152] that 27% of the hydrogen ortho to the hydroxyl group must have been incorporated into the product prior to the hydrolysis in accordance with a radical mechanism i.e. at some stage a phenyl radical must have been present in the reaction mixture which abstracted a hydrogen radical from the solvent prior to work-up. Whitesides[100] obtained similar results when he hydrolysed an aliquot from the reaction between $(C_6H_5)_2CuLi$ and 1-iodonaphthalene with D_2O. The naphthalene recovered had the isotopic composition 80% d_1, 20% d_o.

Aryl radicals are known to react with methyl iodide to produce the aryl iodide and a methyl radical[153] - a halogen abstraction reaction. The abstraction of a halogen atom from alkyl halides by carbon radicals is in the order I ⋙ Br ⟩ Cl. Also, phenyl radical abstraction of halide from alkyl iodides is more facile than from aryl iodides.[154]

Thus, a reasonable explanation for the production of 2-iodophenol in this reaction is a radical mechanism formulated in broad outline as either:-

$$ArBr + n\text{-}BuLi \longrightarrow ArLi + n\text{-}BuBr \quad (34)^{1)}$$

$$ArLi \xrightarrow{?} Ar^{\cdot} + ? \quad (35)^{2)}$$

$$Ar^{\cdot} + CH_3I \longrightarrow ArI + CH_3^{\cdot} \quad (36)$$

---

1) Shown to be non-radical by Ward and Lawler.[20]

2) See page 66 for suggested route to $Ar^{\cdot}$.

or, less likely;

$$Li^{\cdot} + ArBr \longrightarrow ArBr^{-\cdot} + Li^{+} \quad (37)$$

$$ArBr^{-\cdot} \longrightarrow Ar^{\cdot} + Br^{-} \quad (38)$$

$$Ar^{\cdot} + CH_3I \longrightarrow Ar{-}I + CH_3^{\cdot} \quad (39)$$

and at least 29% of the reaction must follow this pathway.

A related incorporation of iodine into the products was again encountered when a reaction was undertaken to determine the position of lithiation of 2-fluorophenol. 2-Fluorophenol was stirred in diethyl ether with two equivalents of n-butyllithium for 5 hours at 20°C; 20 equivalents of methyl iodide were then added and the mixture refluxed for 40 hours. Eleven per cent of the total product of the reaction was 2-n-butyl-3-iodophenol; 1,5% of the isomeric 3-n-butyl-2-iodophenol was obtained and 24% of the starting material was recovered. The structures of the iodobutylphenols were verified by dehalogenation over palladium hydroxide on calcium carbonate[135] when the known 2- and 3-butylphenols were obtained.

This "halogen transfer" reaction had been observed before. Forrest[155] found that reacting equal quantities of 2-bromonitrobenzene and 1-iodonaphthalene at 200°C in an Ullmann reaction yielded 30% of 1-bromonaphthalene. The yield was reduced by decreasing the temperature. He rationalized the product in terms of the aryl iodide reacting with the cuprous bromide, but a detailed mechanism was not advanced. Nilsson[156] obtained 1,2-dichlorobenzene as one of the major products from a reaction of 2-chloroiodobenzene with copper. He suggested that the intermediate was a phenyl-copper species which could eliminate cuprous chloride to give an aryne intermediate but did not elaborate further. In our first case and that of Forrest, after Li - Br exchange there is no ortho halogen available for the loss of LiBr so an aryne is an unlikely intermediate and halogen abstraction by an aryl radical is more acceptable.

3.2 Further Proof for Radical Intermediates - the Effect of Oxygen on the Reaction.

Molecular oxygen is a biradical species known to be a radical scavenger. The effect of its presence on the products obtained from the reaction was therefore studied. This involved two reactions. In one oxygen was rigorously excluded from the reaction by degassing the two reagents in peroxide-free diethyl ether prior to mixing and refluxing at 37°C for 5 hours. In the other, the reaction was performed under medical air (20% oxygen, 79,9% nitrogen). The results of these two reactions and those normally obtained from a routine reaction under nitrogen are detailed in Table XI.

TABLE XI.

(For the reaction TBP + $2CH_3Li$ $\xrightarrow{5\text{ hrs},\ 37^{\circ}C,\ DEE}$ Products)

COMPOUND	PERCENTAGE YIELD		
	No O_2	high purity N_2	20% O_2
DBP[2)]	0	7,1	0
BMP	0	1,3	0
DBMP	5	2,4	0
BDMP	8	4,1	0
Sym. biaryl species	35	30,0	30
unsym. biaryl species.	10	8,5	17[1)]
sym. triaryl species (9)	22	15,0	18
unsym. triaryl species (10)	6	11,0	0
TOTAL	86	79,4	64
% ALKYLATION	77,5 (1,88)	60,0 (1,67)	50 (1,43)
% ARYLATION	41,0 (1)	36,0 (1)	35 (1)

1) The unsymmetrical biaryl in this case was 2,2'-dihydroxy-3,5,5'-tribromobiphenyl i.e. the lithium was not replaced by a methyl group to give the usual biaryl product.

2) See page 27 for an explanation of the abbreviations in Table XI.

Some conclusions may be drawn from a study of these results:-

(i) Exclusion of oxygen from the reaction affords the maximum recovery from any reaction. Generally about 80% of product relative to the starting material is recovered. Oxygen can cause oxidation of phenols to semiquinones and quinones.[157] The products from the reactions were always red-brown in colour, an indication of such oxidation.

(ii) No products in which the lithium atom was not replaced by a methyl group (c.f. 2,4-dibromophenol and 4-bromo-2-methylphenol) were obtained in the oxygen-free experiment.

(iii) The percentage arylation is normal taking into account the increased yield of product but the percentage methylation is significantly increased from 60 to 71% in the oxygen-free experiment.

Oxygen reacts rapidly with free radicals. Methyl radicals react with oxygen to form a highly reactive intermediate[158] which breaks down to formaldehyde and a hydroxy radical[158].

i.e.

$$CH_3^{\cdot} + O_2 \longrightarrow CH_3O_2^{\cdot} \longrightarrow HCHO + OH^{\cdot} \qquad (40)$$

and further $$2\ HCHO \longrightarrow CH_4 + CO_2 \qquad (41)$$

Phenyl radicals also react with oxygen but about 600 times more slowly than do alkyl radicals.[159]

Radical anions also react with oxygen in reactions of the type:-

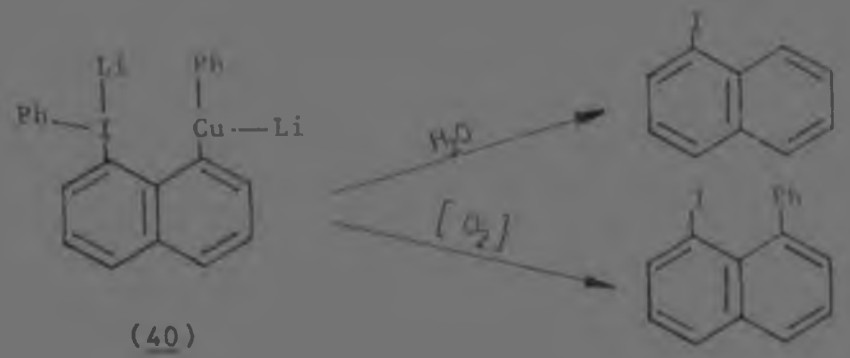
$$Na^+;R^{\cdot-} + O_2 \longrightarrow :R + Na^+,O_2^{\cdot-} \qquad (42)$$

Shirley[39] and others[71] have proposed that organolithium reactions involve radical anions. Thus, the exclusion of oxygen should increase the longevity of these radical anions and promote the reactions they undergo.

The fact that exclusion of most of the oxygen from the reaction mixture increases the amount of methylation suggests that methyl radicals (or radical anions) are generally present in the reaction but a significant proportion of them react with oxygen.

Ward and Lawler[20] have shown that radicals are only involved when both coupling and exchange occur simultaneously (i.e. not during exchange only) suggesting that the methyl radicals are produced during the coupling reaction only.

When the reaction is run under medical air there is a startling absence of monomeric products and a concomitant increase in the biaryl coupled products (taking into account the decreased yields due to oxidation of the phenols). This increase in the yields of biaryl products in the presence of oxygen had been noted by other workers. Whitesides[160] found that reaction of aryl iodide with $Li(CH_3)_2Cu$ usually yielded 30 - 50% of arylmethane but oxidation of the organometallic components prior to hydrolysis increased the yield to 60 - 70%. House[161] had noted that treatment of excess phenyllithium with Cu(I) bromide to give Ph_2CuLi and then further reaction of this with 1,8-diiodonaphthalene gave the supposed intermediate (40) which on hydro-



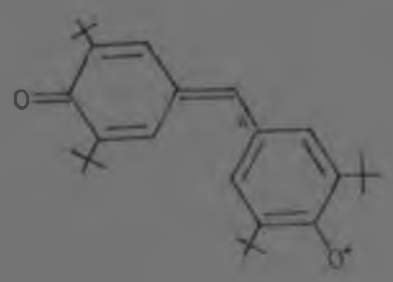
(40)

lysis yielded iodonaphthalene (67%) but on oxidation prior to work-up gave 1-iodo-8-phenylnapnthalene (21%). Other oxidants. e.g. nitrobenzene, have the same effect showing that the role of the oxidising agent in the production of biaryl is merely one of an electron acceptor. This will be discussed further in a later section.

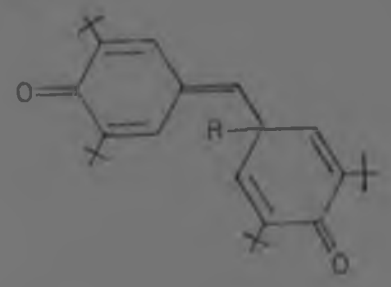
3.3 Attempts to Trap the Free Radicals.

One method of proving the presence of aryl or methyl radicals in the reactions of methyllithium with aryl halides would be to add to the reaction mixture some reagent which would react rapidly with these radicals, and then to isolate the resulting compounds from the reaction. In theory the technique is simple but the choice of radical scavenger

presented some problem as virtually all known scavengers have functional groups (e.g. carbonyl, nitro) which react with organolithium compounds. What was required here was a compound which would couple with the radicals in a manner such that the products could unambiguously be said to arise from reaction with the radicals only and not with the organolithium compound as well. Finally chosen for this purpose was the highly hindered stable free radical known as galvinoxyl[162] — 4-{[3,5-bis(1,1-dimethylethyl)-4-oxo-2,5-cyclohexadien-1-ylidene]methyl}-2,6-bis(1,1-dimethylethyl)phenoxy radical (41)

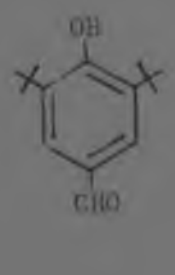


(41)



(42)

The advantage of this compound as a radical scavenger is that free radicals (R·) couple at *C to give (42) which can then be cleaved with basic alumina to yield 3,5-di-t-butyl-4-hydroxybenzaldehyde (43) and the substituted phenol (44).[162]



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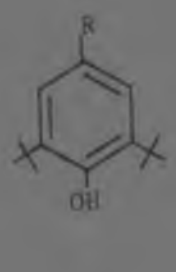
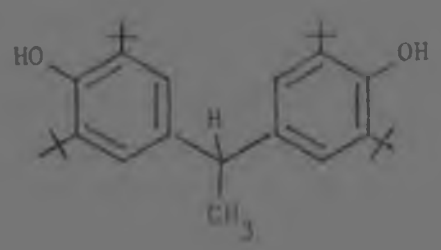


(44)

In initial attempts to trap radical intermediates, an equimolar amount of galvinoxyl was added to the aryl halide substrate. This caused great difficulty in purification of the products as all the column fractions were contaminated with the intensely coloured galvinoxyl. The following reaction was then undertaken: 5 mmoles of 2,4,6-tribromophenol was reacted with 10 mmoles of methyllithium in diethyl ether at 0°C for 30 minutes before 0,335 moles of galvinoxyl in benzene were added. The reaction solution went a deep purple on addition of the galvinoxyl and then rapidly faded to a light orange within 5

minutes. The reaction was quenched with the minimum amount of water and refluxed over excess aluminium oxide prior to work-up in the usual manner. Attempts to cleave the supposed (42) (R = CH_3) were unsuccessful. All the galvinoxyl was found to have been converted to a single crystalline compound which exhibited no carbonyl stretching frequency in the infrared. Mass spectral and NMR data unambiguously verified the compound to be (45). This product must arise from addition of



(45)

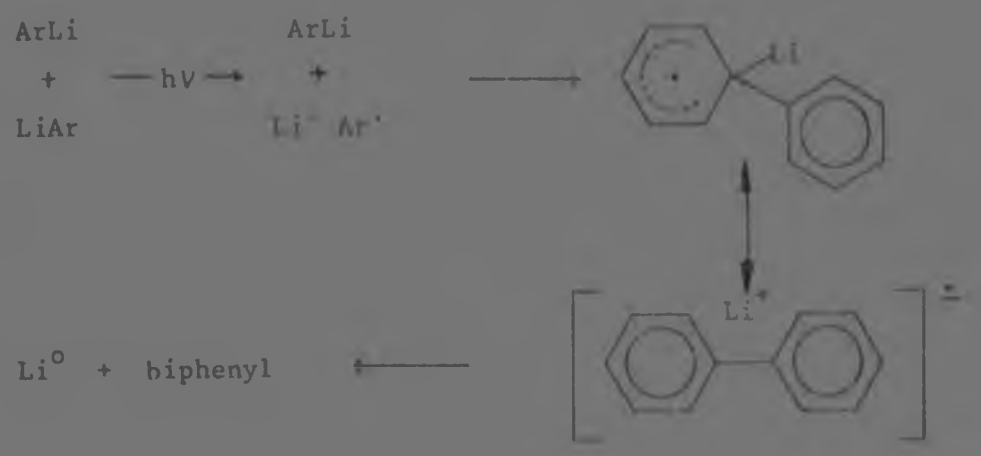
methyllithium across the quinone - methide double bond in (41).

The important finding that emerged here was that methyllithium was still present in the reaction mixture after 30 minutes; this was indeed striking. One factor that was always puzzling in these studies was the apparent "excessive" reactivity of the methyllithium. If metal - halogen exchange precedes coupling in both methylation and arylation then all reactions involving two moles of methyllithium seem to give greater than 100% reactivity (See for example, Table II: 113% reactivity with only 88% of the products analysed.)

All the alkyllithium solutions were quantitatively analysed by the double-titration technique of Gilman.[163] When one equivalent of methyllithium was added to one equivalent of 2,4,6-tribromophenol only the O-lithiate was formed i.e. no bromine - lithium exchange occurred thus verifying the titration.

We deduced, therefore, that the methyllithium was being regenerated during the coupling reaction. Van Tamelen[164] had found that UV irradiation of lithium aryls resulted in aryl coupling with the apparent concomitant production of metallic lithium. Clearly, if lithium metal were produced in the reaction it could react with the methyl bromide formed on metal - halogen exchange to regenerate methyllithium and form

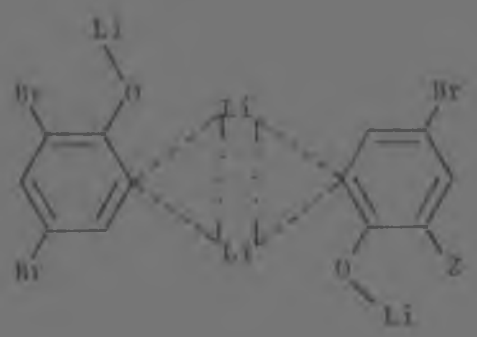
lithium bromide - the commercial mode of production of methyllithium. Van Tamelen postulated the following reaction sequence



He proposed the more stable biphenyl radical anion rather than the simple resonance stabilized radicals as the reaction did not resemble an ordinary homolytic aromatic substitution.[164]

On the basis of these results and considerations we propose that a second type of dimer - DIMER II - (c.f. Dimer I, (26) p 49) may be present in solution and may play an important role in these processes

DIMER II



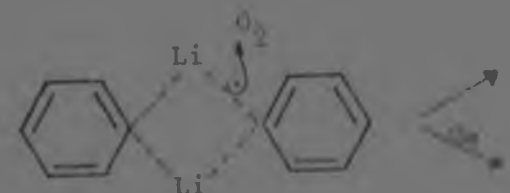
(Z = H, CH_3)

(46)

In Dimer II both the lithium atoms are now directly bonded to carbon atoms of the aromatic rings. This dimer is formulated to collapse via a RADICAL PATHWAY to biaryl products with the elimination of a lithium radical (vide infra).

To explain the results of the reaction run in the presence of 20% oxygen we suggest that Dimer I will be the species which gives rise to most of the bi- and triaryl products of the reactions via an ionic pathway. Dimer II will be more stable and exist for longer periods of time in solution. On work-up with aqueous acid Dimer II will be protonated to yield the monomers 2,4-dibromophenol and / or 4-bromo-2-methylphenol. However, in the presence of oxygen, which is known to help cleave C-metal bonds,[16] Dimer II collapses to the biaryl species and lithium metal. To account for the "excessive" reactivity of methyllithium, some biaryl product must necessarily arise via this route. On breakdown of Dimer II via a radical pathway, the aryl radical formed need not couple with the other aryl ring but may abstract a proton from the solvent (see section 3.1) or react with a methyl radical if there is one present in the immediate vicinity.

A possible mode of breakdown of Dimer II may be formulated as



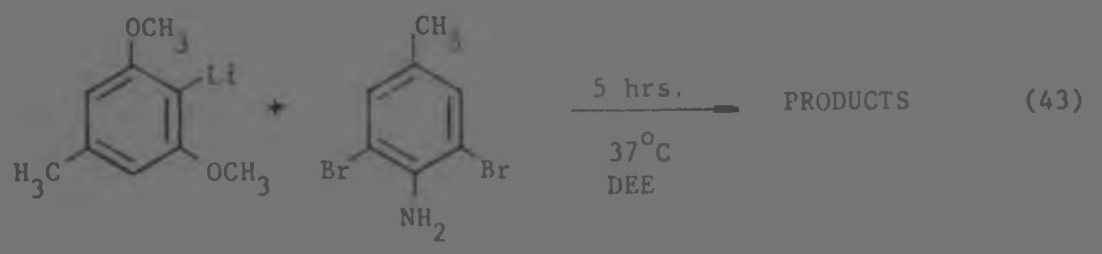
Our postulate of Dimer II is supported by the explanations offered by Whitesides[100] for the increased yields of coupled product on oxidation of mixtures of aryl iodide and lithium dimethyl uprate (I) prior to work-up. He proposed a $(Ph)(CH_3)CuLi$ complex which on oxidation gave $PhCH_3$, but he did not elaborate on the mode of oxidation nor detail the structure of $(Ph)(CH_3)CuLi$ but merely formulated the reaction as

$$(Ph)(CH_3)CuLi \xrightarrow{O_2} PhCH_3$$

In fact, the crux of the usefulness of metals for the coupling reactions may be their varying abilities to form dimers of this kind and the ease of subsequent collapse of such dimers on losing an electron.

3.4 A Test for the Mechanism of the Reaction.

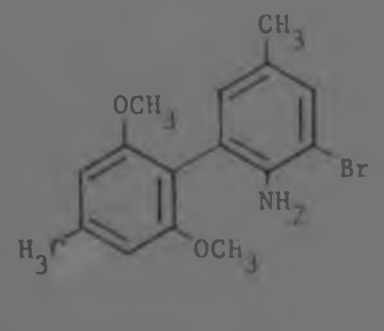
Dimer I and its mode of breakdown are novel and further work was necessary to bolster this postulate. The following reaction was initially undertaken for this purpose.



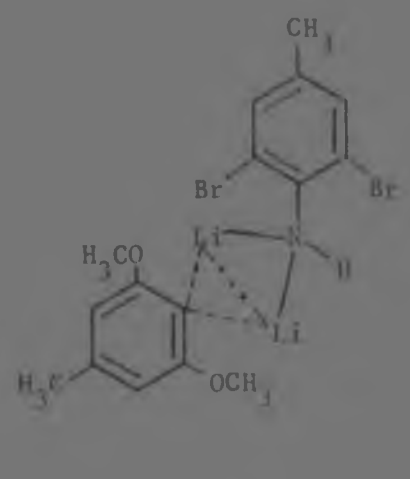
(43)

(See Chapter 4 for the reason for the choice of these reactants and for further research done on the coupling of these two compounds.)

The main product of the reaction was expected to be the biaryl (47) arising from the dimer (48). Instead, the two starting materials and the two



(47)

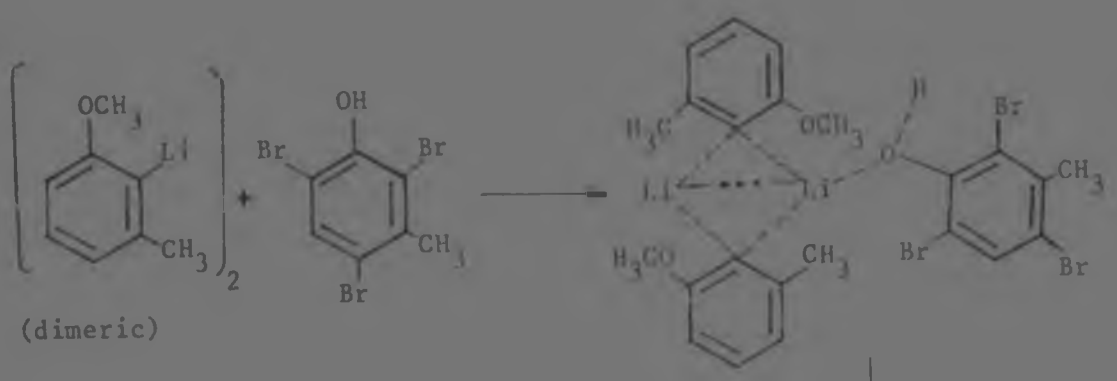


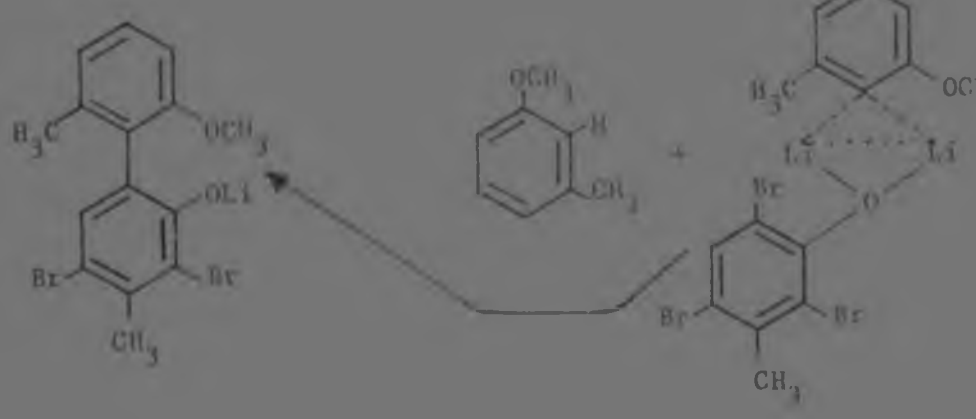
(48)

exchange products (viz. 2-bromoorcinol dimethyl ether and 2-bromo-4-methylaniline (20,8%)) were obtained from the reaction. The main biaryl product (18%) was 2,2'-diamino-3-bromo-5,5'-dimethylbiphenyl and none of the desired product, 2-amino-3-bromo-2',6'-dimethoxy-4,5'-dimethylbiphenyl, was obtained. This result did however lead to further understanding of the mechanism of the reaction.

When Perold[119] had reacted 2,4,6-tribromo-3-methylphenol with two

moles of 2-lithio-3-methoxytoluene, he had no difficulty in obtaining 33% of the desired coupled product 3,5-dibromo-4,6'-dimethyl-2-hydroxy-2'-methoxybiphenyl. In this case, however, the use of one partner of the desired biaryl product to lithiate the other must have facilitated the formation of the required dimer - i.e. a QUASI-INTRAMOLECULAR reaction as sketched below may have occurred.



