FORMATION OF ADDUCTS FROM *IPSO* NITRATION OF CHLOROMESITYLENE AND THEIR REAROMATIZATION

by

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ABSTRACT

Nitration of 2-chloromesitylene with nitric acid in acetic anhydride at temperatures below -50°C gives, in addition to the expected nitro substitution product, the adducts 4-chloro-1,3,5-trimethyl-4-nitro-1,4-dihydrophenylacetate (2) and 3-chloro-2,4,6-trimethyl-4-nitro-1,4-dihydrophenylacetate (3), each as a pair of diastereoisomers. Three of the four adducts have been isolated and characterised. The stereochemistry of 4-chloro-1,3,5-trimethyl-4-nitro-1,4-dihydrophenylacetate has been elucidated using the lanthanide shift reagent, tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-d_6-4,6-octanedione)-europium(III). The mechanism of the formation of the diene adducts is discussed in terms of *ipso* attack of an incipient or free nitronium ion at the halo substituted site, or the alkylated position, in the parent aromatic nucleus followed by attack of the acetate nucleophile at the *para* position to yield the 1,4-addition product.

4-Chloro-1,3,5-trimethyl-4-nitro-1,4-dihydrophenylacetate (2) undergoes exchange reactions in which the acetate group is replaced by other nucleophilic groups (e.g. $\bar{\text{O}}$Me) in an acid catalysed S_N1 type substitution. More vigourous conditions result in rearomatization yielding both nuclear substituted and side-chain substituted arenes.

These have been characterised by g.l.c. and g.l.c.-m.s. techniques. In the side-chain arenes the methyl group *para* to the chlorine atom and *ipso* to the acetate group in the precursor adduct is substituted. Under strongly acidic conditions the formation of 2-chloro-4-nitro-1,3,5-trimethylbenzene (1) is dominant. 3-Chloro-2,4,6-trimethyl-4-nitro-1,4-dihydrophenylacetate (3) gives 3-chloro-2,4,6-trimethylphenylacetate (5) under almost all conditions. The different behaviour of the structurally isomeric adducts is discussed in terms of the stabilities of the carbonium ions formed by competitive loss of the nitro group and acetate group.

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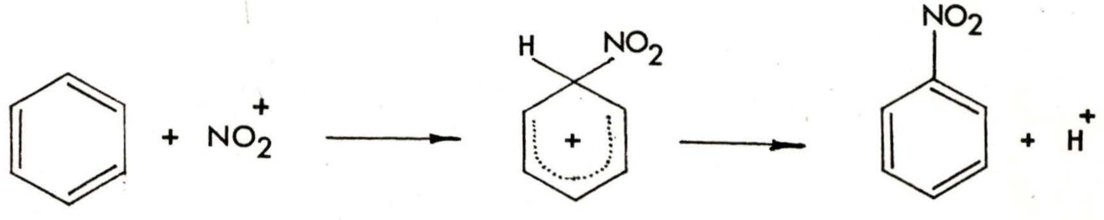
CHAPTER I

INTRODUCTION

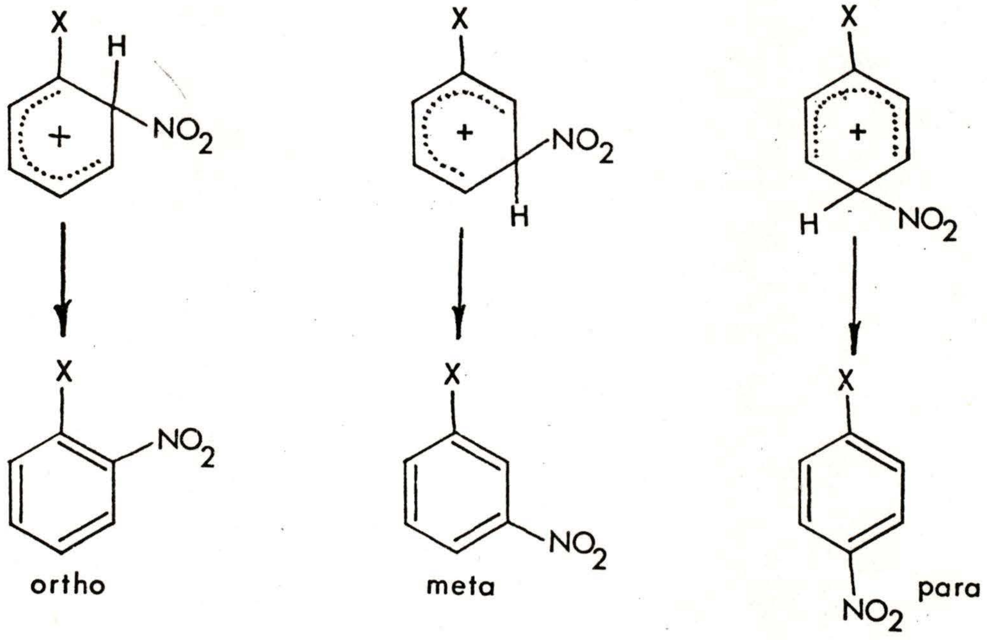
1.1

Aromatic nitration is one of the most widely studied and commonly used electrophilic substitution reactions in organic chemistry, and is frequently used for the preparation of aromatic nitro compounds, among the most valuable intermediates in organic synthesis.

The means which have been used for effecting nitration are numerous (1). However, most commonly preparative nitration is carried out using nitric acid either in sulfuric acid or in an organic solvent. Such systems nitrate aromatic compounds by a process known as 'electrophilic substitution', and extensive mechanistic studies (1) have established, or made probable, the identity of the attacking electrophile. In most cases, though not quite all, the active electrophile has proved to be the nitronium ion, NO_2^+. In its most elementary form, the mechanism for aromatic nitration is thus written as

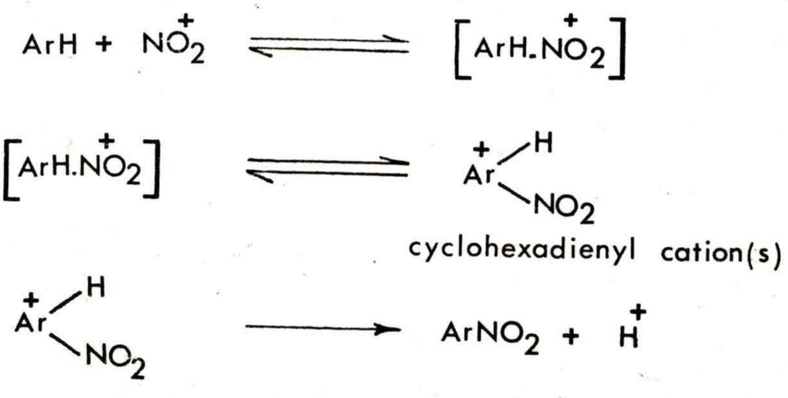


If the aromatic substrate contains a single substituent, there results three isomeric intermediate ions, each of which leads to a different isomeric substitution product.



The intermediate cation has been variously called a Wheland intermediate, a σ-complex or a phenonium (benzenonium) ion and is of course a substituted cyclohexadienyl cation.

This nitration has been dealt with by a number of excellent reviews and books (2) and the enormous amount of evidence relating to the mechanism will not be reviewed here. However, mention must be made of a recent refinement to the mechanism shown above. The pioneering studies of mechanism and of relative reactivities of arenes by Ingold (3) and his school were carried out in many instances, under conditions in which the slow step of the overall reaction was the formation of the nitronium ion. It was possible to measure relative reactivities by choosing two different aromatic substrates to compete for the nitronium ion as it was formed. When Olah (4) developed the use of nitronium salts, the rate determining barrier to the formation of the nitronium ion was removed. He found when nitronium salts were used for reactivity studies their positional selectivity was maintained (*i.e.* ratio of *ortho:meta:para*), whereas substrate selectivity (the relative rates of nitration of *e.g.* benzene and toluene) was not. Incomplete mixing, *i.e.* reaction at a rate faster than mixing of the nitronium salt could occur, has been implicated as the complicating factor in his work. The work does suggest that encounter control might be of importance in nitration and Schofield and his co-workers (5) have shown for a variety of different conditions for nitration that when the substrate is sufficiently reactive it is possible to observe the reaction at the encounter rate between nitronium ion and the substrate. In this situation, further increase in the reactivity of the substrate does not increase the rate of nitration even when studied by the competitive method. Thus it is necessary to introduce an 'encounter pair' whose formation may become rate-determining in appropriate circumstances in the mechanistic scheme above.



An 'encounter pair', represented by $[ArH.NO_2^+]$ of undefined structure is known to be produced when the nitronium ion and the aromatic compound come together during reaction. The 'encounter pair' produces Wheland intermediates (W's) which, by loss of proton, generate nitro compounds. Positional selectivity can thus be maintained in reactions occurring at the encounter rate. Depending on the reaction conditions and the aromatic substrate any of the above steps (or the one that produces the nitronium ion) may be rate determining.

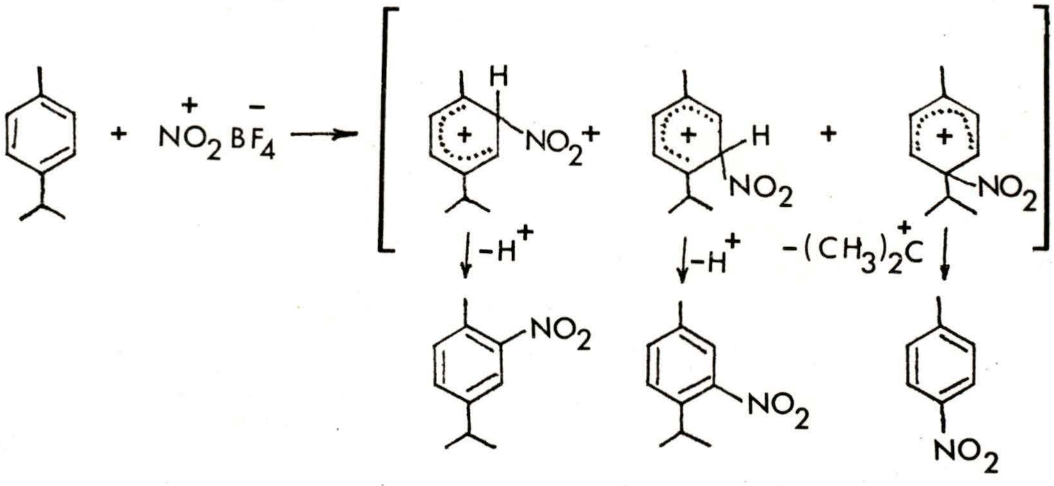
1.2 *'Ipso' Attack:*

The reversible character of some aromatic substitutions is one indication that electrophilic attack may also occur directly at the *ipso* site, the site bearing the substituent on the aromatic, and need not be restricted to the aromatic carbon bearing hydrogen. Nitration of propylated and butylated alkyl benzenes with nitronium tetrafluoroborate, $\overset{+}{N}O_2\overset{-}{B}F_4$, in tetramethylene sulfone solution has shown that, besides intact nitration, direct electrophilic dealkylating nitration occurs with the isopropyl or t-butyl group being lost as a cation (6). Perhaps the most investigated case is the nitration of *o*- and *p*-cymene (6,7) where the nitro group indeed replaces the isopropyl group to give the 2-nitro and the 4-nitro toluenes respectively as the sole nitro-dealkylated products from each reaction without the presence of any other isomer.

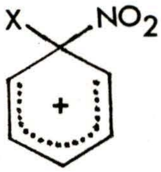
Thus, this loss of the isopropyl group via direct dealkylating nitration is attributed to a rapid *ipso* attack by the nitronium ion. Even at -40°C, *p*-nitro toluene (12.0%) appears to be the only dealkylated product obtained from *p*-cymene (7d).

Data obtained are summarised in Table 1.1 (6).

Nitration of *p*-cymene can schematically be represented as



Thus, in the general mechanism for aromatic nitration given above (p. 2) allowance should be made for the formation of a fourth isomeric Wheland intermediate



Perrin and Skinner (8) coined the term *ipso* attack after their exploratory work on nitration of anisole and *p*-haloanisoles.

TABLE 1.1

NITRATION OF PROPYLATED AND BUTYLATED ALKYLBENZENES WITH $\overset{+}{NO_2}\overset{-}{BF_4}$ IN TETRAMETHYLENE SULFONE SOLUTION AT 25^o

AROMATIC HYDROCARBON	INTACT* NITRATION		DEALKYLATING NITRATION	
	% YIELD	ISOMER DISTRIBUTION	% YIELD	ISOMER DISTRIBUTION
p-cymene	90.5	94.2% 2-nitro-4-isopropyltoluene 5.8% 3-nitro-4-isopropyltoluene	9.5	100% *p*-nitrotoluene
o-cymene	59.0	42.2% 4-nitro-2-isopropyltoluene 38.2% 6-nitro-2-isopropyltoluene 18.6% 5-nitro-2-isopropyltoluene 1.0% 3-nitro-2-isopropyltoluene	41.0	100% *o*-nitrotoluene
o-diisopropyl benzene	100.0	3.3% 3-nitro-*o*-diisopropylbenzene		traces of *o*-nitrocumene
p-diisopropyl benzene	44.0	100.0% 2-nitro-*p*-diisopropylbenzene	56.0	100.0% *p*-nitrocumene
1,3,5-triisopropyl benzene			100.0	100.0% 5-nitro -diisopropyl benzene
p-di-t-butyl benzene	80.0	100.0% 2-nitro-*p*-di-t-butyl benzene	20.0	100.0% *p*-nitro-t-butyl benzene
1,3,5-tri-t-butyl benzene			100.0	100.0% 5-nitro-*m*-di-t-butyl benzene

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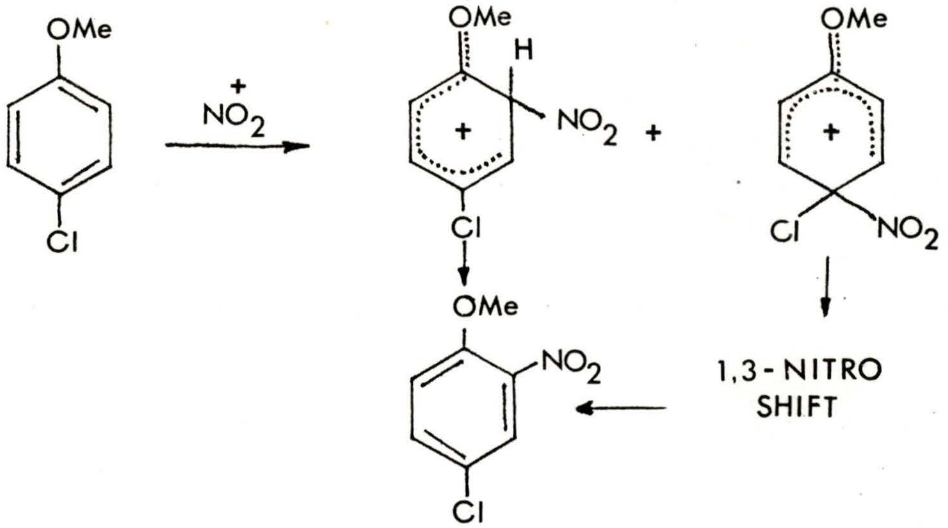
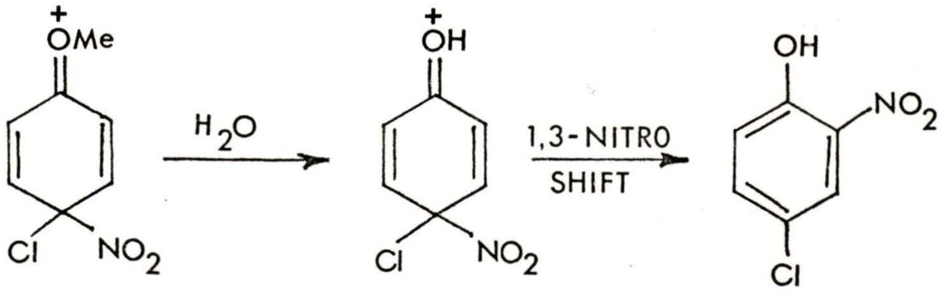
*Intact nitration implies nuclear nitration.

They used quantitative data to relate the directive effects of halo substituents on *ipso* attack.

Evidence of the significant formation of 4-chloro-2-nitroanisole (28%) from *p*-chloroanisole was attributed to *ipso* attack at the chloro-carbon, followed by 1,3 intramolecular nitro shifts. Difficulties, however, arose in deciding as to how much of the 4-chloro-2-nitroanisole resulted directly via initial *ipso* attack, or determining its extent, since the same product results directly from the 'normal' *ortho* attack.



This was overcome by trapping the intermediate formed via initial *ipso* attack by performing the nitration reaction in aqueous acetic acid, which is a poorer nitrating medium than acetic anhydride, to give 4-chloro-2-nitrophenol from the *ipso* intermediate as well as the nitroanisole from direct nitration. The extent of *ipso* attack was obtained by measuring the maximum yield of 4-chloro-2-nitrophenol. Justification of the above case is based on the fact that both reactant *p*-chloroanisole and the 'normal' product 4-chloro-2-nitroanisole are stable to demethylation under the reaction and work up conditions.



The 2-position on the benzene ring was thus shown to be less reactive than it appears from overall result of the reaction.

A vast amount of data is now available on the directive effects of substituents in electrophilic aromatic substitution reactions. Substituents have been classified as activating or deactivating (the substituted benzene being more, or less, reactive, respectively than benzene), and *ortho-para* or *meta* directing, depending on whether *ortho* plus *para* isomers are produced predominantly, or the *meta* isomer. These effects may be measured quantitatively. A substituent, R, has a directive effect expressed by partial rate factors o_f^R, m_f^R, p_f^R, each signifying the rate of electrophilic attack at a position *ortho*, *meta* or *para* to the substituent relative to the rate of attack at a single position of benzene. The directive effect of the substituent R for attack directly at an *ipso* site may be quantitatively expressed by an *ipso* partial rate factor (*ipso* factor) which can be gotten from the equation:

$$i_f^{R} = \frac{k_{ArR}^{total}\% \text{ attack at R}}{k_{ArH}^{total}\% \text{ attack at H}}$$

The *ipso* factor i_f^{R} is characteristic of the substituent type, aromatic substrate, the attacking electrophile, and the reaction conditions. The *ipso*-cyclohexadienyl cation which results via *ipso* attack of an electrophile on an aromatic substrate may undergo a variety of transformations. The possible fates of such *ipso* cyclohexadienyl intermediates are:

1. return to encounter pair or starting materials.
2. loss of X (i.e. *ipso* substitution).
3. rearrangement by migration of nitro group, with subsequent loss of a proton, the net result giving aromatic substitution.
4. similar migration of X, with subsequent loss of proton, the net result giving aromatic substitution with rearrangement.
5. loss of a proton or related group from a substituent remote from *ipso* position.
6. capture by a nucleophile.

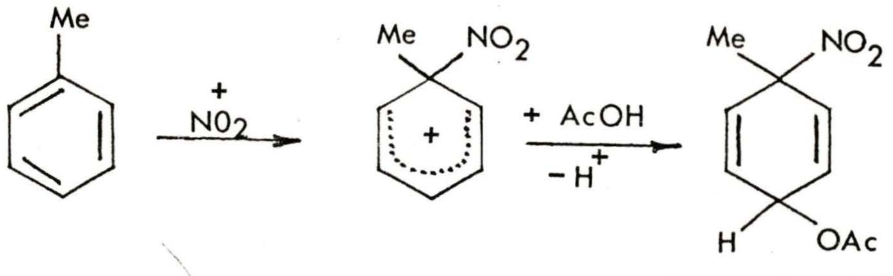
1.3 *Formation of Adducts in Nitration*

This last mentioned fate of an *ipso* cyclohexadienyl cation is important in a solvent such as acetic anhydride (refer to Tables

1.2, 1.3, 1.4 and references cited therein). In fact, since its first use by Orton (9) in 1902, it has become widely used as the medium for carrying out nitration reactions. It is now known (10) that nitric acid in organic solvents such as acetic anhydride is a milder nitrating agent than in a mineral acid such as H_2SO_4 and provide an excellent medium in which almost all aromatics are soluble. Nitric acid and acetic anhydride react rapidly and almost quantitatively to yield acetyl nitrate as the reactive species (11).

$$Ac_2O + HNO_3 \rightleftharpoons AcOH + AcONO_2$$

Arguments have been advanced that the protonated acetyl nitrate, $Ac\overset{+}{O}NO_2H$, is the active electrophile (12) in solutions of nitric acid in acetic anhydride. However, the behaviour of this nitrating medium is most readily understood in terms of its ability to transfer a nitronium ion, $\overset{+}{N}O_2$, to an aromatic substrate under quite mildly acidic conditions. The reaction of nitric acid to form acetyl nitrate results in the replacement of the stronger nitric acid by the weaker acetic acid and this reduces the acidity below what it would otherwise be. The acetic anhydride or acetic acid acts as an effective nucleophile and captures the *ipso*-cyclohexadienyl cation, when formed, to yield 1,4-acetoxynitro adducts which are stable in the reaction medium. Since decomposition of the adducts is catalysed by strong acids, the importance of the reduced acidity of nitric acid solutions in acetic anhydride is evident.



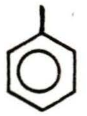
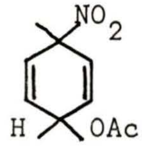
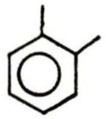
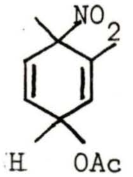
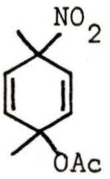
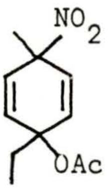
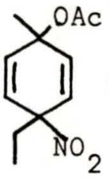
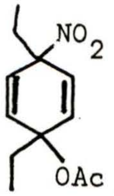
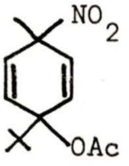
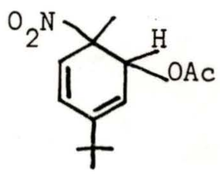
diastereoisomers

Extensive information is now available on the formation of 1,4-acetoxynitro adducts, along with normal substituted aromatic compounds, during the course of nitration of a variety of suitably substituted aromatic substrates (Tables 1.2, 1.3 and 1.4).

The adducts are generated when an aromatic carbon bearing a substituent undergoes *ipso* attack by the nitronium ion at the substituted position, thereby generating a phenonium ion, which looses neither nitro group nor substituent as a cation, but adds a nucleophile to yield a pair of diastereoisomeric adducts. Adduct formation, thus has a similar initial cyclohexadienyl cation-forming step as substitution, and the ratio of addition to substitution products reflects the relative rates of attack by the electrophile at *ipso* and unsubstituted positions.

TABLE. 1.2

ADDITION COMPOUNDS OBTAINED IN THE NITRATION OF MONO- AND DIALKYLATED BENZENES.

AROMATIC HYDROCARBON	ADDUCT(S)	REFERENCE
		(13)
		(14)
		(15)
	 + 	(16)
		(17)
	 	(18)

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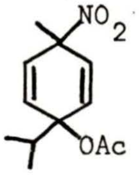
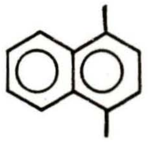
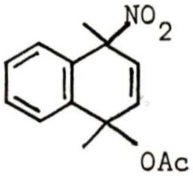
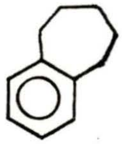
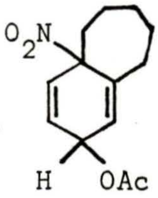
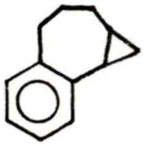
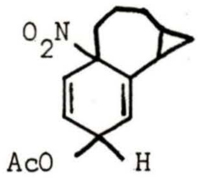
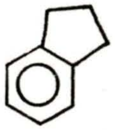
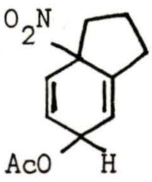
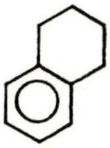
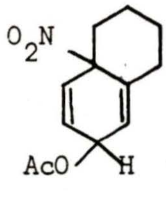
		(7d)
		(19)
		(20)
		(20b)
		(21)
		(22)

TABLE. 1.3

ADDITION COMPOUNDS OBTAINED IN THE NITRATION OF TRI-SUBSTITUTED BENZENES.

