IPSO-NITRATION OF ARYLOXYALKANOIC ACIDS AND REARRANGEMENT AND AROMATIZATION REACTIONS OF *IPSO*-ADDUCTS

by

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ABSTRACT

Nitration of 2-methyl-2-(2-methylphenoxy)propanoic acid with nitric acid in acetic anhydride gives *E*- and *Z*-diastereomers of 3,3,10-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one. 2-Methyl-2-(2,3,5-trimethylphenoxy)propanoic acid under similar conditions affords one of the diastereomers of 3,3,7,9,10-pentamethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one. Nitration of (2-methylphenoxy)acetic acid in acetic anhydride results in the formation of the diastereomers of 10-methyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one. 2-Methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid on nitration with nitric acid in a mixture of trifluoroacetic anhydride and acetic anhydride gives 3,3,10-trimethyl-8,10-dinitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one. In cases of 2-methyl-2-(2-methylphenoxy)propanoic acid and (2-methylphenoxy)acetic acid, 4-nitrosubstituted products are also formed. No 6-nitrosubstituted products are formed on nitration of any of the substrates.

The formation of the spirodienes can be explained by addition of the nitronium ion at the position *ipso* to the methyl group and *ortho* to the ether function and subsequent capture of the *ipso*-Wheland intermediate by the carboxyl group in the side chain. The absence of 6-nitrosubstituted

products is explained by steric effects.

Under neutral conditions the conjugated spirodienes undergo a thermal rearrangement of the nitro group which is shown to be a [1,5] sigmatropic nitro shift. 3,3,10-Trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one rearranges stereospecifically to 3,3,6-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one. The non-stereoselective rearrangement of 3,3,7,9,10-pentamethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one to 3,3,6,7,9-pentamethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one is shown to be a [1,5] sigmatropic shift overshadowed by radical epimerization of the product. A similar concurrent sigmatropic nitro shift and radical epimerization is also observed in the rearrangement of 3-*t*-butyl-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate, while 2-cyano-3,4-dimethyl- and 2-cyano-4,5-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate each undergo a stereospecific [1,3] sigmatropic nitro shift.

Under acidic conditions, the adducts obtained from (2-methylphenoxy)acetic acid and 2-methyl-2-(2-methylphenoxy)propanoic acid undergo rapid epimerization followed by a competing acid-catalyzed [1,5] sigmatropic nitro shift and a 1,3 extramolecular nitro shift to the 4-position. Some leakage of the nitronium ion also occurs. In hydroxylic solvents 2-methyl-6-nitrophenol is also formed. 3,3,8-Trimethyl-8-nitro-1,4-dioxaspiro[4,5]deca-

6,9-dien-2-one, obtained by the nitration of 2-methyl-2-(4-methylphenoxy)propanoic acid with nitric acid in acetic anhydride, reacts with acids in hydroxylic and non-hydroxylic solvents to give 4-methyl-4-nitrocyclohexa-2,5-dienone (or its further reaction products) and 2-methyl-2-(4-methyl-2-nitrophenoxy)propanoic acid. Under basic conditions it gives 4-methyl-4-nitrocyclohexa-2,5-dienone as the sole primary product.

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CHAPTER I

INTRODUCTION

1.1

Aromatic nitration is one of the better understood electrophilic substitution reactions. It has been used as a model reaction in the development of theories of the substitution process. Directing effects of substituents in substitution reactions were first studied for nitration reactions.[1] The classification of substituents as *ortho:para* and *meta*-directing, the connection between orientation and activation and rules determining further substitution in disubstituted benzenes were all developed on the basis of extensive data from aromatic nitration.[2] Nitration can be performed in various solvents and with various nitrating agents, but the effective electrophile (NO_2^+) over a wide range of conditions was found to be the same. Dilute nitric acid, nitric acid in sulphuric acid; metal nitrates in sulphuric acid, in trifluoroacetic acid, in acetic anhydride; nitric acid in oleum, nitric acid in organic solvents like nitromethane, sulpholane, carbon tetrachloride, acetonitrile; nitric acid in acetic acid; acyl nitrates in acetonitrile; alkyl nitrates and sodium ethoxide; nitronium salts in inert organic solvents can be used to affect nitration of substrates of different solubilities and reactivities.

The identification of the electrophile made theoretical calculations much easier. Aromatic nitration was the reaction used as a testing ground for molecular orbital theories relating structure to reactivity. It was used in the development of various reactivity indices,[3] and later to develop the frontier orbital theory of polar reactions.[4]

1.2 *Mechanism of nitration*

The steps involved in the conversion of reactants to products are well understood and can be represented as shown below.[5]

1) $HNO_3 + H^+ \rightleftharpoons NO_2^+ + H_2O$

2) $ArH + NO_2^+ \rightleftharpoons \overline{ArH \quad NO_2^+}$ (encounter pair)

3) $\overline{ArH \quad NO_2^+} \rightleftharpoons W$ (Wheland intermediate)

4) $W \rightleftharpoons$ Products

Any of the above steps can be the rate determining step. In fact, to a certain extent the rate determining step can be changed by adjusting the reaction conditions and the various steps were identified using this method.

1.2.1 Identity of the Electrophile

Nitration of benzene homologs in nitromethane, in acetic acid, in sulpholane, in carbon tetrachloride and in acetonitrile was found to have zeroth order dependence on

the concentration of the substrate.[6] The dependence was between zeroth and first order for benzene and halogenobenzenes and first order for di- and tri-halogenobenzenes. For benzene and toluene, the dependence varied from complete first order to complete zeroth order on varying the solvent. However, the higher homologs always showed zeroth order dependence. If all the processes in steps 2-4) in the above mechanism can be described by a composite rate constant k_2', then the observations can be explained by the balance between k_{-1} and $k_2'[ArH]$. When $k_{-1} << k_2'[ArH]$ the reaction became zeroth order in the aromatic compound. This zeroth order process was identified as the process involving the formation of the electrophile. Under a variety of conditions the relative amount of *o*-, *p*- and *m*-products did not change significantly. Thus the same electrophile was seen to be involved in all the processes. The identity of the electrophile was determined by cryoscopic measurements in sulphuric acid and by Raman spectrocopy. It was shown to be the nitronium ion. This identity was confirmed when Olah obtained the same product ratios using nitronium salts as nitrating agents.[7]

1.2.2 Encounter Pair : Loss of Substrate Selectivity.

Reactivity of toluene with respect to benzene (k_T/k_B) has long been a measure of medium effects in aromatic nitration. This ratio has been determined by competitive and absolute rate measurements under many conditions. It

has been found to vary within a very narrow range (k_T/k_B = 17 to 38) and this has been forwarded as evidence for a common rate determining step and a common electrophile. According to the classical mechanism this step was identified as step 3 (the phenomenon of encounter control was not known). Based on this mechanism, the Brown selectivity-reactivity relationship was proposed,[8] which stated that in competitive processes if the substrate selectivity is lost, positional selectivity should also be lost, and both of these depended on the reactivity of the electrophile.

Nitronium salt nitrations by Olah showed that k_T/k_B ratio fell to 1.5 - 2.5 under these conditions, but the positional selectivity in toluene did not change. This led Olah to propose an intermediate prior to the Wheland intermediate. Formation of the earlier intermediate was said to be rate determining and positional selectivities were determined in the next step. Since the substrate and positional selectivities were not determined in the same step, the reactivity-selectivity relationship need not be true under these conditions. Further Olah proposed that the low k_T/k_B value was due to the high reactivity of the nitronium ion and the intermediate formed in the rate determining step was a π-adduct.[9] A similar loss of substrate selectivity without loss of positional selectivity was observed by Schofield and coworkers in the nitration of

benzene homologs in mixed acid.[10] They proposed that this was due to the onset of diffusion control and the intermediate formed in the rate determining step was an encounter pair. They did not propose any structure for the encounter pair. Olah[11] suggested that the encounter pair may in fact be a π -adduct. Loss of substrate selectivity in nitronium salt nitrations was later shown to be due to incomplete mixing of reagents and the observed low value of k_T/k_B due to macroscopic diffusion control and not microscopic diffusion control.[12] Further Rys and coworkers[13] showed that observed relative rates of nitration of benzene homologs with nitronium salts did not correlate well with π -adduct stabilities of these aromatic compounds (correlation coefficient = 0.91). The evidence forwarded for π -adducts is not sufficient but there is no reason why encounter pairs cannot be π -adducts. This can be decided only after more conclusive evidence is available. Recently Kochi and coworkers[14] have observed a charge transfer band at 400 nm in the nitration mixture of *m*-toluonitrile with nitronium tetrafluoroborate. Thus π -adducts proposed by Olah may in fact be charge-transfer complexes.

1.2.3 Encounter Pair : Retention of Positional Selectivity

Since the recognition of the role of encounter control in mixed acid nitrations,[10] similar encounter controlled rate limit leading to the loss of substrate selectivity has

been observed in trifluoroacetic acid, in nitromethane, in perchloric acid, in sulpholane, in methanesulphonic acid, in phosphoric acid,[15] in aqueous nitric acid[17] and in acetic anhydride. Table 1.1 shows the observed relative rate for mesitylene with respect to benzene (k_M/k_B) and the encounter controlled rate limit in different media along with calculated k_M/k_B based on the additivity principle.