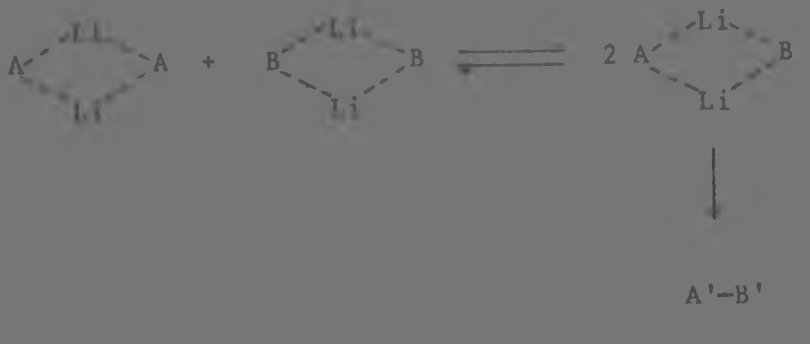


The 2-lithio-3-methoxytoluene should exist as a dimer in solution[23] and this dimer will break down on lithiation of the hydroxyl group of the 3-methyl-2,4,6-tribromophenol. As the monomeric O-lithiate of the 3-methylphenol derivative is produced it may form a mixed dimer with the other molecule of 2-lithio-3-methoxytoluene still in the micro-environment at the instant of the reaction.

(The crucial need for this 2:1 molar ratio of lithiating reagent to substrate may explain the success of the lithium cuprates, e.g. $(CH_3)_2CuLi$, in the coupling reaction. This had been suggested by Pearson[104] who stated that 'the unusual reactivity and usefulness of the lithium

cuprate reagent was probably as a result of its dimeric structure'. Copper, like lithium, forms a bond of low ionic character to carbon.[98])

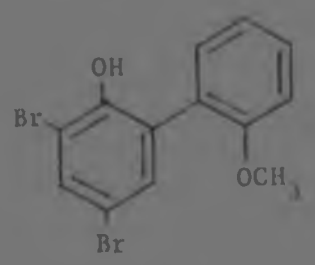
If the two aryl compounds to be coupled (A and B) are lithiated prior to mixing, each exists as a dimer in solution and formation of the desired dimer would demand the pre-dissociation of these 2 existing dimers - an equilibrium phenomenon and hence thermodynamic and kinetic factors are introduced.



This interpretation would also explain why methylation always predominates over arylation. The lithiation of the aryl halide will occur on the surface of the methyllithium aggregate[70] in an INTRACLUSTER reaction. Methyl bromide will be eliminated. The newly formed aryllithiate is now conveniently attached to the $(CH_3Li)_{n-1}$ aggregate for further reaction to occur.

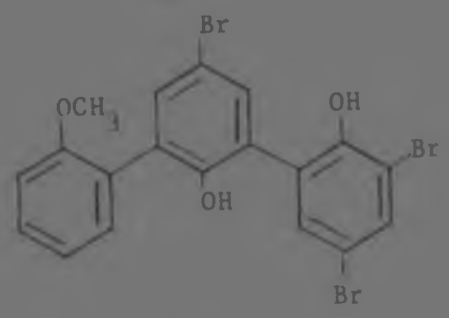
To substantiate the above proposals, three further reactions were carried out.

(i) Two moles of O-lithioanisole were refluxed with 1 mole of 2,4,6-tribromophenol. i.e. the O-lithioanisole was now serving as the lithiating agent for the hydroxyl group of the tribromophenol. The results from the reaction seemed disappointing initially in that only 18% of the desired biaryl species (49) was obtained.



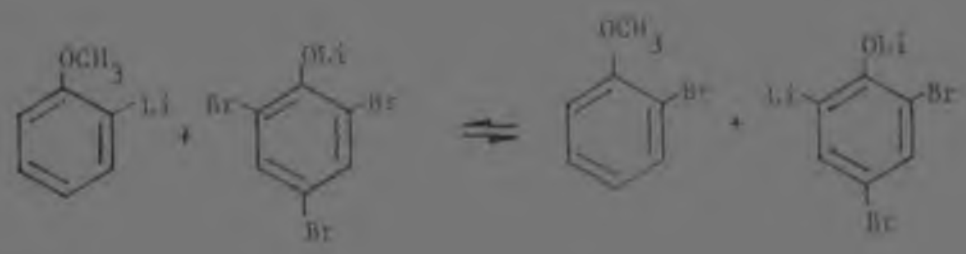
(49)

However, 8% of the trimer (50) was also isolated from the reaction



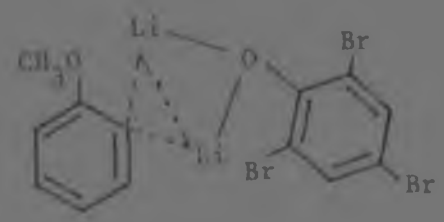
(50)

mixture showing that some of (49) had been consumed owing to the fact that a second ortho bromine atom was available for further reaction. Also, 2,4-dibromophenol (15%), 2-bromoanisole and 3,3',5,5'-tetrabromo-2,2'-dihydroxybiphenyl (22%) were formed during the reaction. 2,4,6-Tribromophenol is a more electronegative species than anisole and the following reaction



(51)

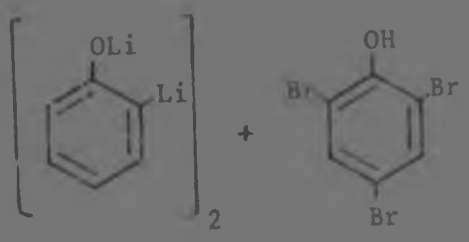
may be formulated to occur within the dimer (52) formed on lithiation of the hydroxyl group of the tribromophenol.



(52)

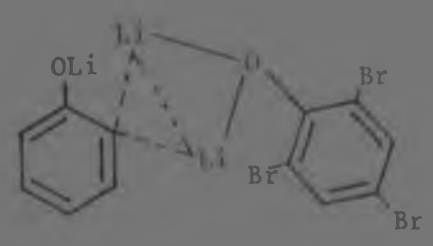
As the lithium on anisole is replaced by bromine, dimer (52) may break down and yields of the biaryl product decrease. Also, once 2-lithio-4,6-dibromolithiumphenolate (51) is formed, it can attack another molecule of tribromophenol-O-lithiate present in solution to form the 3,3',5,5'-tetrabromo-2,2'-dihydroxybiphenyl obtained.

(ii) To overcome this problem of Br – Li exchange leading to the breakdown of dimer (52), reaction (44) was carried out.

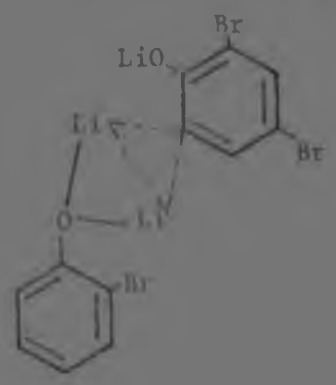


$$\xrightarrow[37^{\circ}C,18\ hrs]{DEE} \text{PRODUCTS} \qquad (44)$$

Dimer (53) should form on lithiation of the hydroxyl group of 2,4,6-tribromophenol and if lithium-bromine exchange should occur then dimer

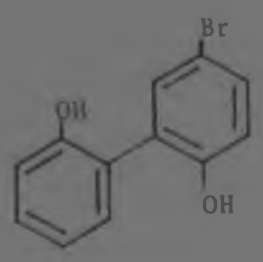


(53)

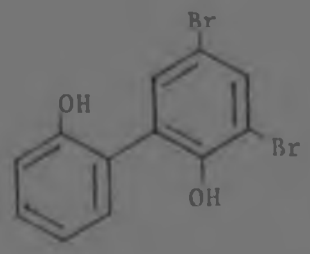


(54)

(54) could form in solution which could collapse to form the desired biaryl product. When the reaction was carried out about 33% of a mixture of (55) and (56) [1] was obtained together with 8% of (57), i.e. an increase from 26 to 41% of the desired coupling reaction.



(55)



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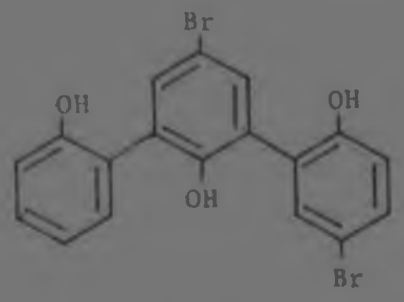
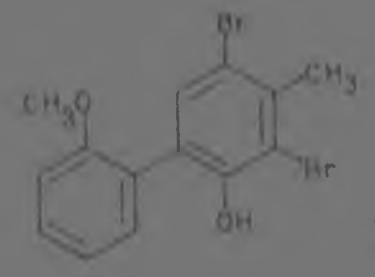


(57)

1) The two compounds could not be separated fully so an estimate of the relative amounts of the two were made.

(iii) When two moles of 2-lithioanisole were reacted with two moles of the already lithiated 2,4,6-tribromophenol, the yield of 3,5-dibromo-2-hydroxy-2'-methoxybiphenyl (49) dropped to below 10%. (The yield was probably enhanced by some metal - halogen exchange between the two dimeric aggregates facilitating formation of the dimer required to yield (49) on loss of lithium bromide.)

To eliminate this undesirable metal - halogen exchange between the two dimeric aggregates, 2 moles of 2-lithioanisole were reacted with one mole of 2,4,6-tribromo-3-methylphenol. Bromine - lithium exchange on the methylphenol is reduced as an alkyl group retards lithiation.[42] The yield of coupled product (58) now rose sharply to at least 50%. The other products of this reaction were not investigated, nor was this yield maximised.



(58)

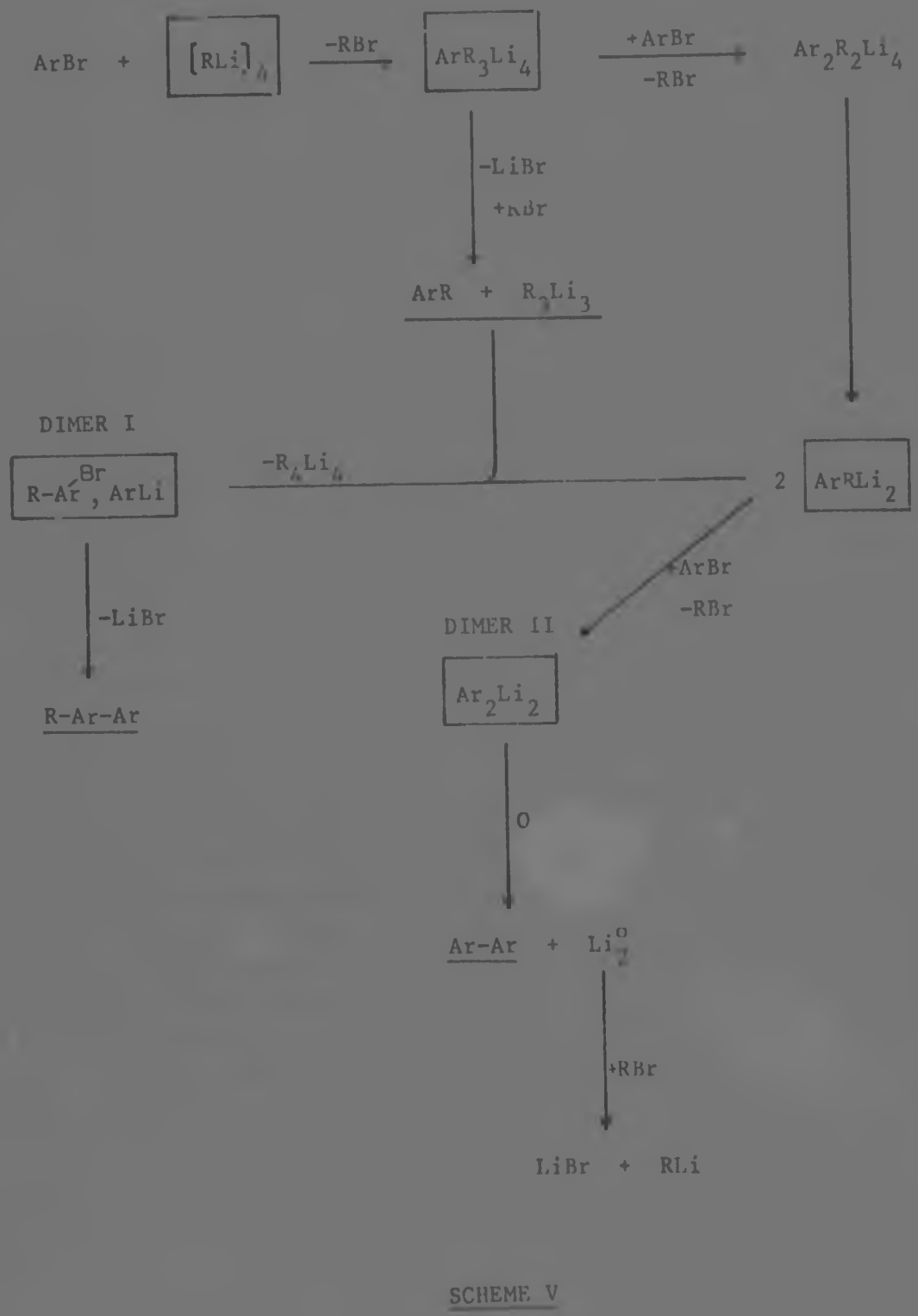
These results do suggest that dimers are formed in solution faciii-tated by the lithiation of the one aryl partner by the other.

3.5 The Intracluster Reaction Pathway.

A schematic outline of the possible pathway of the reaction between an aryl halide and alkyllithium compounds may then be presented as in Scheme V.

The species in square brackets are of the type shown by the NMR studies of Brown[17] to be present in a solution containing both phenyl-lithium and methyl- or ethyllithium. Ar-R will be lithiated more slowly than Ar-Br owing to the fact that the alkyl group is inductively electron-donating - this allows Dimer I to form. Dimer I will only form if the substituent ortho to the bromine on the ring has a lone pair of electrons or a hydrogen atom which may be replaced by a lithium atom (vide supra, section 2.6.2). Dimer I will collapse to Ar-Ar only if

there is a second bromine on the ring allowing for the loss of lithium bromide from the dimer.



SCHEME V

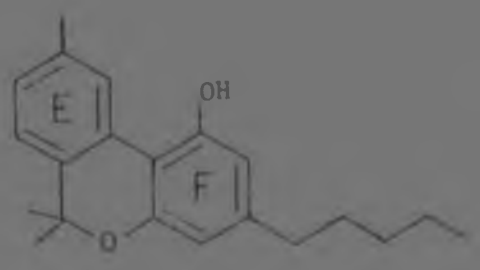
CHAPTER 4.

SOME APPLICATIONS OF THE COUPLING REACTION BETWEEN ARYL HALIDES AND ARYLLITHIUM COMPOUNDS.

Applications of the results of this research were studied in two directions. First, a suitable natural analogue was chosen and its synthesis by the coupling reaction was explored. Secondly, the optimization of the parameters favouring reaction via an ionic mechanism was investigated.

4.1 Choice of a Natural Product Analogue.

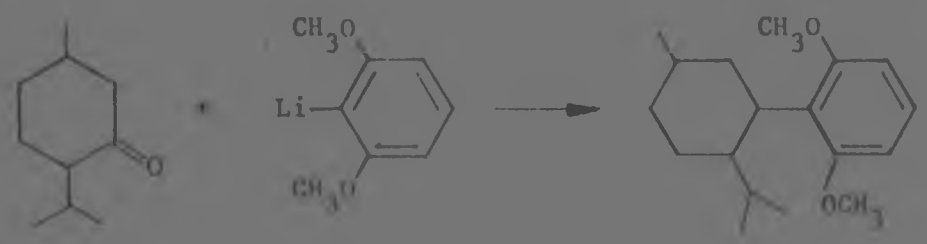
Cannabinol (59), a substituted biaryl system, was selected as a target for the synthesis because of the presence of the two (modified) hydroxyl groups ortho to the site of the biaryl ring junction. Our earlier studies (see section 2.6.2) had shown that the coupling reaction was particularly favoured when there was a hydroxyl or methoxyl group on the aromatic ring adjacent to the position of lithiation and subsequent coupling.



(59)

Cannabinol is a minor constituent of the Cannabis plant and is not psychotomimetically active.[167] Much of the earlier work on the position of the linkage between the two rings in the cannabinoids was done by Adams.[168] More recently, Mechoulam[169,170,171,172] has been one of the

most active researchers in this field. As it is well known that treatment of resorcinol with n-butyllithium results in metallation between the two hydroxyl groups,[171] it was considered that the coupling reaction between aryllithiums and organohalides would be well suited for the synthesis of the cannabinoids. Adams[168] had indeed used the dimethyl ether of 2-lithioresorcinol to verify the position of linkage between the two rings but had employed it in a different type of reaction.



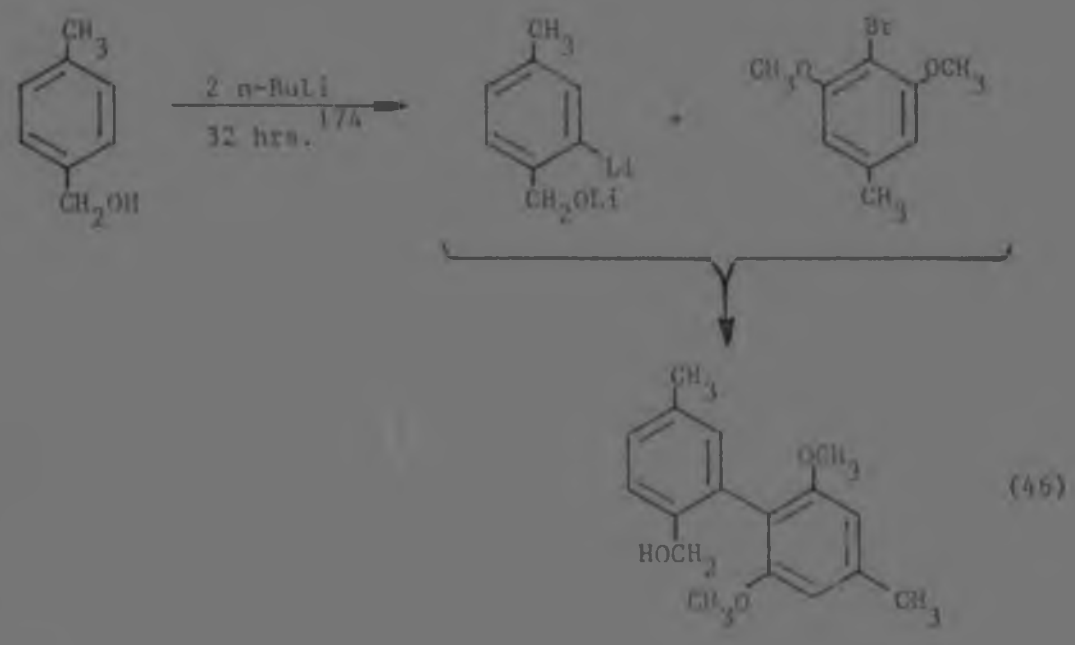
(45)

4.2 Attempted Routes to a Cannabinol.

Cannabinol can be dissected into two portions; olivetol and an aromatic ring bearing a methyl group and another functional group in para positions. Rather than olivetol, the readily available orcinol was chosen for ring F where the methyl group would represent a general alkyl function. Ring E had to carry some functionality which would be ortho to the site of the proposed ring junction and which could later be modified for the elaboration of the pyran ring. Various functional groups were studied. The functional groups chosen and their value in the synthesis of biaryls via coupling between an aryl halide and an aryllithium compound are discussed hereunder.

4.2.1 Via the Arylcarbinol.

One of the first routes studied for the synthesis of a cannabinol analogue was via the arylcarbinol.



(46)

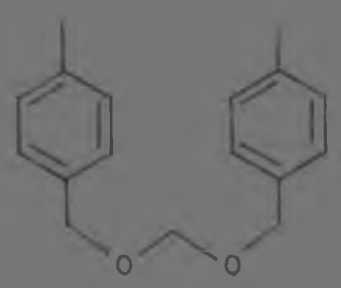
Instead of the desired coupling occurring, extensive Br - Li exchange took place to yield 48% (isolated) of 2-bromo-4-methylbenzyl alcohol, 18% of 4-methylbenzyl alcohol, 66% of 3,5-dimethoxytoluene and 18% of 4-bromo-3,5-dimethoxytoluene (based on the sum of the moles of arylcarbinol and orcinol derivative used).

This bromine - lithium exchange may be explained by the circumstance that the aromatic ring of orcinol is more electronegative than that of the 4-methylbenzyl alcohol. Bromination of the benzyl alcohol ring could make it sufficiently electronegative to prevent this exchange. As it was furthermore possible that O-lithiation of the carbinol group (in addition to lithiation on the ring) might also be a complicating factor in the reaction, protection of the alcohol by etherification was undertaken.

4.2.2 Protection of the Arylcarbinol.

The methoxymethyl ether group was an immediate choice as a protecting group in view of its ease of removal[175,176] after coupling of the two rings. Initial attempts to prepare this compound according to the method of Fieser[175] yielded interesting but unexpected results: only 20%

of the desired methoxymethyl ether of 4-methylbenzyl alcohol was formed, while 74% of the crystalline bis-ether (60) was obtained.



(60)

Even the very gradual addition of the sodium salt of the benzyl alcohol to a twenty-fold excess of the chloromethyl methyl ether did not greatly improve the yield of the methoxymethyl ether of 4-methylbenzyl alcohol. Difficulty was also experienced in purifying the latter compound. The methyl ether of 4-methylbenzyl alcohol was therefore prepared instead.[177] A reaction to monitor the rate of lithiation of this compound showed that some undesirable side reaction was occurring. Lansbury had found[178] that with some ethers e.g. $ArCH_2OR$, if α-metallation occurred to give (61), rearrangement could occur resulting in (62).



(61) (62)

This probably occurred in the case of the methyl ether of the arylcarbinol.

This possible α-metallation and positive inductive effect of the carbinol render it unsuitable as a functional group on substrates intended for coupling reactions with aryllithium compounds.

4.2.3 Via the Benzoic Acid.

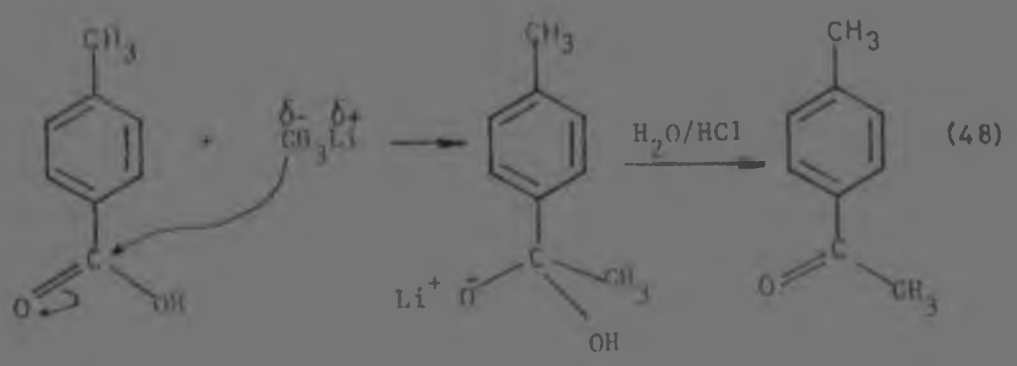
The possibility of using the carboxyl functionality was also examined. The carboxyl group is a powerful electron-withdrawing group

and could reduce the electron density on the aromatic ring considerably to make it more susceptible to attack by a carbanionic species.