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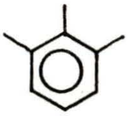
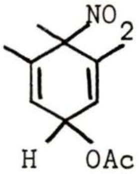
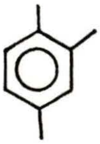
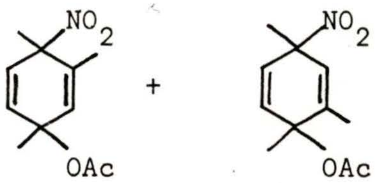
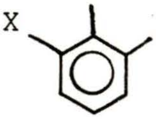
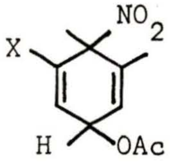
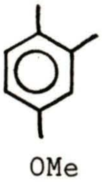
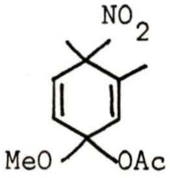
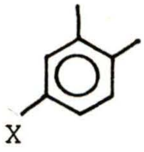
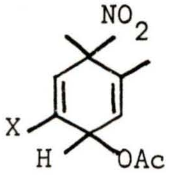
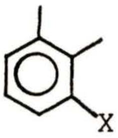
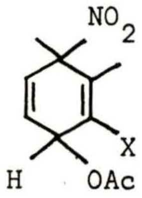
			(14)
			(23)
		X=F	(24)
		X=Cl	(25)
		X=Br	(26)
			(27)
		X=CN	(28)
		X=COMe	(29)
		X=COPh	(29)
		X=NO_2	(30)
		X=CN	(28)
		X=NO_2	(31)

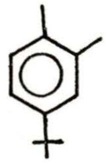
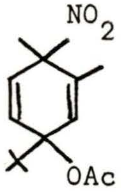
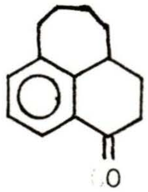
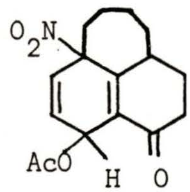
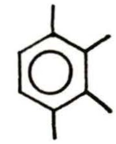
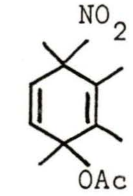
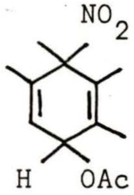
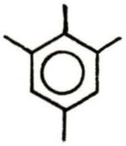
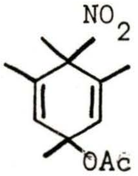
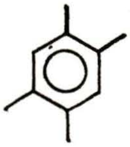
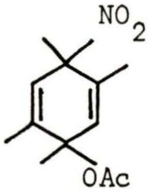
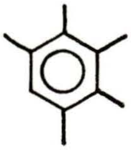
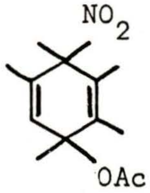
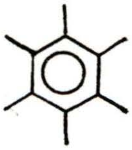
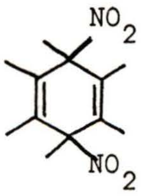
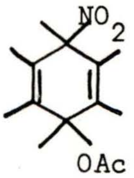
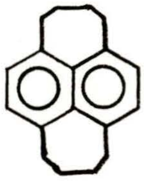
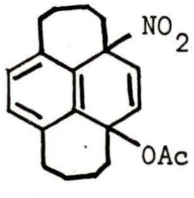
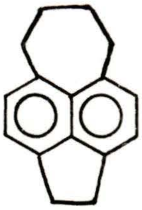
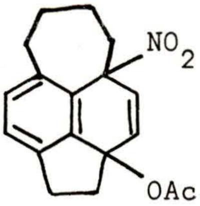
AROMATIC HYDROCARBON	ADDUCT(S)	REFERENCE
		(32)
		(22)

TABLE. 1.4

ADDITION COMPOUNDS OBTAINED IN THE NITRATION OF TETRA-,PENTA-, AND HEXA-SUBSTITUTED BENZENES.

AROMATIC HYDROCARBON	ADDUCT(S)			REFERENCE
		+		(33)
				(33)
				(33)
				(34)
		+		(31)
				(22)*

AROMATIC HYDROCARBON	ADDUCT(S)	REFERENCE
		(22)*

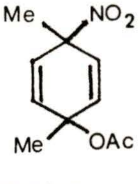
* These diene adducts were not isolated,but have been proposed to bear the assigned structures through the aromatic products obtained in the reactions.These could only have arisen from these 1,4-acetoxynitro adducts.

1.4 *Reactions of Adducts*

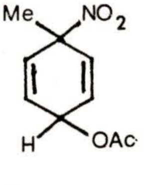
The adducts obtained by such nucleophilic capture undergo a variety of reactions, the most dominant of which is rearomatization. This gives rise to unexpected 'nitration' products in which there is continuing current interest (35). However, the simplest reactions are those in which acetoxynitro dienes are converted into other dienes in which the acetate group has been replaced by (exchanged for) some other nucleophiles.

1.4.1 *Exchange Reactions*

The formation of diastereoisomeric 1,4-acetoxynitro adducts in *ipso* nitration of polysubstituted benzenes is well established. Adducts may be secondary or tertiary acetates *e.g.*

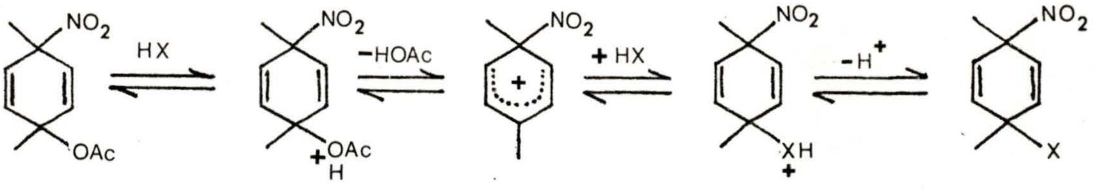


Tertiary



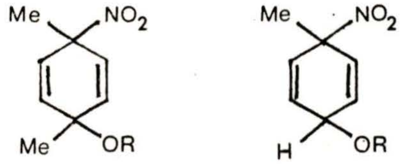
Secondary

Both the above types of adducts, under suitable conditions of acidity, should be able to regenerate the *ipso* cyclohexadienyl cations by acid-catalysed loss of acetate. The so generated cyclohexadienyl cation should then be able to combine with other nucleophiles to form other (acetate-exchanged) adducts.



Thus it should be possible to form the hydroxy, methoxy and formoxy dienes from the acetoxy dienes by reaction with aqueous acid, acidified methanol or formic acid, respectively.

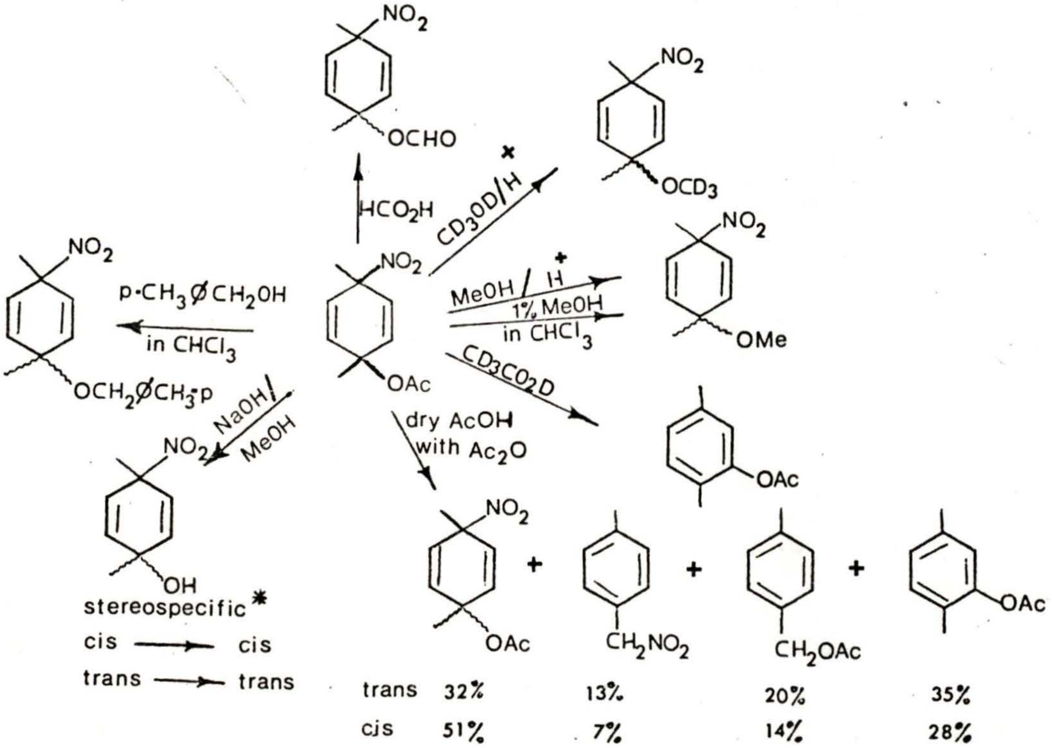
e.g.



R = H, Me, CHO

These expectations are realised in the case of tertiary acetate adducts. Fischer and Ramsay (15) successfully obtained exchanged diene adducts from the tertiary acetate 1,4-adducts of *p*-cymene and pseudocumene. In certain circumstances, the exchange reactions can become complicated by competing or subsequent rearomatization reactions, to yield aromatic compounds (*e.g.* aryl acetates, nitroarenes) and substituted side-chain aromatics. Schemes 1, 2, 3 and

4 have been drawn out below showing exchange reactions on adducts of *p*-xylene (15), pseudocumene (36), *p*-isopropyltoluene (7d) and *p*-t-butyltoluene (37).



SCHEME.1 Reactions of 1,4 adducts of p-xylene.

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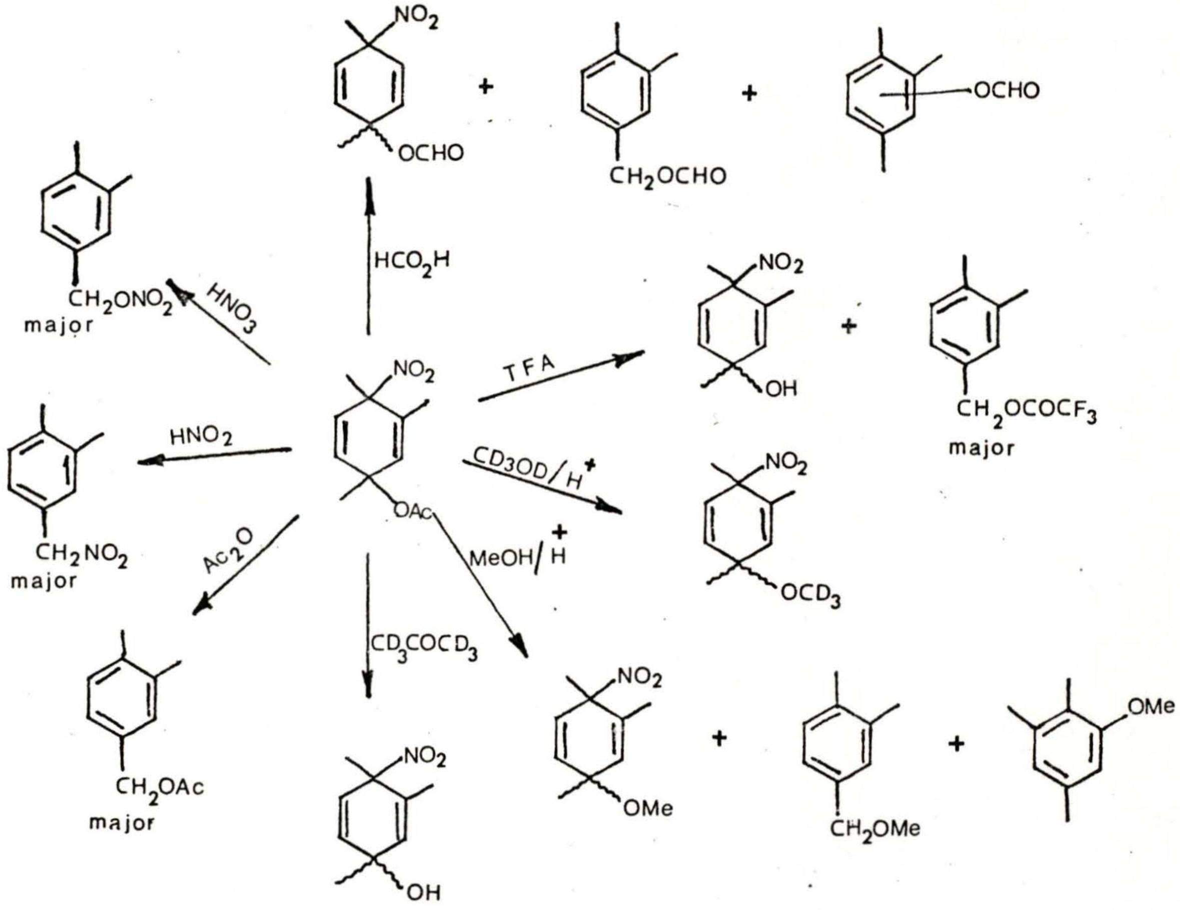
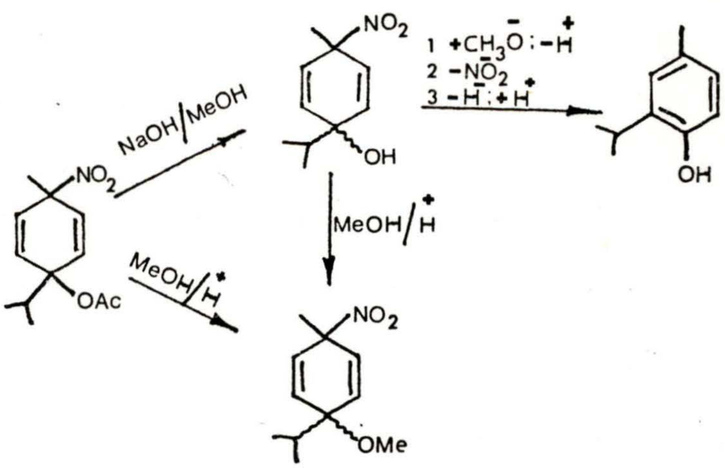
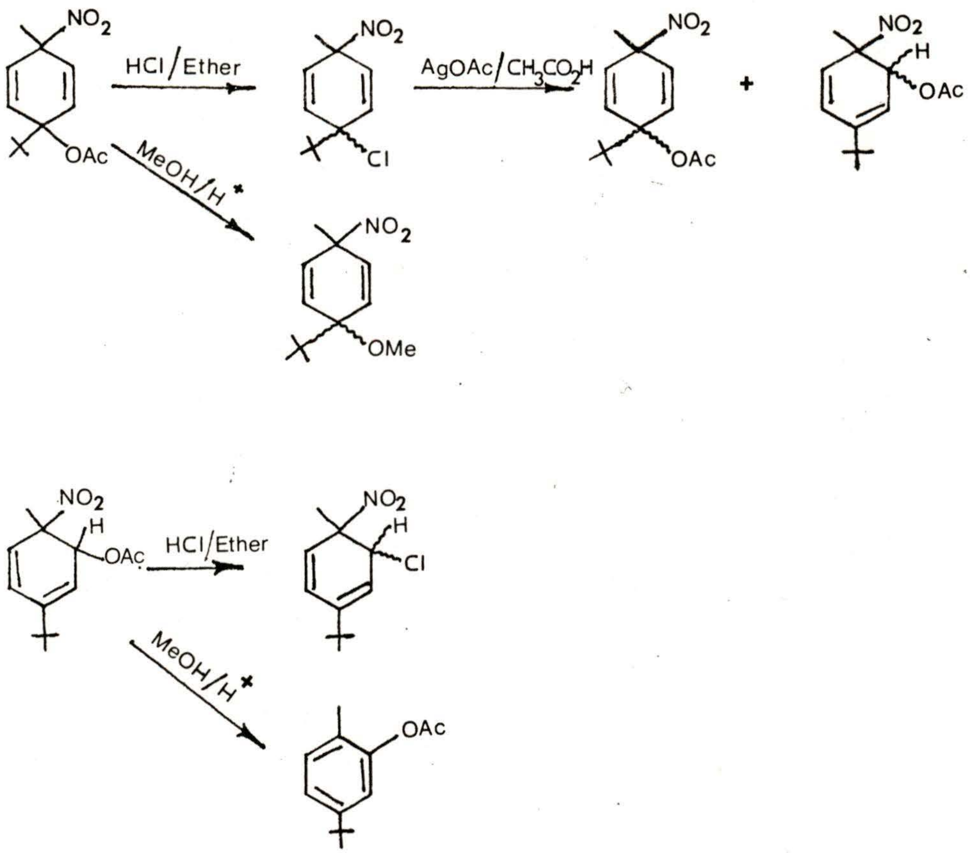
[*] The methoxide must have cleaved the ester by attack at the acyl rather than the alkyl group, otherwise methoxy dienes would have been formed.



SCHEME. 2. Reactions of 1,4 adduct of pseudocumene.



SCHEME. 3 Reactions of 1,4 adduct of p-isopropyltoluene



SCHEME.4. Reactions of 1,4 and 1,2 adducts of p-t-butyltoluene

Thus, under the appropriate conditions it is possible to observe exchange reactions of tertiary acetate adducts, although considerable care is always necessary to avoid competing rearomatization reactions. Exchange reactions have not been observed with secondary acetate adducts, possibly because under the conditions necessary to bring about formation of the *ipso*-cyclohexadienyl cation it is even more difficult to avoid the competing rearomatization reactions. However, Myhre (38) has shown that in rearomatization of the adduct of 1,2,3 trimethylbenzene in aqueous sulfuric acid phenols are formed. The latter must have as precursor the hydroxy diene, formed by exchange of the acetate in aqueous acid. However, the hydroxy diene was not observed directly.

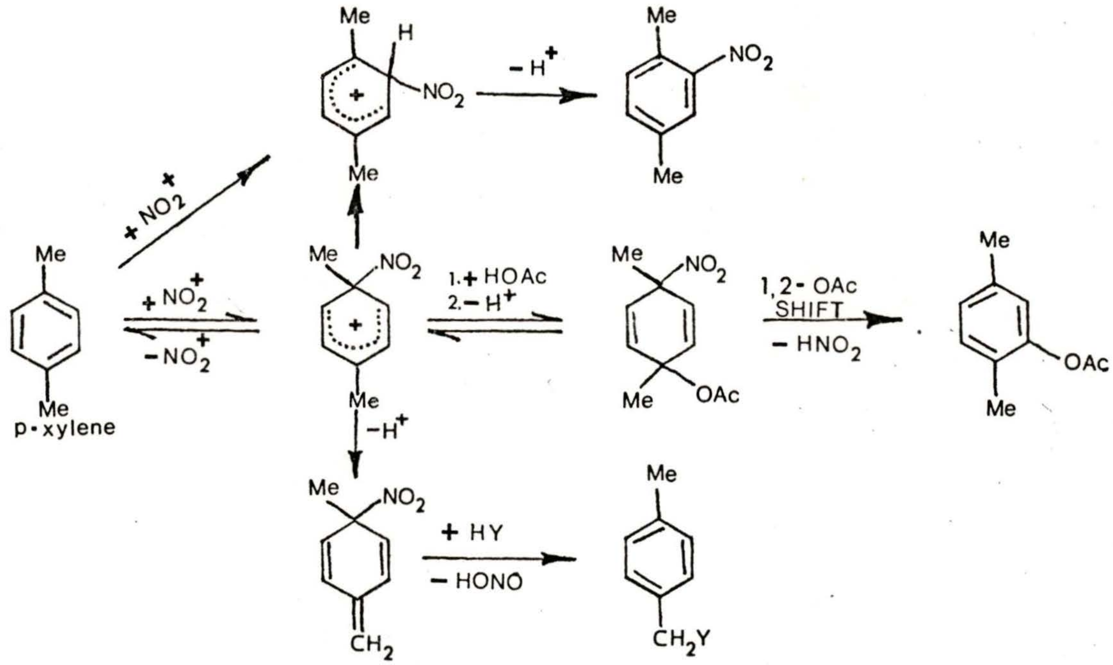
1.4.2 *Rearomatization Reactions*

The acetoxynitro adducts undergo rearomatization to give different aromatic products under a variety of reaction conditions. The three normally formed rearomatization products are:

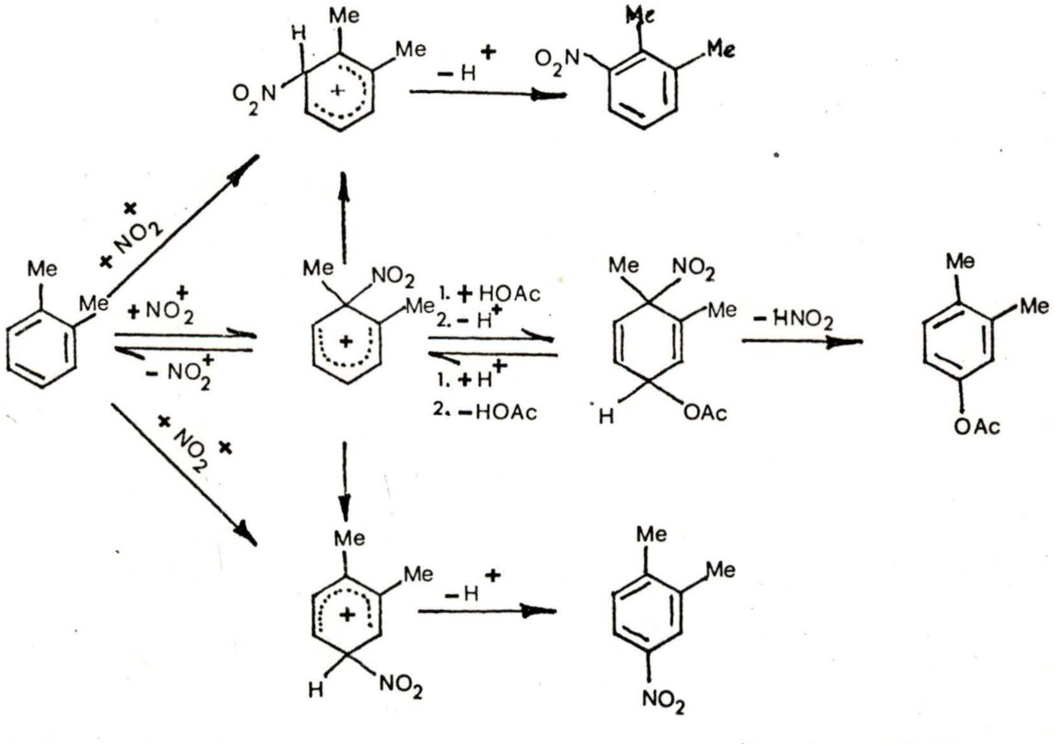
1. the (rearranged) nitroarene.
2. side chain (benzylic) derivatives.
3. aryl acetates which, in the case of tertiary acetate adducts, are rearranged.

Reactions involving nitrative coupling, and oxidation to cyclic ketones are also known (2g) (discussed later).

One need not go far to find diversity in adducts derived from *ipso* attack. *p*-Xylene exhibits behaviour that differs strikingly from that of *o*-xylene adducts (15,36). The most notable feature, the side chain substitution in *p*-xylene type systems but the absence thereof in *o*-xylene type systems, can be explained with reference to 1,4 adducts possessing an alkyl (methyl or ethyl) group *para* to the site of *ipso* attack. Many studies of side chain substitution have been reported and many different mechanistic schemes have been devised (29,33,36,39). Fischer *et al* (29,33) have devised two schemes 5 and 6, which are presented below, which best explain how the parent

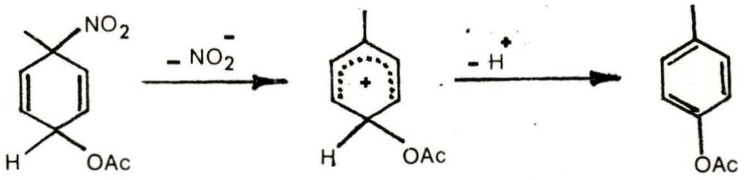


SCHEME.5. Formation and Rearomatization reactions of p-xylene type systems.

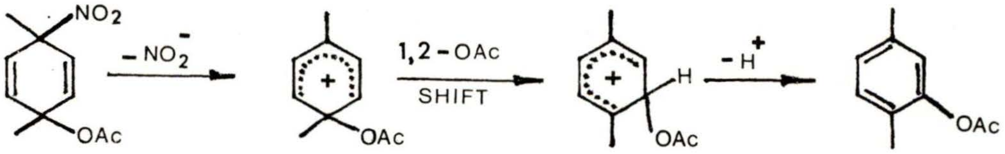


SCHEME.6. Formation and Rearomatization reactions of o-xylene type systems.

tertiary acetate adduct from *p*-xylene type cases rearomatizes to give nitroarenes, side chain benzylic derivatives and aryl acetates, whilst the secondary acetate adducts from *o*-xylene systems afford aryl acetates by elimination of nitrous acid, and nitroarenes by elimination of acetic acid followed by nitro group migration. Elimination of acetyl nitrate and reversion to the original aromatic is also observed in some cases. Myhre (38) has produced convincing evidence that the elimination of nitrous acid to form aryl acetate in secondary acetate adducts occurs by an E1 type mechanism:



Myhre has also argued that tertiary acetate adducts should form rearranged aryl acetates by a similar mechanism:



It is known that migration of the acetate group can occur without exchange with the solvent (*e.g.* in acetic acid-d_4) and is therefore intramolecular.