Table 1.1[a]

Relative Rates of Nitration of Mesitylene in Various Media

Medium	kM/kB (observed)	Encounter limit	kM/kB (calculated)
Trifluoroacetic acid	88	100 ± 20	
Nitromethane	400	400	
61.05% Perchloric acid	78	80 ± 10	
Sulpholane	350	500 ± 200	
63.2% Sulphuric acid	68	68	16000
68.3% Sulphuric acid	36	38	
88% Methanesulphonic acid	387	350 ± 50	
83.8% Phosphoric acid	3.5	3.5	
Acetic anhydride[b]	650	650 ± 50	
Aqueous nitric acid[c]	380	380	

a. adapted from Ref. 15, *b*. Ref. 16, *c*. Ref. 17

In the case of sulphuric and phosphoric acids the limiting rate has been shown to be dependent on solvent viscosity. For other solvents such a relationship does not hold well because changes in solvation and activity coefficients in different media are not known. The limiting rate is sharp in mineral acids but is diffuse in other media because of nitration via C-nitrosation which occurs in activated compounds in such other media.[15] The existence of encounter pairs is now well established. Their formation may become rate-limiting depending on reactivity of the substrate and viscosity of the medium. However retention of positional selectivity has not been conclusively explained yet.[18] Apart from the π-adducts discussed earlier, there are two theories which try to explain the retention of positional selectivity in the absence of substrate selectivity. Schofield[19] has shown that if the rate constant for separation of the components by diffusion of a non-interacting encounter pair is of the order of 10^9 - $10^{10} s^{-1}$ and the upper limit for the rate constants determining positional selectivity is of the order of 10^{12} - $10^{13} s^{-1}$ (i.e. the magnitude of a vibration frequency) then even a non-interacting encounter pair can give rise to positional selectivities of the order of ≥ 100. Positional selectivities in pseudocumene were explained assuming a non-interacting encounter pair.[20] Using the same limits for the rate constants, Perrin showed that in durene and pentamethylbenzene all the positions would be equally

reactive. Since positional selectivity is retained even in pentamethylbenzene, Perrin[21] proposed that the encounter pair is stabilized by interactions increasing the barrier to separation by diffusion and thus enabling retention of positional selectivity. He further proposed an alternative mechanism involving encounter controlled electron transfer and collapse of the resulting radical-radical cation pair. The site of bond formation is determined by relative spin densities. This could explain the positional selectivities even when substrate selectivity was lost in the encounter controlled step. As an evidence for this, Perrin showed that all aromatics more reactive than toluene could transfer an electron to NO_2^+ in an exothermic step, thus leading to an intermediate of lower energy than the non-interacting encounter pair. The reaction of naphthalene radical cation, generated in controlled-potential electrolysis at a Pt anode, with nitrogen dioxide gave 1-nitro : 2-nitro (α/β) product ratio of 9.2 $\pm$ 1 equal to that observed in nitration in conventional media. The almost equal value of α/β was proposed as supporting evidence for the electron transfer mechanism. The result in the nitration experiment was later shown to be due to electrophilic nitration of naphthalene catalyzed by anodically generated acid.[22] Mesitylene radical cation generated independently with ceric ammonium nitrate in the presence of nitrogen dioxide reacted to give both ring-substitution and side chain substitution

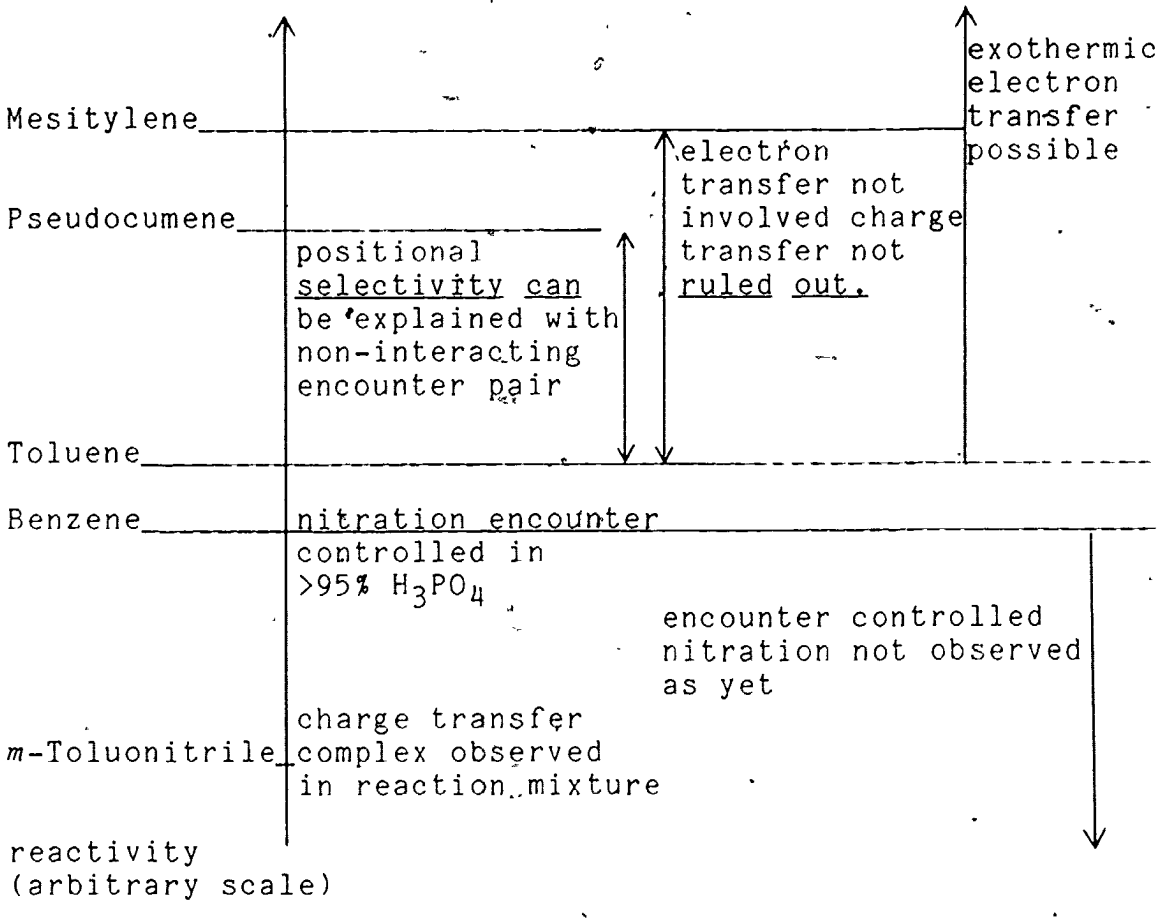
products.[23] Nitration of mesitylene with nitric acid gives only ring-nitration. So electron transfer process need not be considered for aromatic compounds less reactive than mesitylene. Ridd[23], however points out that partial charge transfer cannot be ruled out by this experiment. Nitration of naphthalene with nitronium tetrafluoroborate gave rise to an intense red solution containing the binaphthalene radical cation.[24] The presence of the radical cation does not necessarily mean that the radical cation is on the pathway of nitration by nitronium ion. Nitrous acid or other N(III) species can catalyze nitration by an electron transfer process under conditions where no C-nitrosation occurs. Such nitrous acid catalyzed nitration giving rise to a radical cation has been observed in the case of *N*, *N*,4-trimethylaniline and the following mechanism has been proposed.[25]

$$ArN^+Me_2H + NO^+ \longrightarrow ArNMe_2^{+\cdot} + NO\cdot + H^+$$

$$NO\cdot + NO_2^+ \longrightarrow NO^+ + NO_2\cdot$$

$$ArNMe_2^{+\cdot} + NO_2\cdot \longrightarrow \text{Products}$$

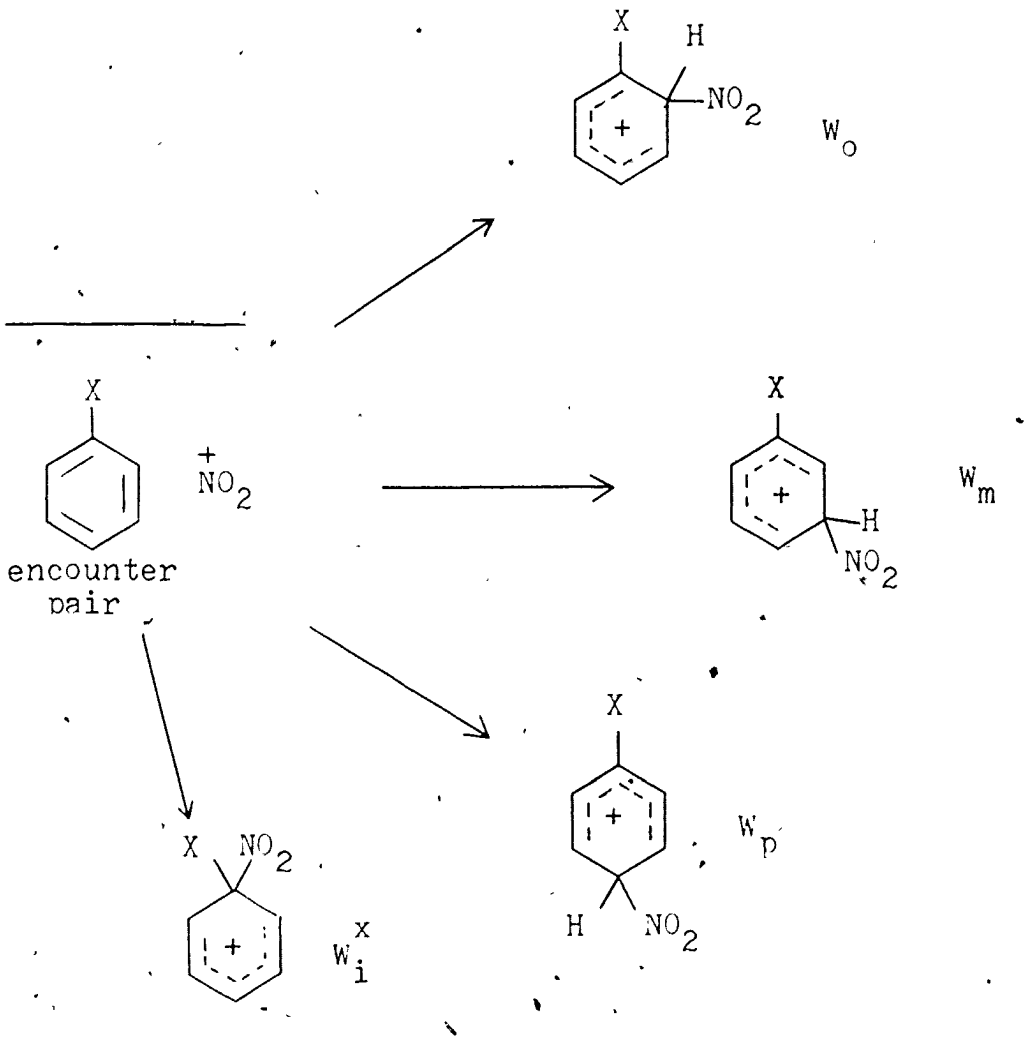
The question of the structure of the encounter pair is not yet settled. It is even possible that encounter pairs involving aromatic compounds of different reactivity have different structures. The present situation can be shown pictorially as below.