Gilman had found[36] that treatment of benzoic acid with n-butyllithium for four minutes at −75°C followed by quenching the reaction by pouring the reaction mixture on to solid subliming carbon dioxide gave phthalic acid as the major product (yield not quoted). On the basis of this work, 4 methyl benzoic acid was allowed to react with n-butyllithium at −75°C for four minutes before eight equivalents of methyl iodide were added to determine the position of lithiation. Forty per cent of butyl 4-tolyl ketone and 45% of methyl 4-tolyl ketone were isolated: the major position of reactivity was therefore at the carboxylic carbon and not on the ring as desired.

The methyl 4-tolyl ketone probably arose because all the n-butyllithium had not been consumed within the four minute period prior to the addition of the methyl iodide so that the following could then occur:-

$$\underset{(\ll 1\ \text{eq.})}{\text{n-BuLi}} + \underset{(8\ \text{eq.})}{CH_3I} \longrightarrow CH_3Li + \text{n-BuI} \qquad (47)$$



(48)

These results show that the carboxyl group is not suitable as a functional group in these coupling reactions of aryl halides and organolithium compounds.

4.2.4 The Ortho-Ester as a Functional Group.

The use of the ortho-ester[179] of 4-methyl-2-bromobenzoic acid in coupling to 2-lithioorcinol dimethyl ether was next explored. Here the absence of α-hydrogen atoms on the ortho-ester carbon would prevent any undesirable rearrangement from occurring. The group is furthermore highly elecron-withdrawing and would hence favour the coupling reaction. A survey of the literature revealed that the yields of ortho-esters from aromatic (as opposed to aliphatic) nitriles are low[180] (<27%) and especially in the case of ortho-substituted benzonitriles.[181] Ortho-esters are furthermore attacked by organolithium reagents to yield a ketone and an alcohol[182] by way of side reactions.

4.2.5 Via the Aniline.

The suitability of the amino functionality in coupling reactions of aryl halides and organolithium compounds was then investigated. Here, as in the case of the hydroxyl group, the amine itself can be lithiated by the aryllithium if desired and could thus facilitate the formation of a dimer analogous to Dimer I ((26), p 49). The substrate chosen was 2,6-dibromo-4-methylaniline, to be coupled with 2-lithio-4,6-dibromo-orcinol dimethyl ether.

Before this reaction was undertaken it was necessary to conduct an experiment to determine the rate of metal-halogen exchange of 2,4,6-tribromoorcinol dimethyl ether by n-butyllithium. A reaction to this effect in diethyl ether monitored by glc showed that lithiation was complete within one hour at 0°C and if left for longer a second product started forming. As the resultant lithiated compound was not very soluble in diethyl ether, the lithiation experiment was repeated in tetrahydrofuran but in this case glc analysis of a sample taken after 15 minutes already exhibited four products. Thus, despite the solubility problems, diethyl ether was chosen as the solvent for the reactions.

The product from lithiation, isolated after quenching with aqueous acid, was initially thought to be 2,6-dibromo-3,5-dimethoxytoluene but was later found to be the 2,4-dibromo- isomer. Coupled products (63)

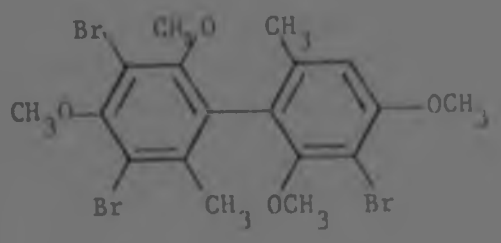
and (64) (vide infra) from the reactions of the lithiated dibromo-3,5-dimethoxytoluene further confirm that lithiation occurs between the methyl and a methoxyl group in position two and not between the two methoxyl groups in position four as anticipated.

Three reactions between a brominated aniline and 2-lithio-4,6-dibromo-3,5-dimethoxytoluene were carried out.

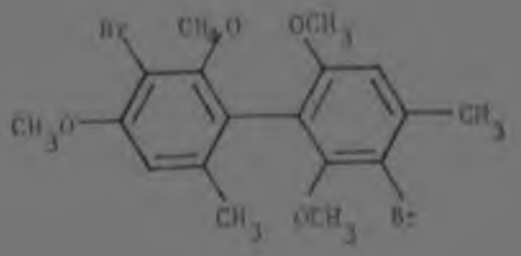
Firstly, equivalent amounts of 2,6-dibromo-4-methyl-N,N-dilithioaniline and the 2-lithio-4,6-dibromo-3,5-dimethoxytoluene were allowed to react. See Chapter 3.4 for the discussion of the results of this experiment.

The reaction was then repeated using four equivalents of 2-lithio-4,6-dibromo-3,5-dimethoxytoluene to each equivalent of 2,6-dibromo-4-methylaniline i.e. the former reagent was now used to lithiate the aniline.

Two dimeric products were isolated from the reaction. Both arose from coupling of the dimethyl ether of dibromoorcinol with itself to yield 38% of (63) and 17% of (64).

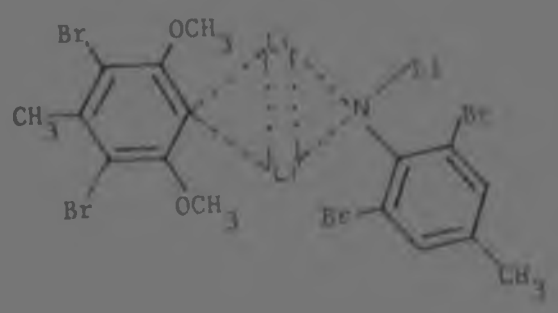


(63)



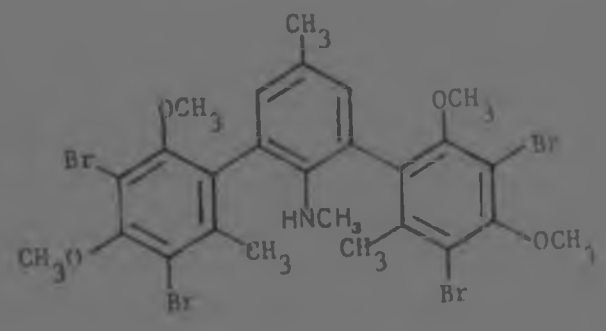
(64)

As di-lithiation of the amine might have been a complication preventing the formation of dimer (65) the reaction was then carried out on

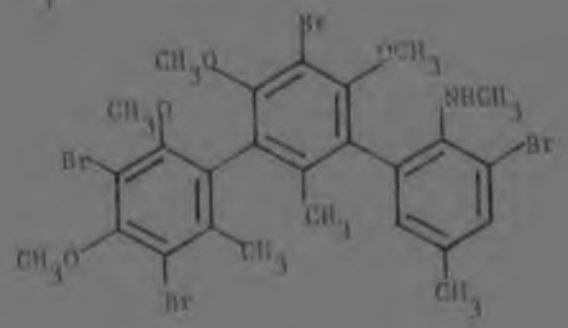


(65)

the N-methyl derivative of 2,6-dibromo-4-methylaniline with four equivalents of 2-lithio-4,6-dibromo-3,5-dimethoxytoluene. While a small amount (< 10%) of a compound whose mass spectra corresponded to a compound $C_{26}H_{27}Br_4NO_4$, i.e (66) or (67), was obtained, the major coupled



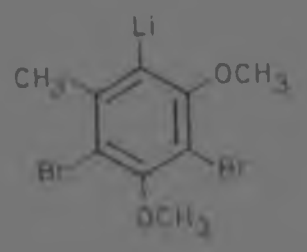
(66)



(67)

products from the reaction were once again (63) and (64), together with a large amount (30%) of 2,4-dibromoorcinol dimethyl ether.

It thus seemed that 4-lithio-2,6-dibromoorcinol dimethyl ether (68) could exist as a monomer in solution. Benzyllithium, believed to be dimeric in benzene,[15] is known to exist as a monomer in diethyl ether[17] and it is possible that the lithiated species of the dimethyl ether of dibromoorcinol (68) is similarly sufficiently stable for it to exist as a monomer in solution.



(68)

4.3 Physical Measurements on the State of Aggregation of Aryllithium Compounds.

There is still uncertainty as to the state of aggregation of aryllithium compounds in various solvents. While ebullioscopic measurements by Wittig[23] and others,[18] NMR studies by Brown,[17] and differential vapour pressure studies by West[18] have suggested that phenyllithium and 2-methyllithium are dimeric in diethyl ether solution, ^{7}Li - NMR studies by Ladd[18] on equimolar amounts of phenyllithium (PhLi) and 4-methylphenyllithium (TolLi) at temperatures down to -100°C have been interpreted in terms of monomeric aryllithium species. Ladd's results are not conclusive: the NMR spectrum of the PhLi : TolLi mixture at -100°C shows one sharp peak with a shoulder and one rather broad peak which may have split further had the temperature been lowered sufficiently. (c.f. NMR of CH_3Li : C_2H_5Li mixture studied by Brown[17]).

To substantiate the suggestion that (68) is monomeric in diethyl ether, a study of its colligative properties was undertaken. The cryoscopic technique was initially chosen for the measurements. Unfortunately, while the dimethyl ether of 2,4,6-tribromoorcinol is soluble in diethyl ether and benzene, the product arising from Br - Li exchange is not. In fact, the product obtained by quenching 2-lithio-4,6-dibromo-3,5-dimethoxytoluene with aqueous acid viz. 2,4-dibromo-3,5-dimethoxy-

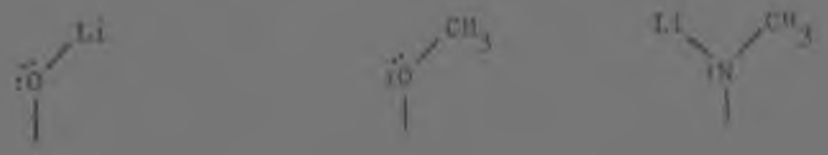
toluene, is soluble only in acetone and sparingly at that. As the state of aggregation of organolithium compounds varies in different solvents, with greatest aggregation occurring in the less polar solvents,[20] one cannot undertake the study of the colligative properties in one solvent and then extrapolate to other solvents. Thus, no measurements of the colligative properties of 2-lithio-4,6-dibromo-3,5-dimethoxytoluene was possible. (This insolubility of the lithio-compound may also account for its lack of the reactivity desired.)

Formation of a dimer analogous to Dimer I (p 49) requires that the aryllithium itself exist as a dimer in solution at the time of its lithiation of the functional group on the aryl halide partner. Thus, 2-lithioanisole (believed to be dimeric in diethyl ether[20]) was allowed to react with 4-methyl-2,6-dibromo-N-methylaniline in a further study of the eligibility of the amino group as a functional group on the aryl halide in its coupling reactions with aryllithium compounds. Once again the desired coupling did not occur.

Finally, in a reaction more precisely analogous to that between 2-lithioanisole and 2,4,6-tribromophenol (see section 3.4) which gave at least 18% of the desired coupled product (and overall 26% coupling between aryl halide and ar lithium compounds), 2,4,6-tribromo-N-methylaniline was allowed to react with two equivalents of 2-lithioanisole for 24 hours at 37°C. If coupling between the anisole and aniline rings did not occur it would have to be attributed to the presence of the nitrogen functionality on the ring: coupling also occurred with 2,4,6-tribromoanisole so the methyl group on the hetero-atom should not as such affect the coupling reaction.

When the reaction was performed, extensive decomposition occurred and half the product of the reaction was a black tar insoluble in all organic solvents. TLC and glc analysis of those compounds soluble in organic solvents showed them to be mainly anisole and unchanged 2,4,6-tribromo-N-methylaniline.

Accepting the intrinsic differences between nitrogen and oxygen, comparison of the results of these analogous reactions with the three functional groups,



strongly suggests that <u>both</u> lone pairs of electrons on the oxygen atom are involved in either formation or the stabilization of any dimers formed in solution.

The above reactions also suggest that the amino group is unsatisfactory for the coupling reaction on account of the extensive oxidation of the amine possibly followed by reaction of the aryllithium with the resultant oxidation products. Further study would be necessary if the effect of working in degassed media were to be evaluated.

Attempts to prepare the cannabinol analogue in this manner therefore failed on three counts:

(i) The undesired position of lithiation of 2,4,6-tribromo-3,5-dimethoxytoluene.

(ii) The possibility that the resultant lithiated compound (<u>viz.</u> 2-lithio-4,6-dibromo-3,5-dimethoxytoluene) exists as a monomer in solution, together with its inherent insolubility in diethyl ether.

(iii) Our lack of success in finding a suitably functionalized aromatic ring with which to couple the orcinol moiety.

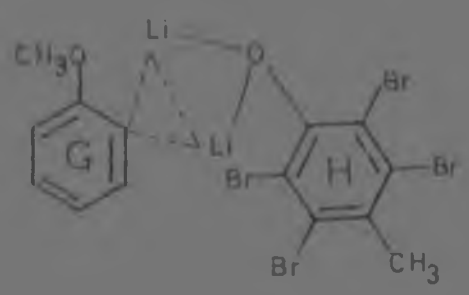
These studies did show that the presence of the functional groups $-COOH$, $-CH_2OH$ or $-NH_2$ on the aromatic ring in the coupling reactions of aryllithiums and aryl halides is not satisfactory.

4.4 <u>Maximization of Ionic Steering in the Coupling Reaction</u>.

In this application of the coupling reaction a substrate was so chosen as the aryl halide partner in the coupling reaction that the outcome of its reaction with an aryllithium in terms of an ionic mechanism could be predicted.

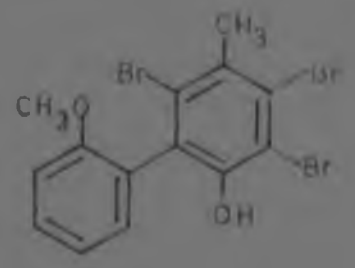
To this end, 2,3,5,6-tetrabromo-4-methylphenol was chosen as the substrate. The polyhalogenation of the ring should greatly increase the electrophilicity of the aromatic ring. The tetrachloro species was not chosen even though chlorine is the more electronegative halogen, owing to the fact that chlorinated intermediates, after metal - halogen exchange, can react via an elimination - addition pathway involving a benzyne intermediate.

The purpose of the alkyl group was three-fold: It would serve as an analogue for any other alkyl group, it has potential for elaboration to further functionalities, and it should decrease the possibility of metal - halogen exchange.[40,41] The hydroxyl functionality would ensure the attack of the aryllithium dimer on the substrate during lithiation of the oxygen and facilitate the formation of a dimer of type I (69).

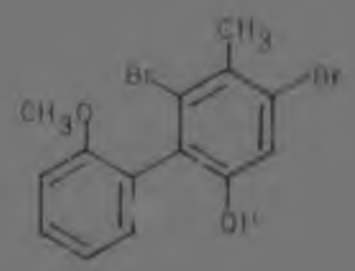


(69)

Two equivalents of 2-lithioanisole (ArLi) were reacted with one equivalent of 2,3,5,6-tetrabromo-4-methylphenol ($Ar'Br_4$). The reaction was expected to proceed with ease to give the coupled product (70) in high yield on collapse of (69) via an ionic pathway with attack of the



(70)

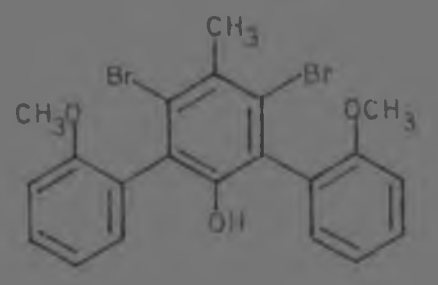


(71)

carbanion of ring G on the highly electropositive ring H. The possibility of some Br - Li exchange occurring to produce (71) as well could not be discounted.

When the reaction was carried out, 1,5 mmoles of 2,3,5,6-tetrabromo-4-methylphenol were added slowly in two portions (see experimental) to 3 mmoles of pre-generated 2-lithioanisole - RUN 1.

Fourteen per cent of the starting material was recovered from this reaction together with 9% of (71), 18% of (70) and, highly significantly, at least 12,5% of the triaryl species (72)



(72)

On repeating the reaction on a slightly larger scale (4 mmoles ArLi, 2 mmoles $Ar'Br_2$), the mixed reactants were left for a longer period of time so as to reduce the amou of starting material recovered and to increase the yields of couple ducts. Again the tetrabromocresol was added slowly to the 2-lit .ioanisole in two portions - RUN 2. The increased amount of tetrabromocresol (2 mmoles as opposed to 1 5 in the previous run) resulted an even greater proportion of the compound being added in the secon aliquot. This caused an even greater percentage of starting material to be recovered from the reaction despite the longer reaction time. The results of this and the preceeding reaction are detailed in Table XII.

These results suggest that the reaction is so fast as to be DIFFUSION controlled and that it is complete before the second aliquot of tetrabromocresol in diethyl ether was added. The 2-lithioanisole must couple so rapidly to both sides of the tetrabromocresol that almost all of it is consumed by the time the second aliquot of tetrabromocresol is added.

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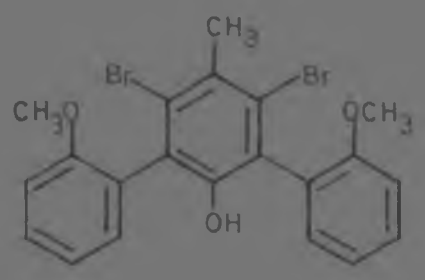

(72)

On repeating the reaction on a slightly larger scale (4 mmoles ArLi, 2 mmoles $Ar'Br_4$), the mixed reactants were left for a longer period of time so as to reduce the amount of starting material recovered and to increase the yields of coupled products. Again the tetrabromocresol was added slowly to the 2-lithioanisole in two portions - RUN 2. The increased amount of tetrabromocresol (2 mmoles as opposed to 1,5 in the previous run) resulted in an even greater proportion of the compound being added in the second aliquot. This caused an even greater percentage of starting material to be recovered from the reaction despite the longer reaction time. The results of this and the preceeding reaction are detailed in Table XII.

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TABLE XII

	ANISOLE	$Ar'Br_4$	(70)	(71)	(72)
RUN 1 (3 mmoles ArLi, 1,5 mmoles $Ar'Br_4$ in 2x10 ml Et_2O)	40%	14%	18%	9%	12,5%
RUN 2. (4 mmoles ArLi, 2 mmoles $Ar'Br_4$ in 2x10 ml Et_2O)	30%	27%	7%*	7%*	24%*

(* this corresponds to 62% coupling [7 + 7 + (24x2)%] between aryllithium and aryl halide - the highest percentage ever obtained during the course of this work.)

To substantiate this, the rate of the reaction was monitored and shown to be complete within 10 seconds after mixing the two reagents. When a two-bulb reaction flask was employed in such a manner that all the tetrabromocresol was added essentially simultaneously to the 2-lichioanisole, virtually no starting material was recovered and, more importantly, no triaryl species (72) was obtained - RUN 3.

When the tetrabromocresol was added over 8 minutes to the 2-lithioanisole, the triaryl species became the major product of the reaction with smaller amounts of the two biaryl products being obtained - RUN 4. Table XIII gives a comparison of the relative amounts of products obtained from the two reactions.

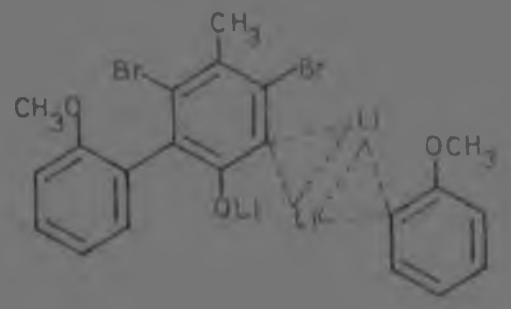
No compound of the nature of the triaryl species (72) (i.e. Ar coupling to both sides of $Ar'Br_4$ to give [Ar - Ar' - Ar]) had been obtained from any previous coupling reaction. The usual triaryl species (cf. (50) and (57)) arose from Li - Br exchange on Ar'Br to produce Ar'Li which then coupled to the already formed Ar - Ar' to give an [Ar - Ar' - Ar'] species.

TABLE XIII

Mode of Addition	% $Ar'Br_4$	% (70)	% (71)	% (72)
RUN 3 (rapid mixing)	9	59	32	0
RUN 4 (slow addition)	36	23	14	26

(Percentages are based on the area under that peak on the glc trace relative to the sum of the areas under all four peaks.)

It is unlikely that there is sufficient time (and there is certainly insufficient 2-lithioanisole) for Br - Li interchange to occur on (70) to enable a dimer of type II (73) to form which can collapse via a radical pathway to the triaryl product.



(73)

The isolation of 4',6'-dibromo-2,2''-dimethoxy-2'-hydroxy-5'-methyl-m-terphenyl (72) from this reaction therefore provides the strongest evidence that the reaction between an aryllithium and an aryl halide can proceed via direct attack of the carbanion (of the aryllithium) on a suitably functionalized electropositive ring of an aryl halide.

The results of this reaction also answer the query posed at the beginning of this work: unsymmetrical biaryl compounds can be synthesized

via an ionic mechanism if on one of the aryl partners a negative charge can be established sufficiently strongly and, more importantly, if the other ring is made sufficiently electron-deficient for such a nucleophilic substitution to occur on it.

It is believed that metallation of the aromatic ring occurs without marked disturbance of the π electron system of the molecule during the process[186] and is assisted if an ortho-substituent bearing lone pairs of electrons is present on the ring for co-ordination to the lithium atom. Likewise, formation of dimers of type I accompanied by partial Br - Li bond formation may facilitate coupling between the two ring carbons in an assisted "pseudo-nucleophilic" substitution in such a way that the π electron system is again essentially undisturbed.

Electron-withdrawing groups on the aromatic ring will decrease the electron density on the ring and make it more accessible to attack by a nucleophile, but the actual coupling reaction with concomitant loss of LiBr may not involve the π electrons of the aromatic ring but merely a relocation of the electrons of the C - Li and Br - C bonds in 4-centre mechanism.

The results of the reaction between 2-lithioanisole and 2,3,5,6-tetrabromo-4-methylphenol show that reactions between aryllithium and aryl bromide compounds can proceed by a pathway involving charged species and that the reaction proceeds faster in accordance with a more pronounced development of charge polarization on the aromatic ring of the substrate.

While the latter reaction therefore seems to proceed via a heterolytic pathway, our other results (see chapter 3) even so provide evidence for the presence of radical species in these reactions. The extent to which either pathway is followed for a specific reaction between an aryl halide and an organolithium compound will therefore depend on the nature of the two species and, from the results of other workers,[82,89] on the solvent employed in the reaction.

4.5 Summary.

The following points have been established for the reactions between aryl halides and organolithium compounds here studied:

(1) Two types of dimers are postulated to exist in solution, viz.

dimers of type I, (see p 49, (26)), which break down to biaryl products via an ionic or semi-ionic pathway involving charged species with elimination of lithium bromide, and

dimers of type II (see p 65, (46)), which require an electron acceptor (oxygen) to cause their collapse to biaryl products via a radical (or, less likely, radical anion) pathway with the elimination of metallic lithium.

(2) There is evidence that as much as 29% of the aryl reactants exist as radicals at some stage of the reaction in some of the reactions studied.

(3) It is highly likely that alkyl radicals are also present during the reaction, especially when methyllithium is used to generate the aryllithium species.

(4) The organolithium reagent is probably regenerated during the reaction.

(5) Bromine was the halogen used extensively during this research and is the halogen of choice for the coupling reaction. Iodine is not sufficiently electronegative and the more electronegative halogens, fluorine and chlorine, may react via a benzyne intermediate which can then give rise to further products.

(6) This coupling reaction can be used for the synthesis of unsymmetrical biaryls, and is specifically of value for the synthesis of unsymmetrically substituted biphenols where one of the aromatic rings contains a hydroxyl group ortho to the site of the ring junction.