In benzylic derivatives, the alkyl group substituted is that which in the original adduct was *ipso* to the acetate group. It is thus understandable that secondary acetate adducts do not give rise to benzylic products. Formation of benzylic products can be envisaged as occurring through the triene (scheme 5) by nucleophilic attack at the methylene group with concomitant loss of the nitro group as nitrite.

Competition between the formation of nitroarenes plus benzylic derivatives, on the one hand and aryl acetate, on the other, will be determined by the relative rates of formation of the *ipso*-nitrocyclohexadienyl cation and the *ipso*-acetoxycyclohexadienyl cation, respectively. These in turn will be affected by the ionizing power of the solvent and its acidity. A good ionizing solvent favours the loss from the diene, of the nitro group as nitrite. The more acidic medium favours the acid-catalysed loss of acetate. The internal competition between nitroarene and benzylic products, both of which are formed via the same intermediate *ipso*-nitrocyclohexadienyl cation, will be determined by the competition between deprotonation and nitro shift. The more basic the solvent the more likely it is that deprotonation at the alkyl group will occur prior to the migration of the nitro group. Thus, highly acidic solutions *e.g.* in neat trifluoromethane sulphonic acid, favour exclusive formation of the nitroarene.

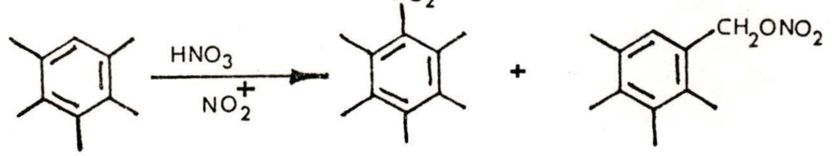
In comparing reactions of secondary and tertiary acetate adducts it would be expected that loss of the acetate from a tertiary centre should occur more readily under milder acidic conditions than loss of the acetate from a secondary centre, and that for this reason the competing aryl acetate formation should be more predominant in the case of the secondary acetate adducts.

Information regarding the competition between aryl acetate formation, and nitroarene formation and formation of benzylic derivatives should be obtainable by the study of rearomatization reactions as a function of solvent ionizing power and acid strength.

Rearomatization reactions have been attempted on such tertiary- and secondary acetate adducts by Fischer and co-workers. Their results indicate that the dominant reaction of adducts which do not have an alkyl group at the site of acetate is 1,4 elimination of nitrous acid, HNO_2 (13,25,33,40).

1.4.3 *Nitro-oxylation Reactions*

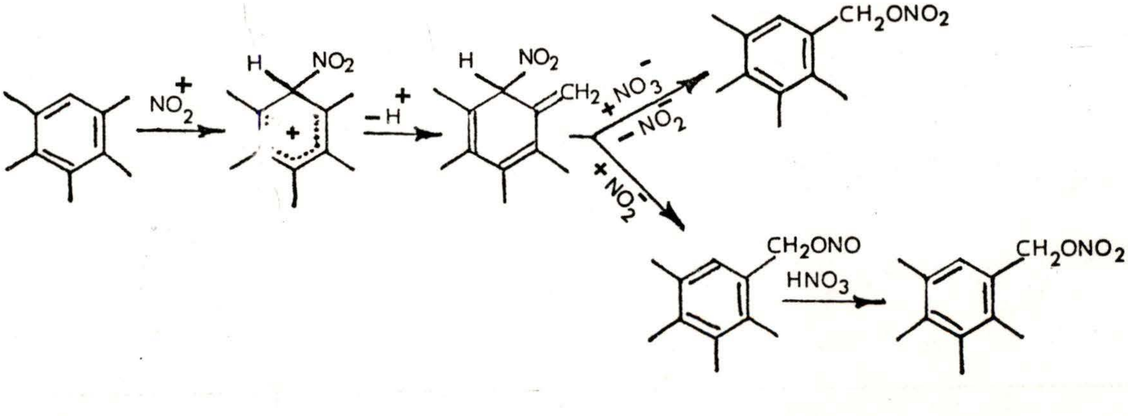
Suzuki (41) has observed a further side-chain product when fuming nitric acid is used as a reactant; *e.g.* with pentamethylbenzene in methylene chloride below 0°C, a mixture of nitropentamethylbenzene and 2,3,4,5-tetramethylbenzyl nitrate was obtained. Other isomeric nitrates are not formed in any significant amount.



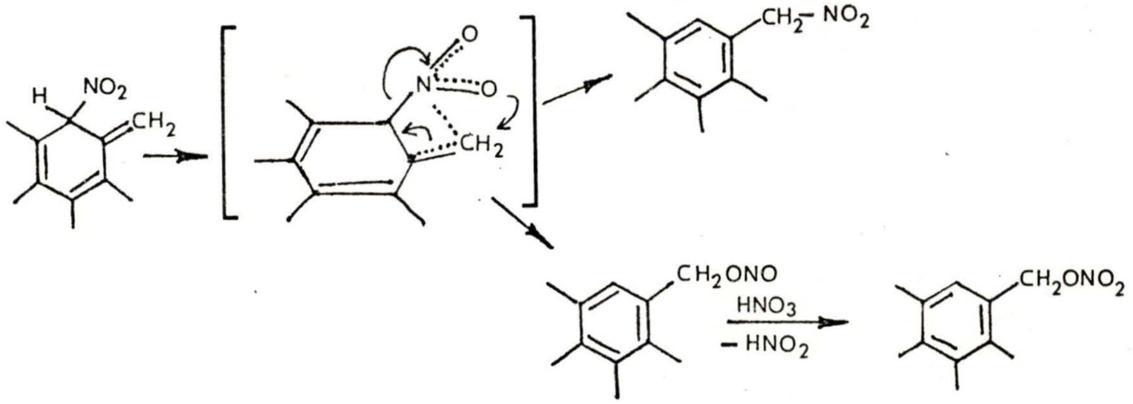
This process can be envisaged through the attack of the nitronium ion at a ring carbon to generate a phenonium ion, which is a common intermediate for nuclear nitration, and in suitable circumstances (conc. nitric acid/acetic anhydride solvent), for adduct formation. The generated ion releases a proton from an *ortho-* or *para* methyl group to produce an *ortho-* or *para*quinoid system which undergoes nuclear migration of the nitro group to produce a benzyl nitrite, which transforms into the benzyl nitrate (42).

Two plausible mechanisms for the formation of side chain compounds are:

1. intermolecular attack of nitrite or nitrate anion at the exo-methylene group with simultaneous loss of nitro group as a nitrite anion (42b).



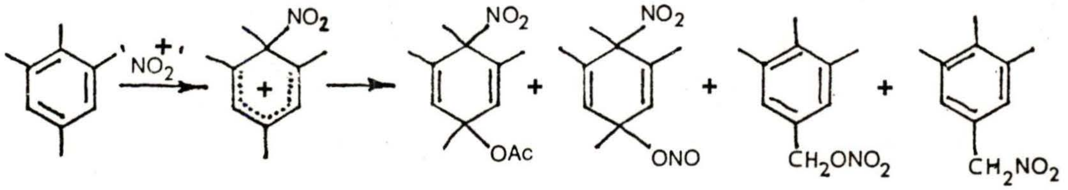
2. ion paired intramolecular association of nitrite anion and carbonium ion (43) as shown below:



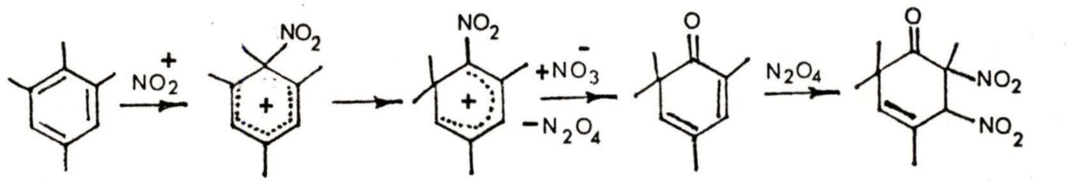
Suzuki has argued that intramolecular attack is favoured in the nitration of methylbenzenes in dilute acetic acid, as considerable amounts of benzyl nitrate and benzyl acetate were seen to be formed early on in the reaction. It will be evident that the derivatives could equally well be formed, like other benzylic derivatives through the cross-conjugated triene (*cf.* Scheme 5) by attack of nitrous acid.

1.4.4 *Formation of Carbonyl Compounds*

In Suzuki's review paper (2g) on side-reactions in aromatic nitration, he points out that nitration of polymethylbenzenes and their halogeno derivatives, with fuming nitric acid leads to side chain nitro-oxylation (discussed above) and oxidation to unsaturated cyclic ketones (cyclohexanones and cyclohexadiones), as competing reactions. It is, however, established that nitration of 1,2,3,5-tetramethylbenzene with concentrated nitric acid in acetic anhydride at -65°C gave 1,4-acetoxynitro adducts and the 1,4-nitritonitro adducts along with the side-chain aromatic nitrates and nitrites (33).

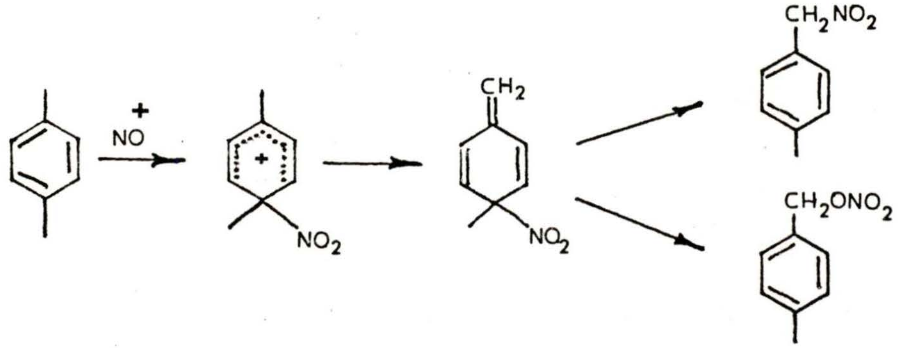


Nitration of the same compound with excess nitric acid in methylene chloride below 0°C is also known (2g) to give a small amount of cyclic ketone in addition to the normal substitution products, and the mechanism formulated shows it to proceed via the same *ipso*-cyclohexadienyl cation intermediate.

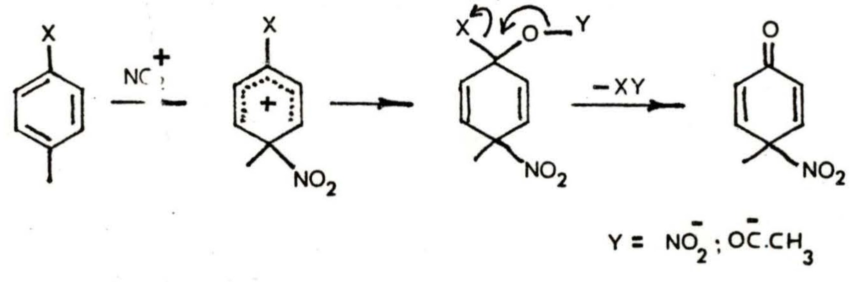


It is postulated that when a substrate contains two methyl groups *para* to each other, preference for the side chain substitution dominates. The dichotomy of the reaction would presumably be determined by the structure of the most favoured intermediate ion.

(a) If the ion has the structure in which the *ipso*-cyclohexadienyl cation has a methyl group *para* to *ipso* position, proton release from the *para* methyl entity gives a nitrocyclohexatriene which could be transformed to give benzyl nitrate or a phenylnitromethane compound.

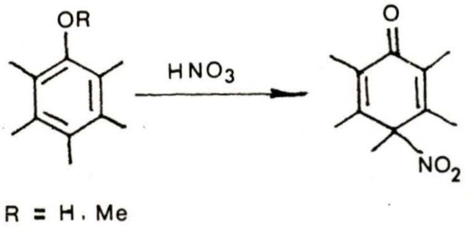


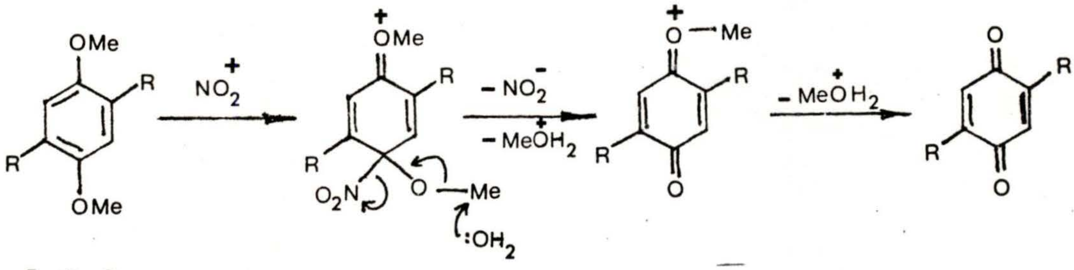
(b) If the ion has the structure with a halogen atom *para* to the *ipso* position, capture of an anion (7d) (*e.g.* nitrate, acetoxy) by the ring carbon bearing the halogen would yield an addition product, which would be converted to carbonyl compound as shown.



The above guidelines are known to work well depending on the structure of the starting aromatic compound.

Nitration of phenols and phenolic ethers is known to form nitrocyclohexadienones (*e.g.* pentamethylphenol, pentamethylanisole) (39) and quinones as shown.

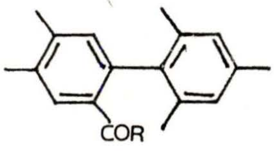




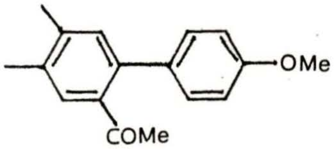
1.4.5 *Nitrative Coupling*

The coupling of arenes to form biaryls under nitrating conditions is well established. This has been shown to be a further elaboration of the chemistry of *ipso* ions (44).

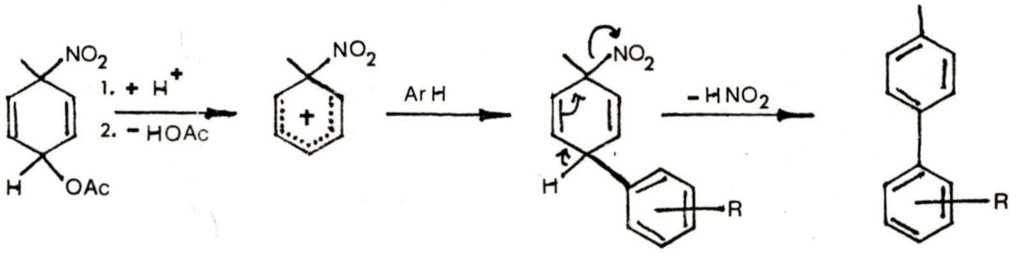
Fischer *et al.* (29) suggest the *ipso*-cyclohexadienyl cation, derived from the secondary 1,4-acetoxynitro adduct, is responsible in the formation of biphenyl derivatives. Addition of diluted solutions of boron-trifluoride etherate to a solution of 1,4-acetoxynitro adducts of 3,4-dimethylacetophenone or 3,4-dimethylbenzophenone with mesitylene or anisole gave high yields of biphenyl derivatives.



R = Me, Ph



It should be noted that these results lend support to the, now, fundamental assumption of stepwise addition of acetyl nitrate to aromatics to yield 1,4 adducts. That is, the existence of dimerization tells us that the life time of the *ipso* ion can be relatively long. In the above example, secondary acetate adducts undergo an exchange reaction by the formation of the cation, and its subsequent combination with a sufficiently activated aromatic substrate. Thus, substitution of the aromatic at the acetate site gives rise to a nitroaryl adduct, which readily undergoes elimination of nitrous acid to form the biphenyl



The coupling reaction is quite sensitive to the structure of the hydrocarbon, and it is significant that such coupling takes place with substrates which when reacted with nitric acid in acetic anhydride are known to, or would be expected to, give good yields of secondary acetate adducts, and does not occur with substrates which do not form adducts, (*e.g.* mesitylene) or which form only tertiary acetate adducts (*e.g.* *p*-xylene).

Toluene itself was not observed to couple (44) but since only a small amount of *ipso* attack occurs in toluene (45) only a very small amount of coupling product would be expected. Cross-coupling of two different arenes also occurs but only if one of the components is the type required for successful self-coupling. Clearly, the second component is merely filling the role of the aromatic which is substituted, not that which becomes the active electrophile. This reaction has the potential for development as a synthesis of mixed biaryl compounds.

1.5 *Objectives of Present Work*

We have explained in some detail above how *ipso* adducts are formed, can rearrange, etc. for a variety of substituted aromatics.

One interesting system that has not yet been studied is chloromesitylene where the possibility of isolating an adduct with the nitro group *ipso* to the chloro-carbon occurs The object then of this work is to study the formation, characterization and rearrangements of the products arising from *ipso* nitration of chloromesitylene.

CHAPTER II

EXPERIMENTAL PROCEDURES AND RESULTS

2.1 *Instrumentation*

^{1}H.m.r. spectra were measured on a Perkin-Elmer R12A (60 MHz) or a Perkin-Elmer R32 (90 MHz) spectrometer with tetramethylsilane as internal reference. Spectra were routinely recorded in carbontetrachloride solution but deuterochloroform was also used occasionally. I.r. spectra were obtained on a grating Perkin-Elmer 337 or on a Pye Unicam SP1000 spectrophotometer, and were calibrated with polystyrene, either in Nujol for solid samples or as thin liquid smears between sodium chloride plates for oils. U.v. spectra were obtained on Unicam SP800 B, Varian Techtron model 635 or Cary 17, spectrophotometers. Mass spectra were obtained with a Perkin-Elmer-Hitachi RMU 7 spectrometer at 70 eV. A Finnegan 3300 g.l.c.-m.s. system was used for obtaining the mass spectra of components of mixtures.

2.2 *Reagents*

Acetic anhydride was certified ACS, Fisher; mesitylene was Puriss, Aldrich; nitric acid (fuming, Fisher) was purified by distilling (300 cm^3) at 0.005 mm of Hg from urea (10 g, reagent, Fisher) and sulfuric acid (555 cm^3) and stored at -25°C. Solvents: anhydrous ether (reagent grade, Amachem) and pentane (reagent grade, Fisher) were dried over sodium followed by distillation and storage in glass bottles containing molecular sieves. Non-deuterated solvents used for spectral examination were certified ACS, spectranalysed (Fisher). Deuterated solvents including methylenechloride-d_2, chloroform-d_1, methanol-d_1, methanol-d_4 , acetic acid-d_4 , deuterium oxide-d_2, and acetone-d_6 were obtained from Merck, Sharp and Dohme. Basic alumina (Activity I) (Camag) used in chromatography was deactivated with 3% of 10% glacial acetic acid (reagent ACS, Fisher). All evaporations were carried out under reduced pressure.

Pure chloromesitylene was prepared by two general methods:

1. A solution of chlorine (31.3 g, 0.88 mol) in chloroform was prepared by passing chlorine gas (supplied by Matheson of Canada Ltd.) into cold chloroform (dry ice-acetone) (46). Mesitylene (60 g, 0.5 mol) was added to the above solution maintained at -60^{o}C. The reaction was kept at that temperature for several hours until the yellow colouration of the chlorine solution disappeared. Evaporation of the solvent, after treatment of the reaction with water (500 cm^3), 20% sodium hydroxide (2 x 500 cm^3) and drying over anhydrous magnesium sulfate, gave a crude product which contains some unreacted starting material.
2. Chlorine gas was passed into mesitylene (180 g, 1.5 mol) at room temperature for approximately 18 h. The gas flow was stopped when traces of small white crystals were observed in the reaction.

These are due to the presence of di- and trichloromesitylene. Products from the above two reactions were combined and fractionally distilled under reduced pressure. Fractions collected between the temperature range (84-87°C) at 7.0 mm Hg pressure were shown by n.m.r. to contain monochloromesitylene. After redistillation at 67°C and 4.25 mm Hg the chloromesitylene was pure by g.l.c. and had *i.r.* (neat liquid sample) 1460(s), 1365(w), 1173(m), 1056(s), 850(s), 702(m), 623(w) cm^{-1}; ^{1}*H.m.r.* τ(60 MHz, neat sample) 3.43 (s,2,4-<u>H</u> and 6-<u>H</u>), 7.82 (s,6,1-$C\underline{H}_3$ and 3-$C\underline{H}_3$) and 7.93 (s,3,5-$C\underline{H}_3$) with no peaks attributable to any impurities.

2.3 *Small-scale Nitration Reaction Monitored by N.M.R.*

The reaction was performed to maximize the extent of diene formation and determine the temperature at which adducts decomposed to give aromatic products.

A solution of chloromesitylene (50 mg, ∿ 0.32 mmol) in acetic anhydride (100 mm^3) in an n.m.r. tube was frozen at -70°C. Nitric acid (40 mg, 0.68 mmol) was added to acetic anhydride (200 mm^3) at -70°C, and the mixture brought to 0°C, recooled and added to the hydrocarbon at -70°C, the resulting reaction mixture was warmed to -30°C, shaken and its ^{1}H.m.r. spectrum recorded. Two further ^{1}H.m.r. spectra were obtained at temperatures of -20°C and 0°C respectively. The instrument was locked on acetic anhydride at τ7.85. Best results were obtained at -30°C; almost all the chloromesitylene had been consumed in the reaction giving a total yield of 21% diene adducts. At the higher temperature the adducts tended to decompose. This was evidenced by the presence of side-chain compounds in the spectrum (τ4.5-4.9). Two further separate reactions done on slightly larger scales at varying temperatures and reaction times of -40°C for 0.75 h and -55°C for 1.5 h using chloromesitylene (50 mmol) in acetic anhydride (50.0 cm^3) and nitric acid (100 mmol) in acetic anhydride (50.0 cm^3), gave similar yields (28 to 30%) of diene adducts after work up. All further large scale preparative reactions were performed at the temperature of -50°C.

2.3.1 *Preparative Scale Nitration of Chloromesitylene*

Nitric acid (28.5 g, 0.45 mol) at -20°C was added in small portions with stirring to acetic anhydride (75.0 cm^3) at -78°C. After complete addition, the mixture was warmed to 0°C to complete the formation of acetyl nitrate, and then cooled to -78°C. The acetyl nitrate in acetic anhydride was then added to a vigorously stirred slurry of chloromesitylene (23.3 g, 0.15 mol) in acetic anhydride (150.0 cm^3) at -78°C. The reaction temperature was raised to -50°C and maintained at that temperature for 2.0 h. Repeated experiments where reaction times varied from 1.5 to 5.0 h showed complete reaction of starting material with some decomposition in those cases where reaction mixtures were left for longer periods.

Observations indicated 2.0 h as being the best time for this reaction.

2.3.2 *Work-up Procedures*

The crude reaction mixtures were cooled to −78°C in a solid carbon dioxide-acetone bath, and pre-cooled ether (1 litre) at −78°C was added. Liquid ammonia, condensed from the gas phase by passage through a condenser at −78°C, was passed into the stirred solution such that the temperature did not rise above −40°C. When the temperature no longer rose on further addition of ammonia, and the reaction appeared alkaline to moist litmus paper, the addition was stopped and the excess ammonia removed by an aspirator over 4-5 h at −20°C. The reaction mixture was treated with water (800 cm^3) at 0°C and the ether layer collected. The aqueous layer was extracted with ether (4 x 400 cm^3), and the combined ethereal extracts were treated with saturated sodium bicarbonate solution (400 cm^3). The ethereal fraction was dried over anhydrous magnesium sulfate and evaporated at room temperature to yield the crude product (in the range 32 to 34 g) which was stored at −20°C. Integration of the ^{1}H.m.r. spectrum of the crude reaction product indicated that the diene adducts constituted approximately 30% of the reaction mixture, the remaining 70% largely being 2-chloro-4-nitromesitylene.

2.3.3 *Chromatography*

Separation of the crude reaction products was carried out at low temperatures (-30°C to -50°C). Cold methanol was circulated through the middle jacket of the chromatography column by means of a pump (Jabsco self-priming) and through a coil which pre-cooled the solvent. This insulated coil, connected in series with the jacket was supported on top of the column. The jacket was itself enclosed by an air jacket which had a drying tube on its top end. The methanol was cooled in a refrigerated tank and then passed through a copper coil set in a Dewar vessel of solid carbon dioxide-acetone. (Refer to Figure 2.1.)

The columns were packed with basic alumina, deactivated with 3% of 10% acetic acid. The ratio of alumina to the crude reaction product was normally kept at 40:1. Experience later showed that a ratio of 60:1 gives much better separations, which may be further improved by very slow variations (by 2.5% each time) of the composition of the ether in pentane solvent used for elution.