1.2.4 Wheland Intermediates : Product Determining Step

A monosubstituted aromatic compound and the nitronium ion in an encounter pair can combine to give four isomeric Wheland intermediates. These are shown in Scheme 1.1. Considering steps 3) and 4) in the nitration mechanism, the Wheland intermediate can revert back to the encounter pair with a rate constant k_{-3} or go to the products with rate constant k_4. The demonstration of the existence of Wheland intermediates was obtained by the negligible isotope effect (<1.19) in the nitration of tritiobenzene.[26] This required the presence of an intermediate from which the product was formed with the rate constant $k_4 >> k_{-3}$.

Scheme 1.1 Isomeric Wheland Intermediates from a Mono-substituted Benzene



The structure of the Wheland intermediate was deduced by noting the similarities in the trends for rates of nitration (rate determining intermediate formation) and the σ-basicities of the corresponding aromatic compound. There was a linear relationship between the logarithms of relative rate constants for nitration in acetic anhydride and relative basicities.[27] Protonated aromatics have a

cyclohexadienyl cation structure as shown by crystallographic and NMR studies[28] and by analogy a similar structure was assigned to the Wheland intermediates.[29] After the recognition of *ipso*-nitration this structure was confirmed by NMR of several W_i^{Me}'s obtained by nitration of trifluoromesitylene, hexamethylbenzene and halopentamethylbenzenes.[30,31]

The Wheland intermediates formed by attack of the nitronium ion at unsubstituted positions generally undergo a fast proton loss to give substituted nitro compounds. The *ipso*-Wheland intermediates can give rise to several products. The routes to these products will be examined after discussing the observations that led to the recognition of *ipso*-attack.

1.3 *Nitration in Acetic Anhydride*

Nitric acid reacts quantitatively with acetic anhydride to give acetyl nitrate (a commonly used name for acetic nitric anhydride) within minutes.[32] With excess of nitric acid, dinitrogen pentoxide is observed as one of the products.[33]

$$Ac_2O + 2HNO_3 \rightleftharpoons N_2O_5 + 2AcOH \qquad -1)$$

$$N_2O_5 + Ac_2O \rightleftharpoons 2AcONO_2 \qquad -2)$$

With a large excess of acetic anhydride another equilibrium is obtained.

$$Ac_2O + HNO_3 \rightleftharpoons AcONO_2 + AcOH \qquad -3)$$

But there is no reason why equilibria 1) and 2) should not

be involved even when acetic anhydride is used as solvent. Acetyl nitrate can generate the nitronium ion in the following way --

$$AcONO_2 + AcOH \rightleftharpoons AcONO_2H^+ + OAc^- \qquad -4)$$

$$AcOHO_2H^+ \rightleftharpoons AcOH + NO_2^+ \qquad -5)$$

Thus $AcONO_2$, NO_2^+, N_2O_5, $AcONO_2H^+$ are some of the potential nitrating agents in the system. High *o:p* ratios of products in many cases, the advent of zeroth order kinetics at high concentrations of mesitylene (0.05 mol dm^{-3}) as opposed to low concentrations (10^{-3} mol dm^{-3}) required in other media frequent acetoxylation accompanying nitration and uncertainty about the nature of the electrophile were some of the reasons why the mechanism of nitration in acetic anhydride was considered, for some time, to be different from that followed in other solvents.

1.3.1 High *o:p* ratios

Nitration of halogenobenzenes in acetic anhydride gave lower *o:p* ratios than in other media.[34] Since halogenobenzenes are polarized with the positive charge towards the ring, the *o*- position should be more positively polarized than the *p*- position. Thus acetic anhydride, a solvent of lower dielectric constant than the mineral acids, gives lower *o:p* ratios due to the electrostatic effect. For the same reason anisole and acetanilide with dipole moments opposite to those of halogenobenzenes were thought to give higher *o:p* ratios. But in acetic acid, a solvent of still

lower dielectric constant, the *o:p* ratio was not affected. An alternate explanation was nitration by dinitrogen pentoxide preferentially at *o*- position, superimposed on nitration by nitronium ion giving normal *o:p* ratio.[35] Similar high *o:p* ratios were observed for benzylic compounds, biphenyl and styrene. No independent evidence is available for any of the proposed mechanisms.

1.3.2 Kinetics; Pseudo-zeroth Order Reactions

The observed zeroth order kinetics in acetic anhydride for high concentrations of aromatics was found to be a medium effect.[36] For benzene and homologs, the nature of the medium changed so much on increasing the concentration of the aromatic that the reaction changed from first order to zeroth order. This transition depended only on the concentration and not on the reactivity of the aromatic. However the initial rate depended not only on the initial nitric acid concentration as in normal zeroth order reaction but also on the reactivity of the aromatic. Hence the reaction was described as a pseudo-zeroth order process.

The rate of nitration in purified acetic anhydride was markedly retarded by trace amounts of nitrate ion, so the effective nitrating agent had to be a positive ion in low concentration.[16] Of the four possible nitrating species in the medium, only protonated acetyl nitrate and nitronium ion can therefore be the effective nitrating agent.

1.3.3 Identification of the Electrophile

Wepster and coworkers[37] showed that the plot of log(1/2 *o*/*p*) from nitration of various alkylbenzenes in acetic anhydride against that in sulphuric acid was linear and had a slope of unity. This implied that $\Delta\Delta G^{\ddagger}$ for attack at *o*- and *p*- positions was the same in both the media and thus a common electrophile, the nitronium ion, was suggested. There were reservations about these results because nitromethane was used as a solvent. Ridd[16] performed the nitration of various aromatic hydrocarbons in purified acetic anhydride and in acetic acid. From the encounter controlled rate constants for mesitylene in the two solvents he could calculate the rate constants for toluene in the two media which were found to be equal. Since the identity of the electrophile is known in acetic acid, this showed that the same electrophile, namely the nitronium ion, is involved in acetic anhydride. After identifying the electrophile, the pseudo-zeroth order process could also be explained. Ridd showed that the mesitylene reaction could not be made zeroth order after correcting for medium effects, even when its concentration was as high as 0.5 mol dm^{-3}. The back reaction must therefore have a rate coefficient of $>10^{10} s^{-1}$ as mesitylene reacted at the encounter rate. Thus, the half-life of the electrophile had to be below 10^{-10}s. This could be explained by a pre-association mechanism, viz., formation of an encounter pair consisting of the aromatic

substrate and protonated acetyl nitrate, formation of the nitronium ion within the encounter pair and subsequent nitration.[38]

$$ArH + AcONO_2H^+ \rightleftharpoons \overline{ArH \cdot AcONO_2H^+}$$

$$\overline{ArH \cdot AcONO_2H^+} \rightleftharpoons \overline{ArH \cdot NO_2^+ \cdot AcOH}$$

$$\overline{ArH \cdot NO_2^+ \cdot AcOH} \rightleftharpoons ArHNO_2^+ + AcOH$$

1.3.4 Nitration and Acetoxylation

Nitration and acetoxylation of *o*-xylene were observed in the same study where the pseudo-zeroth order kinetics was first observed and protonated acetyl nitrate was proposed as an electrophile.[39] The ratio of acetoxylation and nitration products was constant under a variety of conditions and a common electrophile, protonated acetyl nitrate was therefore proposed. But just as the reasons for pseudo-zeroth order kinetics became known and the electrophile was identified as the nitronium ion, the origin of acetoxylation products was also determined. Fischer and coworkers[40] showed that the acetoxylation and nitration products were formed from a common precursor, an adduct of *o*-xylene and acetyl nitrate. This adduct was isolated from the reaction mixture and shown to give the acetoxylation product. Thus the basic mechanism of nitration in acetic anhydride is not different from that in other solvents.

1.4 Ipso-*Wheland Intermediates*

After the isolation of the acetyl nitrate adduct from *o*-xylene, similar adducts were obtained from several benzene homologs. All adducts were formed through the capture of Wheland intermediates formed by the nitronium ion attacking a position *ipso* to a substituent. Substituents can activate or deactivate the *ipso*-position in the same way they activate or deactivate *o*-, *m*- and *p*- positions. The degree of activation can be expressed in terms of partial rate factors. For toluene the partial rate factors are - o_f 44, m_f 2·1, p_f 54, i_f 4·7.[41] Thus a methyl group activates the *ipso*-position twice as much it activates the *meta* position. For alkylbenzenes *ipso*-partial rate factors of other alkyl groups have been determined relative to the methyl group.[42] They are $i_f^{Me} : i_f^{Et} : i_f^{i\text{-}Pr} : i_f^{t\text{-}Bu}$ 1 : 0·3 : 0·2 :0·0. Similar *ipso*-partial rate factors for halogen substituents have been determined by Perrin.[43] They are i_f^{I}=0.18, i_f^{Br}=0.079, i_f^{Cl}=0.061. Thus the methyl group activates the *ipso*-position the most relative to other substituents. Even for the methyl group the *ipso*-position is 9-12 times less reactive than the *o*- and *p*- positions. It follows that if *ipso* - attack at a substituent is to be facilitated, the substituent has to be *o*- or *p*- to another powerful activating substituent.