(7) These studies have shown that homolytic and heterolytic processes occur together in the reactions of a range of alkyllithium reagents with

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(7) These studies have shown that homolytic and heterolytic processes occur together in the reactions of a range of alkyllithium reagents with

halogenated aromatic substrates; they also indicate the role that may be played by intracluster interactions in these reactions.

CHAPTER 5

EXPERIMENTAL

A. General Procedures.

All melting points were obtained using a Kofler micro-hotstage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 521 spectrophotometer or on a Jasco IRA-1 diffraction grating spectrophotometer. Liquids were run as films between sodium chloride plates while the p tassium bromide dispersion techniqu was used for solids. Band positions are given in cm^{-1}. Abbreviations used are s = strong, m = medium, w = weak, br = broad.

Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi-Perkin-Elmer R-20A high resolution spectrometer (60 MHz) or on a Varian HA-100 spectrometer (100 MHz). The chemical shifts were measured on the δ scale in ppm. relative to tetramethylsilane used as an internal standard. Coupling constants (J values) were read directly off the spectra. Abbreviations used are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, imp = imperfect.

Mass spectra (ms) were recorded on a Varian CH5 spectrometer at 70eV and 100μA. Only peaks of relative abundance greater than 5% are reported. Data are quoted; m/e value (relative abundance %). Mass spectral peaks due to halogen isotopic abundance are quoted by giving all the peaks in the multiplet but the abundance of the largest peak only is given (e.g. doublet at m/e 188/186 (53)).

Gas chromatograms were run on a Pye Series 105 (model 5) chromatograph. Column packings used were 5% GE SE-52 on Supelco (0,006 x 1,5m), 5% GE SE-30 on Supelco (0,004 x 1,5m) and 10% GE SE-30 on Anakrom (0,004 x 1,5m). Nitrogen was used as the carrier gas. Unless otherwise stated, the following conditions were used; N_2 0,6 kg cm^{-2}, the column was preheated to 150°C and immediately after injection of the sample

the temperature was programmed to increase at 12°C/minute to 300°C. Generally 100 μg of reaction products (mixtures) and 10 to 20 μg of pure samples were injected. Abbreviations used are R_T = retention time.

The silica gel used in all the column chromatography was Merck Kieselgel, 0,063 - 0,200mm particle size.

All thin layer chromatograms (TLC) were run on (Merck) silica gel GF_{254} plates. After running the plates, they were first viewed under ultraviolet light. The phenolic components were made visible by spraying with Pauly's reagent.[188] Other compounds were detected either by exposing the plate to iodine vapour for several minutes or spraying with chromic acid[188] and then heating the TLC plate in an oven at 120°C for 3 minutes.

All the diethyl ether used in reactions was dried over calcium chloride for 2 days with intermittent shaking before filtering and adding soldium as a finely extruded wire.

All n-butyllithium and some methyllithium was supplied by Merck. The remainder of the methyllithium and all the phenyllithium was prepared according to the method of Gilman.[34] All organolithium samples were analysed according to the Gilman double titration technique[163] using 1,2-dibromoethane. The organolithium reagents were stored in dark bottles fitted with a rubber septum and were transferred with syringes to the reaction flasks. All apparatus was oven dried and cooled in a stream of nitrogen.

General Procedure for all Reactions between an Aryl halide and an Organolithium Compound.

Unless otherwise stated, all reactions were carried out in a nitrogen atmosphere. A two-necked round-bottomed flask containing a bar magnet was fitted with a condenser carrying a nitrogen balloon. The whole apparatus was flushed with nitrogen before the second neck of the reaction flask was closed with a septum. A calculated amount of the organolithium reagent was drawn up into a graduated syringe from the

reagent bottle and transferred to the reaction flask via the septum. The flask was then cooled in ice. A weighed amount of aryl halide was transferred to a second two-necked flask fitted with a nitrogen balloon. This flask was flushed gently with nitrogen before sealing it with a septum. Ten ml of diethyl ether was added. This solution was withdrawn into a clean dry syringe and added dropwise from the syringe via the septum into the organolithium solution while the latter was stirred vigorously. The syringe and second two-necked flask were then washed with a further five ml of diethyl ether and added to the main reaction flask. The ice bath was removed and the reaction flask immersed in an oil bath which was heated to the required temperature. On completion of the reaction, the flask was again cooled in ice before 4 ml of 2M hydrochloric acid were added slowly via the septum. The apparatus was then dismantled and the solution extracted twice with a benzene / diethyl ether 2:1 mixture. The organic layers were washed with brine, combined and dried over anhydrous sodium sulphate before filtering into a round-bottomed flask. The solvent was removed from the product under vacuum on a rotary evaporator to constant weight. This sample was then taken up in solvent and 100 μg were analysed by gas chromatography. After a suitable solvent system had been found by thin layer chromatography, the products were separated by column chromatography. The amounts of starting materials were chosen such that about one gram of product was obtained from the reaction.

Column Chromatography.

The product of the reaction was dried on to twice its weight of silica gel. This was loaded on to the top of a pre-packed column of dry silica gel. Unless otherwise stated, the dimensions of this column were constant at 32 mm diameter and a height of 190 mm - COLUMN A. This required 80 g of silica gel. The sample was protected with a 10 mm layer of sand and some cotton wool. The column was usually eluted with SOLVENT SYSTEM A:-

Pet. ether (40 - 60°C) + benzene	(1 + 19)	200 ml
Pure benzene		200 ml
Benzene + ethyl acetate	(29 + 1)	150 ml
Benzene + ethyl acetate	(19 + 1)	200 ml

Benzene + ethyl acetate	(9 + 1)	200 ml
Benzene + ethyl acetate	(1 + 1)	200 ml.

Twenty millilitre fractions were collected. To follow the course of the separation, 10 µl of each fraction were spotted on TLC and run in benzene + ethyl acetate (9 + 1). On the basis of the TLC, after detection of the compounds, the fractions from the column were combined, dried and analysed by glc. The triaryl products were not eluted from the gas chromatography column under the conditions employed.

Melting Points of Known Compounds.

Unless otherwise stated, the literature m.p. of all known compounds are those quoted in Beilsteins Handbuch der Organischen Chemie.

B. Experimental Procedures Relating to Chapter 2.

The Reaction between 2,4,6-tribromophenol and methyllithium.

Six or 9 mmoles (2 or 3 equivalents) of methyllithium were transferred by means of a syringe to the reaction flask which was then cooled in ice. Three mmoles (0,993 g) of 2,4,6-tribromophenol dissolved in diethyl ether (10 ml) was added dropwise to the methyllithium. The ice bath was removed and the reaction heated to a specific temperature for a certain period of time before quenching and working up the reaction in the general manner and separating the products by column chromatography using solvent system A.

Purification of the products of the reaction between 2,4,6-tribromophenol and methyllithium.

The symmetrical biaryl product and 4-bromo-2-methylphenol always emerged from the column simultaneously. They were separated by microdistillation. The monomer distilled over at 65 - 70°C at 2mm Hg and then crystallized in the tube leaving the crystalline biaryl product in the rear bulb of the tube. All products from the reactions were purified and analysed as follows:-

(i) 2,4-dibromophenol. The crude reddish oil obtained from the column was distilled under reduced pressure of 2mm Hg at 70°C. The resulting colourless liquid was cooled and scratched to initiate crystallization. The compound was recrystallized from benzene, m.p. 38°C (lit.m.p. 40°C)

Analysis: C, 20.78; H, 1.76 ($C_6H_4Br_2O$ requires C, 20 ; H, 1.56)

ms M^+ at m/e 254/252(100)/250, other major peaks at m/e 223(3) 172(8)145(16)127(5)92(10)63(14).

IR ν_{max}(KBr) 3400(br,OH)1580,1470(m,Ar C=C)1160(m,C-O)1060,1030, 857,800(Ar C-H,1,2,4-trisubs ring)

NMR($CDCl_3$) δ 6,82(d(1H)ArH-6,$J_{5,6}$=9Hz)7,36(dd(1H)H-5,$J_{3,5}$=2Hz,$J_{5,6}$=9Hz) 7,51(d(1H)H-3,$J_{3,5}$=2Hz)5,0(s,br(1H)-OH,peak disappears in D_2O)

(ii) 4-bromo-2-methylphenol was recrystallized from pet. ether (40 - 60°C) after distillation, m.p. 63°C (lit.m.p. 64°C)

Analysis; C, 45.19; H, 3.74 (C_7H_7BrO requires C, 45.00; H, 3.78)

ms. M^+ at m/e 188/186(68), other peaks at m/e 160/158(7)145(8) 107(100)90(10).

IR $\bar{\nu}_{max}$(KBr) 3200(br,OH)2900(w,aliphatic CH)1470(m,C-O)1070, 1030,860,802(1,2,4-trisubs Ar ring,C-H)

NMR(CCl_4) δ 7,19(s(1H)ArH-3)7,10(d(1H)H-5,$J_{5,6}$=8Hz)6.51(d(1H)H-6,$J_{5,6}$=8Hz)4,17(s(1H)-OH,disappears in D_2O)?,1?(s(3H)-CH_3)

To prove the position of the methyl group on the aromatic ring, the benzoate of 4-bromo-2-methylphenol was prepared. The NMR spectrum of the benzoate in CCl_4 showed no shift in the position of the methyl peak relative to the position of the peak for 4-bromo-2-methylphenol in CCl_4. No shift in the peak implies an ortho methyl group[89] as meta and para methylphenols show a resonance shift of about +0,1 ppm on formation of the benzoate.

(iii) 4-bromo-2,6-dimethylphenol was purified either by microdistillation at 80°C and 2mm Hg where it crystallized on cooling or by sublimation. It was recrystallized from pet. ether, m.p. 79°C (lit.m.p. 79.5°C)

Analysis; C, 48.04; H, 4.55 (C_8H_9BrO requires C, 47.85; H, 4.48)

ms. M^+ at m/e 202/200(42), other major peaks at m/e 121(100)103 (21)93(21)91(71).

IR. $\bar{\nu}_{max}$(KBr) 3300(br,OH)2900,2840(w,aliphatic C-H)1600,1465(m, Ar C=C)1170(m,Ar C-O)840(1 free Ar H)

NMR(CCl_4) δ 6,93(s(2H)ArH)4,3(s(1H)-OH, peak disappears in D_2O)2,17 (s(6H)-CH_3)

(iv) 2,4-dibromo-6-methylphenol always emerged from the column first and crystallized on removal of the solvent. It was purified by sublimation at 40 - 50°C and 0,09mm Hg and had a m.p. 56 - 57°C (lit.m.p. 58°C)

Analysis; C, 31.43; H, 2.16 ($C_7H_6Br_2O$ requires C, 31.52; H, 2.25)

ms. M^+ at m/e 268/266(100)/264, other peaks at m/e 187/185(57) 169(5)158(10)106(15)77(96).

IR $\bar{\nu}_{max}$(KBr) 3400(s,br,OH)1580,1460(m,Ar C-C)1200(Ar C-O)840 (1 free Ar H)

NMR (CCl_4) δ 7,31(d(1H)H-3,$J_{3,5}$=2,3Hz)7,07(d(1H)H-5,$J_{3,5}$=2,3Hz)5,39(s (1H)-OH, peak disappears in D_2O)2,22(s(3H)-CH_3)

(v) 5,5'-dibromo-2,2'-dihydroxy-3,3'-dimethylbiphenyl (symmetrical biaryl product) was separated from any monomeric material by microdistillation, and recrystallized from benzene + ethanol (1 + 1) to give white needles, m.p. 175,5 - 176°C.

Analysis; Calc. for $C_{14}H_{12}Br_2O_2$: C, 45.36; H, 3.23
Found: C, 45.77; H, 3.04

ms. M^+ at m/e 374/372(25)/370, other major peaks at m/e 293/291 (7)212(100)184(7)169(8)139(5)106(11)105(12)91(10)82(8)76(13)

IR $\bar{\nu}_{max}$(KBr) 3350(s,br,OH)2900(w, aliphatic CH)1560, 1465(m,Ar C=C)1200(s,Ar C-O)840(CH bend of 1 free Ar H)

NMR(CCl_4) δ 7,09(d(2H)H-4,H-4',$J_{4,6}$=2,2Hz)7,26(d(2H)H-6,H-6',$J_{4,6}$=2,2Hz) 5,08(s,(2H)OH, peak disappears in D_2O)2,26(s(6H)Ar-CH_3)

(vi) 2,2'-dihydroxy-3'-methyl-3,5,5'-tribromobiphenyl (unsymmetrical biaryl product) was obtained as tiny crystalline clusters on removal of solvent. Recrystallized from benzene + hexane (4 + 1) to give cream needles, m.p. 193 - 194°C.

Analysis; Calc. for $C_{13}H_9Br_3O_2$; C, 35.55; H, 2.06
Found: C, 35.52; H, 2.00

ms. M^+ at m/e 439/437/435(78)/433, major peaks at m/e 359/357(12)/355, 344/342(54)/340, 315/313(15)/311, 278/276(100)263/261(12) 250/248(15)236/234(26)197(31)169(46)139(71)125(29)115(35)

IR $\bar{\nu}_{max}$(KBr) 3400(br,OH)2900(w,aliphatic CH_3)1545,1450(Ar C=C) 1200(Ar C-O)850(1 free Ar H)

NMR(DMSO) δ 7,65(d(1H)H-4,$J_{4,6}$=2Hz)7,21(d(1H)H-6,$J_{4,6}$=2Hz)7,20(d(1H) H-6',$J_{4',6'}$=2,0Hz)7,02(d(1H)H-4',$J_{4',6'}$=2,0Hz)3,5(s(2H)-OH) 2,17(s(6H)Ar-CH_3)

(vii) 3,3"-dimethyl-5,5'5"-tribromo-2,2';2"-tribydroxy-m-terphenyl (9) (symmetrical triaryl product) was recrystallized from a benzene + hexane (6 + 1) mixture,m.p. 275°C

Analysis; Calc. for $C_{20}H_{15}Br_3O_3$ C, 44.0; H, 2.8
Found: C, 43.3; H, 3.3[1]

ms. M^+ at 546/544/542(100)/540, 384/382(86)364(31)303(26)302(27) 192(31)191(32).

IR. $\bar{\nu}_{max}$(KBr) 3400(br,OH)2910(w,C-H)1465(s,Ar C=C)1200(m,Ar C-O) 855(s,1 free Ar H).

NMR($(CD_3)_2CO$) δ 7,0 - 7,15(m(6H)Ar-H's)4 - 5(br,s(3H)Ar-OH, disappears in D_2O)2,19(s(6H)Ar-CH_3)

(viii) 3"-methyl-2,2';2"-trihydroxy-3,5,5';5"-tetrabromo-m-terphenyl (10) (unsymmetrical triaryl product) did not melt below 340°C and could not be analysed by ms. as the melting point was so high.

NMR($(CD_3)_2CO$) δ 7,47(d(1H)H-4",$J_{4",6"}$=2,5Hz)7,20(s(3H)H-6,H-4',H-6')7,0 - 7,10(s+d(2H)H-4,H-6",$J_{4",6"}$=2,5Hz)5,60(s,Ar-OH peak disappears in D_2O)2,20(s(3H)Ar-CH_3)

The compound was dehalogenated over $Pd(OH)_2$ on $CaCO_3$ to give a compound recrystallized from ethanol with a m.p. of 136 - 137°C.

Analysis; Calc. for $C_{19}H_{16}O_3$; C, 74.60; H, 5.49
Found: C, 74.11; H, 5.69

ms M^+ at 292(100) and other major peaks at 274(73)202(14)141(13) 131(13)105(14).

IR. $\bar{\nu}_{max}$(KBr) 3400(br,m,OH)2900(w,CH_3)1560(w)1450(m)1429(s,Ar C=C) 1200(C-O)835(m)818(m)796(m)764(m)744(s.Ar C-H)

NMR($(CD_3)_2CO$) δ 7,47(d(1H)Ar H-1,$J_{1,2}$=2Hz)7,20(s(3H)Ar H-3,H-4,H-5)7,10 (s+d(2H)Ar H-2,H-6)5,62(s(3H)Ar-OH,peak disappears in D_2O) 2,20(s(3H)Ar-CH_3).

(ix) 2,2'-dihydroxy-3-methyl-5,5'-dibromobiphenyl.

In the reactions run in 20% oxygen and those to which galvinoxyl was added, this new biaryl product was obtained which had the same R_f value on TLC in benzene + ethyl acetate (9 + 1) as the unsymmetrical biaryl product (2,2'-dihydroxy-3'-methyl-3,5,5'-tribromobiphenyl) and the same re-

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1) Difficulty was experienced in separating the two trimers fully as they are so similar in overall structure. There was always slight contamination of each by the other.

tention time on glc as the symmetrical biaryl product (5,5'-dibromo-2,2'-dihydroxy-3,3'-dimethylbiphenyl). It was recrystallized from benzene + hexane (6 + 1), m.p. 158,5 - 159,5°C.

Analysis; Calc. for $C_{13}H_{10}Br_2O_2$; C, 43.60; H, 2.79
Found: C, 43.33; H, 2.79

ms. M^+ at 360/358(85)/356,279/277(13)278/276(11)199(31)198(100) 197(23)170(24)169(24)141(22)139(18)155(24)99(28).

IR. $\bar{\nu}_{max}$(KBr) 3360(s,OH)2905(w,aliphatic C-H)1460(s,Ar C=C) 1200(s,Ar C-O)850(m,1 free Ar H)805(s,2 adj H)

NMR($CDCl_3$) δ 7,50(d(1H)Ar H-4',$J_{3',4'}$=7Hz)7,35(d(1H)Ar H-3',$J_{3',4'}$=7Hz) 7,32(s(2H)Ar H-4,H-6)7,03(m(1H)H-6')2,30(s(3H)Ar-CH_3)

Every time products (i) to (viii) were obtained from the reaction their identity was confirmed by R_f on TLC, R_T on glc, an IR spectrum and a melting point.

Gas Chromatography.

Products from these reactions were analysed using the 5% GE SE-52 on Supelco packing. Using the general conditions (see page 92) the compounds had the following retention times: 4-bromo-2-methylphenol and 2,4-dibromophenol (4,5 - 5 min.) 4-bromo-2,6-dimethylphenol (5,5 - 6 min) 2,4-dibromo-6-methylphenol (6,5 - 7 min) 5,5'-dibromo-3,3'-dimethyl-2,2'-dihydroxybiphenyl (~19 min), and 2,2'-dihydroxy-3'-methyl-3,5,5'-tribromobiphenyl(22 min). The 4-bromo-2-methylphenol and 2,4-dibromophenol were separated on the same column but using the following conditions: N_2 0,4 Kg cm^{-2}, and the temperature isothermal at 125°C. The retention times were then 9,0 and 8,5 minutes respectively.

The reaction between 2,4,6-tribromophenol and n-butyllithium.

n-Butyllithium (15 mmoles) and 2,4,6-tribromophenol (3 mmoles, 0,993g) in diethyl ether (10 ml) were refluxed at 37°C for 40 hours. After work-up, the product of the reaction (299 mgs) was dried on to silica gel (1,2 g), loaded on to the top of a column of silica gel (50 g, 28 x 140 mm) and eluted with pet. ether (40 - 60°C) + benzene (1 + 19) (50 ml) followed by pet. ether + benzene (1 + 9) (300 ml). Ten-ml fractions were collected. Ten µl of each fraction were spotted on TLC and run in the latter

solvent system. The following products were obtained:-

(i) 2-butylphenol (120 mgs) was purified by microdistillation (65 - 70°C at 0,5 mm Hg) to give a colourless liquid.

Analysis: C, 79.89; H, 9.28 ($C_{10}H_{14}O$ requires C, 80.0; H, 9.34)

ms. M^+ at m/e 150(100) Other peaks at m/e 121(13)108(61)107(98) 94(17)91(18)79(40)77(61).

IR. $\bar{\nu}_{max}$(film) 3500(br,OH)2965,2940(s)2880,2870(m)(aliphatic -CH_2,-CH_3)1595,1500,1495(m)1458(s)(Ar C=C)1170(m,Ar C-O) 845(w)750(s,4 adj.Ar H)

NMR(CCl_4) δ 6,95(dd(1H)Ar H-5,$J_{5,6}$=8Hz,$J_{4,5}$=3Hz)6,83(d(1H)H-6, $J_{5,6}$=8Hz)6,65(d(1H)H-3,$J_{3,4}$=10Hz)6,57(dd(1H)H-4,$J_{3,4}$=10Hz, $J_{4,5}$=3Hz)5,5(s(1H)Ar-OH, peak disappears in D_2O)2,51(t(2H) Ar-CH_2-)1,75 - 1,15(m(4H)Ar-CH_2-CH_2-CH_2-)0,89(t(3H)R-CH_3)

(ii) 2,6-dibromophen was recrystallized from water or purified by sublimation, m.p. 55°C (Lit.m.p. 56°C)

Analysis: C, 28.25; H, 1.57 ($C_6H_4Br_2O$ requires C, 28.55; H,1.59)

ms. M^+ at m/e 254/252(100)/250, other peaks at m/e 173/171(33) 172/170(40)145/143(46)144/142(40)119/117(40)92(45)91(43) 86(33)85(34)82(26)74(40)72(41)71(34)63(100).

IR. $\bar{\nu}_{max}$(KBr) 3400(br,OH)1570(w)1468,1450,1440(m)(Ar C=C) 1240,1135,758(s)710(m)(Ar C-H,3 adj H)

NMR(CCl_4) δ 7,31(d(2H)Ar H-3,H-5,$J_{3,4}$=8Hz)6,57(t(1H)H-4,$J_{3,4}$=8Hz) 5,6(s(1H)Ar OH)

The reaction between 2,4,6-tribromophenol and phenyllithium.

Phenyllithium (14,8 mmoles) and 2,4,6-tribromophenol (3,7 mmoles 1,224 g) in diethyl ether (10 ml) were refluxed for 94 hours. The product of the reaction (1,5 g) was loaded on to a column of silica gel (100 g, 35 x 196 mm) and eluted with;

Benzene	(pure)	100 ml
Benzene + ethyl acetate	(39 + 1)	100 ml
Benzene + ethyl acetate	(19 + 1)	40 ml
Benzene + ethyl acetate	(9 + 1)	40 ml

Benzene + ethyl acetate	(1 + 1)	40 ml
Ethyl acetate	(pure)	40 ml
Methanol	(pure)	100 ml.

Twenty ml fractions were collected. The major product of the reaction (288 mg) was distilled at 110°C and 1 mm Hg. A light yellow liquid was obtained which solidified in the tube. When hydrogenolysed over palladium hydroxide on calcium carbonate it gave a syrup (170 mg) which was purified on a column (15 g,16 x 130 mm) eluted as above. Fractions of 10 ml were collected.

2-phenylphenol. Fraction 2 - 10(70 mg), light yellow needles, was recrystallized from hexane, m.p. 55,5°C (Lit.m.p. 56°C)

Analysis; C, 84.60; H, 5.95 ($C_{12}H_{10}O$ requires C, 84.65; H, 5.90)

ms. (M+1)171(14),M^+ at m/e 170(100), other peaks at m/e 169(47) 142(15)141(35)139(14)115(59)89(14)77(11).

IR. $\bar{\nu}_{max}$(KBr) 3560,3520(m,OH)1580(w)1485,1480,1450,1435(m, Ar C=C)1350(C-O)750(4 adj. Ar H)730,695(5 adj. ring H)

NMR($CDCl_3$) δ 7,32(s(5H)Ar H of phenyl ring)7,3 - 6,2(m(4H)Ar H of phenol ring)5,0(br,s(1H)Ar-OH)

Reaction between 2-bromophenol and methyllithium.

To methyllithium (8,5 mmoles) was added the 2-bromophenol (2,84 mmoles, 0,493 g) in diethyl ether (4 ml). The mixture was refluxed for 24 hours before quenching the reaction. Attempts to separate the products on a column were unsuccessful and so preparative TLC was employed. A 20 x 40 mm plate was spread to 1 mm thickness with Kieselgel G_{254} (Merck). The plate was activated at 120°C for 45 minutes before 200 mg of reaction product was applied along a line 25 mm from the base of the plate and it was developed in benzene + ethyl acetate (9 + 1). The 2-methylphenol and phenol were identified by co-injection of the authentic compounds on glc, comparison of the IR spectra against the known samples and mass spectral data. A small amount of a biaryl product was also obtained.