The columns were packed in the normal manner and topped up with an inch of ignited sea sand. The sample was taken up in minimum quantities of ether and added to the cold column. Elution with solvent (pentane and pentane-ether mixtures) was begun immediately by forcing it under pressure of nitrogen (2 to 4 *p.s.i*) through the column. This compensated for increased viscosity of

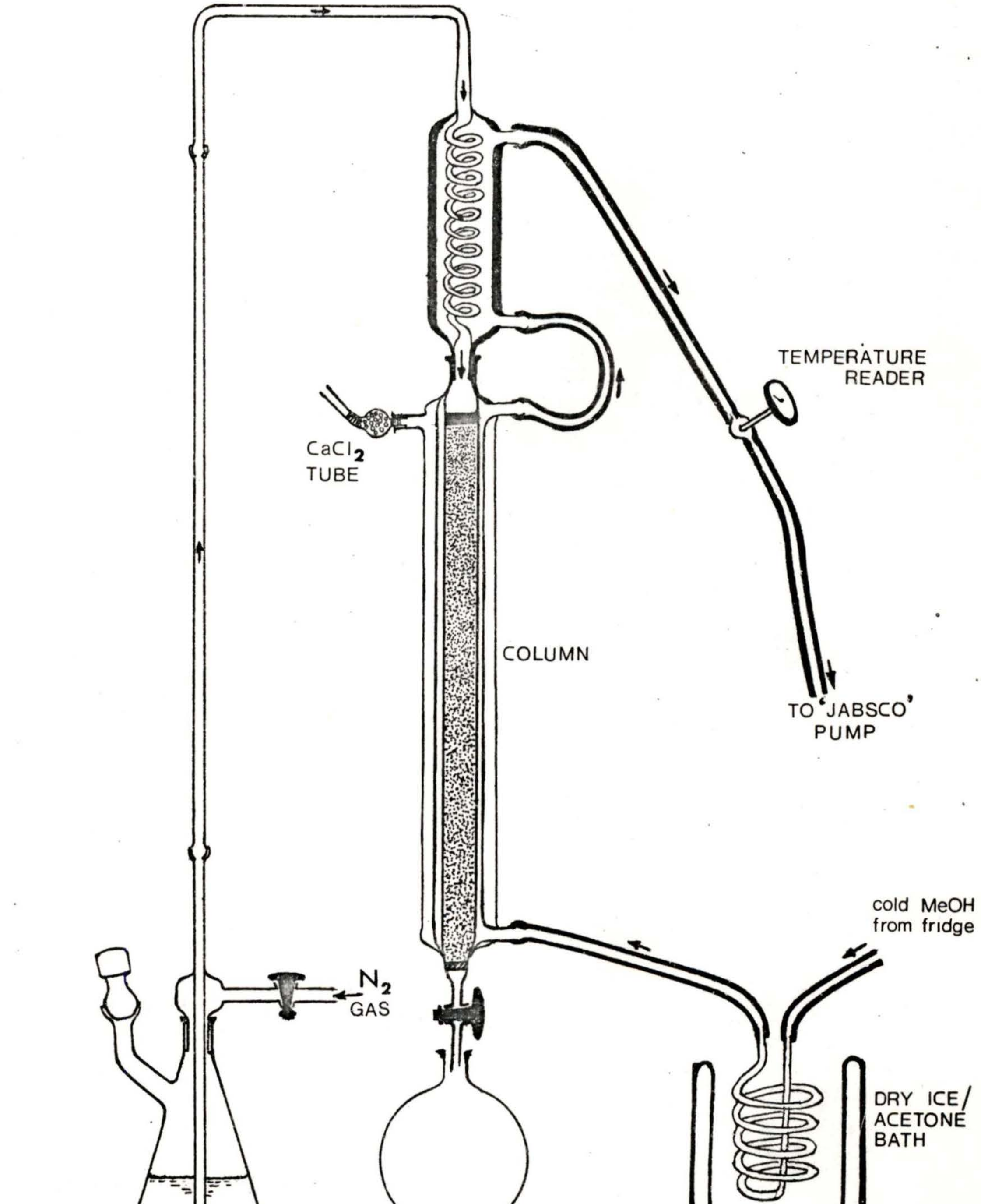
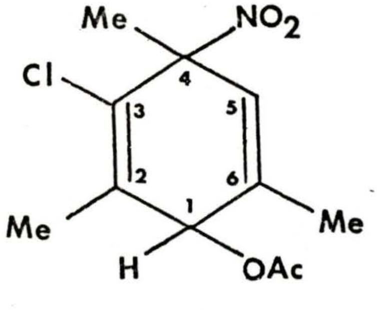


FIGURE.2.1 COLUMN SET UP

solvent at low temperatures and shortened the time that the diene adducts remained in contact with alumina.

Two drops of N,N-di-isopropylethylamine were added to each fraction (400 cm^3) to inhibit acid-catalysed decomposition. The ^{1}H.m.r. spectrum of each fraction in carbon tetrachloride, after evaporation of the solvent, was measured at either 60 MHz or 90 MHz. Examination of the individual chromatography fractions revealed two pairs of diastereomeric dienes to be present in the reaction mixture from nitration of chloromesitylene. That isomer which was eluted first from the chromatography column has been designated as Isomer A, and the other as Isomer B. The system of numbering the adducts is shown below.



3-chloro-2,4,6-trimethyl-4-nitro-1,4-dihydrophenylacetate

Fractions which appeared similar from their ^{1}H.m.r. spectra were combined. Attempts to crystallize the acetoxynitro dienes by dissolving them in minimum amounts of solvent (ether-pentane) followed by cooling in the freezer, with occasional scratching gave three dienes which were successfully characterised. A fourth

1,4-acetoxynitro diene which also formed during reaction in minor proportions could not be isolated, but its presence in certain fractions could be seen from the ^{1}H.m.r. spectra.

In one typical column run elution with pentane and pentane-ether mixtures (up to 40% ether in pentane) gave the aromatic product, 2-chloro-4-nitromesitylene (1) *m.p.* (ethanol) 55-57°C (*lit* (47) 56-57°C); *i.r.* (Nujol) 1530 and 1365 cm^{-1} (NO$_2$); ^{1}*H.m.r.* τ(90 MHz, CCl$_4$), 3.02 (s,1,6-$\underline{H}$), 7.67 (s,3,3-C$\underline{H}_3$), 7.74 (s,3,5-C$\underline{H}_3$), 7.81 (s,3,1-C$\underline{H}_3$); ^{13}*C.m.r.* (CDCl$_3$, ppm), 15.7 and 16.9 (3-$\underline{C}$H$_3$ and 5-$\underline{C}$H$_3$), 20.8 (1-$\underline{C}$H$_3$), 127.0 and 127.8 (C-3 and C-5), 130.4 (C-6), 133.0 (C-2), 138.5 (C-1), and 150.9 (C-4); mass spectrum (70 eV), m/e (relative intensity) 199 (87,M$^+$)[*], 182 (100)[*], 154 (48)[*], 127 (54)[*], 115 (56), 91 (65).

Anal. Calcd. for C$_9$H$_{10}$NO$_2$Cl: C, 54.14; H, 5.01; N, 7.02
Found: C, 54.28; H, 4.60; N, 6.68
C, 53.99; H, 4.92; N, 7.19

The 45% and 50% ether-pentane column fractions gave a diene, which on crystallization from ether-pentane yielded one diastereomer of 4-chloro-1,3,5-trimethyl-4-nitro-1,4-dihydrophenyl acetate (2A) as a white solid. *m.p.* 46-49°C, *i.r.* (Nujol) 1740 and 1240 (OCOCH$_3$), 1560 cm^{-1} (NO$_2$); ^{1}*H.m.r.* τ(90 MHz, CCl$_4$), 3.96 (s,2, 2-$\underline{H}$ and 6-$\underline{H}$), 8.06 (s,3,OCOC$\underline{H}_3$), 8.13 (s,6,3-C$\underline{H}_3$ and 5-C$\underline{H}_3$), 8.44 (s,3,1-C$\underline{H}_3$); ^{13}*C.m.r.* (CDCl$_3$, ppm), 17.5 (3-$\underline{C}$H$_3$ and 5-$\underline{C}$H$_3$), 21.7

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[*] Mass peaks associated with ^{35}Cl are denoted by an asterisk.

Mass units representing ^{37}Cl were also observed but have not been included.

($OCO\underline{C}H_3$), 26.9 (1-$\underline{C}H_3$), 74.0 (C-1), 104.7 (C-4), 129.9 (C-3 and C-5), 132.2 (C-2 and C-6), 170.0 ($O\underline{C}OCH_3$). Mass spectrum (70 eV), m/e (relative intensity), 213 (30, M-NO_2)*, 171 (100)*, 154 (71)*, 135 (30), 119 (22).

Anal. Calcd. for $C_{11}H_{14}ClNO_4$: C, 50.86; H, 5.39; N, 5.39
Found: C, 50.58; H, 5.33; N, 4.91
C, 50.15; H, 5.47; N, 4.90

The 55% ether-pentane fraction contained a 1:1.5 mixture of dienes 2A and 2B respectively, which was combined with fractions richer in diene 2B from other columns and after crystallization from ether-pentane gave the other diastereomer of 4-chloro-1,3,5-trimethyl-4-nitro-1,4-dihydrophenylacetate as a white solid (2B). *m.p.* 63.5-64.5°C, *i.r.* (Nujol) 1745 and 1237 ($OCOCH_3$), 1570 cm^{-1} (NO_2), ^{1}*H.m.r.* τ(90 MHz, $CDCl_3$), 3.83 (s,2,2-$\underline{H}$ and 6-$\underline{H}$), 8.00 (s,3,$OCOC\underline{H}_3$), 8.15 (s,6,3-$C\underline{H}_3$ and 5-$C\underline{H}_3$), 8.48 (s,3,1-$C\underline{H}_3$); ^{13}*C.m.r.* ($CDCl_3$, ppm), 17.0 (3-$\underline{C}H_3$ and 5-$\underline{C}H_3$), 21.8 ($OCO\underline{C}H_3$), 25.3 (1-$\underline{C}H_3$), 74.9 (C-1), 103.0 (C-4), 129.7 (C-3 and C-5), 133.6 (C-2 and C-6), 169.8 ($O\underline{C}OCH_3$). mass spectrum (70 eV), m/e (relative intensity), 224 (13, M-Cl), 213 (25, M-NO_2)*, 171 (100)*, 154 (62)*, 135 (13), 119 (10)

Anal. Calcd. for $C_{11}H_{14}ClNO_4$: C, 50.86; H, 5.39; N, 5.39
Found: C, 50.67; H, 5.51; N, 5.67

The 60% ether-pentane fraction gave mixtures of dienes 2B, 3A and 3B with very little amounts of each and in the ratio

1.0:1.2:1.0 respectively. Attempts to isolate each isomer in such low concentration proved unsuccessful. However, the presence of diene 3A was clearly evident from the ^{1}H.m.r. spectra and it had τ(90 MHz, CCl_4), 4.04 (s,1,1-$\underline{H}$), 4.27 (s,1,5-$\underline{H}$), 7.90 (s,3, $OCOC\underline{H}_3$), 8.10 (s,3,2-$C\underline{H}_3$), 8.18 (s,3,4-$C\underline{H}_3$), 8.26 (s,3,6-$C\underline{H}_3$).

Further elution with solvent ranging from 65% ether-pentane to 100% ether gave 3-chloro-2,4,6-trimethyl-4-nitro-1,4-dihydrophenylacetate (3B) which was crystallized from ether-pentane, to give a white solid. *m.p.* 54-56°C, *i.r.* (Nujol) 1735 and 1220 ($OCOCH_3$), 1550 cm^{-1} (NO_2); *^{1}H.m.r.* τ(90 MHz, $CDCl_3$), 4.07 (s,1,1-$\underline{H}$), 4.27 (s,1,5-$\underline{H}$), 7.82 (s,3,$OCOC\underline{H}_3$), 8.08 (s,3,2-$C\underline{H}_3$), 8.14 (s,3,4-$C\underline{H}_3$), 8.24 (s,3,6-$C\underline{H}_3$); *^{13}C.m.r.* ($CDCl_3$, ppm), 16.8 (2-$\underline{C}H_3$), 19.1 (6-$\underline{C}H_3$), 20.7 ($OCO\underline{C}H_3$), 24.7 (4-$\underline{C}H_3$), 69.8 (C-1), 89.3 (C-4), 125.0 (C-5), 128.5 (C-3), 134.0 (C-2), 136.4 (C-6), 170.9 ($O\underline{C}OCH_3$). Mass spectrum (70 eV), m/e (relative intensity), 213 (100, M-NO_2)*, 171 (25)*, 154 (35)*, 123 (82) ; *u.v.* (CH_3OH) 217.5 nm (800 m^2mol^{-1}).

Anal. Calcd. for $C_{11}H_{14}ClNO_4$: C, 50.86; H, 5.39; N, 5.39

Found: C, 50.32; H, 5.11; N, 5.35

C, 50.84; H, 5.53; N, 5.61

2.4 *Shift Reagent Study*

The shift reagent (1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-d_6-4,6-octanedionato-d_3) europium (III) (48), ($Eu(fod)_3$-d_{27}) was added in small increments (∿ 3 - 5 mg) to a solution of the pure diene (∿ 50 - 100 mg), in each case, in carbon tetrachloride or deuterated chloroform at 0°C. The weight of the reagent added and the ^{1}H.m.r. spectrum (tetramethylsilane as reference) were determined after each addition. Normally, plots of chemical shifts v/s amount of reagent added were linear until the weight ratio of reagent to diene reached almost 1:1. The volume increase on addition of the reagent was ignored. The relative gradients of the chemical shifts of the protons in dienes **2**A, **2**B and **3**B are shown in Table 2.1.

2.5 *G. L. C. Analysis*

G.l.c. traces were taken on a Varian Aerograph 2400 instrument using 1.3 m long 3% SE 30 column of stainless steel. Column packings were prepared by suspending the support in a solution of the liquid phase in chloroform, and after thorough mixing, the solvent was removed by slow rotation on a rotary evaporator.

The instrument was equipped with a hydrogen flame ionization detector, with Helium as carrier gas used at flow rates of 15 cm^3/min at 52 *p.s.i.*

Injector and detector temperatures were *ca.* 50°C above that of the column temperature (180°C). All runs were isothermal. Satisfactory separations were achieved on the 3% SE 30 column,

Table 2.1

Relative Gradients of Proton Chemical Shifts for Diene Adducts **2A**, **2B** and **3B** Resulting from the Addition of Eu(fod)$_3$-d$_{27}$

Assignment	Relative Gradient[a]		Assignment	Relative Gradient[a]
	2A	**2B**		**3B**
1-CH_3	0.64	0.71	1-H	1.60
2-H	0.80	0.86	2-CH_3	0.50
3-CH_3	0.14	0.17	4-CH_3	0.09
5-CH_3	0.14	0.17	5-H	0.22
6-H	0.80	0.86	6-CH_3	0.51

[a] Gradient 1-$OCOCH_3$ = 1.00; absolute gradients of 1-$OCOCH_3$: **2A**, 0.07; **2B**, 0.16; **3B**, 0.08 ppm mg^{-1}

and identification of the aromatic compounds was achieved by comparison of retention times of authentic samples where available, and also by g.l.c./mass spectral analysis.

2.6 *Synthesis of Samples Used for Comparative Purposes*

This section describes the preparation of compounds required for comparison with products isolated from decomposed or undecomposed diene mixtures. The n.m.r. and i.r. data are contained in Table 2.2.

1. *4-Chloro-3,5-dimethylphenylnitromethane* (4)

Crystallization from ethanol, of the product obtained from autodecomposition of diene 2A and also diene 2B gave a crystallized product (described under Reactions of diene adducts) of 4-chloro-3,5-dimethylphenylnitromethane. *m.p.* (ethanol) 92°-93°C; *i.r.* (Nujol) 1545 cm^{-1} (NO_2); *^1H.m.r.* τ(60 MHz, $CDCl_3$), 2.88 (s,2,2-<u>H</u> and 6-<u>H</u>), 4.71 (s,2,benzylic protons), 7.63 (s,6, 3-$C\underline{H}_3$ and 5-$C\underline{H}_3$); *^{13}C.m.r.* ($CDCl_3$, ppm), 20.7 (3-$\underline{C}H_3$ and 5-$\underline{C}H_3$), 79.4 ($\underline{C}H_2NO_2$), 127.3 (C-4), 128.9 (C-1), 129.7 (C-2 and C-6), 137.2 (<u>C</u>-3 and <u>C</u>-5). Mass spectrum: (70 eV), m/e (relative intensity), 199 (2,$M^{+\cdot}$)*, 181 (4)*, 164 (1,M-Cl), 153* (100,M-NO_2).

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.14; H, 5.01; N, 7.02

Found: C, 54.29; H, 5.07; N, 7.11

2. *3-Chloro-2,4,6-trimethylphenylacetate* (5)

3-Chloro-2,4,6-trimethylphenylacetate was obtained from a decomposed diene (3B) as an oil which appeared pure from g.l.c. It was also prepared by acetylation of the corresponding phenol using acetic anhydride in pyridine (48). *i.r.* (neat liquid smear), 1770 and 1212 cm^{-1} ($OCOCH_3$); ^{1}*H.m.r.* τ(60 MHz, CCl_4), 3.13 (s,1,5-$\underline{H}$), 7.71 (s,3,4-$C\underline{H}_3$), 7.76 (s,3,$OCOC\underline{H}_3$), 7.87 (s,3,2-$C\underline{H}_3$), 7.97 (s,3,6-$C\underline{H}_3$); τ(60 MHz, $CDCl_3$), 3.08 (s,1,5-$\underline{H}$), 7.69 (s,6,4-$C\underline{H}_3$ and $OCOC\underline{H}_3$), 7.83 (s,3,2-$C\underline{H}_3$), 7.93 (s,3,6-$C\underline{H}_3$); ^{13}*C.m.r.* ($CDCl_3$, ppm), 14.0 (2-$\underline{C}H_3$), 15.7 (6-$\underline{C}H_3$), 20.2 ($OCO\underline{C}H_3$), 20.3 (4-$\underline{C}H_3$), 128.2 (C-6), 218.5 (C-2), 129.8 (C-5), 132.4 (C-3), 133.7 (C-4), 146.5 (C-1), 169.2 ($O\underline{C}OCH_3$). Mass spectrum: (70 eV), m/e (relative intensity), 212 (10, $M^{+\cdot}$)*, 170 (100, M-CH_2CO)*, 135 (75, M-CH_2CO-Cl), 91 (70).

3. *3-chloro-2,4,6-trimethylphenol* (6)

The phenol was prepared from 2-chloro-4-nitromesitylene. Reduction (49) of the nitro compound (8.0 g, 0.04 mol) with a stirred solution of tin(II) chloride-dihydrate (27.3 g, 0.12 mol) in concentrated hydrochloric acid (37 cm^3) gave the arylamine (3.32 g) (7) after work-up of the reaction. *i.r.* (smear) 3460 and 3395 (m,NH_2), 1627 (s), 1474 (s) and 985 cm^{-1}; ^{1}*H.m.r.* τ(60 MHz, CCl_4), 3.40 (5-$\underline{H}$), 6.75 (1-$N\underline{H}_2$), 7.83, 7.88, 8.03 (2-,4- and 6-$C\underline{H}_3$). The signal at τ6.75 disappeared on treatment with D_2O. Diazotization of a solution of arylamine (3.0 g) in concentrated sulfuric acid

(30 cm^3) with $NaNO_2$ (1.5 g) in water (10 cm^3) and its subsequent hydrolysis (50) by water gave crude phenol. Thick layer chromatography was successfully used to isolate the pure phenol from the crude product. After crystallization from ethanol the phenol had *m.p.* 84-85°; *i.r.* (Nujol) 3350 cm^{-1} (OH); ^{1}*H.m.r.* τ(60 MHz, CCl_4), 3.21 (s,1,5-$\underline{H}$), 5.54 (s,1,3-O$\underline{H}$), 7.73 (s,6,2-C$\underline{H}_3$ and 6-C$\underline{H}_3$), 7.83 (s,3,4-C$\underline{H}_3$); ^{13}*C.m.r.* ($CDCl_3$, ppm), 13.2 (2-$\underline{C}H_3$), 15.6 (6-$\underline{C}H_3$), 20.0 (4-$\underline{C}H_3$), 121.2 (C-6), 121.9 (C-2), 127.7 (C-4), 129.5 (C-5), 132.4 (C-3), 150.6 (C-1). Mass spectrum: (70 eV), m/e (relative intensity), 170 (73, M^+)*, 155 (24, M-CH_3)*, 135 (100, M-Cl), 105 (21), 91 (42), 77 (39).

Anal. Calcd. for $C_9H_{11}ClO$: C, 63.53; H, 6.47
Found: C, 63.42; H, 6.58

Some of this phenol was used to prepare the arylacetate derivative described above.

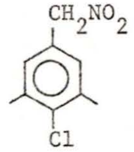
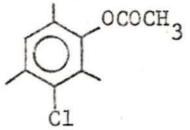
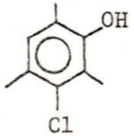
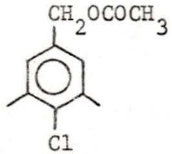
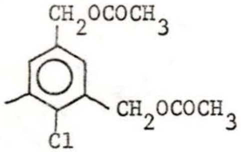
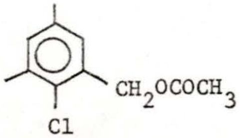
4. *Benzylacetates* (8, 9, 10)

A solution of chloromesitylene and N-bromosuccinimide (51) in CCl_4 on refluxing under u.v. light gave a product containing monobromides (symmetrical and unsymmetrical) and dibromo compound. Refluxing the crude product in 95% ethanol with potassium acetate gave a mixture of side-chain acetates. These were successfully isolated via column chromatography (Silica gel), eluting with ether-pentane mixtures. The 12.5% ether-pentane fraction gave 4-chloro-3,5-dimethylbenzylacetate (8), *i.r.* (neat liquid smear), 1735 and 1215 cm^{-1} (OCOCH$_3$); ^{1}*H.m.r.* τ(60 MHz, CCl$_4$), 3.06 (s,2,2-$\underline{\text{H}}$ and 6-$\underline{\text{H}}$), 5.17 (s,s,1-C$\underline{\text{H}}_2$OAc), 7.73 (s,6,3-C$\underline{\text{H}}_3$ and 5-C$\underline{\text{H}}_3$), 8.04 (s,3, OCOC$\underline{\text{H}}_3$); ^{13}*C.m.r.* (CDCl$_3$, ppm), 20.6 (OCO$\underline{\text{C}}$H$_3$, 3-$\underline{\text{C}}$H$_3$ and 5-$\underline{\text{C}}$H$_3$), 65.6 ($\underline{\text{C}}$H$_2$OAc), 128.3 (C-2 and C-6), 134.0 (C-1), 134.4 (C-4), 136.3 (C-3 and C-5), 170.4 (O$\underline{\text{C}}$OCH$_3$). Mass spectrum: (70 eV), m/e (relative intensity), 212 (53, M$^{+\cdot}$)*, 170 (100, M-CH$_2$CO)*, 153 (56, M-OAc)*, 135 (74, M-CH$_2$CO-Cl), 117 (47), 91 (22), 77 (20). The 22.5% ether-pentane fraction gave the unsymmetrical diacetate (9), 2-chloro-3-methyl-1,5-diacetoxymethylbenzene. *i.r.* (neat liquid smear), 1740 and 1225 cm^{-1} (OCOCH$_3$)$_2$; ^{1}*H.m.r.* τ(60 MHz, CCl$_4$), 2.88 (s,2,4-$\underline{\text{H}}$ and 6-$\underline{\text{H}}$), 4.96 (s,2,3-C$\underline{\text{H}}_2$OAc), 5.1 (s,2,1-C$\underline{\text{H}}_2$OAc), 7.66 (s,3,3-C$\underline{\text{H}}_3$), 7.96 (s,3,1-OCOC$\underline{\text{H}}_3$), 8.00 (s,3,5-OCOC$\underline{\text{H}}_3$).