Once the nitronium ion attacks *ipso* to a substituent, the resulting *ipso*-Wheland intermediate can give rise to a

variety of products. Most of these products are not normal substitution products. A vast amount of data on these unusual products has accumulated over the years and the data have been summarized by Nightingale[44] and Suzuki.[45] Hartshorn[46] pointed out that all of the reactions of the *ipso*-Wheland intermediate can be classified into six categories:

i) loss of the original substituent - *ipso*-substitution

ii) loss of the nitro group - no net reaction.

iii) migration of the original substituent

iv) migration of the nitro group

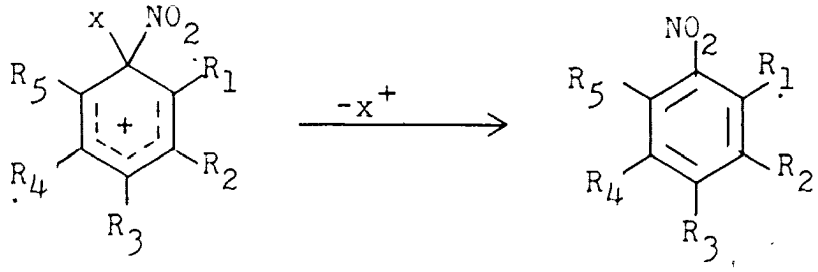
v) modification of a substituent *o*- or *p*- to the *ipso*-position

vi) capture by a nucleophile

1.4.1 *Ipso*-Substitution

Perrin has ranked the electrofugal abilities of various groups in S_N2 and S_N1 processes.[47] In an S_N1 process the leaving group abilities are $NO_2^+ < i\text{-}Pr^+ \sim SO_3 < t\text{-}Bu^+ \sim ArN_2^+ < ArCHOH^+ < NO^+ < CO_2 < B(OH)_3$. In S_N2 processes the leaving group abilities are $CH_3^+ < Cl^+ < Br^+ < D^+ \sim RCO^+ < H^+ \sim I^+ < Hg^{2+} < Me_3Si^+$. The electrofugal abilities in the two series can be compared under suitable conditions and a limited series $Me^+ < Cl^+ < NO_2^+ < Br^+$ has been suggested. If the nitronium ion attacks *ipso* to any group which is a better electrofuge, *ipso*-substitution might be expected. Some

substituents which undergo *ipso*-substitution during nitration are shown below.[48]

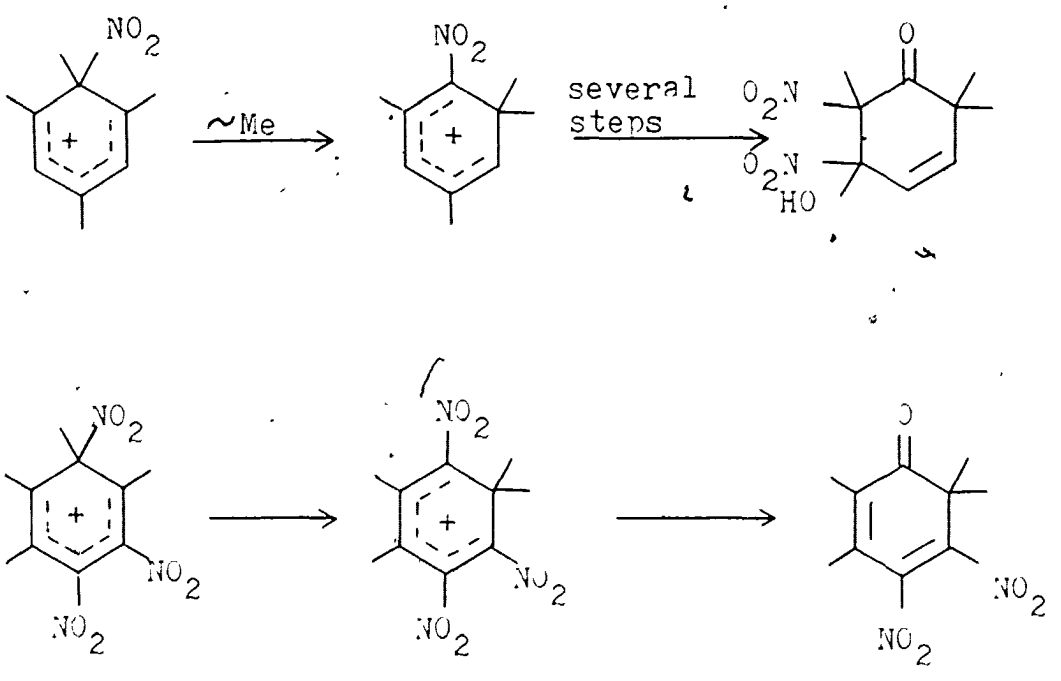


X = CHO, CH_3CO, COOH, OMe, *i*-Pr - *t*-Bu, $ArCH_2$, Br, I, $SiMe_3$, SO_3H.

i-Propyl, *t*-butyl, bromo and iodo substituents can be lost when the *ipso*-position is activated even by a single substituent. For other substituents, the *ipso*-position has to be activated by several substituents with one of them being an *o*- or *p*- OH, OMe or NR_2. In highly substituted compounds, loss of chlorine has also been observed.

1.4.2 Migration of the Original Substituent

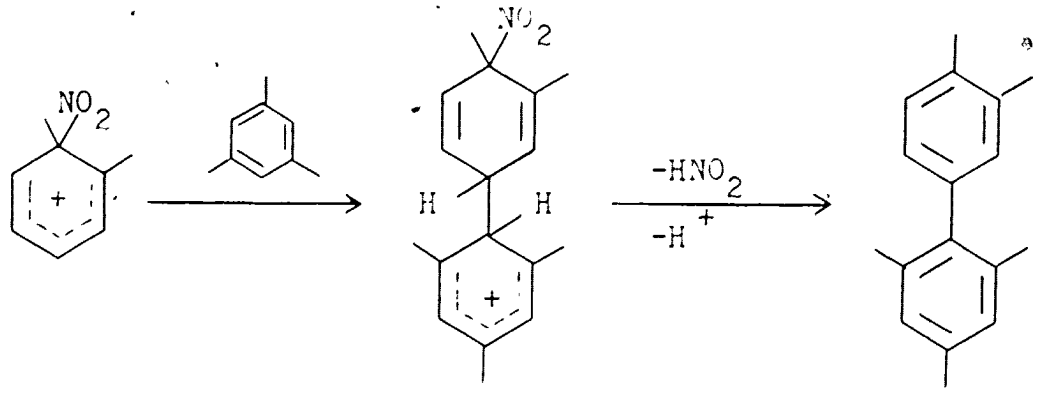
Migration of a methyl group after *ipso*-attack by the nitronium ion has been observed in alkyl benzenes and fully substituted aromatics.[49]

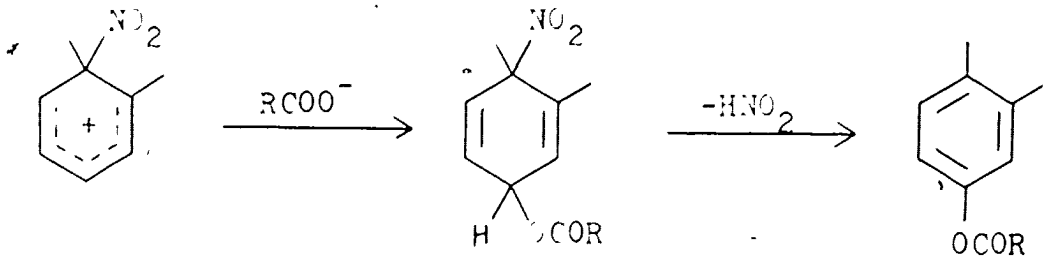


1.4.3 Nucleophilic Capture of the *Ipso*-Wheland Intermediate

The *ipso*-Wheland intermediate can be captured by other reactive aromatic compounds to give unsymmetrical biphenyls.[49] It can also be captured by various acyloxy anions when nitration is carried out with the corresponding acyl nitrate.[50] (Scheme 1.2)

Scheme 1.2 Aromatic Compounds obtained by Nucleophilic Capture





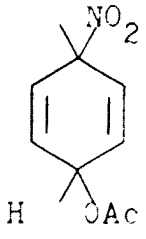
R = Et, *n*-Pr, $CH_3(CH_2)_3$-, $CH_3(CH_2)_4$-.

Capture by the above nucleophiles leads to aromatic products but when acetate is the nucleophile, the intermediate cyclohexadiene can be isolated. Several of these adducts resulting from capture by acetate have been isolated and characterized. Representative examples are shown in Table 1.2.

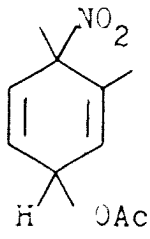
Table 1.2

Adducts Obtained by *Ipso*-Attack of the Nitronium Ion

a) *Ipso* to a methyl group, secondary acetates



(Ref. 51)



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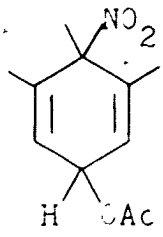
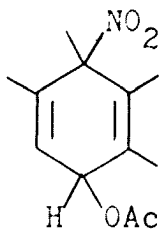
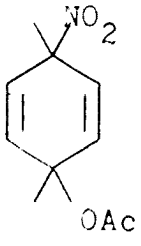


(Ref. 52)

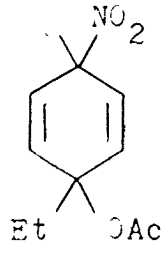


(Ref. 53)

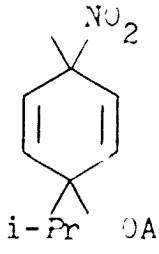
b) *Ipso* to a methyl group, tertiary acetates



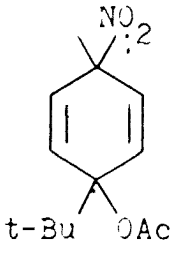
(Ref. 54)



(Ref. 42)

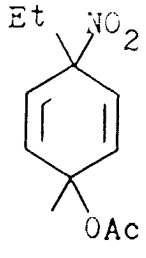


(Ref. 55)



(Ref. 56)

c) *Ipso* to primary and secondary alkyl groups.