2,2'-dihydroxybiphenyl was recrystallized from benzene + hexane,m.p. 110 - 112°C (Lit.m.p. 109°C ex toluene). It was identified by ms and

infrared spectra only.

ms. m/e at 187(13)186(100,M^+)185(15)158(31)157(31)130(16)
127(18)105(34)77(31)

IR. $\bar{\nu}_{max}$(in $CHCl_3$) ~3200(br,m,O-H)1600(w)1425(s)1350(s)(Ar C-C)
1170(m)1095(w)(C-H in-plane).

The amount of material was insufficient for an NMR spectrum to be run, and no commercial material was available for a mixed run.

Reaction between 4-bromophenol and methylsilicon.

This was carried out in a similar [illegible] to the reaction with 3-trimethylsilyl but yielding with D_2O no other 2-deuterio-4-bromophenol as a product of the reaction.

ms. Peaks at 174/172 due to C_6H_5OBr (M^+) of the absence of the peaks at 177/175 due to C_6H_4DOBr)

IR. $\bar{\nu}_{max}$ (Nujol) Most important point of difference between the spectra of (I) (C-H out-of-plane bend) was noticeably disappeared. The peak at 1590 was increased and the peak at 1610 (C-C [illegible]) was [illegible].

The [illegible] CCl_4 solution of [illegible] showed the peak at (I) [illegible] was [illegible] the [illegible] of phenolic [illegible] which [illegible] the [illegible] of the peak at 3 [illegible].

Reaction of 4-methyl-2-trimethylsilyl with benzoyl chloride and aluminium chloride

The experiment [illegible] was carried out [illegible] aluminium chloride in [illegible] as in previous [illegible] the [illegible] was [illegible] The [illegible] of the product of the [illegible] between [illegible] and benzoyl chloride in [illegible] would be an [illegible]. However, the [illegible] of the reaction between [illegible] and benzoyl chloride in [illegible] was known to [illegible] and [illegible] to be [illegible]. The [illegible] was [illegible] and [illegible] to [illegible]. The [illegible] was [illegible] to [illegible]

infrared spectra only.

ms. m/e at 187(13)186(100,M^+)185(14)158(31)157(31)130(26) 127(18)105(34)77(31)

IR. $\bar{\nu}_{max}$(in $CHCl_3$) ~3200(br,m,O-H)1600(w)1475(m)1440(s)(Ar C=C) 1170(m)109.(w)(C-H in-plane).

The amount of material was insufficient for an NMR spectrum to be run, and no commercial material was available for a mixed m.p.

Reaction between 4-bromophenol and methyllithium.

This was carried out in a manner identical to the reaction with 2-bromophenol but quenched with D_2O to obtain 2-deutero-4-bromophenol as a product of the reaction.

ms. Peaks at 174/172 due to C_6H_4DBrO 18,7% of the abundance of the peaks at 173/171 due to C_6H_5BrO.

IR. $\bar{\nu}_{max}$(KBr). When compared with that of authentic 4-bromophenol the peak at 935 (C-H out-of-plane bend) had virtually disappeared. The peak at 1095 had increased and the peak at 1110 (C-H in-plane bend) had decreased in size.

NMR.(CCl_4+THF) δ 7,20(d(2H)Ar H-5,H-3)6,60(d(1,7H)H-2,H-6)8,07(s(1H)Ar OH, peak disappears in D_2O). This was identical to the NMR spectrum of authentic 4-bromophenol except for the decrease in the integral of the peak at 6,0 ppm.

Reaction of 4-bromo-2,6-dimethylphenol with methyllithium and n-butyllithium.

The alkyllithium (9 mmoles) was refluxed with the 4-bromo-2,6-dimethylphenol (3 mmoles, 0,603 g) in diethyl ether (5 ml) for 48 hours after mixing the reagents at 0°. The TLC of the product of the reaction between methyllithium and 4-bromo-2,6-dimethylphenol showed virtually no 2,6-dimethylphenol. However, the product of the reaction between n-butyllithium and 4-bromo-2,6-dimethylphenol (0,418 g) was shown by TLC and glc to be mainly 2,6-dimethylphenol. The two compounds were separated by microdistillation. The 2,6-dimethylphenol distilled over at 46 - 54°C

at 0,05 mm Hg and crystals formed on cooling (240 mg, 65%). It was purified by sublimation (175 mg), m.p. 49°C, undepressed when mixed with authentic 2,6-dimethylphenol (Lit.m.p. 49°C). The IR spectrum (KBr) was identical to that of authentic 2,6-dibromophenol.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 2.3

Reaction between 2-fluorophenol and n-butyllithium.

To n-butyllithium (10 mmoles) cooled in ice was added 2-fluorophenol (3,33 mmoles, 0,373 g) in diethyl ether (2 ml). The mixture was refluxed for 24 hours prior to work-up. The product (0,486 g) was dried on to silica gel (1 g) and loaded on to the top of a prepacked column of silica gel (30 g, 21 x 100 mm). The column was eluted with SOLVENT SYSTEM A. (pg. 94). Two main products were obtained.

(i) 2-butylphenol (238 mg) This compound had been obtained before in the reaction between 2,4,6-tribromophenol and n-butyllithium (see pg 101). Its IR spectrum was shown to be identical to that of the earlier product; it had the same R_f value on TLC in benzene + pet. ether (9 + 1) and co-injection of the two compounds on glc gave a single peak; the ms gave M^+ at m/e 150.

(ii) 3-butylphenol (51 mg) This was purified by distillation under reduced pressure and analysed by spectra only.

ms. m/e at 151(22)150(75,M^+)121(33)109(38)108(100)107(84)101 (22)79(30)77(42).

IR. (film) 3300(br,s,O-H)2920(s)2860(m)(Aliphatic CH_3)1590(s) 1490(m)1450(s)(Ar C=C)1150(m)1100(w)1060(w)(Ar C-H in-plane) 870(m,1 free Ar H)775(m,3 adj Ar H).

NMR (CCl_4) δ 7,1 - 6,6(m,H-4,H-5,H-6)6,50(s,H-2)(area under δ = 6,5 - 7,1 (4H))5,50(s(1H)Ar-OH)2,45(t(2H)Ar-CH_2-CH_2- -)1,2 - 1,7 (m(4H)-CH_2-CH_2-CH_2-CH_3)0,90(imp.t(3H)R-CH_2-CH_3)

Reaction between 2-fluorophenol and phenyllithium.

This was carried out on the same quantities of reactants and followed the same procedure as in the previous reaction with n-butyllithium. The product (351 mg) was loaded on to the top of a prepacked column of silica gel (30 g, 21 x 100 mm) and eluted with;

pet. ether (40 - 60°C) + benzene	(1 + 4)	250 ml,
pet. ether + benzene	(1 + 9)	250 ml,
benzene + ethyl acetate	(9 + 1)	200 ml,

Two main products were obtained.

(i) 2-phenylphenol (130 mg), m.p. 55,5°C, m.p. undepressed when mixed with the 2-phenylphenol obtained previously. (see pg 102).

(ii) 3-phenylphenol (35 mg) was purified by microdistillation and solidified in the tube. It was recrystallized from hexane, m.p. 76°C (Lit. m.p. 78°C).

Analysis: C, 84.29; H, 5.62. ($C_{12}H_{10}O$ requires C, 84.60; H, 5.88)

ms. m/e at 171(35)170(100,M^+)141(43)115(32)105(14).

IR. $\bar{\nu}_{max}$ (KBr) 3400(br,O-H)1590,1560,1480,1470(all m,Ar C=C) 1410(s,C-O)1160,1185,1199(C-H in-plane)780(w,3 adj Ar H) 879(m,1 free Ar H)745,690(s,5 adj Ar H).

NMR (CCl_4) δ 7,4 - 6,5(m(9H)Ar-H)5,8 - 5,2(br(1H)Ar-OH)

Reaction between 2-bromo-4,6-dichlorophenol and methyllithium.

To a chilled solution of methyllithium (15 mmoles) was added 2-bromo-4,6-dichlorophenol (5 mmoles, 1,210 g) in diethyl ether (20 ml) The ice bath was removed and the solution refluxed for one hour before work-up. The products were separated by column chromatography according to the standard procedure to give 7 products.

(i) 2,4-dichloro-6-methylphenol (86 mg) was purified by sublimation at 37°C and 1 mm Hg, m.p. 53 - 54°C (Lit.m.p. 54°C), and was analysed by spectra only.

ms. m/e at 178(40)176(60)143(34)141(100)113(13)112(11)111(15) 77(75)75(27).

IR. $\bar{\nu}_{max}$(KBr) 3400(br,m,O-H)2980,2955,2925(w,CH_3)1600(m)1470(s) (Ar C=C)1405(m,C-O)1235(OH deform)1160,1100(C-H in-plane) 855(s,1 free Ar H)

NMR ($CDCl_3$) δ 6,94(d(1H)Ar H-5)6,80(d(1H)Ar H-3)5,32(s(1H)O-H)2,20 (s(3H)Ar-CH_3)

(ii) 2,4-dichlorophenol (65 mg) had a m.p. 44,5 - 45°C (Lit.m.p.45°C), undepressed when mixed with authentic 2,4-dichlorophenol.

NMR ($CDCl_3$) δ 6,95(dd(1H)Ar H-5,$J_{3,5}$=3Hz,$J_{5,6}$=15Hz)6,8?(d(1H)Ar H-6, $J_{5,6}$=15Hz)6,61(d(1H)Ar H-3,$J_{3,5}$=3I 5,40(Br,s(1H)O-H).

(iii) 4-chloro-2-methylphenol (79 mg) was distilled at 48 - 55°C at 0,5 mm Hg to give a colourless liquid which crystallized,m.p.50°C (Lit. m.p. 51°C)

Analysis: C, 58.32; H, 4.5. (C_7H_7ClO requires C, 58.8; H, 4.8)

ms. Peaks at m/e 144(25)142(67)107(100)99(14)79(26)77(53).

IR. $\bar{\nu}_{max}$(KBr) 3300(br,OH)2920(w,CH_3)1600(w)1480(s)1450(m) (Ar C=C)1410(m,C-O)1200(O-H deform)1180,1120(C-H in-plane) 800(s,2 adj Ar H) 890,880(m,1 free H)

NMR (CCl_4) δ 6,97(d(1H)Ar H-3,$J_{3,5}$=2,5Hz)6,64(dd(1H)Ar H-5,$J_{5,6}$=9Hz, $J_{3,5}$=2,5Hz)7,19(d(1H)Ar H-6,$J_{5,6}$=9Hz)5,80(s(1H)OH,peak disappears in D_2O)2,16(s(3H)Ar-CH_3).

(iv) 2,2'-dihydroxy-3-methyl-3',5,5'-trichlorobiphenyl (240 mg) was recrystallized from benzene,m.p. 165 - 167°C.

Analysis: Calc. for $C_{13}H_9Cl_3O_2$ C, 51.75; H, 2.97
Found: C, 51.63; H, 2.97.

ms. m/e at 306(33)/304(95)/302(100)269(28)267(44)232(60)203(18) 139(18)

IR. $\bar{\nu}_{max}$(KBr) 3400(s,br,OH)2920,2960(w,CH_3)1585(w)1560(m)1460(s) (Ar C=C)1390(C-O)1200(OH deform)1150,1220(m,C-H)855(s,1 free Ar H)

NMR($(CD_3)_2CO$) δ 7,20(d(1H)Ar H-4',$J_{4',6'}$=3Hz)6,97(d(1H)Ar H-6',$J_{4',6'}$=3Hz) 7,00(s(1H)Ar H-6)6,89(s(1H)Ar H-4)4,5 - 5,5(br,s(2H)OH, peak disappears in D_2O)2,20(s(3H)Ar-CH_3)

(v) 2,2'-dihydroxy-3,5,5'-trichlorobiphenyl(74 mg) was recrystallized from benzene, m.p. 177 - 178,5°C and analysed by spectra only.

ms. Peaks at m/e 292(30)290(95)288(100)255(24)254(22)253(36) 227(14)225(22)220(18)219(15)218(50)217(14)189(25)162(22) 161(13)160(10)155(13)126(28)99(14)98(13).

IR. $\bar{\nu}_{max}$(KBr) 3350(s,br,OH)1560(w)1490(m)1460(s)(Ar C=C)1390 (C-O)1192,1100,1050(m,Ar C-H)860(m,1 free Ar H)810(m,2 adj H)

NMR$(CD_3)_2CO$ δ 7,22(d(1H)Ar H-4,$J_{4,6}$=2,5Hz)7,04(d(1H)Ar H-6',$J_{4',6'}$=2Hz) 7,02(d(1H)Ar H-6,$J_{4,6}$=2,5Hz)7,01(dd(1H)Ar H-4',$J_{4',6'}$=2Hz, $J_{3',4'}$=9Hz)6,80(d(1H)Ar H-3',$J_{3',4'}$=9Hz), OH peak under aromatics - integral decreases on addition on D_2O.

(vi) 3-methyl-2,2',2''-trihydroxy-3'',5,5',5''-tetrachloro-m-terphenyl (12)
This product was recrystallized from benzene + acetone, m.p. 263°C.

Analysis: Calc. for $C_{19}H_{12}Cl_4O_3$; C, 53.20; H, 2.80.
Found: C,53.7; H, 3.19.

ms. m/e at 434(11)432(51)430(97)428(76)398(8)396(27)394(30) 167(27)149(100).

IR. $\bar{\nu}_{max}$(KBr) 3400(br,s,OH)2920(w,CH_3)1560(w)1460(m)(Ar C=C) 1400(C-O)1200(OH deform)1140(m,C-H in-plane)860(m,1 free Ar H).

NMR$(CD_3)_2CO$ δ 7,17(d(1H)Ar H-4'',$J_{4'',6''}$=2Hz)7,02(s(4H)Ar H-4,H-4',H-6, H-6')6,9(d(1H)Ar H-6'',$J_{4'',6''}$=2Hz)4,6 -5,1(br,s,OH)2,19 (s(3H)Ar-CH_3)

(vii) 2,2',2''-trihydroxy-3,5,5',5''-tetrachloro-m-terphenyl (13) was purified by sublimation, m.p. 243°C and analysed by ms only.

ms. Peaks at m/e 420(?)418(10)416(19)414(16)188(32)186(33) 167(18)149(39)144(21)142(47)107(100).

Reaction between 2,4,6-triiodophenol and methyllithium.

2,4,6-Triiodophenol (3 mmoles, 1.416 g) and methyllithium (6 mmoles) in diethyl ether (10 ml) were refluxed for 5 hours before work-up and separation of the products by column chromatography using SOLVENT SYSTEM A. Three main products were obtained. The monomeric and major biaryl products emerged from the column simultaneously. Microdistillation

separated the monomer from the biaryl species.

(` 4-iodo-2-methylphenol (70 mg) was distilled at 80 - 90°C at 0,5 mm Hg and was recrystallized from hexane. m.p. 70 - 71°C (Lit.m.p. 72°C) Analysed by spectra only.

ms. Peaks at m/ 234(100)220(100)127(11)107(38)93(49)79(18) 78(18)77(47)65(46)

IR. $\bar{\nu}_{max}$(KBr) 3300(br,OH)1570(m)1475(s)1415(m)(Ar C-C 1160,1100 (C-H in-plane)810(s,1 free Ar H)795(m,2 adj Ar H).

NMR (CCl_4) δ 7,52(imp.d(2H)Ar H-3,H-5,$J_{5,6}$=10Hz)6,60(d(1H)Ar H-6, $J_{5,6}$=10Hz)5,3(br,s(1H)OH, peak disappears in D_2O)2, 0 (s(3H)Ar-CH_3).

(ii) 2,2'-dihydroxy-5,5'-diiodo-3,3'-dimethylbiphenyl (221 mg) was the major product from the reaction and was recrystallized from benzene, m.p. 159 - 160°C.

Analysis: Calc. for $C_{14}H_{12}I_2O_2$; C, 36.10; H, 2.58.
Found: C, 36.46; H, 2.69.

ms. Peaks at m/e 467(12)466(70)354(17)340(17)213(19)212(100) 211(20).

IR. $\bar{\nu}_{max}$(KBr) 2900(br,C-H) 1450(m,Ar C=C)1200(s,OH deform)1140 (m,C-H in-plane)850(m,1 free Ar H).

NMR($(CD_3)_2CO$) δ 7,57(d(2H)Ar H-6,$J_{4,6}$=3Hz)7,40(d(2H)Ar H-4,$J_{4,6}$=3Hz) 7.10(br,s(2H)Ar-OH, peak disappears in D_2O)2,27(s(6H)Ar-CH_3)

(iii) 2.2'-dihydroxy-5,5'-diiodo-3-methylbiphenyl (165mg) was recrystallized from benzene, m.p.177 - 178,5°C.

Analysis: Calc. for $C_{13}H_{10}I_2O_2$; C, 34.63; H, 2.21
Found: C, 34.79; H, 2.18.

ms. Peaks at m/e 453(23)452(100)452(100)340(43)325(15)213(26) 212(13)199(29)198(100)197(30)170(22)169(24)141(25)115(28) 99(26).

IR. $\bar{\nu}_{max}$(KBr) 3380(br,s,OH)2940,2900(w,C-H)1480(m)1450(s) (Ar C=C)1200(w)1120(m)1060(w)(C-H in-plane)860(m,1 free Ar H)798(· ^ adj Ar H).

NMR($(CD_3)_2CO$) δ 8,00(br,s(2H)Ar-OH,peak disappears in D_2O)7,59(dd(1H) Ar H-4',$J_{3',4'}$=10Hz,$J_{4',6'}$=2Hz)7,60(d(1H)Ar H-6',$J_{4',6'}$=2Hz) 7,45(s(2H)Ar H-4,H-6)6,88(d(1H)Ar H-3',$J_{3',4'}$=10Hz) 2,29(s(3H)Ar-CH_3).

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 2.4

Reaction between 2,4,6-tribromo-3-methylphenol and methyllithium.

To a chilled solution of methyllithium (6 mmoles) was added 2,4,6-tribromo-3-methylphenol (3 mmoles, 1,035 g) in diethyl ether (5 ml). The ice bath was removed and the solution was heated to reflux for 2 hours before quenching. The product (0,757 g) was dissolved in ethanol (40 ml). $Pd(OH)_2$ on $CaCO_3$ (2%, 2PM) was added and the solution stirred under hydrogen until no further uptake of gas occurred. Calcium carbonate was dissolved by the careful addition of HCl and the solution was filtered through celite to remove all palladium and then analysed by glc on 5% GE SE-52 on Supelco. The conditions used were; temperature 100°C to start and then increased at 6°C/minute, N_2 0,4 Kg cm^{-2}. The various dimethylphenols emerged at the following temperatures: 2,6- (132°C),2,4- and 2,5-(137°C) and 2,3-dimethylphenol (141°C).

Bromination of the dimethylphenol

Each dimethylphenol (12 mg) was dissolved in CCl_4 (3 ml) and titrated with a 0,5M solution of bromine in CCl_4 to the first permanent red colour. The solution was shaken for 10 minutes before both the solvent and excess bromine were removed in vacuo. The dehalogenated product of the reaction was treated in the same manner. The brominated compounds were analysed on the glc on the 5% GE SE-52 column, temperature isothermal at 160°C, N_2 0,4 Kg cm^{-2}.

A NOVEL MODE OF CHLORINATION OF AROMATIC COMPOUNDS.

Chlorination of the dimethylphenols.

Chlorine gas was bubbled through a weighed solution of CCl_4 cooled in a dry ice / acetone bath until there was no further colour change in the CCl_4. The increase in weight and hence the concentration of the chlorine in the CCl_4 was determined. The solution was then titrated against the product of the reaction (40 mg) in CCl_4 to the first permanent yellow colour. (The Cl_2/CCl_4 solution was stored in the dark in a sealed container for 6 months and was still effective after that time even though the exact molarity was no longer known.) The solution was stirred for 20 minutes before the excess Cl_2 and CCl_4 were removed and theproduct was analysed by glc against the similarly chlorinated authentic dimethylphenols under the same conditions as were employed for the brominated dimethylphenols. The results showed that co-injection of the chlorinated product of the reaction and chlorinated 2,4- or 2,6-dimethylphenol resulted in new peaks appearing on the gc trace (retention times 6,0 and 8,7 min. respectively) while co-injection of the chlorinated product of the reaction and chlorinated 2,3- or 2,5-dimethylphenol caused an increase in two peaks of retention time 6,7 and 7,4 minutes respectively.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 2.5

To 2,4,6-tribromophenol (3 mmoles, 0,993 g) in diethyl ether (8 ml) cooled in ice was added n-butyllithium (6 mmoles) dropwise from a syringe while stirring the tribromophenol solution rapidly. The ice bath was removed and the solution stirred at room temperature for one hour before recooling in ice and the appropriate amount of methyl iodide (3,21 or 3,7 mmoles) in diethyl ether was added. Then the solution was refluxed for 5 hours before work-up. The product was analysed by glc on the 5% OV SE-52 column - temperature isothermal at 125°C; N_2 0,4 Kg cm^{-2}. The reaction products were worked up in the normal way and the products separated by the standard procedure on column A using SOLVENT SYSTEM A.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 2.6.1

All reactions were performed according to the general procedure (see pg 93) using 5 mmoles of aryl [illegible] and 15 mmoles of methyllithium. These two compounds were refluxed together in diethyl ether (10 ml) for 5 hours before quenching the reaction with aqueous acid. The products were all separated on column A using SOLVENT SYSTEM A.

FOR Y = CH_3 (i.e. 2,6-dibromo-4-methylphenol.)

The following products were obtained:-

(i) 2-bromo-4,6-dimethylphenol (117 mg) was purified by microdistillation under reduced pressure at 80°C and 0,5 mm Hg. (Lit b.p$_{4}$ 105 - 106°C)

Analysis: C, 48,04; H, 4.55. (C_8H_9BrO requires C, 47.85; H, 4.48.)

ms. Peaks at m/e 202/200(100)187/185(20)122(33)121(22)91(54) 77(40)

IR. ν_{max}(film) 3500(m,OH)2910(m,CH_3)1440(m,Ar C=C)1240,1180, 1100(C-H in-plane)840(w, 1 free Ar H)

NMR (CCl_4) δ 6,78(br,s(1H)Ar H-3)6,58(Br,s(1H)Ar H-5)5,12(s(1H)Ar OH) 2,15(b.,s(6H)Ar-CH_3)

(ii) 2,4,6-trimethylphenol (mesitol) (58 mg) was purified by sublimation at 65°C and 0,3 mm Hg, m.p. 71 - 72°C (Lit.m.p.72°C) undepressed when mixed with authentic 2,4,6-trimethylphenol.

Analysis: C, 78.84; H, 8.82 ($C_9H_{12}O$ requires C, 79.00; H, 8.83)

NMR (CCl_4) δ 6,44(s(2H)Ar-H)4,42(br,s(1H)Ar-OH, peak disappears in D_2O)2,06(imp s(9H)Ar-CH_3).

(iii) 2,4-dimethylphenol (88 mg) was purified by distillation from a biaryl product at 70 - 80°C at 0,5 mm Hg. Its structure was verified by ms and comparison of IR (liquid film) with that of authentic 2,4-dimethylphenol.

ms. Peaks at m/e 123(18)122(100)121(94)108(15)107(97)91(30) 79(24)78(15)77(44).

(iv) 2,2'-dihydroxy-3,3';5,5'-tetramethylbiphenyl (254 mg) remained as a solid in the rear of the distillation tube after removal of the 2,4-dimethylphenol and was recrystallized from ethanol, m.p. 137 - 138°C. (Lit m.p. 137,5 - 138,5°C)

Analysis; C, 78.9; H, 7.17 ($C_{16}H_{18}O_2$ requires C 79.2; H, 7.44)

ms. Peaks at m/e 243(25)242(100)241(11)227(47)226(15)225(20) 209(17)199(21).