The 10% ether-pentane fraction from the above column which contained a mixture of isomeric monoacetates was rechromatographed to obtain the 2-chloro-3,5-dimethylbenzylacetate (10). It was obtained from the 12.5% ether-pentane fraction in the second column. *i.r.* (neat liquid smear), 1740 and 1230 (broad) cm^{-1} (OCOCH$_3$); ^{1}*H.m.r.* τ(60 MHz, CCl$_4$), 3.08 (broad singlet, 2,4-$\underline{\text{H}}$ and 6-$\underline{\text{H}}$), 5.00 (s,2,1-C$\underline{\text{H}}_2$OAc), 7.73 (s,3,3-C$\underline{\text{H}}_3$), 7.77 (s,3,5-C$\underline{\text{H}}_3$), 8.00 (s,3,1-OCOC$\underline{\text{H}}_3$); ^{13}*C.m.r.* (CDCl$_3$, ppm), 20.2 and 20.7 (3-$\underline{\text{C}}$H$_3$, 5-$\underline{\text{C}}$H$_3$ and OCO$\underline{\text{C}}$H$_3$), 64.1 ($\underline{\text{C}}$H$_2$OAc), 128.0 (C-6), 130.7 (C-2), 131.5 (C-4), 133.4 (C-1), 136.1 (C-5), 136.3 (C-3) and 170.5 (O$\underline{\text{C}}$OCH$_3$). Mass

Table 2.2

N.M.R. and I.R. Spectral Data of Compounds Used for Comparative Purposes

COMPOUND	N.M.R. (τ)				I.R.
	Ar-H	-CH$_2$-	Ar-CH$_3$	Ar-OCOC$\underline{H}_3$	
	2.88(s)	4.71(s)	7.63(s)		1545 cm^{-1} (NO$_2$)
	In (CCl$_4$) 3.13(s) In (CDCl$_3$) 3.08(s)		7.71(s) 7.87(s) 7.97(s) 7.69 7.83 7.93	7.76(s) 7.69	1770 and 1212 cm^{-1} (OCOCH$_3$)
	3.21(s)		7.73 7.83	5.54 (Ar-OH)	3350 cm^{-1} (-OH)
	3.06(s)	5.17(s)	7.73(s)	8.04 (Ar-CH$_2$OCOC$\underline{H}_3$	1735 and 1215 cm^{-1} (OCOCH$_3$)
	2.88(s)	4.96(s) 5.10(s)	7.66	7.96 8.00 (Ar-CH$_2$OCOC$\underline{H}_3$)	1740 and 1225 cm^{-1} (OCOCH$_3$)'s
	3.08(s)	5.00(s)	7.73(s) 7.77(s)	8.00 (Ar-CH$_2$OCOC$\underline{H}_3$	1740 and 1230 cm^{-1} (OCOCH$_3$)

spectrum: (70 eV), m/e (relative intensity), 212 (52, $M^{+\cdot}$)*, 177 (68, M-Cl), 170 (63, M-CH_2CO)*, 153 (58, M-OAc)*, 135 (100, M-CH_2CO-Cl), 119 (79), 117 (83), 91 (38), 77 (44).

2.7 *Decomposition and Exchange Reactions*

Addition of the pre-cooled (-78°C) reagent (300-500 mm^3) to the solid diene (0.2 - 0.4 mmol) in an n.m.r. tube was the normal method of preparing reaction solutions. In cases of solubility difficulty, a solution of diene in deuterated chloroform (50-75 mm^3) was preferred. The reactions were then monitored by ^{1}H.m.r. at ∿ 35°C.

The reactions were worked up by pouring the contents of the n.m.r. tube into a small flask (∿ 25 cm^3 capacity), rinsing with methylene chloride (∿ 1.0 cm^3), cooling to -78°C and then passing gaseous ammonia in for five minutes. Addition of anhydrous magnesium sulfate followed by filtration and evaporation of solvent yielded reaction products (see Appendix 1) which were analysed by i.r., ^{1}H.m.r., g.l.c. and g.l.c.-mass spectrometry.

1. *Decomposition*

An initially pure sample of diene **2A** decomposed into three components when introduced into the g.l.c.-m.s. system, at 180°C on a SE 30 column. Analysis of the g.l.c. trace and g.l.c.-mass spectra indicated that the aromatic components consisted of chloromesitylene (22%); m/e (relative intensity) 154 (100, $M^{+\cdot})^*$, 119 (45, M-Cl); 2-chloro-4-nitromesitylene (1) (27%): 199 (100, $M^{+\cdot})^*$, 182 (25, M-17)*, 154 (20), and 3-chloro-2,4,6-trimethylphenylacetate (5) (32%): 212 (37, $M^{+\cdot})^*$, 170 (100, $M-CH_2CO)^*$, 151 (50), 135 (22). The remaining 19% represent unidentified products.

A similar experiment with diene 2B gave largely chloromesitylene (56%), 2-chloro-4-nitromesitylene (1) (14%), and 3-chloro-2,4,6-trimethylphenylacetate (5) (30%).

Diene 3B rapidly decomposed on the g.l.c. column to give the sole product, 3-chloro-2,4,6-trimethylphenylacetate (5).

Prolonged storage of dienes 2A, 2B and 3B at -20°C gave known decomposition products. Dienes 2A and 2B decomposed to give 4-chloro-3,5-dimethylphenylnitromethane (4) whilst diene 3B lost nitrous acid to give the aryl acetate (5). Diene 3B on prolonged exposure at room temperature was seen to produce brown fumes, and the white diene solid changed to a green coloured liquid during the decomposition from which chloro-trimethylphenylacetate (5) could be isolated.

2. *Reaction with 0.1% sulfuric acid in methanol*

Acetoxy diene 2A (50.2 mg, $\sim$ 0.2 mmol) was added to 0.1% H_2SO_4 (vol/vol) in methanol solution (300 mm^3) in an n.m.r. tube at

0°C. The reaction was stirred and examination by ^{1}H.m.r. indicated no appreciable exchange at 0°C. However, exchange of the methoxy group for the acetoxy moiety occurred when the temperature was raised to 20°C, and more rapidly at 30°C. The signal associated with the acetate methyl (τ8.05) gradually decreased and two new signals in the methyl region (τ8.65 and τ8.74) representing the *cis* and *trans* isomers of the methoxynitro diene became more prominent. *i.e.* The methyl signal due to the methyl group *ipso* to the acetate in the original diene (τ8.45) was seen to move to a higher field and split in two as the exchange took place.

The reaction mixture was diluted with methylene chloride (1 cm^3) and cooled to -78°C. Ammonia was bubbled through for five minutes. Evaporation of the solvent after drying (anhydrous MgSO$_4$) gave the mixture of the isomeric methoxy dienes (**11**) in the ratio ∿ 1:1 ^{1}*H.m.r.* τ(60 MHz, CDCl$_3$), 4.20 (broad, 4, two from each diene, 2-$\underline{H}$ and 6-$\underline{H}$), 6.85 and 6.97 (two singlets, 6, three for each methoxy group, 1-OC$\underline{H}_3$), 8.13 (s,12,6, 2 methyls in each diene, 3-C$\underline{H}_3$ and 5-C$\underline{H}_3$), 8.63 and 8.72 (two singlets, 6, three for each methyl group, 1-C$\underline{H}_3$). ^{13}*C.m.r.* (CDCl$_3$, ppm), 17.1 and 17.4 (3-$\underline{C}$H$_3$ and 5-$\underline{C}$H$_3$ for each diene), 26.6 and 27.4 (1-$\underline{C}$H$_3$ for each diene), 52.5 and 52.8 (1-O$\underline{C}$H$_3$ from each diene), 71.92 (C-1 in each diene), 132.3 and 132.5 (C-3 and C-5 in each diene), 134.8 and 136.0 (C-2 and C-6 in each diene). The peaks of C-4 (∿ 90.4) which are of low intensity were not able to be clearly distinguished from the background noise. The methoxy diene is stable up to 60°C.

A similar reaction of diene 3B (55.5 mg, $\sim$ 0.2 mmol) with 0.1% H_2SO_4 in methanol (300 mm^3) gave a single product, 3-chloro-2,4,6-trimethylphenylacetate (5).

3. *Reaction with 10% H_2O in Acetone-d_6*

A solution of acetoxy diene 2A (53.2 mg, $\sim$ 0.2 mmol) in 10% H_2O in acetone-d_6 containing 0.1% H_2SO_4 (vol/vol) (300 mm^3) was prepared at 0°C. The ^{1}H.m.r. was monitored at $\sim$ 35°C. Exchange occurred very slowly. Spectra obtained 65 minutes after the reaction was commenced showed new signals, attributed to the hydroxy diene, appeared at τ3.94 (diene protons), τ8.17 (s,6,3-$C\underline{H}_3$ and 5-$C\underline{H}_3$) and τ8.64 (s,3,1-$C\underline{H}_3$). Another peak at τ8.73 developed along with the τ8.64 signal in the ratio 1:2. This was attributed to the 1-$C\underline{H}_3$ signal for the hydroxy diene diastereoisomer. About 16 hours later the signal at τ8.47 (1-CH_3 of the original acetoxy diene) had largely disappeared. An intense signal at τ8.05 was from the acetic acid liberated during the course of the reaction. After standing for two months the diene had decomposed giving mainly a side chain derivative (τ5.15), probably the alcohol, with a minor amount of 2-chloro-4-nitromesitylene.

4. *Reaction with Dry Hydrogen Chloride Gas*

Dry HCl gas was passed through a solution of acetoxy diene 2A (175 mg, $\sim$0.8 mmol) in ether (15 cm^3) maintained between -10°C and

-15°C for half an hour. The reaction mixture was neutralized with gaseous ammonia (at -15°C), excess NH_4Cl filtered, and the product dried (anhydrous $MgSO_4$). Evaporation of the solvent gave exchanged reaction product with minor quantities of aromatic compounds. Observation of the n.m.r. spectra revealed a complete loss of the acetate methyl signal at τ8.03 and the downfield shift to τ8.23 of the methyl group 'ipso' to the acetate moiety, which appeared at τ8.45 in the original diene, indicated that the chloride anion replaced the acetate group. Integration in the methyl region showed two methyls at τ8.14 (s,6,3-C$\underline{H}_3$ and 5-CH_3) and a methyl at τ8.23 (s,3,1-C$\underline{H}_3$) which favours the dichloro diene structure (12). The diene protons moved slightly downfield to τ3.94 from a value of τ3.99 in the original acetoxy diene. Decomposition products constituted only a minor fraction of the total product (*ca.* 10%). The aromatic compound produced largely appeared to be 2-chloro-4-nitromesitylene (1) and a small amount of 4-chloro-3,5-dimethylphenylnitromethane (4). A similar reaction done at -78°C showed no exchange occurring, and prolonged storage of the reaction at -20°C eventually showed the presence of side chain nitro compound along with the original diene.

5. *Reaction with Silver Nitrate in Methanol*

To a solution of silver nitrate (98.4 mg, 1.15 mmol) in methanol (500 mm^3) in an n.m.r. tube maintained at -78°C was added acetoxy diene **2A** (78.6 mg, ∿ 0.3 mmol), and the reaction monitored by ^{1}H.m.r. at ∿ 35°C. Appreciable amounts of aromatic compounds were formed within an hour of the start of the reaction. Signals developed at τ8.68 and τ8.76 which, on comparison with the reaction with 0.1% H_2SO_4 in MeOH, indicated that the exchange of methoxy group for the acetoxy moiety occurred. These signals represent the methyl groups *ipso* to the methoxy group in the dienes. Signals also developed at τ3.35 and τ8.53, which like the τ8.76 peak of one of the methoxy diene isomers, were gradually reduced in intensity in the course of the reaction while a new peak developed at τ3.45. Prior to work-up *ca.* 85% of the product was aromatic compounds. The reaction mixture, after work-up, showed signals at τ6.81 and τ6.93 representing the methyl groups of the methoxyl moiety in the isomeric pair of the methoxy dienes. These signals also correspond well with those of the methoxy nitro diene characterized earlier. Some additional signals in the methoxyl region at τ6.53 and τ6.84 appear to be associated with a peak in the diene methyl region at τ8.45 (*cf.* τ8.53 in methanol) indicate yet another kind of diene of unknown structure.

G.l.c. peaks, with associated molecular ions and assignments were eluted in the following order. The assignments of compounds (**1**) and (**5**) were confirmed by comparison of retention times with those of authentic samples. m/e (relative intensity), 194 (∿ 15%, 3-hydroxy-2,4,6-trimethylphenylacetate) (**13**), 150 (1%, 2,4,6-trimethylanisole) (**14**), 199 (24%, 2-chloro-4-nitromesitylene) (**1**), 212 (52%, 3-chloro-

2,4,6-trimethylphenylacetate) (5), and 223 (8%, 2,4,6-trimethyl-3-nitrophenylacetate) (15).

The g.l.c.-m.s. trace for m/e at 194 also shows another molecular ion at 166 assigned to 3-hydroxy-2,4,6-trimethylanisole (16A). The compounds appear together, under one peak on the g.l.c. run.

6. *Reaction with Silver Nitrate in Methanol-d_4*

To a solution of silver nitrate (96.5 mg, ∼ 1.1 mmol) in methanol-d_4 (500 mm^3) at 0°C was added diene 2A (86.8 mg, ∼ 0.3 mmol) and the reaction monitored using n.m.r. at ambient temperature. Within the first fifteen minutes of the reaction new signals at τ4.16, τ8.68, and τ8.76 indicated the developing methoxynitro dienes, while the acetate diene peaks at τ3.90 and τ8.50 gradually disappears. The peaks at τ3.3 and τ8.53 also appeared, and disappeared again over 2 h as the τ3.45 peak appeared. The τ4.16 and τ8.76 peaks disappeared over two days. At this stage *ca.* 80% of the product was aromatic compounds. Analysis on g.l.c. and g.l.c.-m.s. gave g.l.c. peaks with associated m/e values (% composition of each compound) at 169 (20%, 3-hydroxy-2,4,6-trimethylanisole) (16B), 199 (21%, 2-chloro-4-nitromesitylene) (1), 212 (45%, 3-chloro-2,4,6-trimethylphenylacetate) (5), and 223 (8%, 3-nitro-2,4,6-trimethylphenylacetate (15) plus some very minor components, in the sequence shown.

7. *Reaction with Silver Nitrite in Methanol-d_4*

To a solution of silver nitrite (81.4 mg, ∿ 0.6 mmol) in methanol-d_4 (500 mm^3) at -78°C was added the diene 2A (93.7 mg, ∿ 0.4 mmol) and the reaction monitored by n.m.r. at ∿ 35°C. A similar sequence of events to those which occurred in the reaction with $AgNO_3$, ensued. An i.r. spectrum on the final products shows bands at 1775 and 1215 cm^{-1} ($OCOCH_3$) and 1540 cm^{-1} (NO_2). Analysis on g.l.c. and g.l.c.-m.s. gave g.l.c. peaks in the following sequence with m/e values 169 (19%, 3-hydroxy-2,4,6-trimethylanisole) (16B), 199 (22%, 2-chloro-4-nitromesitylene) (1), 212 (51%, 3-chloro-2,4,6-trimethylphenylacetate) (5), and 223 (4%, 3-nitro-2,4,6-trimethylphenylacetate) (15) plus some minor components.

8. *Reaction with Borontrifluoride Etherate*

Cold BF_3- etherate solution (200 mm^3) at -78°C was added to the diene 2A (50.0 mg, ∿ 0.2 mmol) in an n.m.r. tube also at -78°C. The reaction progress was monitored by ^{1}H.m.r. spectroscopy, which showed immediate decomposition of the diene to give equal amounts of two major products, 2-chloro-4-nitromesitylene (1), and 4-chloro-3,5-dimethylphenylnitromethane (4).

The similar reaction of diene 2B gave largely the 2-chloro-4-nitromesitylene (1).

Reaction of diene **3B** (57.4 mg, ∿ 0.2 mmol) with BF_3-etherate (300 mm^3), showed after work up only one compound, 3-chloro-2,4,6-trimethylphenylacetate (**5**), the n.m.r. spectra of which was identical to that of the authentic sample.

9. *Reaction with Trifluoroacetic Acid in Trifluoroacetic Anhydride (TFA/TFAA)*

A solution of TFA in TFAA (1:1) (300 mm^3) at -78°C was added to the diene **2A** (107.0 mg, ∿ 0.4 mmol) in $CDCl_3$ (75 mm^3). The mixture turned a brick-red colour immediately and ^{1}H.m.r. monitoring showed the presence of 2-chloro-4-nitromesitylene (**1**).

Similar reaction of diene **3B** (55.2 mg, ∿ 0.2 mmol) with TFA/TFAA produced a single compound, checked by g.l.c. and found to be 3-chloro-2,4,6-trimethylphenylacetate (**5**). The spectrum of this product was identical to that for the authentic compound.

10. *Reaction with Acetic Acid-d_4*

Diene **2A** (86.0 mg, ∿ 0.3 mmol) was added to acetic acid-d_4 (330 mm^3) in an n.m.r. tube at 0°C. The tube was shaken and the reaction monitored by ^{1}H.m.r. at ∿ 35°C. A very slow rearomatization reaction proceeded accompanied by isomerization of the diene. Five days later all the diene had decomposed. Major signals at τ4.42, τ4.64, and τ5.02 in the ratio of 1:2.5:1 indicated the presence of side chain substitution products. A very small signal at τ5.44

was also observed. Comparison of the reaction product, after work-up, with the following reaction in 10% acetic anhydride in acetic acid-d$_4$ showed the predominant products to be 4-chloro-3,5-dimethylphenylnitromethane (4) (55%), 4-chloro-3,5-dimethylbenzylacetate (8) (20%). The above assignments were made using authentic samples of the benzylnitromethane and benzylacetate compounds for comparison of ^{1}H.m.r. The signal at τ4.42 associated with an unknown side-chain derivative disappeared when the product was left to stand for 3 months at ambient temperature. The same component appeared in other reactions (i.e. 11, 12) and is suggested to be 4-chloro-3,5-dimethylbenzylnitrite (17).

A similar reaction of diene 3B (53.2 mg, ∿ 0.2 mmol) with acetic acid-d$_4$ (300 mm^3) yielded a single product assigned as 3-chloro-2,4,6-trimethylphenylacetate (5) with the help of i.r., ^{1}H.m.r. spectra and g.l.c.

11. *Reaction with 10% Acetic Anhydride in Acetic Acid-d$_4$*

To the diene 2B (51.5 mg, ∿ 0.2 mmol) in an n.m.r. tube at 0°C was added a cold (0°C) solution of 10% Ac$_2$O in acetic acid-d$_4$ (200 mm^3) and the reaction monitored by ^{1}H.m.r. Signals corresponding to the isomer 2A were seen to be formed, but decomposition of the dienes occurred more rapidly to give signals at τ4.43, τ4.65, and τ5.03 indicating benzylic products. Signals at τ4.65 and τ5.03

were attributed to 4-chloro-3,5-dimethylphenylnitromethane (4) and 4-chloro-3,5-dimethylbenzylacetate (8), respectively, by enhancement of these signals brought about by addition of solutions of the authentic compounds to the reaction. The signal at τ4.43 is possibly the methylene group of 4-chloro-3,5-dimethylbenzylnitrite (17). It was demonstrated that the τ4.43 signal could not be due to 2-chloro-3,5-dimethylbenzylacetate (10) as the $C\underline{H}_2$ peak of this compound is at τ4.96. Re-examination of the product mixture after 3.5 months by ^{1}H.m.r. showed a complete loss of the τ4.43 signal, with new signals at τ0.17, τ2.25 and τ2.45 which have been attributed to 4-chloro-3,5-dimethylbenzaldehyde (19). This assignment was made in conjunction with the reaction of diene 2A with 10% D_2O in acetic acid-d_4 which gave a similar behavioural pattern. In fact, g.l.c.-m.s. analysis in the following reaction (i.e. 12) showed a molecular ion corresponding to 4-chloro-3,5-dimethylbenzaldehyde (19).

12. *Reaction with 10% D_2O in Acetic Acid-d_4*

To diene 2A (50.5 mg, ~0.2 mmol) at 0°C was added 10% D_2O in acetic acid-d_4 solution (300 mm^3) and the reaction monitored by ^{1}H.m.r. Almost immediately decomposition products analogous to the above two reactions were formed, with the τ4.65 and τ5.03 peaks attributed to phenylnitromethane (4) and benzylacetate (8), respectively. The peak at τ4.43 was also observed and disappeared later giving rise to new minor signals at τ0.12, τ2.2 and τ2.4. The τ4.43 signal was attributed to 4-chloro-3,5-dimethylbenzylnitrite (17). Analysis of g.l.c. and g.l.c.-m.s. gave a molecular ion at 168 corresponding to the benzaldehyde (19) which is presumed to have been formed from (17). This has been discussed in the following chapter.

13. *Reaction with Silver Acetate in Acetone-d_6*

Silver acetate (60 mg, ∿ 0.36 mmol) was added to a solution of diene 2A (53.2 mg, ∿ 0.2 mmol) in acetone-d_6 (500 mm^3) maintained at 0°C. The reaction mixture was thoroughly shaken. Because of the insolubility of silver acetate, ^{1}H.m.r. observation of the progress of the reaction was not possible. The reaction after work-up and examination by g.l.c. showed three major components with very small traces of two minor products. Analysis by g.l.c.-m.s. gave m/e values 154 (3%), 152 (5%), 199 (24%), 212 (54%) and 223 (15%). The components with mass weights of 154, 152, 199, 212 and 223 were assigned as chloromesitylene, 2,4-dihydroxymesitylene (18), 2-chloro-4-nitromesitylene (1), 3-chloro-2,4,6-trimethylphenylacetate (5) and 3-nitro-2,4,6-trimethylphenylacetate (15) respectively. The mass spectral traces for m/e of 199, 212 and 223 were comparable to g.l.c.-m.s. traces of products obtained from $AgNO_3$ and $AgNO_2$ reactions in methanol and methanol-d_4. A similar reaction in which low concentration of silver acetate (0.22 mmol) was reacted with diene 2A (∿ 0.39 mmol) proceeded slowly, finally giving the above products after work-up of the reaction.

14. *Reaction with Trifluoromethanesulfonic Acid (CF_3SO_3H)*

To diene 3B (55.7 mg, ∿ 0.2 mmol) in $CDCl_3$ (75 mm^3) in an n.m.r. tube at -78°C, was added pre-cooled (-78°C) CF_3SO_3H (300 mm^3). An immediate reaction occurred as the reaction mixture thawed. Work-up of the reaction gave a mixture of aromatic compounds, which were eluted in the following order on g.l.c.: 2,4-dihydroxymesitylene (18) (m/e 152, 12%), 3-chloromesitol (6) (m/e 170, 44%), 2-chloro-4-nitromesitylene (1) (m/e 199, 17%) and 3-chloro-2,4,6-trimethylphenyl-acetate (5) (m/e 212, 11%). The identities of (6), (1) and (5) were confirmed by comparison of g.l.c. retention time and mass spectra with those of authentic samples. A fifth component (12%) was not identified but was likely to be the 3-nitro-2,4,6-trimethylphenyl-acetate (15).

CHAPTER III

DISCUSSION

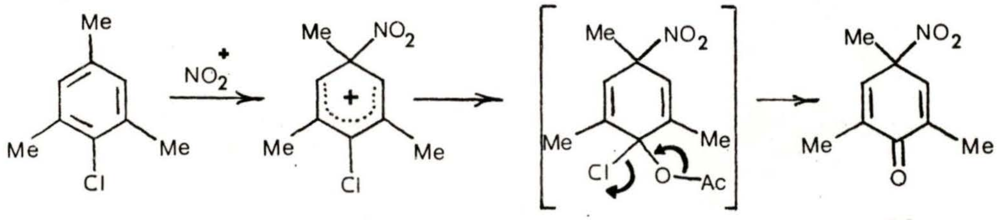
3.1

Nitration of chloromesitylene in acetic anhydride yielded three adducts 2A, 2B, and 3B. These adducts are labile, and readily undergo decomposition at room temperature to give rearomatization products. Acid catalysed decomposition was facile. Manipulation of the dienes during spectral analysis, and reaction studies was difficult, especially in the case of the secondary acetate diene 3B which decomposes very rapidly to the aryl acetate 5. The unstable nature of diene 3B limited the number of rearomatization and exchange reactions which could be performed and necessitated several attempts to obtain the elemental analysis. A larger number of exchange and rearomatization reactions were performed on diene 2A because it was more stable and also available in larger amount from the nitration reactions than diene 3B.

3.2 *Diastereomers 2A and 2B, 4-chloro-1,3,5-trimethyl-4-nitro-1,4-dihydrophenylacetate*

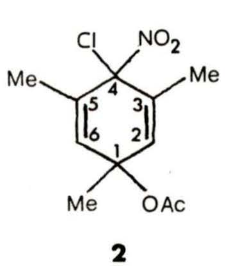
I.r. bands at 1740 and 1240, and at 1560 cm^{-1} established the presence of the acetoxy and nitro groups respectively in 2A, while 2B had corresponding absorptions at 1745 and 1237, and at 1570 cm^{-1}.