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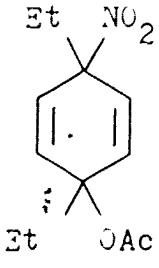
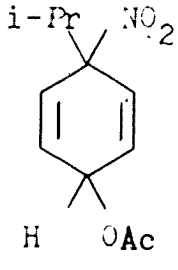
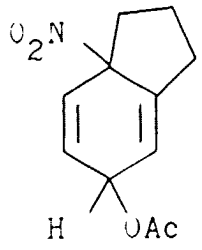


(Ref. 42)

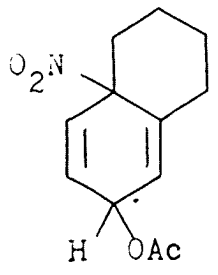


(Ref. 57)

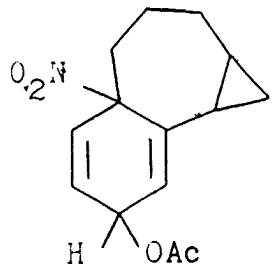
d) *Ipso* a to bridgehead in fused benzocycloalkanes



(Ref. 58)

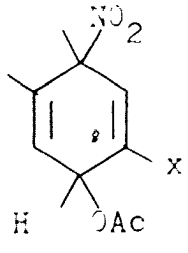


(Ref. 59)

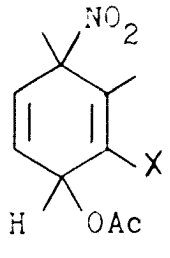


(Ref. 60)

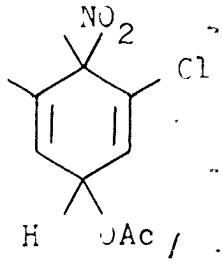
e) Regiospecific *ipso*-attack directed by a substituent



(X = CN^{61}, NO_2^{62}, $COMe^{63}$, $COPh^{63}$)

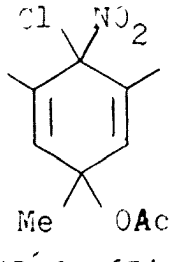


(X = NO_2^{62}, CN^{61})



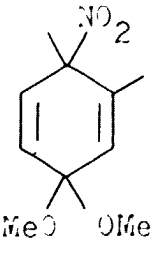
(Ref.64)

f) Attack *ipso* to a hetero substituent

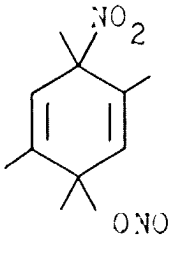


(Ref. 65)

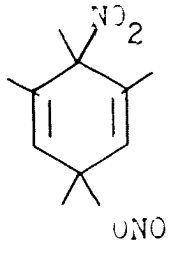
g) Capture by a nucleophile other than acetate



(Ref. 66)



(Ref. 53)

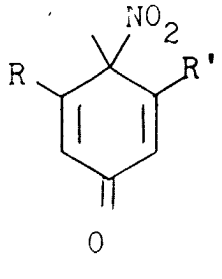


(Ref. 53)

All the adducts shown in Table 1.2 are formed by attack of an external nucleophile. If a substituent with a lone pair is present, intramolecular capture of the Wheland intermediate is also possible. The lone pair may be conjugated with the ring as in phenols, aromatic ethers, aryl acetates and anilines or it may be separated from the ring by a carbon chain. Several dienones, iminium salts and cyclohexadienes resulting from intramolecular nucleophilic capture have also been isolated.

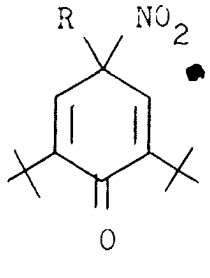
Table 1.3

Ipso Adducts Formed by Internal Nucleophilic Attack



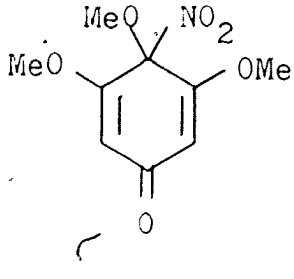
(R,R' = H, Me)

Ref. 67

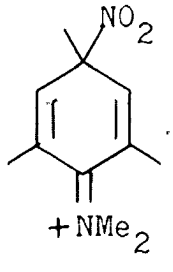


(R = CH_2OMe, CH_2CN)

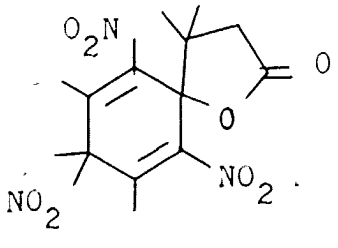
Ref. 68



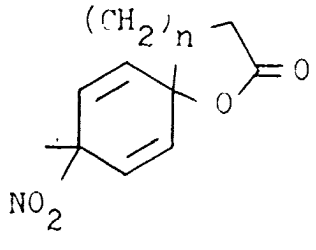
Ref. 69



Ref. 25

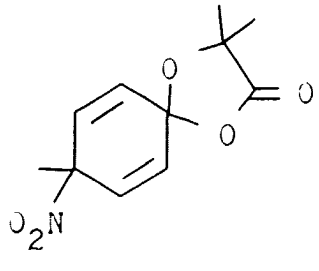


Ref. 70



n = 2,3

Ref. 71

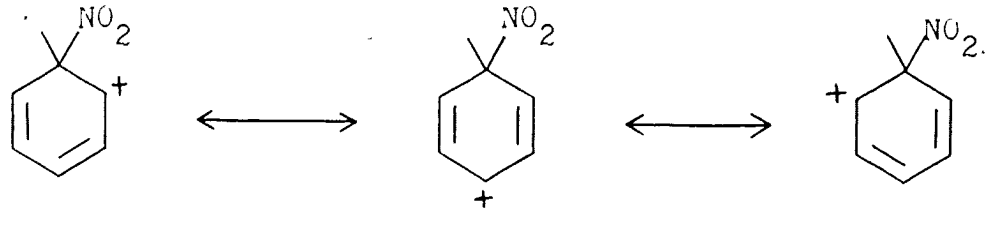


Ref. 72

All the adducts listed in Tables 1.2 and 1.3 are 1,4 adducts. The nucleophile attacks the position *para* to the

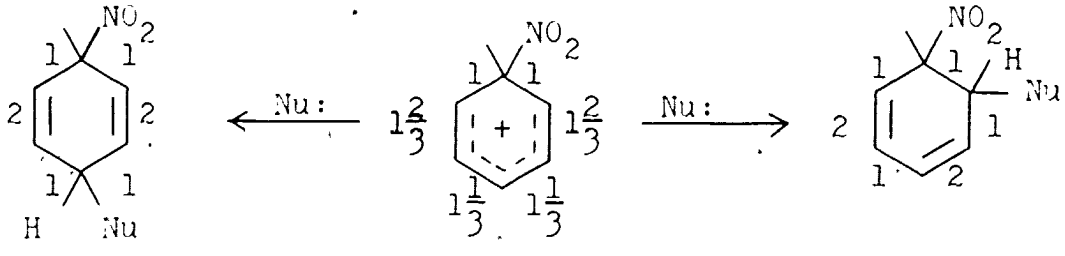
incoming nitro group giving nonconjugated dienes or cross-conjugated dienones. In the Wheland intermediate the positive charge is concentrated at both the terminal carbon atoms, and the central carbon atom of the cyclohexadienyl system. Both 1,4 and 1,2 adducts are therefore possible. Exclusive formation of 1,4 adducts over 1,2 adducts has been explained by the principles of electron correlation[73] and least motion.[74]

Resonance Structures for the *Ipso*-Wheland Intermediate



A B C

Changes in $\sigma + \pi$ Bond Orders

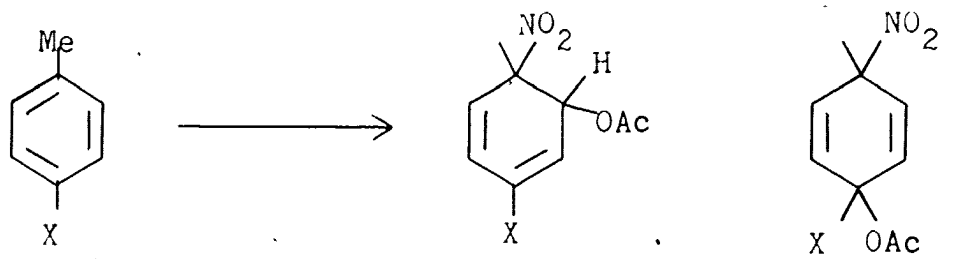


1,4 adduct 1,2 adduct

The principle of electron correlation states that in a cyclic system the electrons tend to stay in pairs which are as far removed from each other as possible. Thus the resonance contributor B is most important leading to excess positive charge at C-4. This, it was proposed, led to

preferential attack at C-4. When applying the principle of least motion, $\sigma + \pi$ bond orders in the Wheland intermediate were calculated giving equal weight to all the resonance contributors. The net changes in bond orders in forming the 1,2 and the 1,4 adducts were calculated. For 1,2 adduct formation the net change is 2 while for the 1,4 adduct the net change is 4/3. Thus less molecular reorganization was required to form the 1,4 adduct. This, it was stated, was, therefore, the favored product according to the principle of least motion. The model Wheland intermediate considered in both the approaches had an unsubstituted dienyl system. With additional substituents, both electronic and steric factors should affect the charge distribution in the dienyl system and the approach of the nucleophile. Several 1,2 adducts have now been isolated (Scheme 1.3) but as yet, there is no satisfactory explanation for the direction of the nucleophilic attack. In some cases only 1,2 adducts were observed while in other cases both 1,2 and 1,4 adducts were obtained.