IR. $\bar{\nu}_{max}$ (KBr) 3400(br,s,O-H)2900(w,CH_3)1480(s)1430(w)(Ar C=C) 1220,1170,1110(all m, C-H in-plane)842(s, 1 free Ar H).

NMR (CCl_4 + $(CD_3)_2CO$) δ 6,64(br s(4H)Ar-H)4,52(s(2H)Ar-OH,peak disappears in D_2O) 2,16(s(12H)Ar-CH_3)

FOR Y = H (i.e. 2,6-dibromophenol)

Three main products were obtained.

(i) 6-bromo-2-methylphenol (80 mg) was purified by microdistillation at 50 - 55°C at 1 mm Hg (Lit $b.p._7$ 71 - 73°C) and analysed by spectra only.

ms. Peaks at m/e 188/186(33)187/185(12)142(32)141(27)107(100) 105(23)79(30)78(36)77(68).

NMR (CCl_4) δ 7,04(dd(1H)H-5,$J_{3,5}$=2Hz,$J_{4,5}$=7Hz)6,85(dd(1H)H-3,$J_{3,4}$=7Hz, $J_{3,5}$=2Hz)6,44(dd(1H)H-4,$J_{3,4}$=7Hz,$J_{4,5}$=7Hz)5,32(s(1H)Ar-OH) 2,22(s(3H)Ar-CH_3).

(ii) 2,6-dimethylphenol (37 mg) was recrystallized from ethanol, m.p. 48°C (Lit.m.p. 49°C) undepressed when mixed with an authentic sample of 2,6-dimethylphenol. Its ms (M^+ at m/e 122) confirmed its identity.

(iii) 2,2'-dihydroxy-3-3'-dimethylbiphenyl (230 mg) was purified by sublimation,m.p. 112°C (Lit.m.p. 113°C)

Analysis: C, 78.41; H, 6.56 ($C_{14}H_{14}O_2$ requires C, 78.50; H, 6.54)

ms. Peaks at m/e 215(17)214(100)213(12)199(23)197(16)195(13) 186(14)185(12)171(25).

IR $\bar{\nu}_{max}$ (KBr) 3200(br s,OH)1600(w)1555(w)1426(s)(Ar C=C)1280 (C-O)1169(m)1120(w)1078(w)(C-H)768(s,3 adj Ar H)

NMR (CCl_4 + $(CD_3)_2CO$) δ 6,45 - 6,95(m(6H)Ar H-4,H-4',H-5,H-5',H-6,H-6')4,50 (s(2H)Ar-OH,peak disappears in D_2O)2,22(s(6H)Ar-CH_3).

FOR Y = Br (i.e. 2,4,6-tribromophenol)

See pages 96 - 99

FOR Y = Cl (i.e. 2,6-dibromo-4-chlorophenol)

Two monomeric and two biaryl products were obtained.

(i) 4-chloro-2,6-dimethylphenol (32 mg) was obtained pure and crystalline from the column and was purified further by sublimation,m.p. 83 - 84°C (Lit.m.p. 83°C)

Analysis: C, 62.01; H, 5.38 (C_8H_9ClO requires C, 62.00; H, 5.75)

ms. Peaks at m/e 158(25)156(75)121(100)103(25)91(33)77(50).

IR. $\bar{\nu}_{max}$(KBr) 3350(br,s,OH)2900(w,CH_3)1470(s,Ar C=C)1180(s,OH deform)850(m, 1 free Ar H).

NMR (CCl_4) δ 6,95(s(2H)Ar H)4,40(s(1H)Ar-OH)2,20(s(6H)Ar-CH_3).

(ii) 4-chloro-2-methylphenol (80 mg) was obtained from the column together with a biaryl product and was separated from the latter by microdistillation at 50°C and 0,5 mm Hg as a colourless liquid which crystallized on cooling,m.p. 50°C, undepressed when mixed with the 4-chloro-2-methylphenol obtained in a previous reaction (see page 106). Its ms confirmed its identity (M^+ 144/142)

(iii) 5.5'-dichloro-2.2'-dihydroxy-3,3'-dimethylbiphenyl (153 mg) was obtained as cream coloured crystals in the rear of the tube after microdistillation (vide supra) and was recrystallized from benzene + hexane (4 + 1),m.p. 154°C.

Analysis: Calc. for $C_{14}H_{12}Cl_2O_2$; C, 59.4; H, 4.24,
Found: C, 59.53; H, 4.24

ms. Peaks at m/e 286(9)284(45)282(57)249(19)247(57)212(100)

IR. $\bar{\nu}_{max}$(KBr) 3300(br,m,OH)1468(m,Ar C=C)858(s, 1 free Ar H)

NMR ($(CD_3)_2CO$) δ 7,0 - 7,3(m,Ar-H, peak due to -OH under Ar-H signal causing broadening of the latter)2,30(s,Ar-CH_3)

(iv) 3-bromo-5,5'-dichloro-2,2'-dihydroxy-3'-methylbiphenyl was obtained from the column contaminated with small amounts of higher molecular weight species. It was not possible to obtain a pure sample of it. Analysis was only by ms in which the base peak was due to $C_{13}H_9Cl_2BrO$ - no peak of higher m/e greater than 2% abundance.

ms. Peaks at m/e 330(24)328(91)326(71)250(10)248(57)246(53) 212(100)

FOR Y = F (i.e. 2,6-dibromo-4-fluorophenol)

One major product and one minor product were obtained.

(i) C_8H_9BrO (10 mg) was obtained together with some biaryl product and was recrystallized but remained impure. The position of the second methyl group was uncertain. Attempts to dehalogenate it over $Pd(OH)_2$ on $CaCO_3$ to the dimethylphenol for comparison with the known dimethylphenols (xylenols) were unsuccessful. An NMR of the mixture suggested that it was mainly 2,4-dimethyl-6-bromophenol (meta splitting of the aromatic protons).

(ii) 5,5'-difluoro-2,2'-dihydroxy-3,3'-dimethylbiphenyl (130 mg) was the major product of the reaction and it was purified either by sublimation at 120°C and 1 mm Hg (m.p. 128 - 130°C) or by distillation at 85 - 90°C at 0,2 mm Hg. It solidified on cooling and was recrystallized from a pet. ether (40 - 60°C) / acetone/benzene mixture, m.p. 130°C. Analysed by spectra only.

ms. Peaks at m/e 251(30)250(100)235(20)234(15)233(13)232(10) 231(21)230(13)229(10)207(21)203(15)203(15)202(39)201(46) 133(38)125(17)

IR. $\bar{\nu}_{max}$ 3100(br,m,OH)2990(w)2935(w)(CH_3)1590(m)1470(s)(Ar C=C) 1225(m,C-O)1178,1120(s,C-H)860(s,1 free Ar H).

NMR ($CDCl_3$ + $(CD_3)_2CO$) δ 6,95(dd(2H)Ar H-4,H-4',$J_{4,6}$=8,5Hz,J_{HF}=3Hz)6,80(dd(2H) Ar H-6,H-6',$J_{4,6}$=8,5Hz,J_{HF}= 3Hz) These peaks coincided to give a triplet of doublets in the ratio 1:2:1) 6,30 - 6,0(br s(2H)O-H, peak disappears in D_2O)2,31(s(6H)Ar-CH_3)

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 2.6.2

The same general method of reaction was followed and the column dimensions for the separation of the products were unchanged (viz. 80 g, 32 x 190 mm) but the solvent system varied for each species.

FOR X = OH (i.e. 2,4,6-tribromophenol)

See pages 96 - 99

FOR X = OCH_3 (i.e. 2,4,6-tribromoanisole)

The products were separated by eluting the column with 100 ml of each of the following solvents; benzene + pet. ether (60 - 80°C) (1 + 1), (4 + 1), (9 + 1); benzene + ethyl acetate (24 + 1), (19 + 1), (9 + 1) to obtain:-

(i) 2,4-dibromo-6-methylanisole (34 mg) which was distilled at 80°C and 1 mm Hg; a colourless liquid.

Analysis: C, 34.04; H, 2.90 ($C_8H_8Br_2O$ requires C, 34.30; H, 2.86)

ms. Peaks at m/e 282/280 / 278(87)268/266/264(60)267/265/263(75) 253/251/249(34)225/223/221(32)158/156(57)157/155(20)90(30) 89(45)77(100).

IR. $\bar{\nu}_{max}$(film) 2950(m,C-H)1580(w)1465(s)1420(m)(Ar C=C)860 (1 free Ar H).

NMR (CCl_4) δ 7,44(d(1H)H-3,$J_{3,5}$=3Hz)7,18(imp.s(1H)H-5,$J_{3,5}$=3Hz) 3,72(s(3H)Ar-OCH_3)2,28(s(3H)Ar-CH_3).

(ii) 2,4-dibromoanisole (60 mg) was purified by microdistillation at 40°C at 0,1 mm Hg.

Analysis: C, 31.75; H, 2.33 ($C_7H_6Br_2O$ requires C, 31.60; H, 2.25)

ms. Peaks at m/e 268/266/264(100)253/251/249(54)225/223/221(34) 172/170(12)96(16)95(28)75(27)74(21)63(96)62(37).

IR. $\bar{\nu}_{max}$ (film) 2945(m,CH_3)1470(w)1445(m)1430(m)(Ar C=C)1380 (s,C-O)1180,1000,968(s,C-H)815(s, 1 free Ar H)745(m, 2 adj. Ar H).

(iii) 5,5'-dibromo-2,2'-dimethoxy-3,3'-dimethylbiphenyl (61 mg) was obtained as a solid and was recrystallized from pet. ether, m.p. 131°C.

Analysis: Calc. for $C_{16}H_{16}Br_2O_2$ C, 48.00; H, 4.00.
Found: C, 47.79; H, 4.03.

ms. Peaks at m/e 402/400/398(100)388/386/384(9)306/304(60) 291/289(48)240(40)226(26)210(36)182/181(26)163/162(25).

IR. $\bar{\nu}_{max}$ (KBr) 2948(m)2920(m)2825(w)(CH_3)1568(w)1463(s)1420(m) (Ar C=C)1400(s,C-O)1155,1005(s,C-H in-plane)862(s, 1 free Ar H).

NMR (CCl_4) δ 7,14(s(4H)Ar-H)3,39(s(6H)Ar-OCH_3)2,25(s(6H)Ar-CH_3)

(iv) 3,5,5'-tribromo-2,2'-dimethoxy-3-methylbiphenyl (148 mg) was recrystallized from benzene + hexane, m.p. 73 - 74°C.

Analysis: Calc. for $C_{15}H_{13}Br_3O_2$ C, 38.80; H, 2.80
Found: C, 39.3; H, 2.77.

ms. Peaks at m/e 468/466/464/462(75)453/451/449/447(100) 371/369/367(41)357/355/353(65)139(50).

IR. $\bar{\nu}_{max}$ (KBr) 2925(C-H)1540(w)1487(m)1457(s)1410(m)(Ar C=C) 1235(s,O-H)856(m, 1 free Ar H).

NMR (CCl_4) δ 7,20(s(4H)Ar-H)3,41(s(6H)Ar-OCH_3)2,29(s(6H)Ar-CH_3)

FOR X = 3 x CH_3 (i.e. 2,4,6-tribromo-1,3,5-trimethylbenzene)

The products of the reaction were separated on a column eluted with pet. ether + hexane (3 + 2) throughout to give two products.

(i) 4,6-dibromo-1,2,3,5-tetramethylbenzene (322 mg) was a crystalline solid and was recrystallized from benzene, m.p. (sealed tube) 198°C. (Lit.m.p. 198°C)

Analysis; C, 41.7; H, 4.08 ($C_{10}H_{12}Br_2$ requires C, 41.3; H, 4.13)

ms Peaks at m/e 294/292/290(100)280/278/276(14)213/211(80) 199/197(26)132(25)131(22)117(33)116(25)115(35).

IR. $\bar{\nu}_{max}$(KBr)2960(m)2860(w)(CH_3)1450(m,Ar C=C).

NMR (C_6D_6) δ 2,04(s(3H)Ar-CH_3,bonded to C5)1,67(s(6H)Ar-CH_3,bonded to C1,C3)1,40(s(3H)Ar-CH_3,bonded to C2).

(ii) 3,3'-dibromo-2,2',4,4',6,6'-hexamethylbiphenyl (65 mg) was a solid and was recrystallized from benzene,m.p. 112°C (Lit.m.p.112 - 113°C)

Analysis: C, 54.59; H, 5.31 ($C_{18}H_{20}Br_2$ requires C, 54.60; H, 5.05)

ms. Peaks at m/e 398/396/394(67)317/315(5)302/300(22)236(100) 221(80)206(27)205(18)203(10)191(19) and several m/2e peaks from 118 to 95,5.

IR. $\bar{\nu}_{max}$(KBr) 2980(w)2950(w)2920(m)2860(w)(CH_3)1450(s,Ar C=C) 1055(s,C-H)865,870(m 1 free Ar H)

NMR (C_6D_6) δ 6,01(s(2H)ArH-5,H-5')1,61(s(6H)Ar-CH_3)1,36(s(6H)Ar-CH_3) 0,94(s(6H)Ar-CH_3)

FOR X = CH_3 (i.e. 2,4,6-tribromotoluene)

Great difficulty was experienced in separating the two products which had virtually identical R_f values in hexane. The product was loaded on to a column (usua size) and eluted with hexane in a cold room at 5°C. The first fraction contained only one compound, two fractions contained both and the rest contained the second compound. The fractions containing both products were recolumned twice more to obtain further pure samples of the two compounds.

(i) 2,6-dibromo-1,4-dimethylbenzene (239 mg) was a solid and was recrystallized from ethanol,.m.p. 35,5°C (Lit.m.p. 36°C).

Analysis; C,36.46; H, 2.70 ($C_8H_8Br_2$ requires C, 36.30; H, 3.0)

ms. Peaks at m/e 266/264/262(100)185/183(67)104(42)103(37) 102(14)77(32).

IR. $\bar{\nu}_{max}$(KBr) 2955(w)2920(m)2865(w)(CH_3)1600(m)1540(m)1460(s) (Ar C=C)1053(Ar C-H)850(s , 1 free Ar H).

NMR (CCl_4) δ 7,17(s(2H)Ar-H)2,46(s(3H)Ar-CH_3)2,20(s(3H)Ar-CH_3).

(ii) 3,5-dibromo-1,2-dimethylbenzene (187 mg) was recrystallized from ethanol, m.p. 63°C.

Analysis; Calc. for $C_8H_8Br_2$ C, 36.30; H, 3.0
Found: C, 36.17; H, 3.38.

ms. Peaks at m/e 266/264/262(100)251/249/247(13)185/183(69) 105(6)104(45)103(46)102(14)77(36).

IR. $\bar{\nu}_{max}$(KBr) 2950(w)2920(m)2860(w)(CH_3)1580(m)1500(m)1458(s) (Ar C=C)1160(Ar C-H)860(m)850(s)(1 free Ar H).

NMR (CCl_4) δ 7,49(d(1H)Ar H-4,$J_{4,6}$=2Hz)7,15(d(1H)Ar H-6,$J_{4,6}$=2Hz) 2,30(s(6H)Ar-CH_3)

FOR X = H (i.e. 1,3,5-tribromobenzene)

Initial reactions between 1,3,5-tribromobenzene and methyllithium gave very poor yields as the products were quite volatile and hence readily lost while removing the solvents unless the temperature of the water bath was kept quite low. The products were separated by column chromatography eluting with benzene + hexane (1 + 9) 100 ml; (1 + 1) 100 ml; and finally with pure benzene. One major product and three minor monomeric products were obtained;

(i) 1,3-dibromo-5-methylbenzene (332 mg) was a crystalline solid which was purified by microdistillation to yield a colourless liquid which crystailized in luminous feathers, m.p. 39°C (Lit.m.p.39°C)

Analysis; C, 33.63; H, 2.44 ($C_7H_6Br_2$ requires C, 33.62; H, 2.40)

ms. Peaks at m/e 252/250/248(100)171/169(48)90(40)89(28).

IR. $\bar{\nu}_{max}$(KBr) 3070,2960,2920,2840(all w, C-H)1585(w)1555(w) 1430(m)(Ar C=C)860(w, 1 free Ar H).

NMR (CCl_4) δ 7,37(imp s(1H)Ar H-2)7,15(imp s(2H)Ar-H-4,H-6)2,30 2,30(s(3H)Ar-CH_3).

The other three monomeric products were identified on the basis of their m only.

Monitoring the reaction between 2,4,6-tribromomesitylene and methyllithium.

2,4,6-Tribromomesitylene (1,071 g, 3 mmoles) was dissolved in dry benzene (20 ml) and cooled in ice. Methyllithium (3 mmoles) was added over 2 minutes and immediately after addition, an aliquot (1 ml) of solution was withdrawn and injected into 2M HCl (2 ml). This was then shaken up with a benzene / diethyl ether solution and the organic layer analysed by glc. Meanwhile, the ice bath was removed and the solution heated to 25°C. Further samples were withdrawn at 5, 11, 16, 20, 37, 60 and 100 minutes after mixing of the two reactants. Glc analysis of the samples showed that some lithiation had occurred within 5 minutes but the starting material was still the major species present for the first 30 minutes. Co-injection of the starting material with the sample taken after 100 minutes showed that a small amount of starting material was still present.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 2.7

Reaction between 2.4.6-tribromophenol and insufficient methyllithium.

To an ice-cold solution of 2,4,6-tribromophenol (1,65 g, 5 mmoles) in dry diethyl ether (10 ml) was added methyllithium (7,5 mmoles) over 3 minutes. The solution was then heated and refluxed for 5 hours before quenching and working up in the usual manner. The products were separated on column A using SOLVENT SYSTEM A to yield as the major product

2.2'2"-trihydroxy-3.3",5,5',5"-pentabromo-m-terphenyl (34) (602 mg) which was recrystallized from benzene / acetone to yield tiny clusters of crystals, m. p. 207 - 208°C. The compound was analysed by its spectra only.

ms. Peaks at m/e 678/676/674/672/670/668(100)598/596/594/592/590(25)516/514/512/510(57)354/352(28)126/(46)125(29)82(54)80(57).

Monitoring the reaction between 2,4,6-tribromomesitylene and methyllithium.

2,4,6-Tribromomesitylene (1,071 g, 3 mmoles) was dissolved in dry benzene (20 ml) and cooled in ice. Methyllithium (3 mmoles) was added over 2 minutes and immediately after addition, an aliquot (1 ml) of solution was withdrawn and injected into 2M HCl (2 ml). This was then shaken up with a benzene / diethyl ether solution and the organic layer analysed by glc. Meanwhile, the ice bath was removed and the solution heated to 25°C. Further samples were withdrawn at 5, 11, 16, 20, 37, 60 and 100 minutes after mixing of the two reactants. Glc analysis of the samples showed that some lithiation had occurred within 5 minutes but the starting material was still the major species present for the first 30 minutes. Co-injection of the starting material with the sample taken after 100 minutes showed that a small amount of starting material was still present.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 2.7

Reaction between 2.4.6-tribromophenol and insufficient methyllithium.

To an ice-cold solution of 2,4,6-tribromophenol (1,65 g, 5 mmoles) in dry diethyl ether (10 ml) was added methyllithium (7,5 mmoles) over 3 minutes. The solution was then heated and refluxed for 5 hours before quenching and working up in the usual manner. The products were separated on column A using SOLVENT SYSTEM A to yield as the major product

2,2',2"-trihydroxy-3,3",5,5',5"-pentabromo-m-terphenyl (34) (602 mg) which was recrystallized from benzene / acetone to yield tiny clusters of crystals, m. p. 207 - 208°C. The compound was analysed by its spectra only.

ms. Peaks at m/e 678/676/674/672/670/668(100)598/596/594/592/590(25)516/514/512/510(57)354/352(28)126/(46)125(29)82(54)80(57).

IR. $\bar{\nu}_{max}$(KBr) 3400(br,s,O-H)1600(w)1535(w)1440(s)(Ar C=C) 1370(OH deform)1200(m,C-O)840(s, 1 free Ar H).

NMR ($(CD_3)_2CO$) δ 7,72(d(2H)Ar H-4,H-4",$J_{4,6}$=3Hz)7,49(s(2H)Ar H-4',H-6') 7,42(d(2H)Ar H-6,H-6",$J_{4,6}$=3Hz)6,20(s(3H)Ar-OH, peak disappears in D_2O).

Reaction between 2,4-dibromo-6-methylphenol and methyllithium.

2,4-dibromo-6-methylphenol (0,798 g, 3 mmoles) in diethyl ether (7,5 ml) was cooled in ice and stirred rapidly while methyllithium (6 mmoles) was added over 3 minutes. The solution was then heated to reflux for 5 hours before the reaction was quenched with aqueous acid. The products were separated by column chromatography according to the general procedure using SOLVENT SYSTEM A to yield 49% (0,391 g) of the starting material and 2-methyl-4-bromophenol (0,202 g) which was purified by sublimation at 30°C and 0,05 mm Hg and identified by its IR and m.p. (63 - 64°C) which was undepressed when admixed with the 4-bromo-2-methylphenol obtained previously. The 4-bromo-2,6-dimethylphenol obtained was identified only by its R_f on TLC and by co-injection on glc with fully characterized material, as was the biaryl product.

Reaction between 2,4,6-tribromophenol, 2,4-dibromo-6-ethylphenol and methyllithium.

2,4,6-tribromophenol (1,65 g, 5 mmoles) and 2,4-dibromo-6-ethylphenol (1,40 g, 5 mmoles) were weighed into the reaction flask. The flask was then flushed gently with nitrogen and sealed with a rubber septum before diethyl ether (15 ml) was added. After cooling the flask in ice, methyllithium (15 mmoles) was added and the reaction was then heated to reflux for 5 hours. The reaction was quenched, worked up and the products separated in the usual manner. The products were identified by their R_f value on TLC in benzene + ethyl acetate (9 + 1), R_T on glc, and mixed melting points with the known compounds. The following compounds were obtained:-

(i) 2,4-dibromo-6-ethylphenol (1,228 g) was distilled under reduced pressure and an IR spectrum run which was found to be identical to that of the starting material.

(ii) 4-bromo-2-ethyl-6-methylphenol (111 mg) was recrystallized from hexane + benzene (3 + 1), m.p. 44°C. It was analysed by its spectra only.

ms. Peaks at m/e 216/214(100,M^+)201/199(94)135(46)115(17) 92(43)91(38)77(17).

IR. $\bar{\nu}_{max}$(KBr) 3400(s,O-H)2960,2920,2870(w,CH_2,CH_3)1470(m, Ar C=C)1310(m,OH deform)1190(s,C-O)1010(m,C-H in-plane) 960(m, 1 free Ar H)

NMR ($CDCl_3$) δ 7,31(s(1H)Ar H-5)7,19(s(1H)Ar H-3)4,35(br s(1H)Ar-OH, peak disappears in D_2O)2,60(q(2H)Ar-CH_2-CH_3,J=7Hz) 2,24(s(3H)Ar-CH_3)1,23(t(3H)Ar-CH_2-CH_3,J=7Hz)

(iii) 4-bromo-2-ethylphenol (58 mg) was purified from the biaryl product by distillation under reduced pressure at 80°C at 0,3 mm Hg. (Lit.b.p.$_3$ = 110°C)

ms. Peaks at m/e 202/200(97,M^+)187/185(100)121(36)91(19) 78(41)77(33).

IR. $\bar{\nu}_{max}$(film) 3400(s,O-H)2960,2920,2860(w,C-H)1600(w)1480 (s)(Ar C=C)1400(m,OH deform)1240(C-O)1100(s,C-H in-plane) 870(m, 1 free Ar H)800(s, 2 adj.H).