Peaks at τ3.96 (2H), 8.06 (3H), 8.13 (6H) and 8.44 (3H) in the ^{1}H.m.r. spectrum of 2A are assigned as vinyl protons, acetate methyl protons, 1- and 3-methyl protons, and 5-methyl protons, respectively (using the enumeration of 2-chloromesitylene). The symmetry evident from the ^{1}H.m.r. spectra, which is preserved through shift reagent studies (below) and which is also evident in the ^{13}C spectra indicates that the compound labelled 2A must be a 1,4- rather than a 1,2-adduct. No 1,2-adduct can have any chemically identical ring protons and methyl groups. Again the symmetry requires the nitro group to be located at C-2 and the acetate at C-5 of the original 2-chloromesitylene, or vice-versa. The decrease in the paramagnetic shift of a proton with an increase in the distance between the site of complexation of europium and the proton in question is well established (52a) and such shift reagent studies allow the ambiguity between the 2-acetoxy-5-nitro and 5-acetoxy-2-nitro structures to be resolved. The acetate methyl protons move downfield most rapidly on addition of the shift reagent, as is appropriate since the europium is preferentially complexed at the acetate group (52b) and hence closest to these protons. This confirms the correctness of the acetate group assignment. The single methyl group (at C-5 of the original 2-chloromesitylene) moves downfield more rapidly than two symmetrical methyl groups (at C-1 and C-3). The europium and thus the acetate group must therefore be closer to the C-5 than to the C-1 and C-3 and hence the 5-acetoxy-2-nitro structure is correct and the alternative 2-acetoxy-5-nitro structure must be rejected. It is also to be noted that the latter structure is unlikely on the chemical grounds since from other systems it is known that the potential geminal arrangement of chlorine and acetate is preferentially converted into a cyclohexadienone, *i.e.* 4-nitro-2,4,6-trimethylcyclohexa-2,5-dienone (**20**) is the expected product of attack by nitronium ion at C-5.



20a **20**

It can be concluded with confidence then that, using its own correct enumeration, **2**A is a diastereomer of 4-chloro-1,3,5-trimethyl-4-nitro-1,4-dihydrophenylacetate and similar arguments can be adduced to demonstrate that **2**B is the other diastereoisomer.

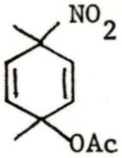
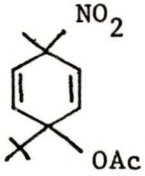
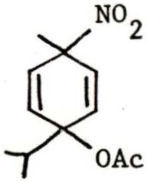
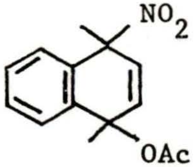


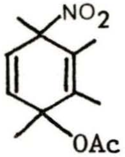
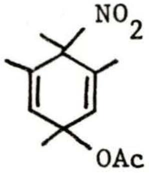
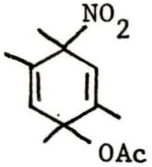
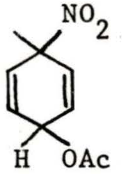
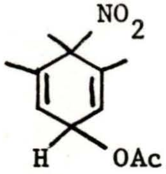
2

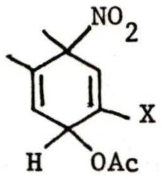
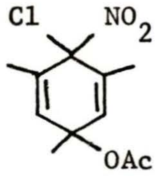
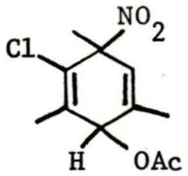
It is somewhat surprising that in the ^{1}H.m.r. of **2**A and **2**B there was no obvious coupling between vinyl protons and the adjacent methyl groups. The vinyl protons of 2B, in particular, appeared as broad singlets and the 3- and 5-methyl protons were also somewhat broad. However, no splitting could be resolved. In six of the seven cases in which the stereochemistry of diastereoisomeric adducts have been assigned, the chemical shift of the acetate group is at lower field in the *cis* isomer than in the *trans*. (Refer to Table 3.1.) This would suggest that 2B is the *cis* isomer and 2A the *trans*. Further support for this tentative assignment is provided by the shift reagent studies. Addition of the shift reagent produces a larger shift in the 2B protons than it does in the corresponding protons of 2A (Figure 3.1). This implies that the shift reagent is complexed more extensively in 2B than in 2A. It is proposed that the nitro group can contribute to the complexing ability of 2B, since the nitro is on the same side of the ring as the acetate in this diastereomer. The nitro group is weakly complexed and the dominant complexing occurs with the acetoxy function (52b). However weak, the europium-nitro group complexing would add to the stability of the europium-diene complex. If both the acetoxy and the nitro group of 2B are involved in the complexing of the europium then the europium should be located closer to the centre of the cyclohexadiene ring in 2B than in 2A, and in consequence the shifts of the ring protons and ring methyl protons should be greater relative to that of the acetate group in 2B, than they are in 2A. This is indeed observed (Figure 3.2). Normally the effect of a shift reagent on C-4 methyl group is used to assign the stereochemistry. Obviously this approach is not possible in the present case where there is no such methyl group in the diene.

Table 3.1

τ Values of Acetate Group and Other Substituents in Known Isomeric Pairs of Dienes

Diene		$OCOC\underline{H}_3$	C-1	C-2	C-3	C-4	C-5	C-6	Assign-ment	Ref.
	a	8.01	8.54	3.93	3.93	8.21	3.93	3.93	*cis*	(15)
	b	8.03	8.51	3.81	3.81	8.29	3.81	3.81	*trans*	
	a	8.02	9.07	3.97	3.79	8.25	3.79	3.97		(18)
	b	8.05	9.04	3.96	3.66	8.30	3.66	3.96		
	a	8.00	7.95 9.12	4.04	3.78	8.21	3.78	4.04		(7d)
	b	8.03	7.79 9.11	3.95	3.67	8.29	3.67	3.95		
	a	7.99	8.39	3.89	3.66	8.05	--	--	*trans*	(19)
	b	8.04	8.31	4.03	3.80	7.93	--	--	*cis*	

	a	8.09	8.57	8.28	8.30	8.27	4.24	4.16	*trans*	(33)
	b	8.06	8.59	8.23	8.32	8.38	4.23	3.76	*cis*	
	a	8.04	8.47	4.18	8.25	8.22	8.25	4.18		(33)
	b	7.98	8.65	4.11	8.20	8.37	8.20	4.11		
	a	8.09	8.57	8.24	4.54	8.25	8.27	4.34	*trans*	(33)
	b	8.04	8.54	8.18	4.49	8.37	8.22	3.91	*cis*	
	a	7.91	4.31	3.85	3.76	8.21	3.76	3.85	*trans*	(13)
	b	7.97	4.48	3.96	3.75	8.31	3.75	3.96	*cis*	
	a	8.00	4.52	8.26	8.32	8.27	8.26	4.22		(14)
	b	8.06	4.52	8.31	8.28	8.35	8.28	4.33		

	X = COMe									
	a	7.98	3.83	7.62	3.08	8.09	8.15	4.00	*trans*	(29)
	b	7.95	3.90	7.62	3.14	8.17	8.13	4.03	*cis*	
	X = COPh									
	a	8.01	3.60	--	3.46	8.04	8.10	3.90	*trans*	(29)
	b	7.99	3.68	--	3.54	8.26	8.10	3.93	*cis*	
	2A	8.06	8.44	3.96	8.13	--	8.13	3.96	*trans* (tentative)	
	2B	8.00	8.48	3.83	8.15	--	8.15	3.83	*cis* (tentative)	
	3A	7.90	4.04	8.10	--	8.18	4.27	8.26	? (not isolated)	
	3B	7.82	4.07	8.08		8.14	4.27	8.24	?	

i) a refers to the diene eluted first, b follows a in a column run

ii) Un-assigned structures drawn were not used for shift reagent study. They have been included for comparison purposes only.

Figure 3.1. Plot Showing Chemical Shifts of Protons of Dienes 2A and 2B as a Function of the Amount of Eu(fod)$_3$-d$_{27}$ Reagent Added

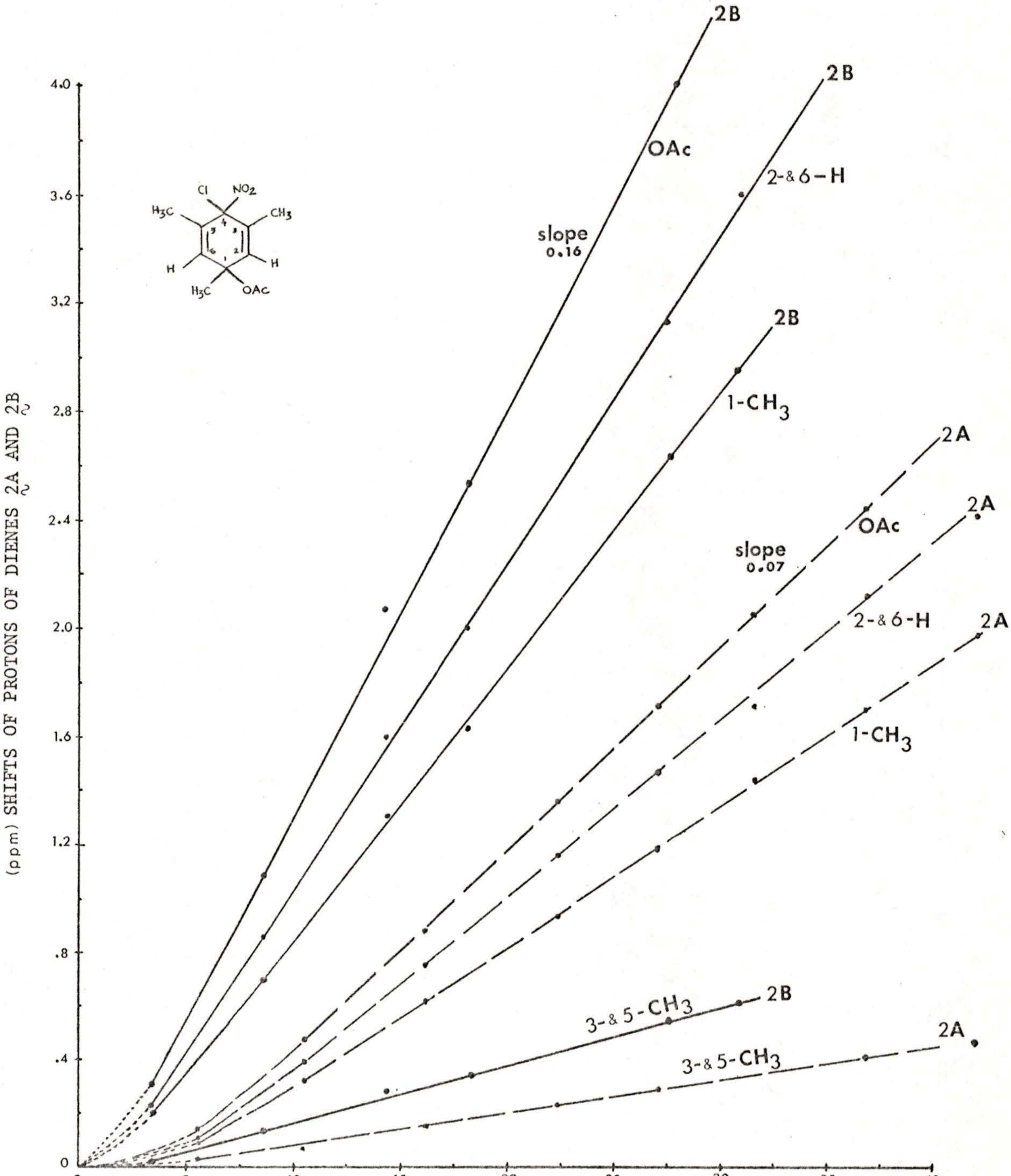
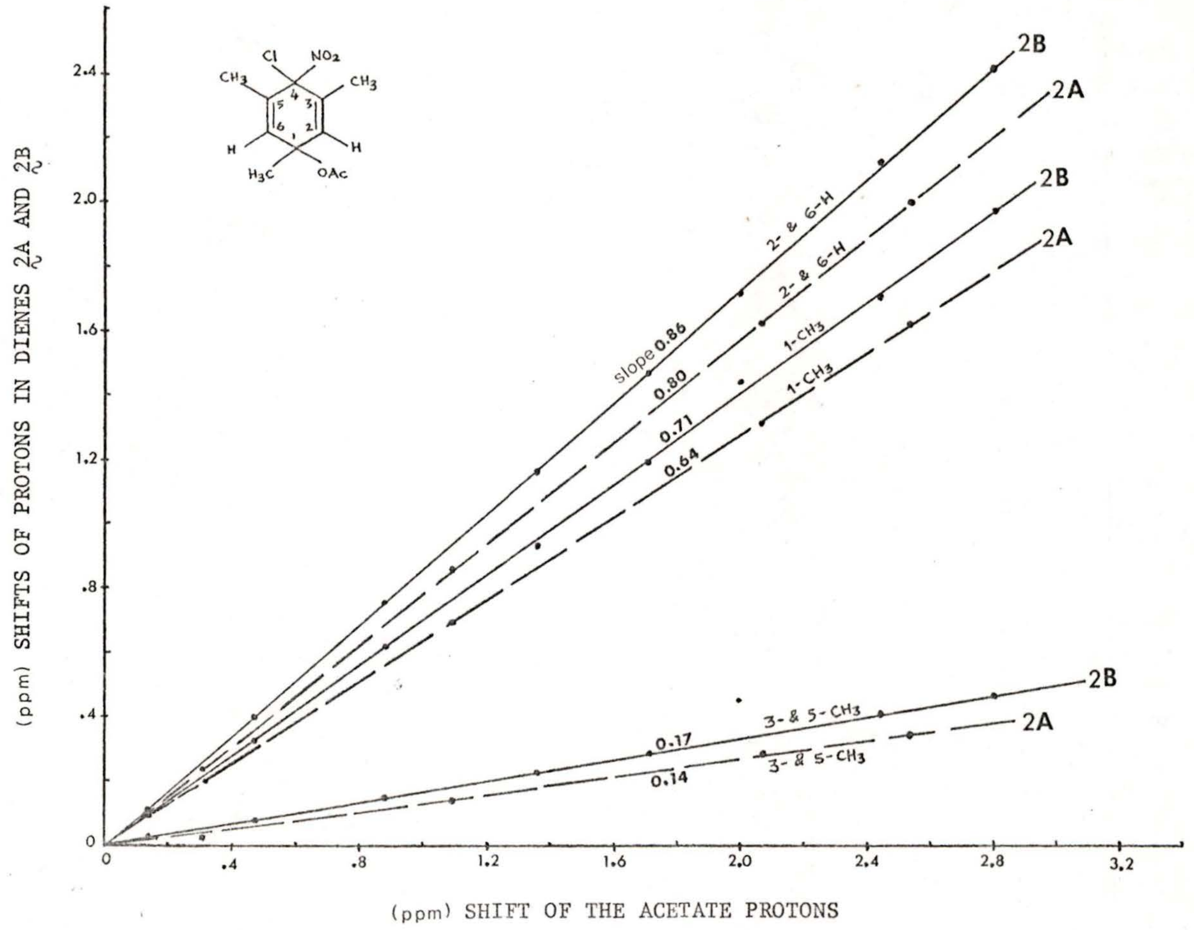


Figure 3.2. Plot Showing the Chemical Shifts of Protons in Diene 2A and 2B v/s the Chemical Shift of the Acetate Protons on the Addition of Eu(fod)$_3$-d$_{27}$ Shift Reagent



The close similarity of the ^{1}H.m.r. spectra of pure diene 2A and that of diene 2B became distinctly clear when small additions of diene 2B to a solution of pure diene 2A in $CDCl_3$ produced three distinct new signals at τ3.86 (2-$\underline{H}$ and 6-$\underline{H}$), 8.01 ($OCOC\underline{H}_3$) and 8.48 (1-$C\underline{H}_3$) — see Appendix 2.

3.3 *Diene 3B, 3-chloro-2,4,6-trimethyl-4-nitro-1,4-dihydrophenylacetate*

I.r. bands appeared at 1735 and 1220, and at 1550 cm^{-1}, consistent with the presence of the acetate and nitro groups in diene 3B.

The ^{1}H.m.r. and ^{13}C.m.r. spectra of 3B reveal that the symmetry present in dienes 2A and 2B is absent in 3B. There are two different ring protons (τ4.07 and 4.27) and four distinct methyl groups (τ7.82, 8.08, 8.14 and 8.24). The shift reagent studies (Figure 3.3) show that one proton (relative slope 1.60) must be attached to the same site as the acetate and the other (relative slope 0.23) is at least two carbon atoms away. Two of the methyl groups (relative slopes 0.50 and 0.51) must be equi-distant from the acetate and closer than the third (relative slope 0.09). These facts can be accommodated by the structure 3-chloro-2,4,6-trimethyl-4-nitro-1,4-dihydrophenylacetate but not by any other 1,4-adduct structures. The absence of u.v. absorption around 255 nm shows that 3A must be a 1,4- and not a 1,2-adduct. The latter would be a conjugated cyclohexadiene which would absorb at 253 nm or greater.

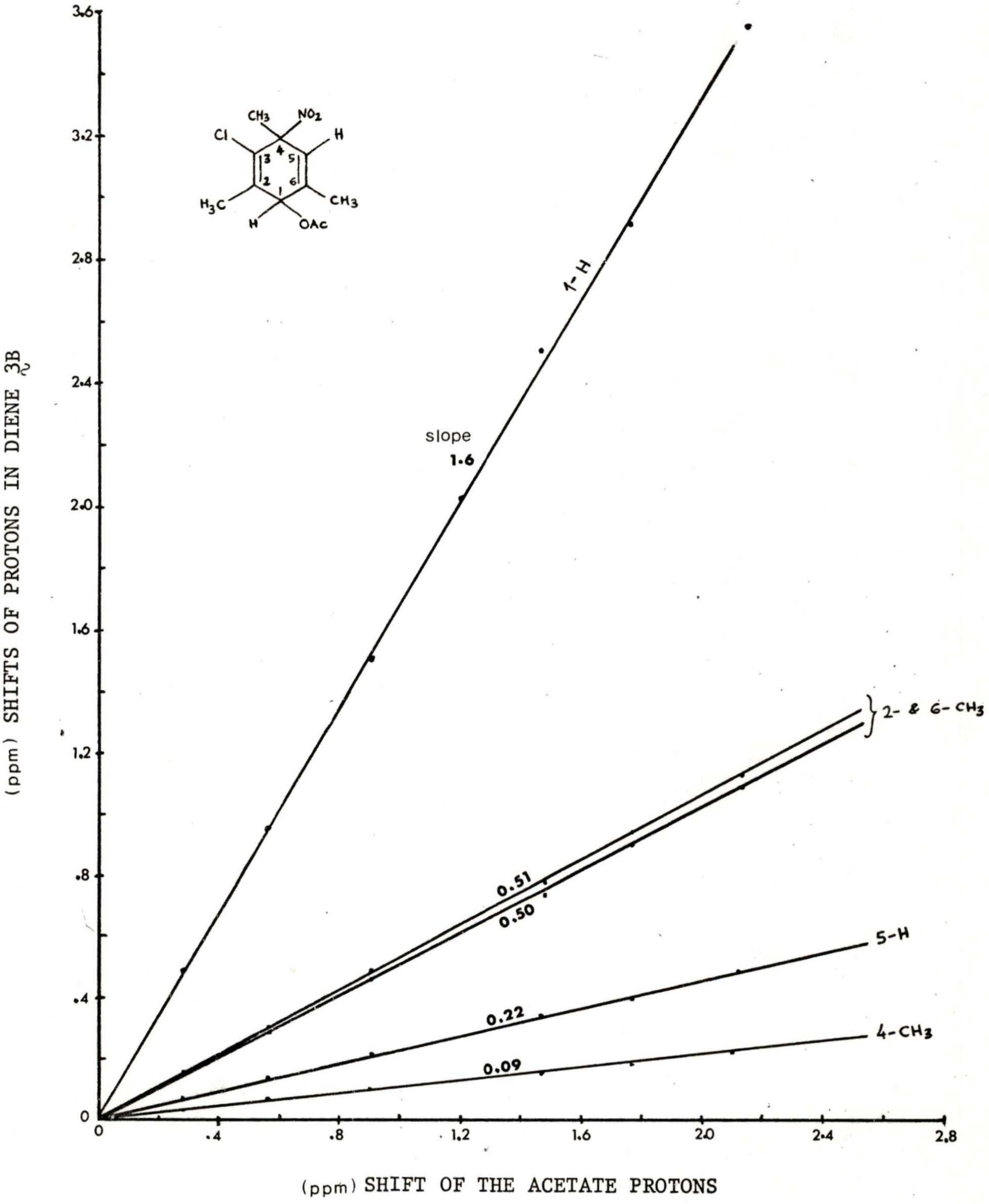
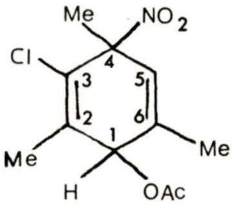


Figure 3.3. Plot Showing the Chemical Shifts of Protons in Diene 3B v/s the Chemical Shift of the Acetate Protons on the Addition of $\text{Eu(fod)}_3\text{-d}_{27}$ Shift Reagent

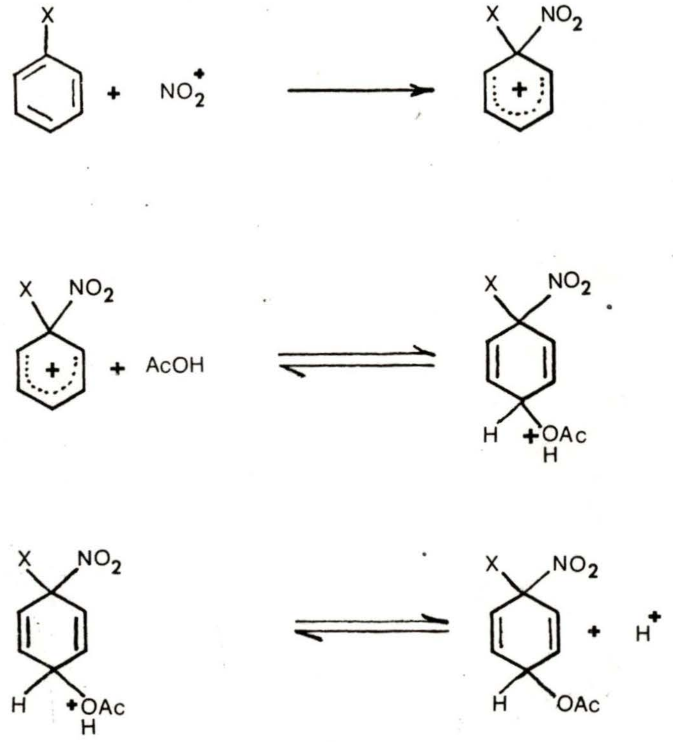


3

Repeated handling of diene **3**B at room temperature caused its decomposition to give the arylacetate **5**. The stereochemistry of the unstable diene **3**B was not assigned since the diastereomer **3**A, although formed, was difficult to isolate and thus was not available for the essential comparison. It seems reasonable also that diene **3**A would like diene **3**B be quite unstable since they are both secondary acetate adducts.

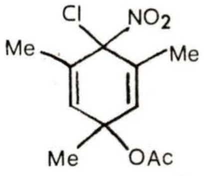
3.4 *The Mechanism of Adduct Formation*

Results obtained in this work show that nitration of chloromesitylene in acetic anhydride leads to the formation of 1,4-acetoxynitro adducts and that both the *cis* and *trans* diastereomeric adducts are formed. Formation of adducts during nitration is presumably the result of a sequence that begins with the bonding of the nitronium ion to a ring carbon bearing a substituent group. The *ipso*-cyclohexadienyl cation that forms as a consequence of *ipso* attack undergoes addition of the acetate from acetic acid or acetic anhydride, either from the same side as that of the incoming nitronium electrophile or the opposite side to yield the *cis* and *trans* 1,4-acetoxynitro adducts, respectively. The addition reaction follows a two-step path and is essentially a nitration which has been diverted in the final step. Thus, adducts are produced when an aromatic carbon bearing a substituent is not substantially less activated than the carbon bearing hydrogen. Attack of an incipient nitronium ion at the *ipso* position competes with attack at the unsubstituted positions.



The initial cyclohexadienyl cation-forming step is similar to that leading to substitution and the ratio of addition to substitution products is controlled by relative rates of attack of the nitronium ion at the *ipso* and unsubstituted positions. The *ipso* attack phenomenon is regarded as a commonly occurring process in the nitration in acetic anhydride (refer to Tables 1.2, 1.3 and 1.4) and possibly for all electrophilic substitution reactions.

The total amount of adducts produced is dependent upon the activation of the substituted positions relative to unsubstituted positions. Nitration reactions on chloromesitylene produced, on average, 30% diene adducts in the total reaction product. (Checked by ^{1}H.m.r.) The major product (∼ 70%) from the nitration reaction was 2-chloro-4-nitromesitylene 1, an indication that the substituted positions are somewhat less activated than the unsubstituted positions. The adducts obtained in the nitration of 2-chloromesitylene show that *ipso* attack occurs at the carbon bearing chlorine (C-2) and the carbons bearing methyl groups *ortho* to the chlorine-carbon position in the parent hydrocarbon (C-1 and C-3). There is a third *ipso* position in the 2-chloromesitylene molecule and thus three pairs (2, 3, 20a) of diastereoisomeric adducts are possible, but no *ipso* attack was detected at the methyl group *para* to the chlorine (see page 68). Several nitration reactions on 2-chloromesitylene, after work-up and chromatography showed that the ratio of the products 1:2:3 was 7:3:1, respectively.