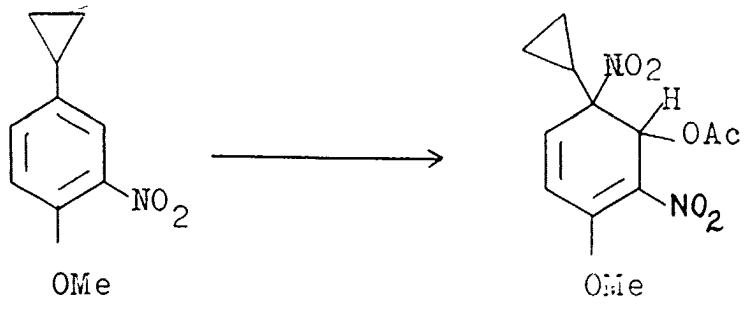
Scheme 1.3 Formation of 1,2 Adducts



X = *t*-Bu, (Ref. 56)
X = F, Cl, Br, OMe, NHAc (Ref. 72)

X = *t*-Bu,F,Cl,Br OMe, NHAc

X = *t*-Bu,F



(Ref. 75)

It is interesting to note that while *p*-*t*-butyltoluene[56] gives 1,2 adduct as the major product, 1-*t*-butyl-3,4-dimethylbenzene[76] and 1-*t*-butyl-3,4,5-trimethylbenzene[77] give only 1,4 adducts.

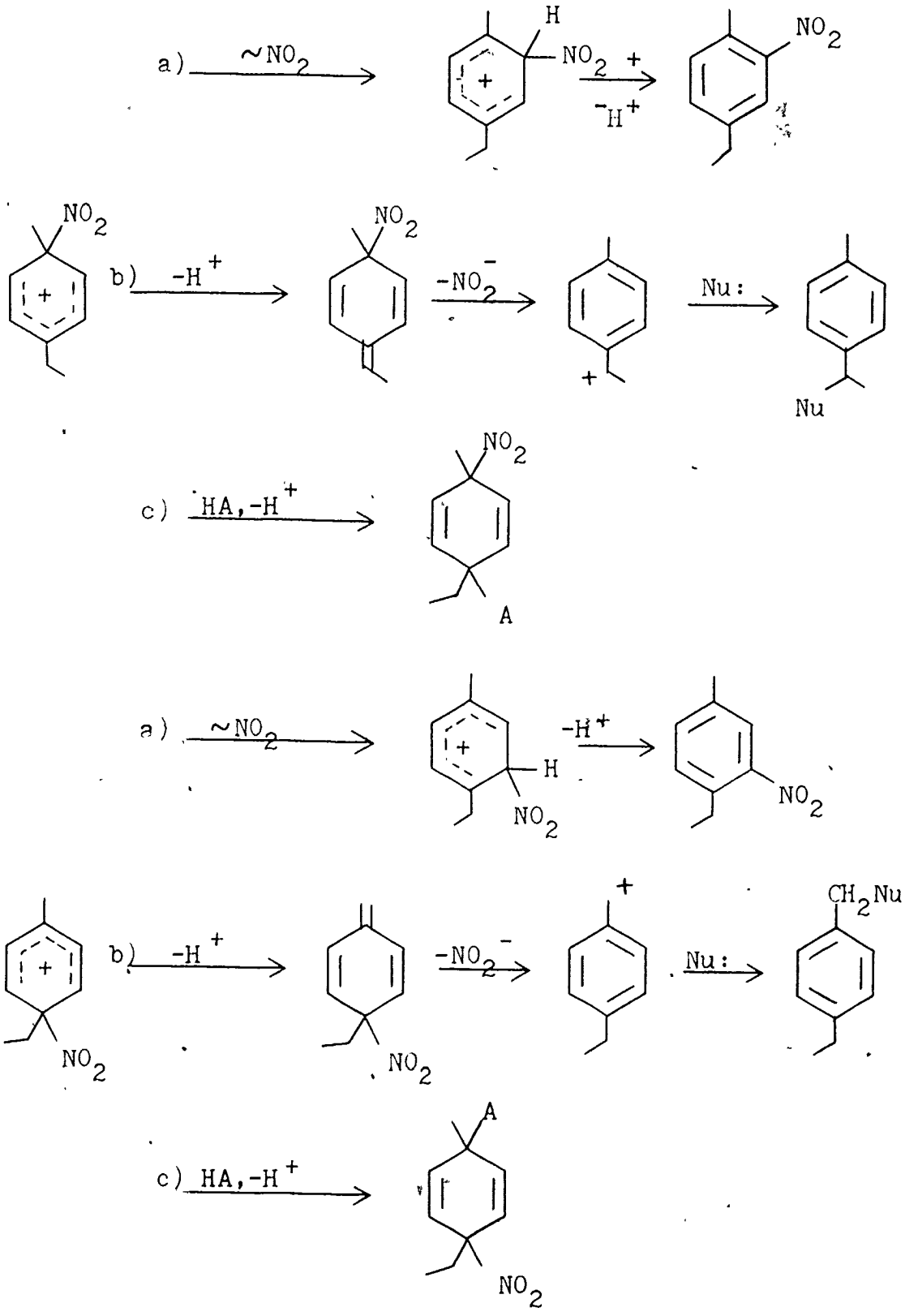
1.5 *Reactions of* Ipso-*Adducts*

Isolation of *ipso*-adducts is important because the *ipso*-Wheland intermediate can be regenerated from the adducts without any complications from the concurrent formation of other isomeric Wheland intermediates. Migration of the original substituent and *ipso*-substitution reactions have already been described. Other reactions can be most readily elucidated and understood by forming the Wheland intermediate from the *ipso*-adducts.

1.5.1 Reactions of the *Ipso*-Wheland Intermediate

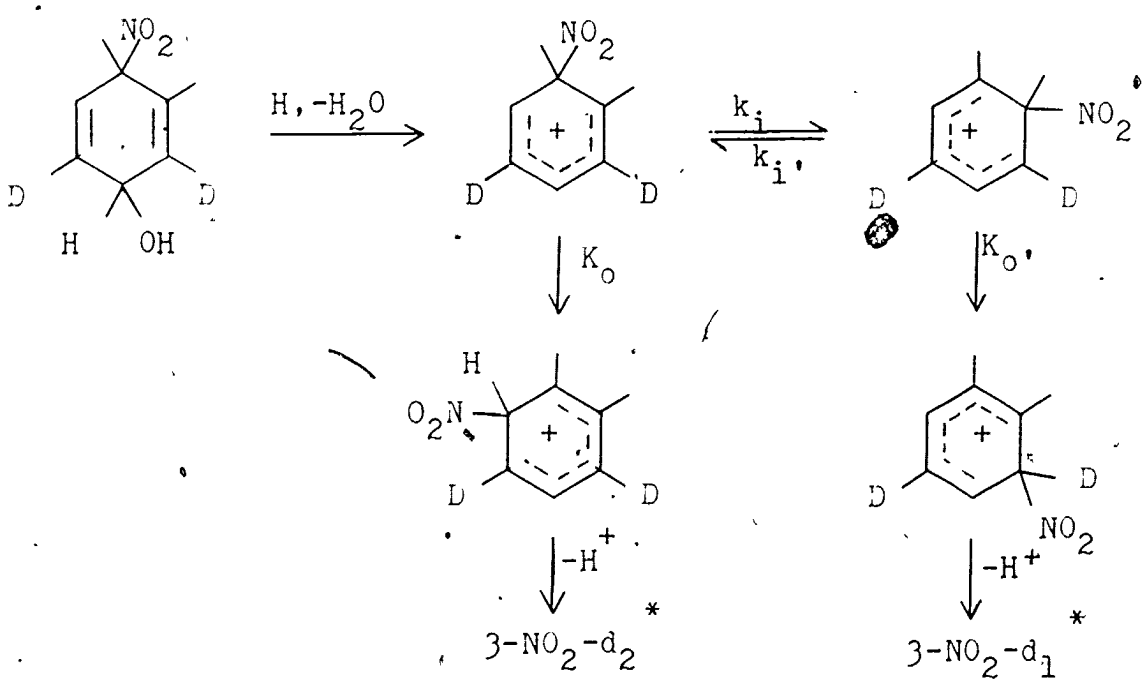
p-Ethyltoluene gave two regioisomeric *ipso*-adducts. The corresponding Wheland intermediates could be obtained by treating the individual adducts with strong acids.[78] Reactions of these Wheland intermediates are representative of a large number of reactions. These reactions are shown in Scheme 1.4.

Scheme 1.4 Reactions of *Ipso*-Wheland Intermediates



a) Migration of the nitro group

The nitro group undergoes a concerted 1,2 shift to give an isomeric Wheland intermediate which loses a proton to give only one nitro compound. No further 1,2 nitro shifts are observed from an unsubstituted positions. If the *ortho* position is substituted, the nitro group may rearrange further, after the initial nitro shift. Myhre[79] has shown by isotopic labelling that the nitro shift to a substituted position is faster by 50 times than the shift to an unsubstituted position.



The ratio of $3\text{-}NO_2\text{-}d_2$: $3\text{-}NO_2\text{-}d_1$ was 1.021 from which Myhre calculated a $k_o:k_i$ ratio of 0.02 assuming $k_i = k_i'$ and $k_o = k_o'$. This showed that the isotopomeric *ipso*-Wheland intermediates were nearly equilibrated before migration to

* 1,2-dimethyl-3-nitrobenzene

an unsubstituted position occurred.