(iv) 5,5'-dibromo-2,2'-dihydroxy-3,3'-dimethylbiphenyl (350 mg)

(v) 2,2'-dihydroxy-3-methyl-3',5,5'-tribromobiphenyl (73 mg)

(i) symmetrical biaryl (14) (144 mg) and

(vii) unsymmetrical biaryl (15) (20 mg) products were also obtained.

All were characterized after recrystallization by their m.p., mixed.m.p. and IR spectra.

C. Experimental Procedures Relating to Chapter 3.

Reaction between 2-bromophenol and n-butyllithium with the addition of methyl iodide.

To an ice-cold solution of 2-bromophenol (0,493 g, 2,84 mmoles) in diethyl ether (8 ml) was added n-butyllithium (5,68 mmoles). The ice bath was removed and the solution stirred at room temperature (25°C) for one hour. Then methyl iodide (56,8 mmoles, 3,6 ml) in diethyl ether (10 ml) was added dropwise over one minute and the reaction was then heated to reflux for 5 hours before quenching. After work-up, the products were separated on the usual column (see general procedures) using SOLVENT SYSTEM A. The first compound to emerge from the column was

2-iodophenol (200 mg) which was purified by distillation at 60°C and 0,1 mm Hg. The liquid crystallized on cooling, m.p. 38 - 39°C (Lit. m.p. 43°C) It was analysed by its spectra only.

ms. Peaks only at m/e 221(8)220(100,M^+)93(35)and66_(51)

IR. $\bar{\nu}_{max}$(KBr)3200(br,m,O-H)1570(m)1442(s)(Ar C=C)1225(m) 1125(m)1040(m)1018(s)(C-H in-plane)745(s. 4 adj.Ar H)

NMR (CCl_4) δ 7,48(d(1H)Ar H-3,$J_{3,4}$=7Hz)7,08(dd(1H)Ar H-5,$J_{5,6}$=8Hz, $J_{4,5}$=9Hz)6,80(d(1H)Ar H-6,$J_{5,6}$=8Hz,6,48(dd(1H)Ar H-4, $J_{3,4}$=7Hz,$J_{4,5}$=9Hz)5,00(s(1H)Ar-OH).

2-methylphenol (98 mg) and phenol (23 mg) were also obtained from the reaction. Both were identified by their IR spectra only which were shown to be identical to that of authentic 2-methylphenol and phenol respectively.

Reaction between 2-fluorophenol and n-butyllithium.

To n-butyllithium (6 mmoles) in an iced reaction flask was added 2-fluorophenol (0,373 g, 3 mmoles) in diethyl ether (5 ml). The resul-

tant solution was stirred at 25°C for 5 hours before re-cooling in ice and methyl iodide (3,67 ml, 60 mmoles) in diethyl ether (5 ml) was added over 10 minutes. The reaction was heated to reflux for 40 hours before quenching. The product was dried on to silica gel (1 g) and loaded on the top of a prepacked column of silica gel (30 g, 21 mm diameter) and eluted with benzene (50 ml); benzene + ethyl acetate (19 + 1) 50 ml; (9 + 1) 100 ml, to obtain two new compounds and recover some of the starting material.

(i) 2-n-butyl-3-iodophenol (70 mg) was obtained pure and crystalline from the column on removal of the solvent, m.p. 49,5°C.

ms. Peaks at m/e 277(36)276(85)246(6)234(41)233(100)220(15) 149(12)121(16)108(18)107(57)106(19)91(25)79(26)78(76).

NMR (CCl_4) δ 7,30(dd(1H)Ar H-4, $J_{4,5}$=6Hz, $J_{4,6}$=3Hz)6,61(d,Ar H-5, $J_{4,5}$=6Hz)6,58(d,Ar H-6, $J_{4,6}$=3Hz) The upfield peaks of the last two protons are co-incident. The resultant 3 peaks integrate for 2 protons. δ 4,68(s(1H)Ar-OH) 2,73(t(2H)Ar-CH_2-CH_2-)~1,5(m(4H)Ar-CH_2-CH_2-CH_2-CH_3) 0,97(t(3H)R-CH_2-CH_3)

The sample was dehalogenated over $Pd(OH)_2$ on $CaCO_3$ to obtain 2-butylphenol. This was purified by distillation at a reduced pressure. Its IR and NMR were run and shown to be identical to that of the 2-n-butylphenol obtained previously (see pg.101).

(ii) 3-n-butyl-2-iodophenol (14 mg) was analysed by its mass spectrum alone.

ms. Peaks at m/e 277(24)276(100,M^+)247(21)235(20)234(85) 233(77)190(8)175(11)151(7)149(25)121(24)120(33)107(100). 91(28)79(21)78(59)77(57)73(56)

It was hydrogenolysed and purified as for 2-butyl-3-iodophenol to obtain just sufficient material to run an IR film which was shown to be identical to that of the 3-butylphenol obtained previously.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 3.2

Reaction in Oxygen-free Atmosphere.

The diethyl ether used was dried in the usual manner over $CaCl_2$ and then sodium added but now benzophenone was added to the diethyl ether standing over sodium wire and the ether was distilled off from the resulting solution on to molecular sieve (3Å). A two-bulbed reaction flask was employed. Into the lower bulb the methyllithium solution (10 mmoles) was introduced via a rubber septum. In the upper bulb the 2,4,6-tribromophenol (5 mmoles) in diethyl ether (10 ml) was added. The contents of both bulbs were frozen solid in liquid nitrogen before evacuating the system with a high-vacuum pump. Once the minimal pressure had been obtained, the system was closed and the solutions warmed to room temperature. The gases present in the solutions bubbled out on warming. The cooling and evacuating procedure was repeated 3 to 4 times until no more gas evolved from the solutions on warming. The lower bulb was then cooled in ice and the contents of the upper bulb gradually poured into the lower. The combined solutions were then heated to reflux for 5 hours before work-up in the usual manner.

Reaction in the Presence of Oxygen.

The method was as for the general procedure but instead of high purity nitrogen, medical air (79,9% nitrogen, 20% oxygen) was used.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 3.3

Reaction between 2,4,6-tribromophenol and Methyllithium with the Addition of Galvinoxyl.

To an iced solution of 2,4,6-tribromophenol (1,665 g, 5 mmoles) in diethyl ether (18 ml) was added methyllithium (10 mmoles) dropwise over 3 minutes. The solution was stirred at $0^{o}C$ for 30 minutes before galvinoxyl (0,15 g, 0,356 mmoles) in dry benzene (10 ml) was added. The

colour of the solution went from deep purple to light yellow within 5 minutes. The ice bath was removed and the reaction solution allowed to come to 25°C. Thirty minutes later the reaction was quenched with the calculated minimum amount of water. Aluminium oxide (17,5 g) was added to the solution which was then refluxed for half-an-hour before cooling, filtering and working up in the usual manner. The products were separated by column chromatography on silica gel using SOLVENT SYSTEM A. The first fraction (145 mg) contained mainly one new compound. This fraction was re-chromatographed on a silica gel column (10 g, 15 mm diameter) eluted with hexane + benzene (3 + 1) 20 ml; (1 + 1) 24 ml; (1 + 3) 20 ml. Two-and-a-half ml fractions were collected. One major product was obtained.

1,1-di-[3,5-bis(1,1-dimethylethyl)-4-hydroxy]phenylethane (45) was recrystallized from pet. ether (40 - 60°C) to yield light yellow crys-tals, m.p. 156°C.

Analysis: Calc. for $C_{30}H_{46}O_2$, C, 82.2; H, 10.56
Found; C, 82.37; H, 10.43.

ms. Peaks at m/e 439(54)438(92,M^+)424(84)423(100)381(28) 379(30)234(35)233(92)204(35)190(26)149(52)57(92)

IR. $\bar{\nu}_{max}$ 3600(s, non-bonded O-H)3400(br,s,OH)2940(s)2845(m) (C-H)1445(m)1425(s)(Ar C=C)1350(m,OH deform)1220(s,C-O) 1145(s)1135,1105(m)(C-H in-plane)865(m,1 free Ar H).

NMR ($CDCl_3$) δ 7,04(s(4H)Ar-H)5,00(s(2H)Ar-OH)3,95(q(1H)CH_3-CH,J=8Hz) 2,62(d(3H)CH_3-CH,J=8Hz)1,41(s(36H)C-(CH_3)$_3$).

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 3.4

Preparation of 2-lithioorcinol dimethyl ether.

To an ice-cold solution of 2-bromoorcinol dimethyl ether (1,155 g, 5 mmoles) in diethyl ether (20 ml) was added n-butyllithium (5 mmoles). The ice bath was removed and the solution heated to reflux for 20 hours. - SOLUTION I.

Preparation of 2,6-dibromo-4-methyl-N,N-dilithioaniline

2,6-Dibromo-4-methylaniline (1,325 g, 5 mmoles) in diethyl ether (8 ml) was cooled in ice and n-butyllithium (10 mmoles) was added dropwise to the solution. This was stirred at 0°C for 20 minutes before solution I was added. The mixture was then refluxed for 5 hours before quenching. The only new products obtained were;-

(i) 2-bromo-4-methylaniline which had been prepared previously.[204] Thus, this compound was identified by its IR spectrum (KBr) which was shown to be identical to that obtained previously. Its m.p. (26°C) was undepressed when it was admixed with the previous sample. The two compounds also had identical R_f values on TLC in benzene + ethyl acetate (9 + 1).

(ii) 2,2'-diamino-3-bromo-5,5'-dimethylbiphenyl (124 mg) which was a solid. It was recrystallized from benzene / hexane, m.p. 108°C.

Analysis: Calc. for $C_{14}H_{15}N_2Br$, C, 58.6, H, 5.15; N, 9.61
Found; C, 58.4; H, 5.29; N, 9,43.

ms. Peaks at m/e 292/290(50)211(17)200(18)196(19)195(28)
194(23)152(18)151(33)106(24)105(70)104(29)94(100)91(62).

IR. $\bar{\nu}_{max}$ (KBr) 3420(m)3336(w)3276(m)(bonded and non-bonded N-H)2910(w,C-H)1616(s,N-H deform,1° amine)1501,1466, 1447(s,C=C)807(s,2 adj Ar H)851(s,1 free Ar H)

NMR ($CDCl_3$) δ 7,36(imp s(1H)Ar H-4)7,12(dd(1H)Ar H-4',$J_{3',4'}$=8Hz, $J_{4',6'}$=2,5Hz)7,00(imp s(2H)Ar H-6,H-6')6,78(d(1H)Ar H-3', $J_{3',4'}$=8Hz)4,09(br s(2H)Ar-NH_2)3,60(br s(2H)Ar-NH_2) 2,25(s(6H)Ar-CH_3)

Reaction between 2-lithioanisole and 2,4,6-tribromophenol.

A solution of 2-bromoanisole (1,122 g, 6 mmoles) in diethyl ether (10 ml) was cooled in ice before adding n-butyllithium (6 mmoles). The ice bath was removed and the solution stirred at 25°C for 1 hour. Then the reaction flask was again cooled in ice and a solution of 2,4,6-tribromophenol (0,993 g, 3 mmoles) in diethyl ether (8 ml) was added rapidly from a syringe via a rubber septum. The solution was heated

to reflux for 16 hours before quenching and working up when 4 main products were obtained.

(i) 2,4-dibromophenol (69 mg) was purified by microdistillation at 55 - 60°C at 0,3 mm Hg and crystallized on cooling; m.p. undepressed when admixed with authentic material, IR spectrum shown to be identical to that of 2,4-dibromophenol.

(ii) 3,5-dibromo-2-hydroxy-2'-methoxybiphenyl (134 mg) was the solid in the rear of the microdistillation tube after removal of 2,4-dibromophenol. It was recrystallized from acetone / diethyl ether, m.p. 135°C.

Analysis: Calc. for $C_{13}H_{10}Br_2O_2$, C, 43.75; H, 2.79
Found; C, 44.08; H, 3.12.

ms. Peaks at m/e 360/358/356(100)264/262(26)248/246(13)199(43) 198(14)183(16)170(19)169(16)155(41)139(20)127(22)126(28) 99(19)63(25)

IR $\bar{\nu}_{max}$(KBr) 3400(s,O-H)2950,2875(w,C-H)1598,1580(w)1495, 1450(m)(Ar C=C)1240(s,C-O)1220(s)1115(m)1010(s)(C-H in-plane)800(m,1 free Ar H)750(s,4 adj Ar H)

NMR ($(CD_3)_2CO$) δ 7,6 - 7,05(m(5H)Ar H-6,H-3',H-4',H-5',H-6')7,73(d(1H) Ar H-4,$J_{4,6}$=3Hz)7,90(s(1H)Ar-OH, peak disappears in D_2O) 3,85(s(3H)Ar-OCH_3)

(iii) 3,3',5,5'-tetrabromo-2,2'-dihydroxybiphenyl (161 mg) was purified by sublimation and recrystallized from $CHCl_3$, m.p. 206 - 207°C, and was analysed by spectra only.

ms. Peaks at m/e 506/504/502/500/498(100,M^+)344/342/340(82) 278/276(15)263/261(11)235/233(19)172/171(M^{2+},32)149(24) 126(24)125(20).

IR $\bar{\nu}_{max}$(KBr) 3400(br,OH)1585,1550(w)1460(s)(Ar C=C)1240 (C-O)1150(m,C-H in-plane)865(s,1 free Ar H).

NMR ($(CD_3)_2CO$) δ 7,80(d(2H). H-4,H-4',$J_{4,6}$=2,5Hz)7,45(d(2H)Ar H-6,H-6' $J_{4,6}$=2,5Hz)3,87(br s,Ar-OH)

(iv) 3,5,5'-tribromo-2,2'-dihydroxy-2"-methoxy-m-terphenyl (50) (65 mg) was recrystallized from benzene / hexane / acetone, m.p. 220 - 221°C.

ms. Peaks at m/e 532/530/528(100)370/368(25)274(15) 226/225/224(23,M^{2+})197(18).

IR. $\bar{\nu}_{max}$(KBr) 3500(s,O-H)2950(w,C-H)1585,1555(w)1500(m)1468, 1450(s)(Ar C=C)1220(s,C-O)1180(m)1020(m,C-H in-plane) 870(m,1 free Ar H)760(s,4 adj Ar H).

NMR ($(CD_3)_2CO$) δ 7,80(d(1H)Ar H-4,$J_{4,6}$=3Hz)7,57(d(1H)Ar H-6,$J_{4,6}$=3Hz) 7,51(s(2H)Ar H-4',H-6')7,4 - 7,1(m(4H)Ar H-3",H-4",H-5", H-6")~7,4(br s,Ar-OH, reduction in peak size in D_2O) 3,91(s(3H)Ar-OCH_3)

Reaction between 2-lithiumphenol-O-lithiate and 2,4,6-tribromophenol

To an ice-cold solution of 2-bromophenol (1,038 g, 6 mmoles) in diethyl ether (10 ml) was added n-butyllithium (12 mmoles) dropwise. The ice bath was replaced by an oil bath and the reaction heated to reflux for 17 hours before quenching with aqueous acid and working up in the usual manner. The resulting oil (1,30 g) was dried on to silica gel (4 g) and the products separated by column chromatography on the standard column using SOLVENT SYSTEM A to obtain:-

(i) 2-bromophenol (410 mg) which was distilled and its IR spectrum (film) shown to be identical to that of authentic 2-bromophenol.

(ii) Phenol (210 mg) which was recrystallized from water, m.p. 43°C, undepressed when admixed with authentic phenol.

(iii) 5-bromo-2,2'-dihydroxybiphenyl (135 mg) was recrystallized from hexane / benzene, m.p. 114 - 115°C.

Analysis: Calc. for $C_{12}H_9BrO$, C, 57.88; H, 3.61
Found; C, 57.35; H, 3.23.

ms. Peaks at m/e 266/264(80)185(100)184(98)157(40)156(72) 139(42)131(37)129(48)128(63)127(33).

IR. $\bar{\nu}_{max}$(KBr) 3300(br,O-H)1580(w)1480,1440(s)(Ar C=C)1200 (C-O)880(m,1 free Ar H)800(s,2 adj Ar H)740(s,4 adj Ar H)

NMR ($(CD_3)_2CO$) δ 7,5(d,Ar H-6,$J_{4,6}$=2,5Hz)7,47(d,Ar H-3,$J_{3,4}$=7,5Hz) 7,30(dd,Ar H-4,$J_{3,4}$=7,5Hz,$J_{4,6}$=2,5Hz)7,2 - 6,9(m,Ar H-3', H-4',H-5',H-6')(area under 7,5 - 6,9 = 7H) δ 8,20(br s, Ar-OH, peak disappears in D_2O)

(iv) 3,5-dibromo-2,2'-dihydroxybiphenyl (25 mg) was recrystallized from hexane / benzene, m.p. 174°C. It was analysed by its ms and IR spectra only.

ms. Peaks at m/e 346/344/342(33,M^+)266/264(27)185(39)184(100) 157(14)156(23)155(19)128(36)127(20).

IR. $\bar{\nu}_{max}$(KBr) 3300(br,O-H)1460,1430(m,Ar C=C)1380(s,C-O) 1200(O-H deform)865(m,1 free Ar H)780(s, 4 adj Ar H).

(v) 5,5'-dibromo-2,2',2"-trihydroxy-m-terphenyl (57) (110 mg) was recrystallized from $CHCl_3$ / benzene / acetone, m.p. 236 - 237°C.

ms. Peaks at m/e 438/436/434(100)277(23)276(99)259(16)258(57) 248(26)247(23)189(21)148(25)139(20)100(20)78(43).

IR. $\bar{\nu}_{max}$(KBr) 3250(br,O-H)1570(w)1495(s)1460(m)(Ar C=C)1390 (s,C-O)1200(s,O-H defrom)860(m,1 free Ar H)815(m,2 adj Ar H)750(s,4 adj Ar H)

NMR ($(CD_3)_2CO$) δ 7,5(br s(3H)Ar-OH, reduction in integral of aromatics when spectrum rerun in D_2O)7,56(s,Ar H-4',H-6')7,6 - 7,3 (m,Ar H-3",H-4",H-6")7,2 - 6,9(m,Ar H-3,H-4,H-5,H-6)

Reaction between 2-lithioanisole and O-lithiate of 2,4,6-tribromophenol.

A two-bulb reaction flask was employed. To a [illegible]-cold solution of 2-bromoanisole (0,516 g, 3 mmoles) in diethyl ether (10 ml) in the lower bulb was added n-butyllithium (3 mmoles). The ice bath was removed and the solution stirred at 25°C for one hour. In the upper bulb a solution of 2,4,6-tribromophenol (0,993 g, 3 mmoles) in diethyl ether (5 ml) was introduced. After the solution in the lower bulb had been stirring for 55 minutes, n-butyllithium (3 mmoles) was added to the now iced tribromophenol solution via a rubber septum. Five minutes after this addition, by tilting the apparatus, the O-lithiate of 2,4,6-tri-

bromophenol was run slowly into the cooled solution of the 2-lithioanisole in the lower bulb. The ice bath was removed and the reaction mixture was heated to reflux for 21 hours before quenching and work-up. The product (0,7 g) was dried on to silica gel (2 g), loaded on to a pre-packed column of silica gel of the usual dimensions and eluted with SOLVENT SYSTEM A to obtain 19% of 2,4-dibromophenol and only 10% of the biaryl 3,5-dibromo-2-hydroxy-2'-methoxybiphenyl. Both products were identified by their IR spectra and their m.p. which were undepressed when these products were admixed with the identical compounds obtained from the previous reactions.

Reaction between 2-lithioanisole and 2,4,6-tribromo-3-methylphenol

2-Bromoanisole (0,374 g, 2 mmoles) was dissolved in diethyl ether (5 ml) and cooled in ice. While stirring vigorously, n-butyllithium (2 mmoles) was added. The ice bath was removed and the solution stirred at room temperature for one hour before re-cooling to $0^{o}C$ and adding the 2,4,6-tribromo-3-methylphenol (0,345 g, 1 mmole) in diethyl ether (5 ml). The solution was then heated to reflux and left for 18 hours before quenching. The product of the reaction (0,40 g) was dried on to silica gel (1 g) and loaded on to the standard silica gel column. The column was eluted with SOLVENT SYSTEM A. Only the major product of the reaction was investigated.

3,5-dibromo-2-hydroxy-2'-methoxy-4-methylbiphenyl (155 mg, 48%) was recrystallized from $CHCl_3$ / Et_2O to yield white needles, m.p. 147,5 - 148°C.

Analysis: Calc. for $C_{14}H_{12}Br_2O_2$, C, 45.40; H, 3.22
Found; C, 45.41; H, 3.99.

ms, Peaks at m/e 374/372/370(100)278/276(18)213(8)212(32) 211(9)190(23)184(18)183(11)169(17)168(9)152(16)141(10) 139(15)115(11)106(12).

IR $\bar{\nu}_{max}$(KBr) 3365(br s,O-H)2915,2830(w,C-H)1592,1575(w) 1490,1455(m)1441(s)(Ar C=C)1115(w)1010(s)(C-H in-plane) 880(m,1 free Ar H)746(s,4 adj Ar H)

NMR ($CDCl_3$) δ 7,50(s(1H)Ar H-6)7,45 - 7,05(m(4H)Ar H-3',H-4',H-5', H-6')6,43(s(1H)Ar-OH, peak disappears in D_2O)3,90(s(3H) Ar-OCH_3)2,63(s(3H)Ar-CH_3)

A second NMR run on the mother liquor from the recrystallization of the compound showed two $-CH_3$ peaks suggesting the presence of the higher melting isomer, 3,5-dibromo-2-hydroxy-2'-methoxy-5-methylbiphenyl, was also formed during the reaction.

The reaction was repeated for a number of times to obtain as the major product the 3,5-dibromo-2-hydroxy-2'-methoxy-5-methyl-

A second NMR run on the mother liquor from the recrystallization of this compound showed two $-CH_3$ peaks suggesting that some of the more hindered isomer, 3,5-dibromo-2-hydroxy-2'-methoxy-6-methylbiphenyl, was also formed during the reaction.

This reaction was repeated on a quarter of the scale to obtain as the major product again the 3,5-dibromo-2-hydroxy-2'-methoxy-4-methyl-biphenyl (50%).

D. Experimental Procedures Relating to Chapter 4.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 4.2.1

1 - Reaction between 4-Methylbenzyl alcohol and 4-Bromo-3,5-dimethoxytoluene.

To an ice-cold solution of 4-methylbenzyl alcohol (1,22 g, 0,01 moles) in diethyl ether (20 ml) was added n-butyllithium (0,02 moles) over 5 minutes. The solution was heated to reflux for 30 hours before the dimethyl ether of 2-bromoorcinol (0,01 moles) in diethyl ether (6 ml) was added. The mixture was refluxed for a further 40 hours before quenching and working up the reaction. The product (3,5 g) was dried on silica gel (7 g) and loaded on to the top of the usual column which was eluted with pet. ether (40 - 60°C) + benzene (1 + 9) 100 ml; (1 + 19) 100 ml; benzene + ethyl acetate (19 + 1) 250 ml; (9 + 1) 250 ml; (4 + 1) 250 ml, to obtain,

(i) 2-bromo-4-methylbenzyl alcohol (216 mg) which crystallized on removal of the solvent and was recrystallized from pet. ether, m.p. 45°C.

Analysis: Calc. for C_8H_9BrO, C, 47.7; H, 4.48,
Found; C, 47.4; H, 4.48.

ms. Peaks at m/e 202/200(M^+,56)121(91)93(100)92(53)91(89)

IR. $\bar{\nu}_{max}$ (KBr) 3240,3120(s,O-H)2280,2820(w,C-H)1590(m) 1545(w)1475(s,Ar C=C)1200(C-O)1040,1015(s,C-H in-plane) 795(s, 2 adj.Ar H).