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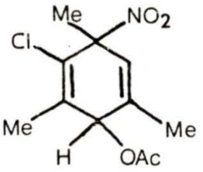

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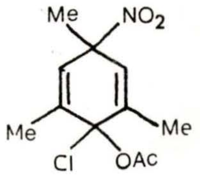
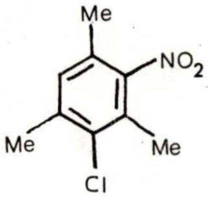
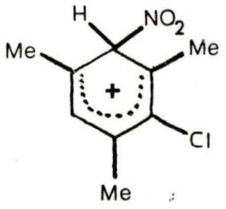


20a



1

In the cyclohexadienyl cation intermediates leading to 2-chloro-4-nitromesitylene (**1**) and diene **2** *viz*



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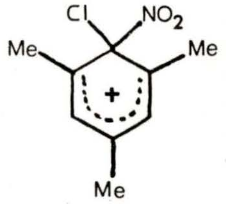
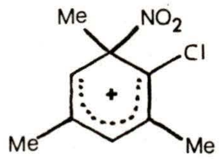


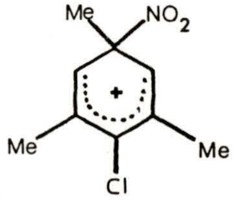
22

the methyl groups are similarly located with respect to the positive charge and the difference between these cations is in the location of the chlorine atom. It is *meta* to the site of addition of the nitronium ion in the first case (**21**) and *ipso* in the second (**22**). Thus, provided that the reaction steps are irreversible, the relative amounts of the nitro compound **1** and diene **2**, when corrected for the statistical factor of 2 favouring substitution, should reflect the substituent effects of the *meta* and *ipso* chlorine atoms and measure the ratio of partial rate factors $m_f^{Cl}:i_f^{Cl}$. The ratio of partial rate factors then, $m_f^{Cl}:i_f^{Cl}$, is 1.2:1. This value is in good agreement with the value (1.1:1) obtained by Perrin and Skinner (8) from the nitration of *p*-chloroanisole. It can be concluded that a chlorine atom has a closely similar deactivating effect at the *ipso* and *meta* positions.

The cyclohexadienyl cations obtained by addition of nitronium ion *ipso* to a methyl group have the structures



23



24

Again, these two structures differ only in the location of the chlorine atom, which is *ortho* to the site of addition of the nitronium ion in the first structure (**23**) and *para* in the second (**24**). The first structure (**23**) is the cation precursor to diene **3** and the second is the precursor to 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dienone (see page 68).

Chlorine in the *para* position is more activating than an *ortho* chlorine. The ratio $p_f^{Cl}:o_f^{Cl}$ is 4.72:1 (2a, p.85 and 2b) and after allowing for the statistical factor of 2 favouring the first cation (23), the second cation (24) should still be formed preferentially, *i.e.* more of the cyclohexadienone (20) should still be formed than diene 3. In fact, no cyclohexadienone (20) was observed in any reaction. However, in the very last nitration reaction carried out on 2-chloromesitylene, benzylic and methyl proton absorptions in the ^{1}H.m.r. spectra of some column fractions appeared to correspond with those of 4-hydroxy-3,5-dimethylphenylnitromethane (25), a product of rearomatization of 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dienone (20), obtained from low temperature nitration of mesitol (52). This would suggest that a small amount of 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dienone (20) could have been formed, at least in this case. It is unlikely that a significant amount of the dienone could have been overlooked since the recovery of the reaction products from the nitration reactions was excellent.

In principle it is possible to calculate from partial rate factors an expected product distribution for attack by the nitronium ion at all of the different nuclear positions of 2-chloromesitylene. In practice this cannot be done with any useful precision as may be illustrated by a comparison of the stabilities of the first member from each of the two pairs of cyclohexadienyl cation intermediates 21, 22 and 23, 24 discussed above. In (21) the methyl groups are at positions *ortho* and *para* to the site of attack by the nitronium ion whereas in 23 the methyl groups are *ipso* and *meta*. The stability difference between (21) and (23) with respect to the methyl groups should be the same as that for attack at unsubstituted and *ipso* positions in mesitylene itself. In terms of reactivities this has been calculated (53) to be a factor of 5000:1 in favour of attack at unsubstituted positions in mesitylene. (It is therefore not surprising that nitration of mesitylene is a very clean reaction leading to nitromesitylene as the only product.) Thus, the methyl groups should favour (21) by a reactivity factor of 5000:1. The chlorine atom is *meta* to the site of addition of the nitronium ion in (21) and *ortho* in (23). The *ortho* chlorine is less deactivating than the *meta* chlorine and the effect of the chlorine is to favour (23). The reactivity factor may be calculated from the partial rate factors, o_f^{Cl} and m_f^{Cl} for chlorine (2a). The chlorine should favour (23) over (21) by a factor of 32:1. Thus, the effect of the methyl groups is to produce exclusive formation of (21) whereas that of the chlorine atom is to produce almost exclusive formation of (23). In principle the combined result should be obtained by multiplying the factors together to produce a resultant factor of 155:1 in favour of (21).

However, small changes in the partial rate factors would drastically alter this result and it is known that partial rate factors can be markedly affected by the reactivity of the system under study. For example, m_f^{Cl} for nitration of chlorobenzene is 9×10^{-4} whereas m_f^{Cl} for nitration of *p*-chloroanisole is 690×10^{-4}. Thus, the fact that the 2-chloro-4-nitrobenzene (1) is formed (via 21) to a greater extent than the diene 3 (via 23) is in accord with the qualitative prediction that (21) should be more stable than (23) but we cannot expect the quantitative prediction to be valid.

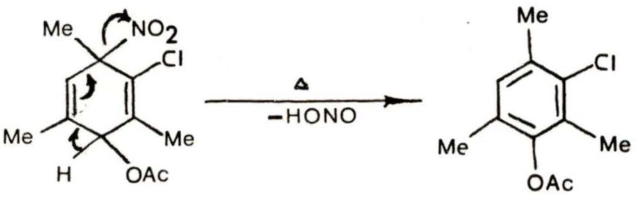
In summary, the relative yields of 2-chloro-4-nitromesitylene (1) and diene 2 are in good accord with prediction based on partial rate factors; the fact that diene 3 is formed in smaller amount than either (1) or (2) is in qualitative accord with prediction but it is somewhat surprising that, at most, only a trace of 2,4,6-trimethyl-4-nitrocyclohexa-2,5-dienone (20) would have been formed.

As mentioned above, attack at substituted positions similar to those encountered in the nitration of 2-chloromesitylene must occur in other electrophilic substitution reactions of suitably substituted aromatic compounds. This provides further reasons to investigate and obtain *ipso* factors for substituents which have not yet been investigated. In the absence of a suitable nucleophile for further reaction with the *ipso*-cyclohexadienyl cation generated by *ipso* attack, the cation could react in other ways mentioned on page 9 (Chapter I). The following section 3.5 describes various reactions of adducts (2) and (3) that are presumed to occur in most cases via regenerated *ipso*-cyclohexadienyl cations.

3.5 *Reactions of the Adducts*

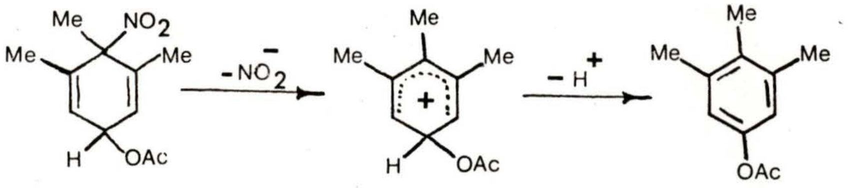
The adducts studied in the present work are very labile, and undergo rearomatization reactions readily. The course of reactions of dienes 2A and 2B, which are tertiary acetates, are markedly different from the secondary acetate adduct 3B.

Various well characterised secondary 1,4-acetoxynitro adducts obtained from hydrocarbons such as toluene (13), *o*-xylene (14), 1,2,3-trimethylbenzene (14, 38), 3,4-dimethylaceto- and 3,4-dimethylbenzophenones (29), 1,2,3,4- and 1,2,3,5-tetramethylbenzene (33) readily eliminate nitrous acid to form arylacetates. This reaction is a characteristic of the secondary acetate adducts (14). Diene 3B, on prolonged exposure at room temperature was seen to produce brown fumes, and the white diene solid changed to a green coloured liquid during decomposition to give the 3-chloro-2,4,6-trimethylphenylacetate (5).



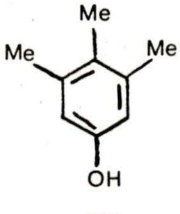
3 **5**

A recent kinetic study (38) on the solvolytic behaviour of 4-nitro-3,4,5-trimethyl-1,4-dihydrophenylacetate, a secondary acetate adduct, prepared by reaction of 1,2,3-trimethylbenzene with acetyl nitrate has produced convincing evidence that elimination of nitrous acid to form arylacetate occurs by an E1 type mechanism.

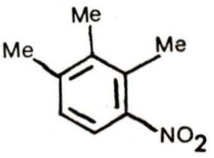


26

In aqueous ethanol and related solvents, the adduct loses nitrous acid, to yield 3,4,5-trimethylphenyl acetate (26). Reactions of the same adduct in aqueous sulfuric acid solutions ranging from 50 to 96% gave 3,4,5-trimethylphenol (27) and 4-nitro-1,2,3-trimethylbenzene (28); the yield of the nitration product increased steadily over the 50 - 70% range and then held near the quantitative mark.

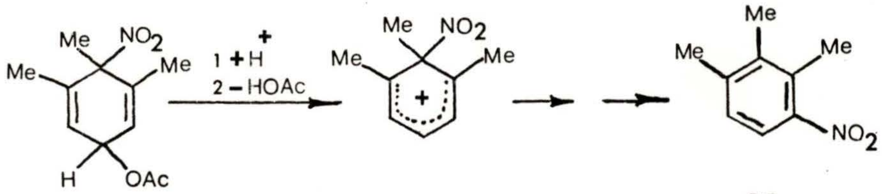


27



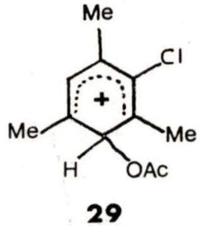
28

The results indicate that uncatalysed elimination of nitrous acid is the preferred route under most weakly acidic conditions and in solvents with increased polarity or ionizing power to yield the arylacetate, or the equivalent phenol if prior exchange of acetate for hydroxy has occurred. In strong acid solutions, the acid-catalysed loss of acetate becomes the pathway of rearomatization.

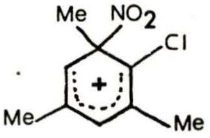


28

The above observations imply that the stability of the *ipso*-acetoxycyclohexadienyl cation and the regenerated *ipso*-nitrocyclohexadienyl cation contributes to the relative ease with which the respective acetoxy- or nitroarenes are formed. The cations generated by loss of the nitro group and acetate group, respectively, from diene **3B** have the structures



29

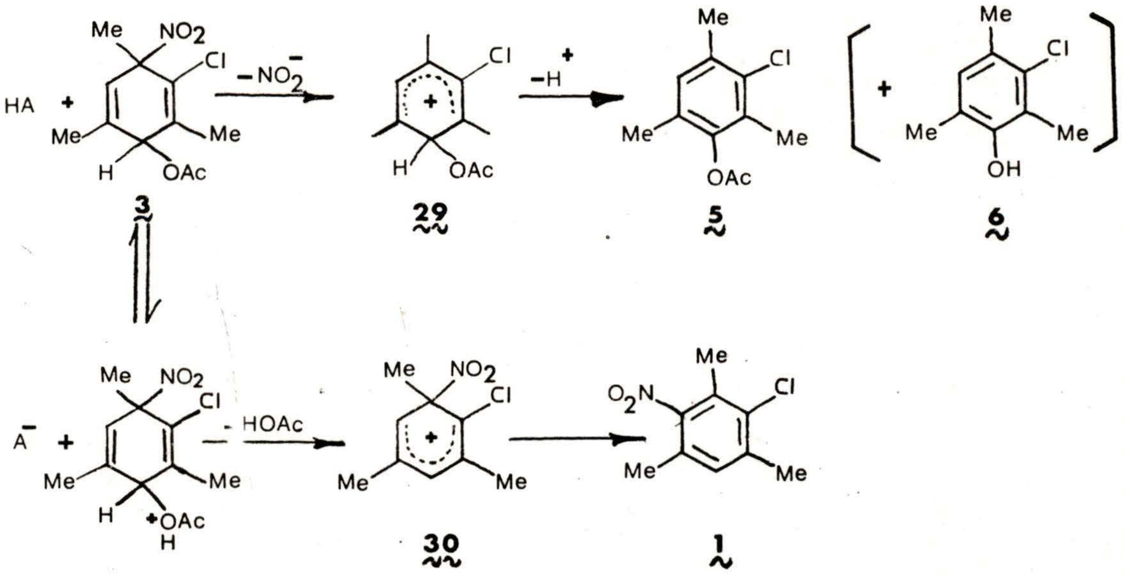


30

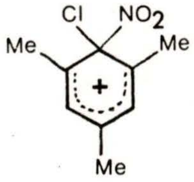
The methyl groups in **29** are more favourably located (*ortho* and *para*) for stabilization of the positive charge than in **30** (*meta* and *ipso*).

On the other hand the chlorine should be less destabilizing in 30 than in 29, but its effect should be outweighed by that of the methyl groups. Thus, it is understandable that the arylacetate (5) which is formed via 29, is the favoured reaction product from diene 3B.

Reaction of secondary acetate diene 3B with 0.1% H_2SO_4 in MeOH,acetic acid-d_4, boron trifluoride-etherate, trifluoroacetic acid in trifluoroacetic anhydride gave a single product, 3-chloro-2,4,6-trimethylphenylacetate (5). Only under very strongly acidic conditions, neat trifluoromethane sulfonic acid, was some 2-chloro-4-nitromesitylene (1) (17%) formed (via 30), and even then the products from 29, 3-chloro-2,4,6-trimethylphenol (6) (44%) and 3-chloro-2,4,6-trimethylphenylacetate (5) (11%), predominated. It is likely that the phenol (6) was formed by hydrolysis of the phenylacetate (5). 2,4,6-trimethyl-1,3-benzenediol (18) (12%) was also produced in this reaction (*c f.* page 96).



In the rearomatization reactions of the tertiary acetate adduct 2 three general types of reactions listed were observed: 1. 1,3-migration of the nitro group to give 2-chloro-4-nitromesitylene (1); 2. formation of side-chain benzylic derivatives; 3. 1,2-shift of the acetate group to yield phenylacetates. In the case of diene 2, intermediate (31), with *ortho* and *para* methyls, is more stable than (32) with *ipso* and *meta* methyl groups.



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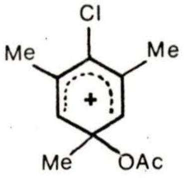
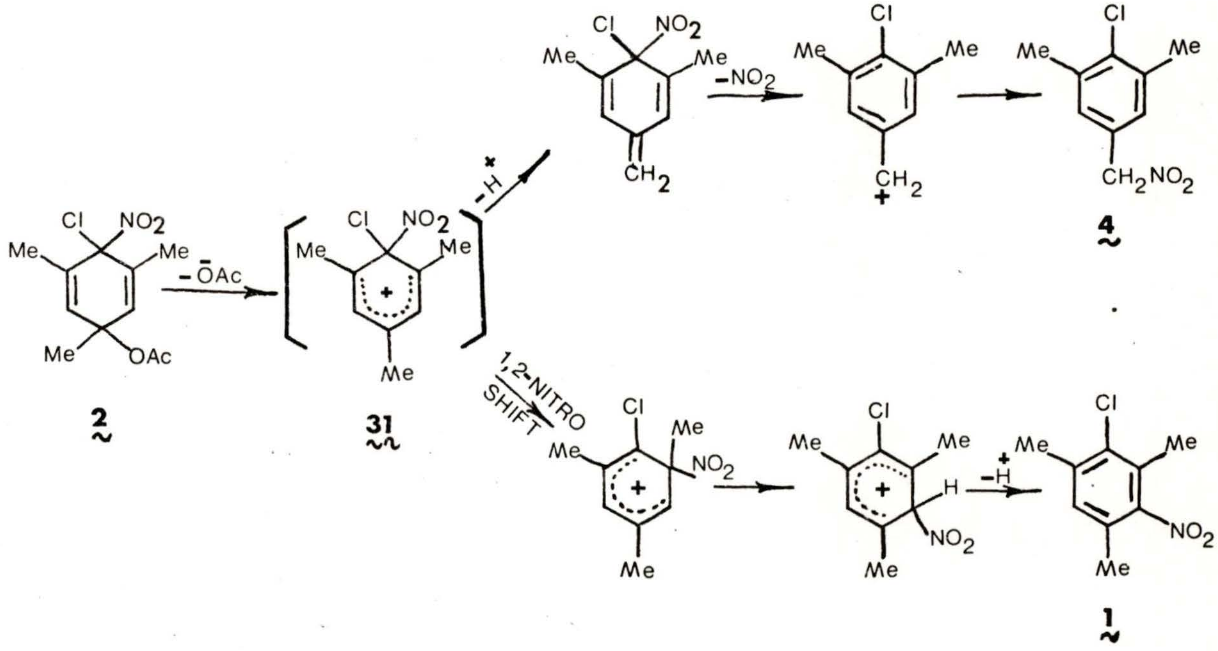


32

Thus, diene 2 preferentially gives rise to nitroarenes and benzylic products both of which are formed via 31. Only under the special conditions of silver nitrate in methanol, silver acetate in methanol-d_4, silver nitrite in methanol-d_4, silver acetate in acetone-d_6 was any appreciable amount of aryl acetate formed.

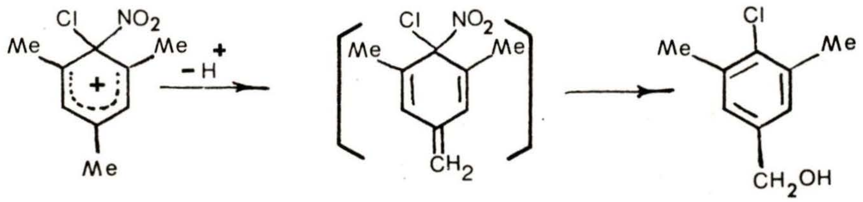
Auto-decomposition of diene 2 gave rise to the benzylic derivative 4-chloro-3,5-dimethylphenylnitromethane (4), with no detectable trace of the nitroarene (1). The *ipso*-nitrocyclohexadienyl cation (31) can generate the nitroarene by a nitro shift and the benzylic products by deprotonation at the alkyl group *para* to the *ipso* site:



In the case of the auto-decomposition reaction the basic species available to accept the proton in the formation of the triene are the nitrite anion, the acetate group of another molecule of the diene and the acetic acid liberated in the course of the reaction. The relative extents of formation of nitroarene and benzylic products will be determined by the competition between nitro shift and deprotonation. The more basic the solvent the more likely it is that deprotonation will occur at the alkyl group before the nitro group migrates. Thus, in highly acidic media the relative amounts of the nitroarene product should increase considerably.

This indeed was observed in the reactions of diene 2. In acetic acid-d_4 benzylic products, 4-chloro-3,5-dimethylphenylnitromethane (4) (55%), 4-chloro-3,5-dimethylbenzylacetate (8) (20%) and

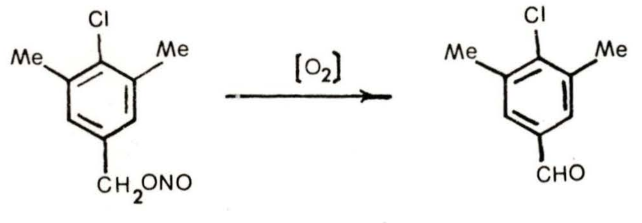
4-chloro-3,5-dimethylbenzylnitrite (**17**) (20%) were formed, essentially exclusively. Reactions with boron trifluoride-etherate solution yielded a 1:1 mixture of (**4**) and 2-chloro-4-nitromesitylene (**1**). Under increased acid conditions of trifluoroacetic acid in trifluoroacetic anhydride only the 2-chloro-4-nitromesitylene (**1**) was formed. Other reactions carried out under mildly acidic conditions showed the predominant formation of benzylic derivatives. Reaction with 10% H_2O in acetone-d_6 gave 4-chloro-3,5-dimethylbenzylalcohol (**33**).



31

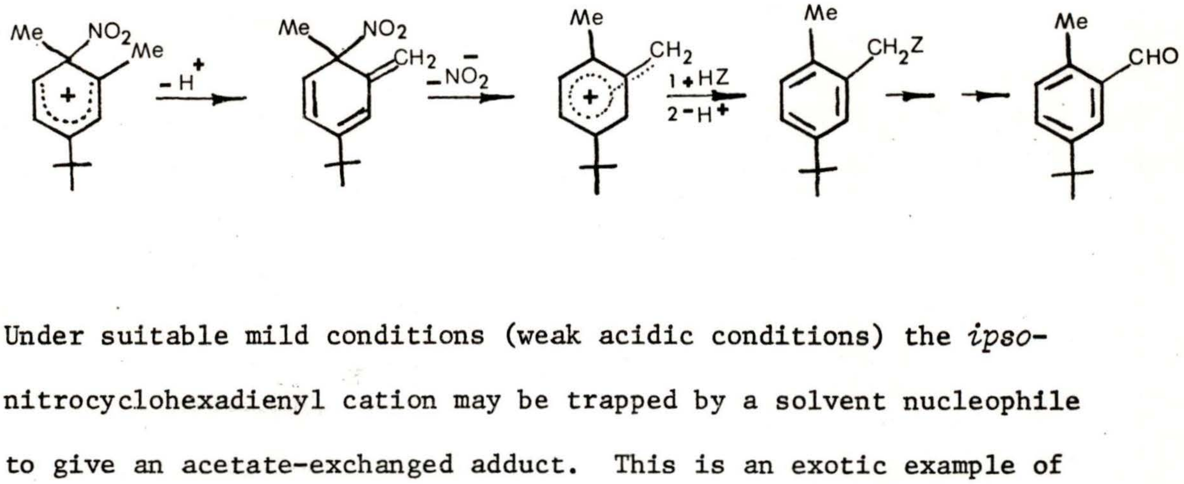
33

A minor trace of 2-chloro-4-nitromesitylene was also detected. Reactions in 10% Ac_2O in acetic acid-d_4 and 10% D_2O in acetic acid-d_4 showed the intermediate formation of deuterated acetoxy-nitro adducts, which eventually decomposed to give three major benzylic products; 4-chloro-3,5-dimethylphenylnitromethane (**4**), 4-chloro-3,5-dimethylbenzylacetate (**8**), and 4-chloro-3,5-dimethylbenzylnitrite (**17**), the last of which eventually produced the 4-chloro-3,5-dimethylbenzaldehyde (**34**).

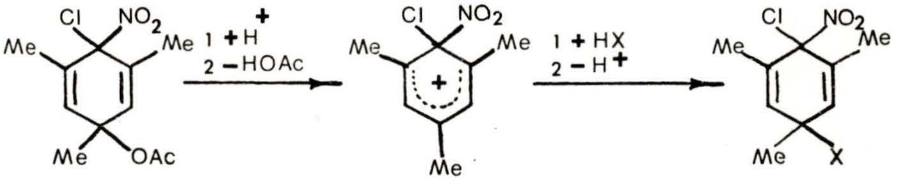


17 34

This observation has been confirmed by g.l.c.-m.s. analysis which showed a peak with the appropriate molecular ion at mass 168. A similar reaction has been observed in the reaction of 1-*t*-butyl-3,4-dimethyl-4-nitro-1,4-dihydrophenyl acetate (35), in less ionizing conditions using acetic acid-d_4 in acetic anhydride (54).



Under suitable mild conditions (weak acidic conditions) the *ipso*-nitrocyclohexadienyl cation may be trapped by a solvent nucleophile to give an acetate-exchanged adduct. This is an exotic example of an S_N1 nucleophilic substitution reaction. Diene 2 underwent exchange reactions with 0.1% H_2SO_4 in MeOH and dry HCl in ether solutions to give the *cis* and *trans* mixtures of methoxy-nitro and the dichloro-nitro dienes, respectively.

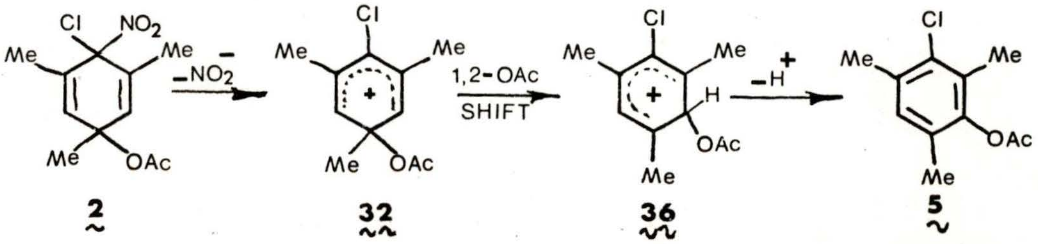


2

X = OMe, Cl

Exchange by other nucleophiles (*e.g.* X = OH, OCD_3, $OCOCD_3$, $-ONO_2$) for the acetate moiety also occurred in the reactions with 10% water in acetone-d_6, 10% acetic anhydride in acetic acid-d_4, 10% deuterated water in acetic acid-d_4, silver nitrate in methanol-d_4, silver nitrate in methanol and silver nitrite in methanol-d_4 but subsequent rearomatization reactions gave more aromatic components in the final products.