b) Benzylic substitution

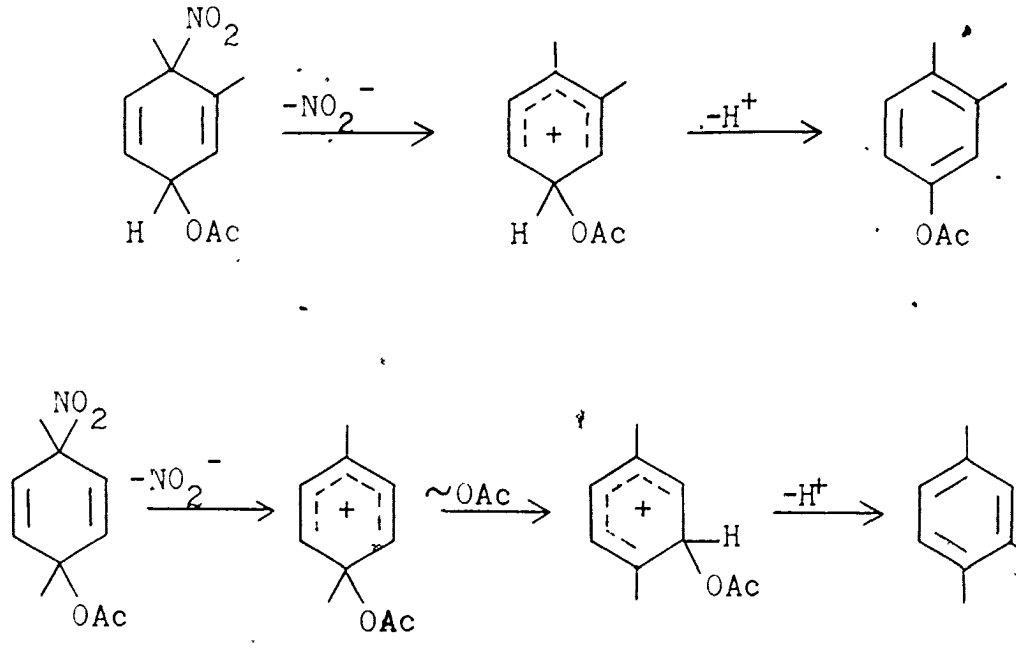
An alkyl group *para* to the *ipso*-position is modified by proton loss to give alkylidene cyclohexadiene intermediates. This is followed by solvolysis of the nitro group to give a benzylic cation which is trapped by a nucleophile to give benzylic substitution products. NO_2^- , ONO^- , ONO_2^- , CH_3COO^- , MeO^- are some of the nucleophiles which have been observed in such benzylic substitutions.[80]

c) Nucleophilic capture of the Wheland intermediate

Dienes where acetate has been exchanged for other nucleophiles have been observed for HA = H_2O, MeOH, HCl and HCOOH in Scheme 1.4.[78] These reactions occur under acidic conditions and can be looked upon as $A_{AL}1$ hydrolyses of the dienyl acetate, followed by capture of the dienyl cation by the nucleophile.

1.5.2 Solvolysis of the *Ipso*-Adducts

Apart from giving rise to the *ipso*-Wheland intermediate, the *ipso*-adducts can also give rise to acetoxy cyclohexadienyl cations by solvolysis of the nitro group under weakly acidic or neutral conditions. If the adduct is a secondary acetate, loss of the proton *ipso* to the acetate is the predominant reaction.[51] In tertiary acetates, the acetate migrates to the adjacent position to give an isomeric cyclohexadienyl cation which loses a proton to give the aromatic acetate.[81]



The intramolecular nature of the 1,2 acetate shift has been demonstrated by carrying out the solvolysis in the presence of propionic acid[52] or acetic acid-d_4[54], when no incorporation of the added nucleophile was observed in the aromatic products.

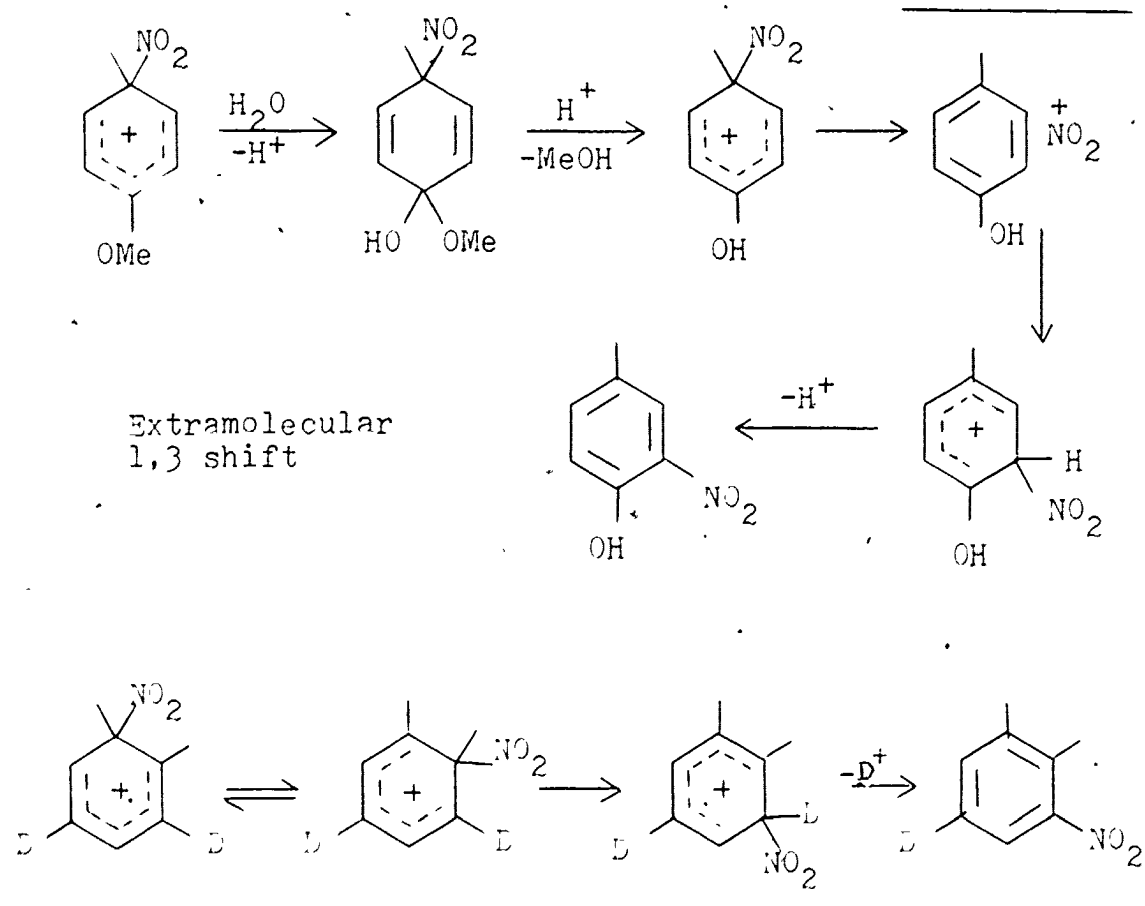
1.5.3 Loss of the Nitro Group

Earlier (Section 1.4) it was mentioned that loss of the nitro group from the *ipso*-Wheland intermediate in the nitration reaction mixture leads to no observable net reaction. When the *ipso*-Wheland intermediate is generated from the *ipso*-adduct, loss of the nitro group leads to an encounter pair (microscopic reversibility). The fate of the encounter pair may by decided in three ways : i) attack of nitro group at the *ipso*-position, which leads to no net

reaction ii) attack of nitro group at another activated position in the molecule or iii) diffusion apart of the components of the encounter pair.

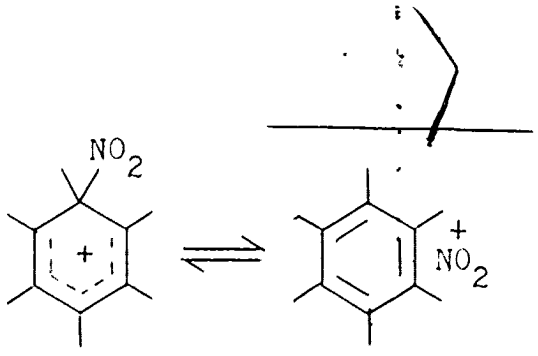
When the nitro group attacks another activated position in the molecule, the reaction is defined as extramolecular migration by Schofield.[82] These migrations are generally observed when the *ipso*-position is activated by a hydroxy or methoxy group. The new position of the nitro group is also *ortho* or *para* to the directing substituent. Overall, extramolecular migration is a formal 1,3 NO_2 shift. This has to be differentiated from apparent 1,3 shifts by sequential 1,2 migrations of the nitro group. Myhre has studied such sequential shifts in detail.[79] An extramolecular nitro shift has been observed during the nitration of *p*-methylanisole in mixed acid.[83] Scheme 1.5 shows mechanisms for both extramolecular and sequential 1,2 nitro shifts.

Scheme 1.5 1,3 Nitro Shifts



Sequential intramolecular 1,2 shifts

When the nitro group diffuses out from the encounter pair, the process is called denitration. For deactivated compounds which do not react at encounter rate such escape from the encounter pair should be common. For compounds reacting at encounter rate denitration has been observed only in a few cases. Olah[30] has showed that nitrohexamethylbenzenium cation could nitrate benzene and mesitylene to nitrobenzene and nitromesitylene respectively.