NMR ($CDCl_3$) δ 7,27(d(1H)H-3,$J_{3,5}$=2Hz)7,08(d(1H)H-6,$J_{5,6}$=7Hz) 6,94(dd(1H)H-5,$J_{3,5}$=2Hz,$J_{5,6}$=7Hz)4,60(s(2H)CH_2OH) 2,38(br s(1H)-CH_2OH)2,25(s(3H)Ar-CH_3).

Two hundred milligrams of 2-bromo-4-methylbenzyl alcohol were oxidised with 70% nitric acid[190] to
2-bromo-4-methylbenzaldehyde which was purified on a silica gel column (8 g, 1,4 mm diameter) eluted with benzene + ethyl acetate (4 + 1), m.p. 31°C (Lit.m.p. 30 - 31°C)

ms. Peaks at m/e 200/198(66)199/197(100)171/169(28)91(43) 90(73)89(57).

IR. $\bar{\nu}_{max}$(KBr)~2900(br s,C-H)1660(C=O)1580(m)1470(w)(Ar C=C) 1020(C-H in-plane)820(2 adj.Ar H).

NMR (CCl_4) δ 10,12(s(1H)Ar-CHO)7,66(d(1H)Ar H-6,$J_{5,6}$=8Hz) 7,32(s(1H)H-3)7,10(d(1H)H-5,$J_{5,6}$=8Hz)2,47(s(3H)Ar-CH_3)

The identities of the dimethyl ether of orcinol and the two starting materials were proved by their ms, mixed m.p. (where applicable) and IR spectra.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 4.2.2

Attempted Preparation of the Methoxymethyl ether of 4-methylbenzyl alcohol.

A solution of 4-methylbenzyl alcohol (2,3 g, 17 mmoles) in dry toluene (15 ml) was stirred vigorously while sodium hydride (0,42 g, 17 mmoles) was added followed by chloromethyl methyl ether (1,28 ml, 17,5 mmoles). The resultant solution was stirred at room temperature for 6 hours before filtering and removing the solvents by distillation. The two products were separated by column chromatography on the standard column by eluting with pet. ether + benzene (1 + 1) 100 ml; (1 + 4) 250 ml; (1 + 9)250 ml: (1 + 19) 250 ml;benzene + ethyl acetate (1 + 1) 250 ml.

(i) bis(4-methylbenzyloxy)methane (60) (1.61 mg) was a sweet-smelling solid, m.p. 34°C.

ms. Peaks at m/e 256(8)151(20)136(12)134(9)133(8)122(18) 121(54)120(21)119(54)107(52)106(100)105(81)104(47)103 (48)93(48)92(22)91(50).

IR $\bar{\nu}_{max}$(KBr) 3020(w)2970(m)2900,2840(s)(C-H)1600(w)1500, 1450(m)(Ar C=C)1080,1020(br s,C-O)790(s,2 adj Ar H).

NMR ($CDCl_3$) δ 7,11(s(8H)Ar-H)4,74(s(2H)-O-CH_2-O-)4,54(s(4H)Ar-CH_2-O) 2,31(s(6H)Ar-CH_3).

(ii) The methoxymethyl ether of 4-methylbenzyl alcohol, (0,42 g) was a yellow liquid which decomposed on microdistillation at reduced pressure Analyses were carried out on the chromatographically pure product.

ms. Peaks at m/e 166(M^+,18)151(13)134(40)121(43)119(93) 107(93)106(100)93(34)91(93)79(43)78(32)77(57)

NMR ($CDCl_3$) δ 7,14(s(4H)Ar-H)4,64(s(2H)-O-CH_2-O-)4,51(s(2H)-O-CH_2-Ar) 3,38(s(3H)CH_2-O-CH_3)2,31(s(3H)Ar-CH_3)

Monitoring the Rate of Lithiation of the Methyl Ether of 4-Methylbenzyl Alcohol.

n-Butyllithium (1 mmole) was added to an ice-cold solution of the methyl ether of 4-methylbenzyl alcohol (0,136 g, 1 mmole) in diethyl ether (5 ml). The solution was then heated to reflux and samples were taken at 5 hourly intervals. TLC of the quenched samples in benzene suggested that the compound had broken down to the starting material plus some other compound that was not examined further.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 4.2.3

Reaction between 4-Methylbenzoic Acid and n-Butyllithium to which Methyl Iodide was added.

To a solution of 4-methylbenzoic acid (0,68 g, 5 mmoles) in diethyl ether (8 ml) cooled in a dry ice / acetone bath was added n-butyllithium (5 mmoles) over 3 minutes. The reaction was stirred at this temperature for 4 minutes before methyl iodide (2,54 ml, 40 mmoles) in diethyl ether was added. The resulting solution was stirred at -75°C for a further 20 minutes before refluxing for 1 hour, quenching and working up the reaction. The product (0,75 g) was dried on to silica gel (2 g) and loaded on to the top of column A (see p. 94) which was eluted with benzene, 250 ml, and benzene + ethyl acetate (19 + 1) 500 ml. Two main products were obtained which were analysed by their spectra only.

(i) butyl p-tolyl ketone (270 mg) was purified by distillation and crystallized on cooling, m.p. 20°C (Lit.m.p. 21°C).

ms. Peaks at m/e 176(M^+,9)135(15)134(91)120(32)119(100, $M^+-C_4H_9$)105(9)92(21)91(94)90(12)89(20)

IR. $\bar{\nu}_{max}$(film) 3020(m)2955,2920,2870(s)(C-H)1690(s,C=O) 1610,1570,1465,1410(a,Ar C=C)810(s, 2 adj Ar H)

NMR ($CDCl_3$) δ 7,67(d(2H)Ar H-2,$J_{2,3}$=8Hz)7,05(d(2H)H-3,$J_{2,3}$=8Hz) 2,78(t(2H)-CO-CH_2-CH_3)2,30(s(3H)Ar-CH_3)1,80 - 1,20 (m(4H)-$CH_2CH_2CH_2CH_3$)0,9(imp. t(3H)-CH_2CH_3)

(ii) methyl p-tolyl ketone (228 mg) was also purified by distillation at 70°C and 1 mm Hg. (Lit.b.p.$_{12}$ 91°C)

ms. Peaks at m/e 135(M+1,5)134(42)120(8)119(86)92(14)91(100) 90(8)89(14)

IR. $\bar{\nu}_{max}$(film) 3030,3000,2950,2920(m,C-H)1680(s,C=O)1610(s) 1575,1435,1410(m,Ar C=C)810(s, 2 adj Ar H)

NMR (CCl_4) δ 7,68(d(2H)Ar H-2,$J_{2,3}$=8Hz)7,03(d(2H)Ar H-3,$J_{2,3}$=8Hz) 2,40(s(3H)-CO-CH_3)2,30(s(3H)Ar-CH_3)

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 4.2.3

Reaction to Monitor the Rate of Lithiation of 2,4,6-Tribromoorcinol Dimethyl Ether.

To an ice-cold solution of the dimethyl ether of 2,4,6-tribromo-orcinol (0,156 g) in diethyl ether (10 ml) was added an equivalent amount of n-butyllithium. The mixture was maintained at 0°C and samples for glc analysis were withdrawn at half hourly intervals for 2 hours, quenched in aqueous acid and shaken up with benzene / ether. Only the organic phase was analysed. A solid appeared in the reaction flask after 20 minutes which was still present after 2 hours when the entire reaction was quenched and worked up to obtain:

2,4-dibromo-3,5-dimethoxytoluene which was recrystallized from ethanol, m.p. 170,5 - 171°C. The literature consulted cited the melting point of the 2,4-dibromo isomer as 161°C[191] and the 2,6-dibromo isomer as 80°C.[192] Assuming the latter to be a printing error as it seemed unlikely that the two isomers could exhibit such vastly different melt-

ing points, the sample was initially taken to be 2,6-dibromo-3,5-dimethoxytoluene and this conclusion was supported by the NMR spectrum (vide infra) which showed a single sharp peak for the supposedly identical methoxyl groups. A later reference[193] to the 2,4-dibromo isomer quoted the melting point as 168 - 169°C and the biaryl products (63) and (64) from the reaction confirmed that the 2-lithio-4,6-dibromo-3,5-dimethoxytoluene is formed on lithiation of the dimethyl ether of 2,4,6-tribromoorcinol.

ms. Peaks of >10% abundance at m/e 312/310/308(100,M^+)269/267/265(35) and 198/196(14) only.

IR. $\bar{\nu}_{max}$(KBr) 2960(m)2820(w)(C-H)1560,1440,1410(s,Ar C=C) 1200(s,C-O)1070,1040(s,C-H in-plane)930(m,1 free Ar H)

NMR ($(CD_3)_2CO$) δ 5,93(s(1H)Ar-H)3,24(s(6H)Ar-OCH_3)2,64(s(3H)Ar-CH_3)

Reaction between 2-lithio-4,6-dibromo-3,5-dimethoxytoluene and 2,6-dibromo-4-methylaniline.

To a chilled solution of the dimethyl ether of 2,4,6-tribromo orcinol (3,112 g, 8 mmoles) in diethyl ether (20 ml) was added n-butyllithium (8 mmoles). After stirring the solution at 0°C for 1 hour, 2,6-dibromo-4-methylaniline (0,530 g, 2 mmoles) in THF (10 ml) was added The resultant solution gradually went a deep red on heating to reflux. The reaction was quenched after refluxing for 52 hours. The products were separated on the standard column (see p. 94) using SOLVENT SYSTEM A. Two major biaryl products were obtained.

(i) 3,5,5'-tribromo-2,2',4,4'-tetramethoxy-6,6'-dimethylbiphenyl (63) 805 mg),was recrystallized from ethanol, m.p. 173,5 - 174°C.

ms. Peaks at m/e 542/540/538/536(8)462/460/458(8)220(10) 219(56)177(32)176(97)134(100).

IR. $\bar{\nu}_{max}$(KBr) 2930(m)2830(w)(C-H)1593(m)1566,1450(s)(Ar C=C) 1200(C-O)1080(s,C-H in-plane)939(m,1 free Ar H).

NMR ($(CD_3)_2CO$) δ 6,89(s(1H)Ar-H)4,01(s(3H)Ar(C2)-OCH_3)3,83(s(3H) Ar(C2')-OCH_3)3,47;3,46(both s(6H)Ar(C4)-OCH_3, Ar(C4')-OCH_3)2,78(s(3H)Ar(C6)-CH_3)2,69(s(3H) Ar(C6')-CH_3)

(ii) 3,3'-dibromo-2,2',4,6'-tetramethoxy-4',6-dimethylbiphenyl (64) (320 mg) was recrystallized from benzene / hexane / ethanol, m.p. 205 - 206°C.

ms. Peaks at m/e 462/460/458(100)351/349(17)350/348(27) 300(15)219(12)176(43)150(9)149(17)134(32)120(21) 119(16)105(21)91(29).

IR. $\bar{\nu}_{max}$(KBr) 2930(m)2840(w)(C-H)1588(s)1560(m)1450(s) (Ar C=C)1200(s,C-O)1100,1085(s,C-H in-plane)938(m) 920(w)(1 free Ar H)

NMR ($(CD_3)_2CO$) δ 6,96(s(1H)Ar-H)6,79(s(1H)Ar-H)4,00;3,78;3,73(each s, (3H)Ar-OCH_3)3,45(s(3H)Ar(C4)-OCH_3)2,79(s(3H)Ar(C6)-CH_3) 2,48(s(3H)Ar(C4')-CH_3)

Reaction between 2-lithio-4,6-dibromoorcinol dimethyl ether and N-methyl-4-methyl-2,6-dibromoaniline.

N-Methyl-4-methylaniline was prepared according to the method of Roberts and Vogt[194] and then brominated.

2,4,6-Tribromoorcinol dimethyl ether (1,56 g, 4 mmoles) was dissolved in diethyl ether (15 ml) and cooled in ice. Then n-butyllithium (4 mmoles) was added and the solution was stirred at 0°C for one hour before N-methyl-4-methyl-2,6-dibromoaniline (0,558 g, 2 mmole) in diethyl ether (10 ml) was added. The mixture was heated to reflux for 50 hours before quenching and working up in the usual manner. The product was dried on to silica gel (3 g), loaded on to the top of the pre-packed column of silica gel of standard size and eluted with pet. ether (40 - 60°C) + benzene (1 + 4) 250 ml; (1 + 9) 200 ml; benzene + ethyl acetate (19 + 1) 200 ml;(9 + 1) 200 ml,to obtain 4 major products.

(i) 2,4-dibromo-3,5-dimethoxytoluene (360 mg) was recrystallized from ethanol, m.p. 171°C, undepressed when admixed with the compound obtained previously. The IR spectrum confirmed its identity.

(ii) and (iii) 3,3',5'-tribromo-2,2',4,4'-tetramethoxy-6,6'-dimethylbiphenyl (272 mg) and 3,3'-dibromo-4',6-dimethyl-2,2',4,6'-tetramethoxybiphenyl (90 mg) were also isolated from the reaction and were identified by comparison of their IR spectra with those of the compounds obtained in the previous reaction. Also, the m.p. of the recrystallized compounds were

undepressed when mixed with the products of the previous reaction.

(iv) $C_{26}H_{27}Br_4NO_4$ (147 mg) was recrystallized from ethanol, m.p. 238 - 240°C.

ms. Base peak at m/e 741/739/737/735/733, no other peaks of greater than 10% abundance.

IR. $\bar{\nu}_{max}$(KBr) 2990(w)2920(m)2820(w)(C-H)1580,1490(m)1440(s) (Ar C=C)1200(s,C-O)1075(s,C-H in-plane)965,935(w,1 free Ar H).

Reaction between 2-Lithioanisole and N-Methyl-4-methyl-2,6-dibromoaniline.

To a chilled solution of 2-bromoanisole (0,748 g, 4 mmoles) in diethyl ether (10 ml) was added n-butyllithium (4 mmoles) and the mixture was then stirred at room temperature for one hour. N-Methyl-2,6-dibromo-4-methylaniline (0,558 g, 2 mmoles) in diethyl ether (10 ml) was then added to the re-chilled solution. The resultant mixture was heated to reflux for 22 hours before quenching and working up to obtain a thick black tar (0,634 g) which glc analysis (by co-injection) showed to be mainly anisole (355 mg) and the unchanged N-methylaniline.

Reaction between 2-Lithioanisole and N-methyl-2,4,6-tribromoaniline.

The method was identical to that of the previous reaction using equivalent amounts of the two starting materials. TLC (in benzene + pet. ether (40 - 60°C) (1 + 1)) and glc (general conditions) again showed the main products of the reaction to be anisole and unchanged amine. A significant amount of an insoluble black tar was also obtained.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 4.4

The Reactions between 2-Lithioanisole and 2,3,5,6-Tetrabromo-4-methylphenol.

RUN 1.

2-Bromoanisole (0,561 g, 3 mmoles) in diethyl ether (10 ml) was cooled in ice before n-butyllithium (3 mmoles) was added. The ice bath was removed and the solution stirred at room temperature for one hour before re-cooling in ice. Difficulty was experienced in dissolving the 2,3,5,6-tetrabromo-4-methylphenol (0,636 g, 1,5 mmoles) in diethyl ether. Two x 10 ml aliquots of diethyl ether were required to dissolve all the tetrabromocresol. Thus, only that amount of 2,3,5,6-tetrabromo-4-methylphenol soluble in 10 ml diethyl ether was added to the 2-lithioanisole solution initially and the remainder was added about 2 minutes later in the second 10 ml aliquot of diethyl ether. The ice bath was then removed and the solution heated to reflux for 24 hours before quenching and working up in the usual manner. The product (0,80 g) was dried on to silica gel (2 g) and loaded on to a pre-packed column of silica gel of usual dimensions and eluted with: pet. ether (40 - 60°C) + benzene (1 + 9) 200 ml;(1 + 19) 200 ml; pure benzene, 200 ml; benzene + ethyl acetate (19 + 1) 200 ml;(9 + 1) 200 ml, to give :

(i) Anisole (230 mg) which was purified by distillation and identified by its R_f on TLC (benzene), co-injection with authentic anisole on glc and its IR spectrum.

(ii) 2,3,5,6-tetrabromo-4-methylphenol (95 mg) was re-crystallized from benzene, m.p. 198 - 199°C, undepressed when admixed with authentic material.

(iii) 2,4-dibromo-6-hydroxy-2'-methoxy-2-methylbiphenyl (71) (51 mg) was obtained from the column together with 6-hydroxy-2'-methoxy-2-methyl 2,4,5-tribromobiphenyl and was separated from it by crystallization from Et_2O / $CHCl_3$ and re-crystallized from acetone / water to give needles, m.p. 160,5 - 161°C.

Analysis: Calc. for $C_{14}H_{12}Br_2O_2$, C, 45.16; H, 3.22,
Found: C, 45.18; H, 3.24.

ms. Peaks at m/e 374/372/370(100)358/356/354(50)294/292(17) 278/276(20)212(26)211(18)198(20)184(14)183(15)169(17) 168(18)152(18)139(27)106(15)105(22).

IR. $\bar{\nu}_{max}$(KBr) 3400(br,m,O-H)3360(m, non-bonded O-H)2920, 288((w,C-H)1580.1565,1480,1450(m)1430,1420(s,Ar C=C) 1220(s,C-O)1000(C-H in-plane)870(m,1 free Ar H)730 (s,4 adj.Ar H).

NMR ($(CD_3)_2CO$) δ 7,5 - 6,9(m(6H)Ar-OH,Ar H-5,H-3',H-4',H-5',H-6') 3,80(s(3H)Ar-OCH_3)2,34(s(3H)Ar-CH_3)

(iv) 2,4,5-tribromo-6-hydroxy-2'-methoxy-2-methylbiphenyl, (70) (122 mg) could not be crystallized from any solvent. It was finally distilled at 180 - 185°C and 0,4 mm Hg to give a transparent super-cooled liquid which finally crystallized after two days. It was re-crystallized from benzene / Et_2O, m.p. 98 - 99°C.

Analysis: Calc. for $C_{14}H_{11}Br_3O_2$; C, 37.38; H, 2.45,
Found: C, 37.69; H, 2.56.

ms. Peaks at m/e 454/452/450/448(100)373/371/369(50)358/356/ 354(100)292/290(36)211(36)139(74).

IR. $\bar{\nu}_{max}$(KBr) 3440(br,s,O-H)2920,2820(w,C-H)1590,1560(m) 1490,1455,1410(s)(Ar C=C)1240(s,C-O)745(s,4 adj.Ar H)

NMR ($(CD_3)_2CO$) δ ~7,50(br s,Ar-OH)7,31(d,Ar H-6',$J_{5';6'}$=3Hz)7,27(dd, Ar H-4',$J_{3';4'}$=6Hz,$J_{4';5'}$=3Hz)7,03(t,Ar H-5',$J_{4';5'}$=3Hz, $J_{5';6'}$=3Hz)6,98(d,Ar H-3',$J_{3';4'}$=6Hz) Integration under peaks from 7,5 - 6,9 is equivalent to 5 protons. 3,68(s(3H)Ar-OCH_3) 2(s(3H)Ar-CH_3)

(v)) 4',6'-dibromo-2"-hydroxy-2,2"-dimethoxy-5'-methyl-m-terphenyl (72) (100 mg) would also not crystallize from any solvent tried but was distilled at 230°C and 0,3 mm Hg to give a light yellow viscous liquid that "cracked" on scratching.

ms. Peaks at m/e 480/478/476(48)400/398(26)384/382(26) 320/318(43)288(30)279(37)255(32)225(56)139(95)91(71) 85(67)83(100).

IR. $\bar{\nu}_{max}$(KBr) 3450(m,O-H)2900,2820(w,C-H)1580(m)1565,1480, 1450,1420,1400(s,Ar C=C)1230(s,C-O)1090,1055,1030(m) 1010(s)(C-H in-plane)740(4 adj.Ar H).

NMR ($(CD_3)_2CO$) δ ~7,60(br s(1H)Ar-OH)7,3 - 6,8(m(8H)Ar-H)3,70(s(6H) Ar-OCH_3)2,58(s(3H)Ar-CH_3)

RUN 2.

This reaction was identical to the previous run except that 4 mmoles of 2-lithioanisole were generated in the usual manner from 2-bromoanisole (0,748 g) and n-butyllithium (4 mmoles). Two mmoles of 2,3,5,6-tetrabromo-4-methylphenol (0,848 g) were again dissolved in 2 x 10 ml aliquots of diethyl ether (i.e. the proportion of the tetrabromocresol in the second aliquot would now be greater than in Run 1.) Samples for glc analysis were withdrawn after 24, 40, 48 and 64 hours. The sample was quenched by injection into aqueous acid which was then shaken up with benzene / ether, Only the organic phase was analysed by glc (N_2 0,4 kg cm^{-2}; 150°C, increase 24°C/min. to 300°C; 10% GE SE-52 on Supelco, 0,004 x 1,0 m)

RUN 3.

2-Bromoanisole (0,374 g, 2 mmoles) weighed into the lower bulb of a two-bulb reaction flask. 2,3,5,6-tetrabromo-4-methylphenol (0,424 g, 1 mmole) was carefully introduced into the upper bulb. The entire apparatus was flushed in a gentle stream of nitrogen before sealing the two bulbs with rubber septa. The lower bulb was cooled in ice and diethyl ether added prior to the addition of n-butyllithium (two mmoles). The ice bath was removed and the solution stirred at room temperature for one hour before again re-cooling in ice. The contents of the upper bulb were dissolved completely in diethyl ether (15 ml) and added essentially all at once to the contents of the lower bulb by rapid tilting of the apparatus. Ten seconds after mixing, a sample was withdrawn, quenched and analysed by glc. Another sample was similarly taken after one minute. The entire reaction was quenched (but not worked up) after 100 minutes and analysed by glc. The glc traces

of the three samples were all identical thus indicating that the reaction was complete at the time of the first sampling.

RUN 4.

To an ice-cold solution of 2-lithioanisole (0,187g, 1 mmole) prepared in the usual manner was added 2,3,5,6-tetrabromo-4-methylphenol (0,212 g, 0,5 mmole) in diethyl ether (8 ml) over 8 minutes and a sample extracted for glc analysis immediately after the addition was complete. The reaction was quenched 10 minutes later and a second sample taken and analysed by glc was found to be identical to the first.

APPENDIX

Preparation of the Starting Materials.

Bromination by the gradual addition of the required number of equivalents of bromine in three times its volume of glacial acetic acid to a stirred solution of the unbrominated commercially available material in water / acetic acid was the mode of preparation of:

(i) 2,4,6-tribromophenol,
(ii) 2,4,6-tribromoanisole,
(iii) 2,4-dibromo-6-methylphenol,
(iv) 2,4-dibromo-6-ethylphenol,
(v) 2,6-dibromo-4-methylphenol,
(vi) 2,6-dibromo-4-fluorophenol,
(vii) 2-bromo-4,6-dichlorophenol.

The following further compounds were prepared as reported previously:

(viii) 2,4,6-tribromotoluene[195]
(ix) 1,2,3,5-tetrabromobenzene[196]
(x) 2,6-dibromophenol,[197]
(xi) 4-fluorophenol,[198]
(xii) 4-methylbenzyl alcohol,[199]
(xiii) 2-bromophenol,[200]
(xiv) 4-bromophenol,[201]
(xv) 2,4,6-triiodophenol,[202]
(xvi) 1,3,5-tribromobenzene,[203]
(xvii) 2,6-dibromo-4-methylaniline,[204]
(xviii) 2,4,6-tribromo-3-methylphenol,[205]
(xix) 2-bromoorcinol,[206]
(xx) methyl ethers of 2-bromophenol and orcinol,[207]
(xxi) N-methyl ethers of 2,6-dibromo-4-methylaniline and 2,4,6-tribromoaniline,[194]
(xxii) 2,3,5,6-tetrabromo-4-methylphenol[208,209]

Attempts to prepare 2,4-difluorophenol from 2,4-difluoroaniline by four different methods[198,210,211,212] were unsuccessful.

2,6-Dibromo-4-chlorophenol was prepared from 2,6-dibromophenol by the novel chlorination technique described on page 110.

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