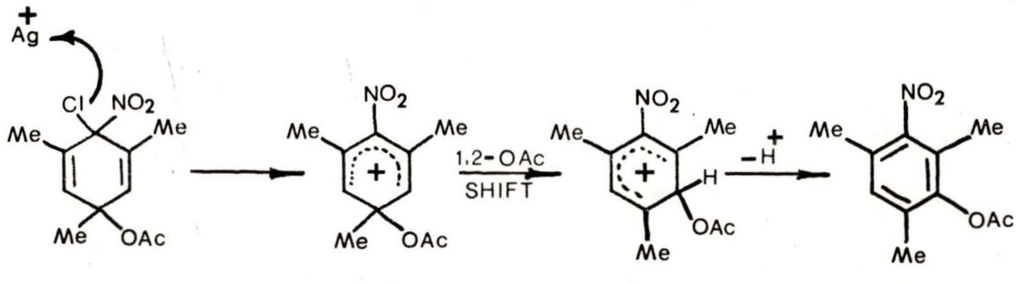
Tertiary acetate adducts under conditions of low acidity undergo loss of nitrous acid accompanied by 1,2- shift of the acetate group to a neighbouring position, to form an arylacetate (14a, 15). This is in line with the recent observations of Myhre and his co-workers (38). In the case of diene 2 formation of arylacetate would follow the following reaction pathway.



2 32 36 5

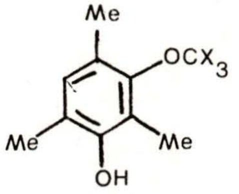
It is evident that formation of (32) is so little favoured that arylacetate (5) was not obtained under conditions which, for other substrates would be conducive to its formation, and in contrast to the reactions of diene 3B. However, reactions of diene 2 in almost neutral (or basic) conditions of reagents like silver nitrate in methanol-d_4, silver nitrate in methanol, silver nitrite in methanol-d_4, and silver acetate in acetone-d_6 did produce 3-chloro-2,4,6-trimethylphenylacetate (5) as a major component, (45% - 54%) in the reaction products. It seems likely that formation of the arylacetate (5) in these instances can be attributed to the ionization of the nitro group being particularly favoured by the ionic media.

In reactions where silver salts were used, 3-nitro-2,4,6-trimethylphenylacetate (15) was also formed (8 - 15%). This product was not obtained in any other reactions. It is proposed that the silver cations assist the loss of the chlorine atom in the tertiary acetate diene 2 to generate the cyclohexadienyl cation (37) which undergoes 1,2-acetate shift followed by the loss of a proton to give the nitrophenylacetate (15).

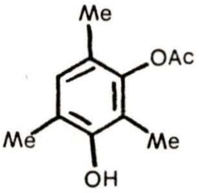


2 **37** **15**

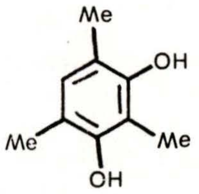
Some minor amounts of other aromatic compounds presumably formed subsequent to exchange with solvent were also detected. Reactions of diene **2** with silver nitrate, and silver nitrite in methanol and methanol-d_4 gave 3-hydroxy-2,4,6-trimethylanisole derivatives (**16**) (15 - 20%). Reactions with silver nitrate in methanol and silver acetate in acetone-d_6 gave some 3-hydroxy-2,4,6-trimethylphenylacetate (**13**) (∿ 15%) and 2,4-dihydroxy-1,3,5-trimethylbenzene (**18**) (∿ 5%), respectively.



16 a X = H
b X = D

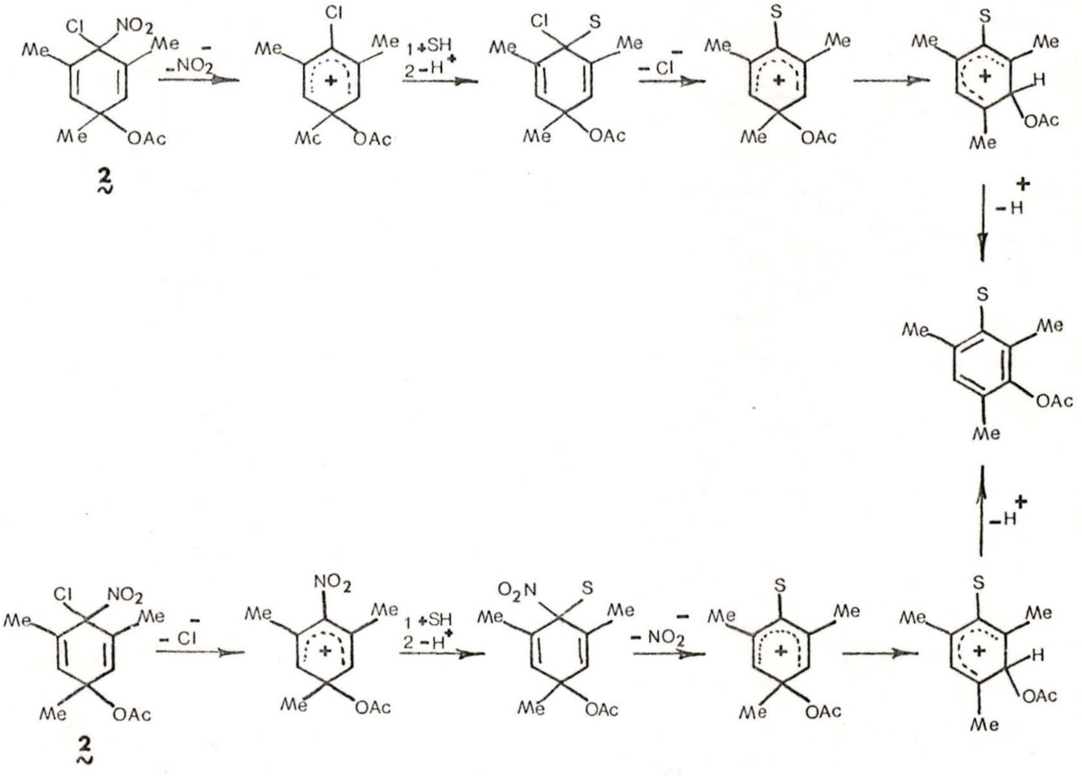


13



18

Since these reactions were carried out in non-acidic good ionizing conditions it is proposed that these solvent-exchanged aromatic products are produced by the initial loss of nitro group as nitrite anion (or chloride anion) followed by addition of a solvent molecule to produce some unstable exchanged diene which rearomatizes immediately by loss of chloride (or nitro) followed by acetate shift.



Products 13, 16 and 18 can be envisaged as being formed via either of the mechanisms shown above.

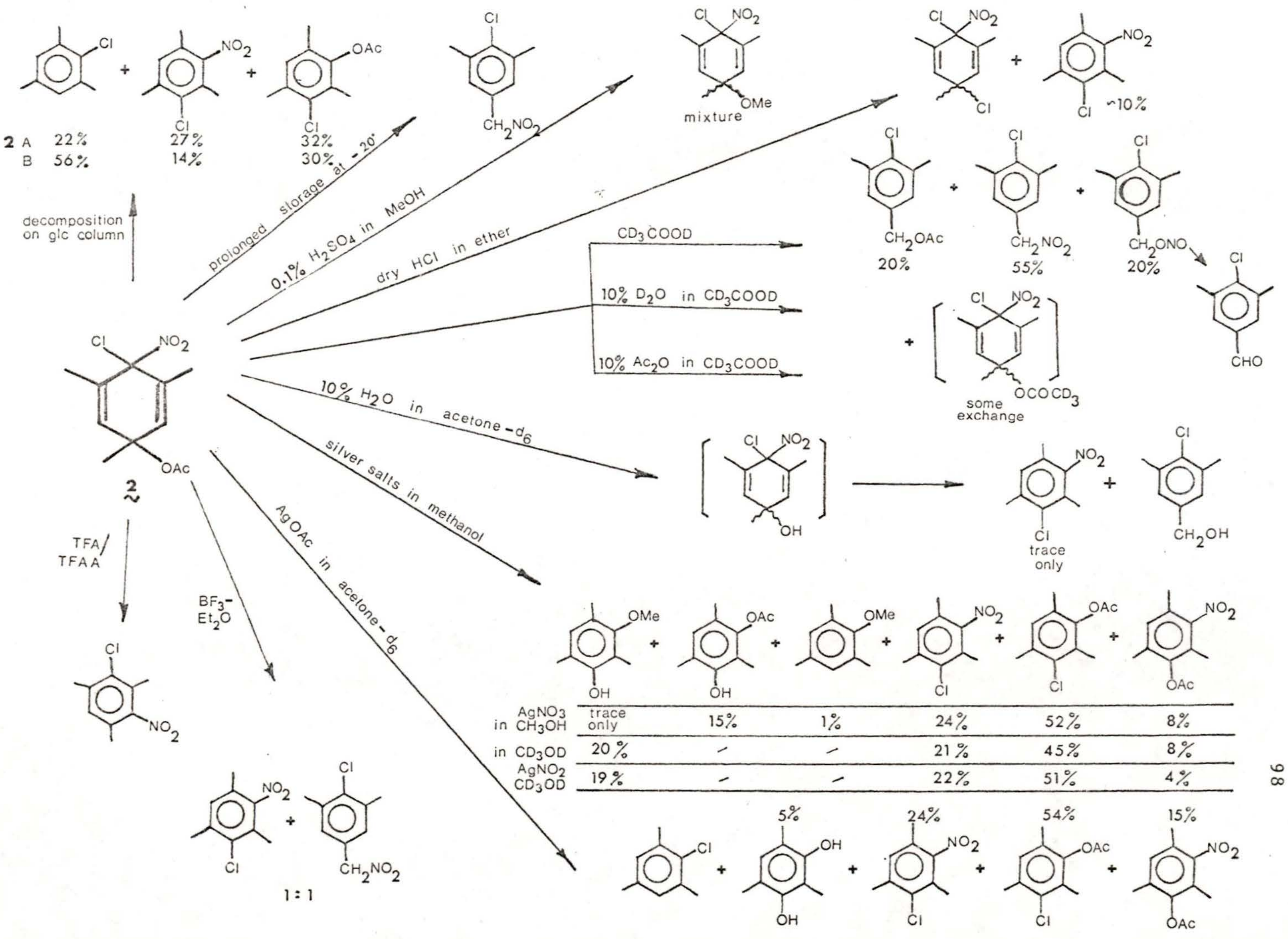
Conclusion

This report describes the formation, isolation, and characterization of the two pairs of diastereoisomeric 1,4-acetoxy-nitro adducts which arise by *ipso* attack of a nitronium ion at substantially activated, substituted positions in 2-chloromesitylene followed by addition of acetate nucleophile at the position *para* to the initial point of attack. Isolation of one particular isomeric adduct of 4-chloro-1,3,5-trimethyl-4-nitro-1,4-dihydrophenylacetate (2) suggests that the *ipso* and *meta* deactivation which chlorine can cause in aromatic compounds is small in comparison to the activation brought about by three *ortho* and *para* methyl groups. This is the first example of an adduct with nitro *ipso* to halogen, formed by nitration.

The acid-catalysed reactions on the secondary acetate diene 3 which produced arylacetate (5) preferentially have been discussed in terms of the greater stability of the acetoxycyclohexadienyl cation generated by loss of the nitro group compared with the nitrocyclohexadienyl cation which would be formed by loss of acetate. Observations on reactions of diene 3 also support the rational developed by Myhre (38) that good ionizing conditions favour the formation of arylacetates and more acidic media caused the acid-catalysed loss of the acetate moiety to produce nitroarenes or benzylic compounds.

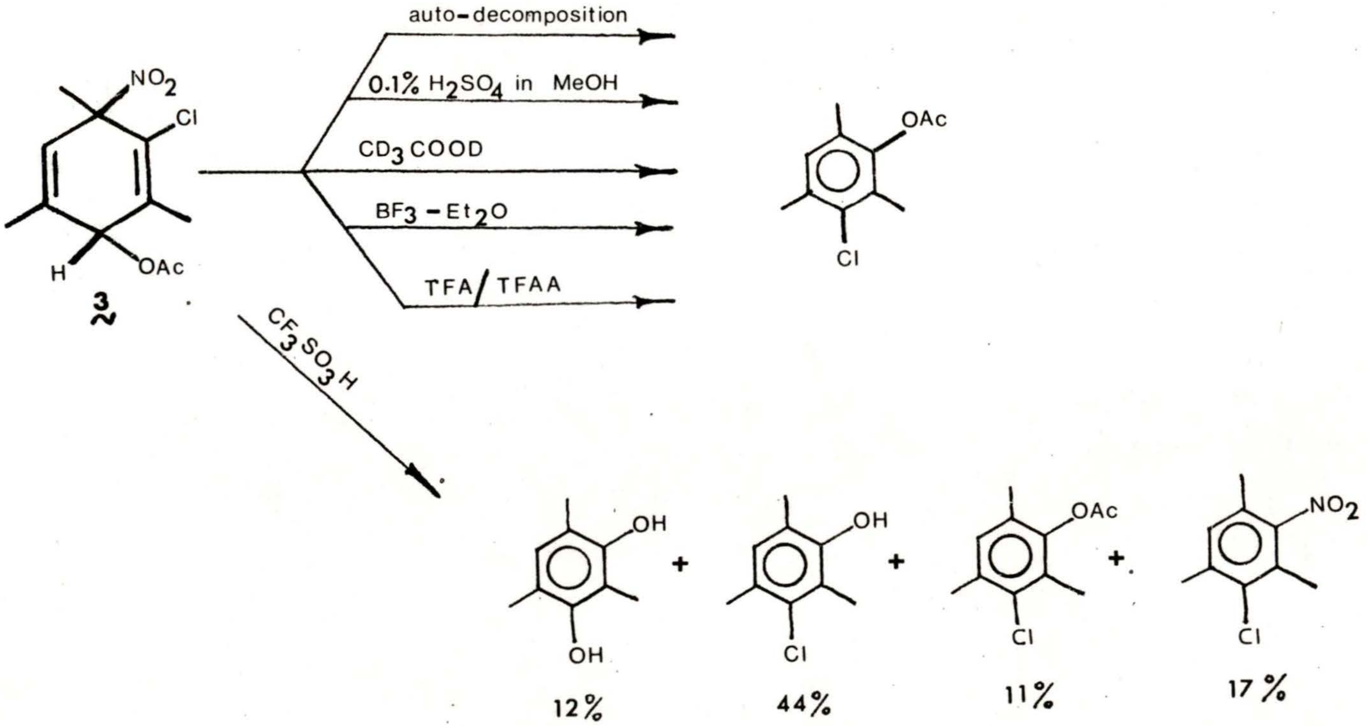
In the case of diene 2 the loss of acetate gives the more stable cyclohexadienyl cation and thus the favoured products are benzylic derivatives and nitroarene.

Reactions of diene 2



$AgNO_3$ in CH_3OH	trace only	15%	1%	24%	52%	8%
in CD_3OD	20%	–	–	21%	45%	8%
$AgNO_2$ CD_3OD	19%	–	–	22%	51%	4%

Reactions of diene 3



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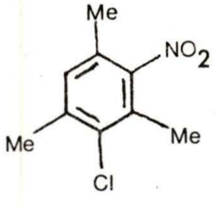
APPENDIX I



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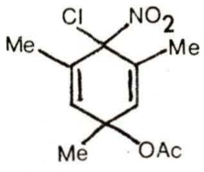

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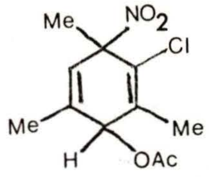

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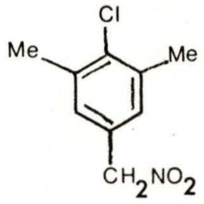

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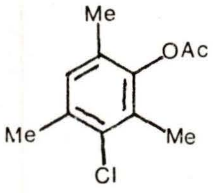

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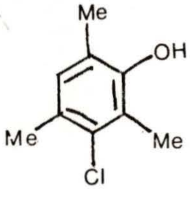

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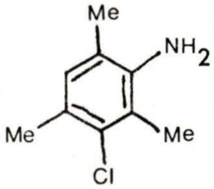

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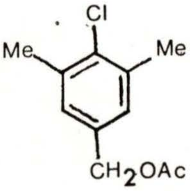

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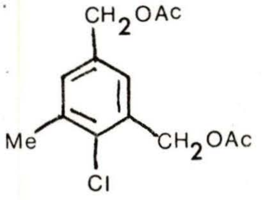

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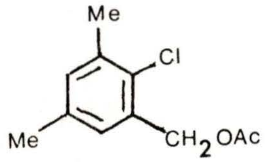

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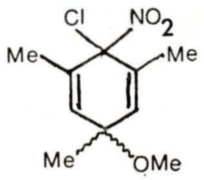

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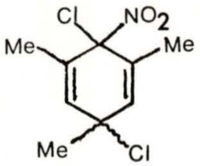

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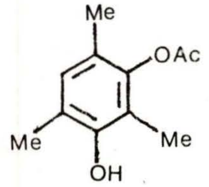

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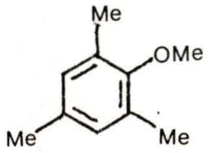

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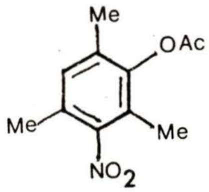

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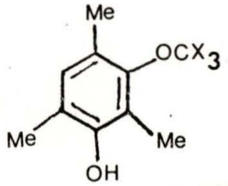

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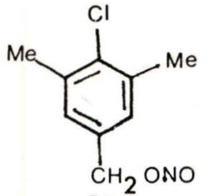

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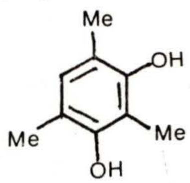

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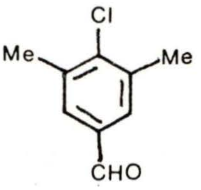

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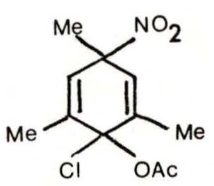

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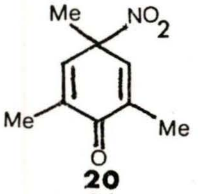

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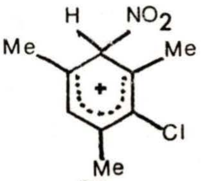

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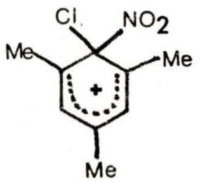

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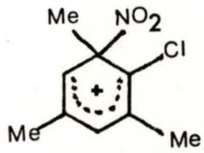

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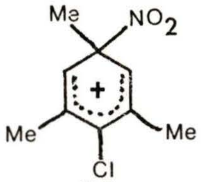

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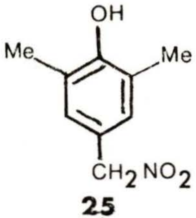

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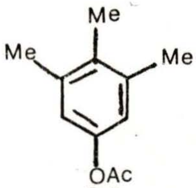

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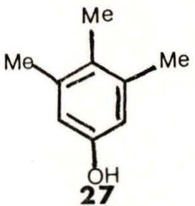

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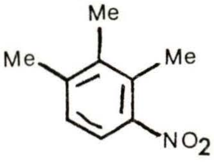

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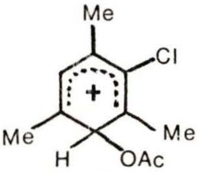

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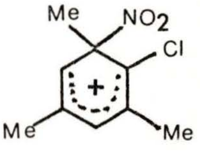

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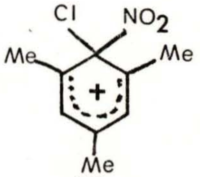

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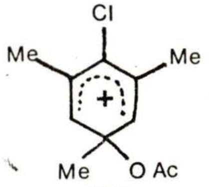

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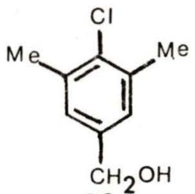

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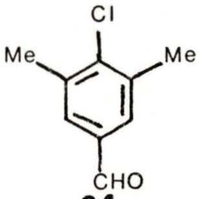

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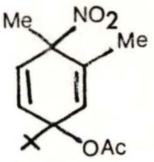

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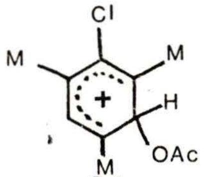

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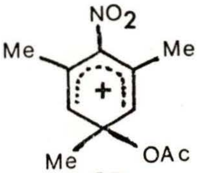

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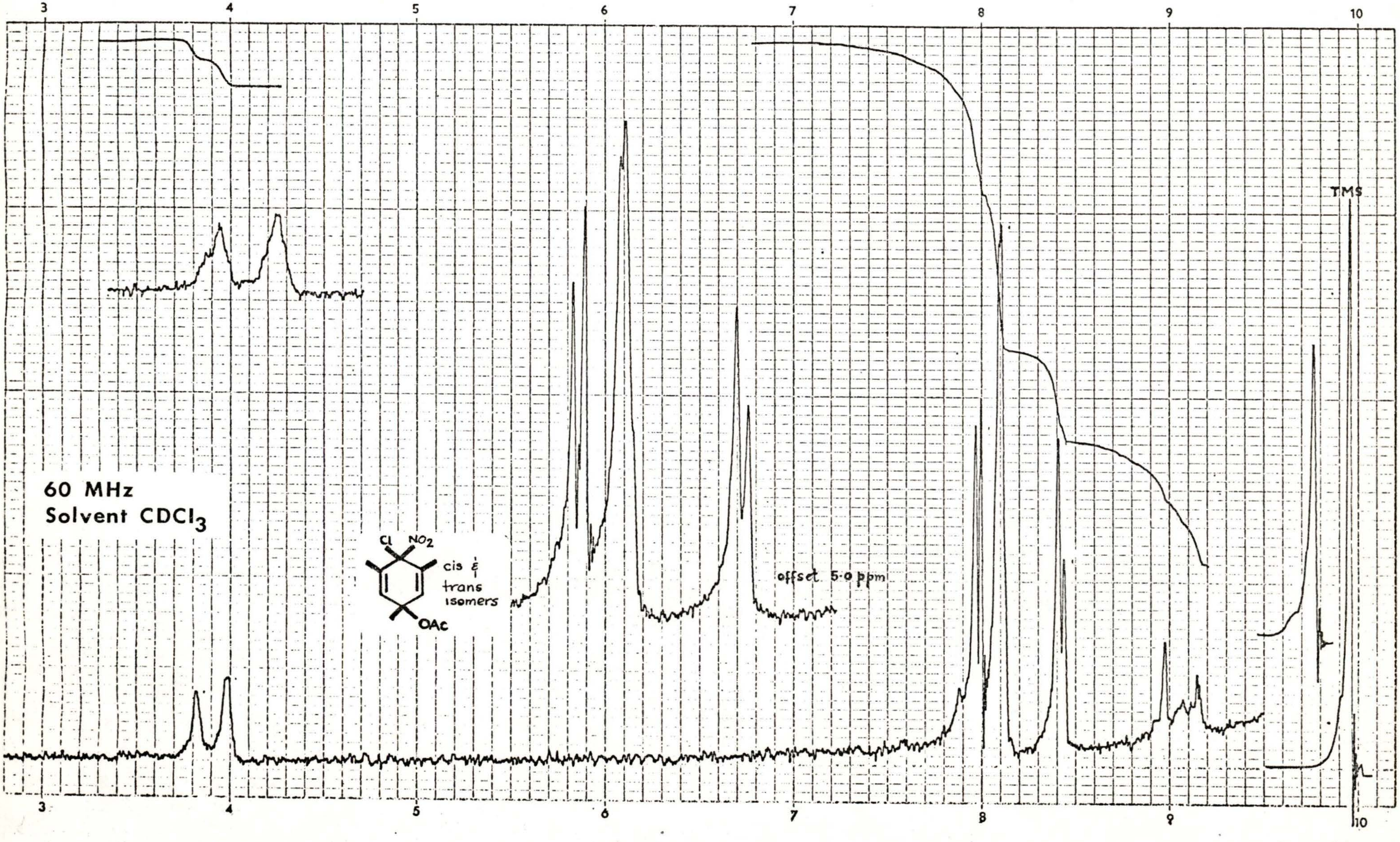
APPENDIX II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Author [redacted]

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Name

23rd September 1977

Date