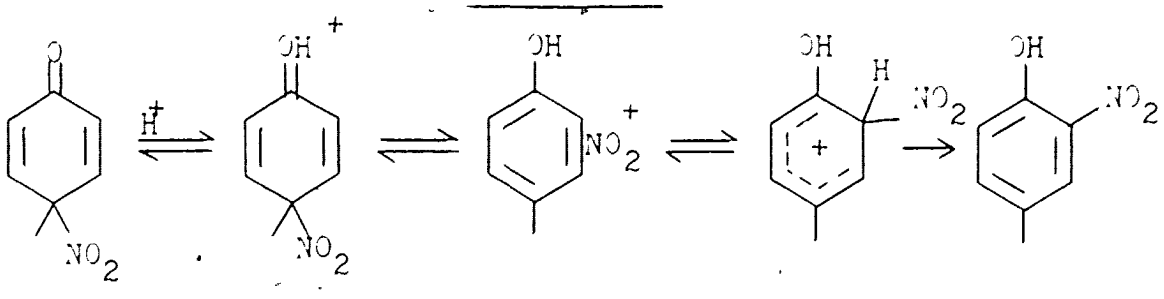


$$C_6Me_6 + NO_2^+ \xrightarrow{ArH} ArNO_2$$

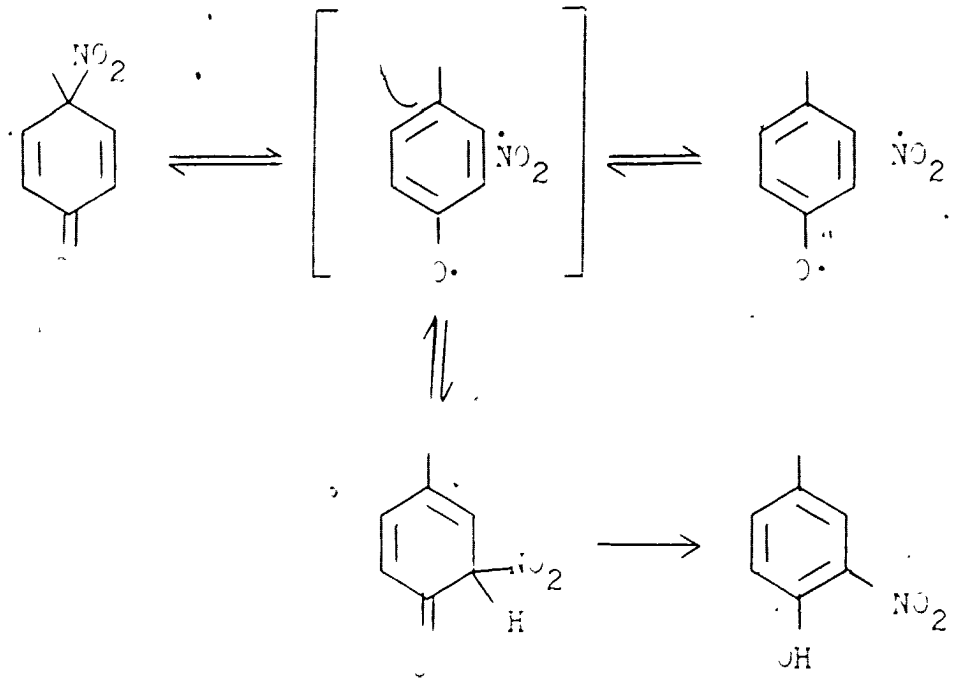
$$ArH = C_6H_6,\ C_6H_3Me_3$$

1.5.4 1,3 Nitro Shifts in Cyclohexadienones.

Cyclohexadienones obtained by *ipso*- nitration of suitably substituted phenols or anisoles undergo a 1,3 nitro shift under two different conditions. Under acidic conditions, the nitro shift is predominantly extramolecular.[84]



In neutral or weakly acidic solvents such as hexane, acetic acid, ethanol, water, dimethylsulphoxide the dienone has been shown to undergo 1,3 nitro shift by a radical dissociation recombination process. Some leakage of the NO_2 radical from the radical pair has been demonstrated by trapping experiments using radical scavengers and crossover experiments using ^{15}N and ^{2}H labelled dienone.[85]



1.6 *Reactions of Wheland Intermediates Containing a Secondary Nitro Group*

In the last step of the nitration mechanism (Section 1.2), deprotonation of the Wheland intermediate was shown to be irreversible. This is the generally observed situation, since the reverse step, protonation of the nitroaromatic *ipso* to a nitro group is a process requiring a high activation energy. The activation energy of the reverse protonation reaction can be reduced by increasing the energy of the nitroaromatic. One possible way to do this is to reduce the conjugation of the nitro group with the aromatic system. 9-Nitroanthracene is such a compound where the *peri* interactions force the nitro group out of the aromatic plane by 64°-90°. Gore[86] tried to protonate 9-nitroanthracene with sulphuric acid in trichloroacetic acid at 90°C. He

isolated 81% free nitric acid indicating that nitro aromatic compounds can be protonated under strong acid conditions, and that deprotonation of the Wheland intermediate can be slowed down enough to observe a competing denitration reaction. Further Cerfontain[87] determined that there is an isotope effect in the nitration of anthracene-9-d_1 (k_H/k_D = 2.6 in sulpholane and 6.1 in acetonitrile) confirming that loss of proton in the σ-adduct can become a rate determining step. Olah et al.[88] showed that there is a similar isotope effect of k_H/k_D = 2.25 in the nitration of anthracene-d_{10} with nitronium hexafluorophosphate in nitromethane. In the same work they showed that pentamethylnitrobenzene and 9-nitroanthracene could nitrate benzene, toluene and mesitylene in the presence of super acids to give the respective nitroaromatic compounds with a low yield of ca. 5%. A similar denitration was observed in the case of 2,4,5-triisopropyl-6-nitroacetanilide by Neal et al.[89] This compound when refluxed with concentrated hydrochloric acid in ethanol gave 2,4,5-triisopropylacetanilide.

Table 1.4

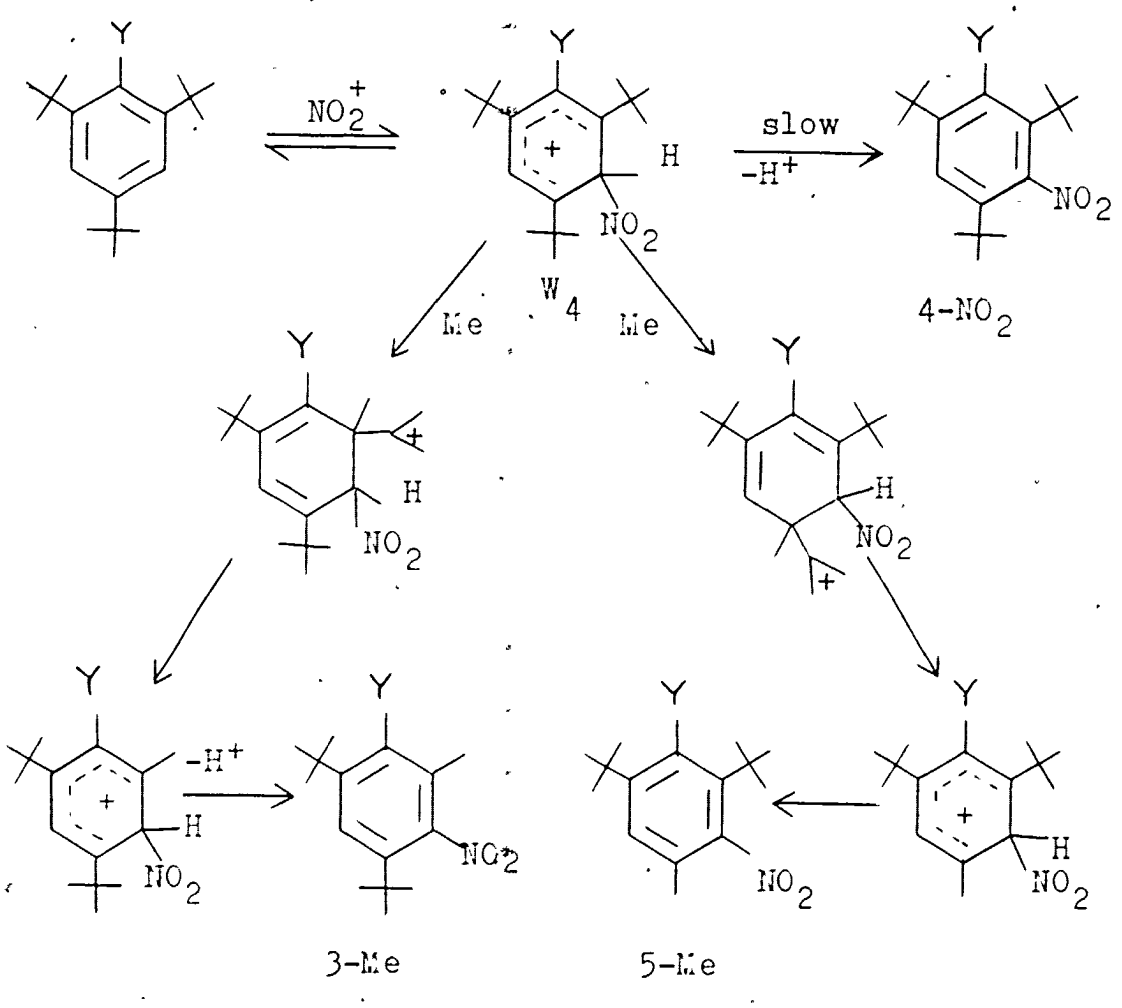
Products[a] and isotope effects in the nitration of 1,3,5-tri-*t*-butyl-2-Y-benzenes

Y	Relative yields of 4-NO_2	3-Me	5-Me	k_H/k_D	Volume of Y($cm^3.mol^{-1}$)
H	100%	-	-	1	----
Me	100%	-	-	3.7	13.7
NO_2	81%	1%	18%	3.0	11.8
F	100%	-	-	2.3	5.8

a Products shown in Scheme 1.6

All the above reactions suggest that the normally very fast proton loss can be slowed down sufficiently to allow alternate pathways to operate. The main alternate pathway is the loss of the nitro group which leads to denitration or transfer nitration products. Myhre et al.[90] have confirmed the slow deprotonation in another isotopic study and also demonstrated the existence of a pathway other than deprotonation and denitration. (Scheme 1.6, Table 1.4)

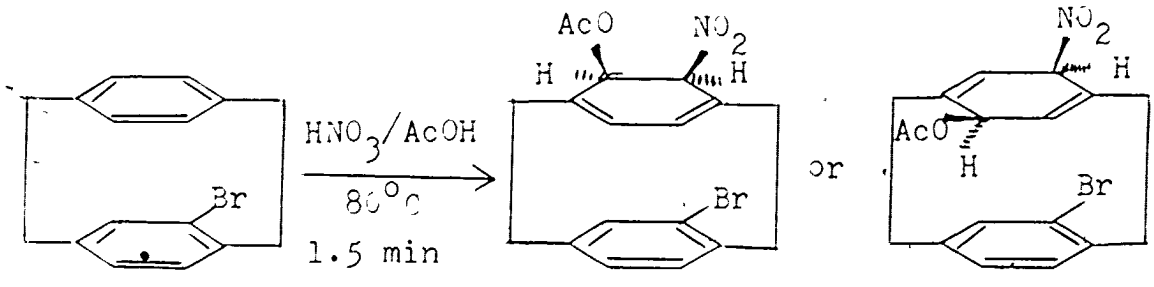
Scheme 1.6 Pathways for Wheland Intermediate with Secondary Nitro Group



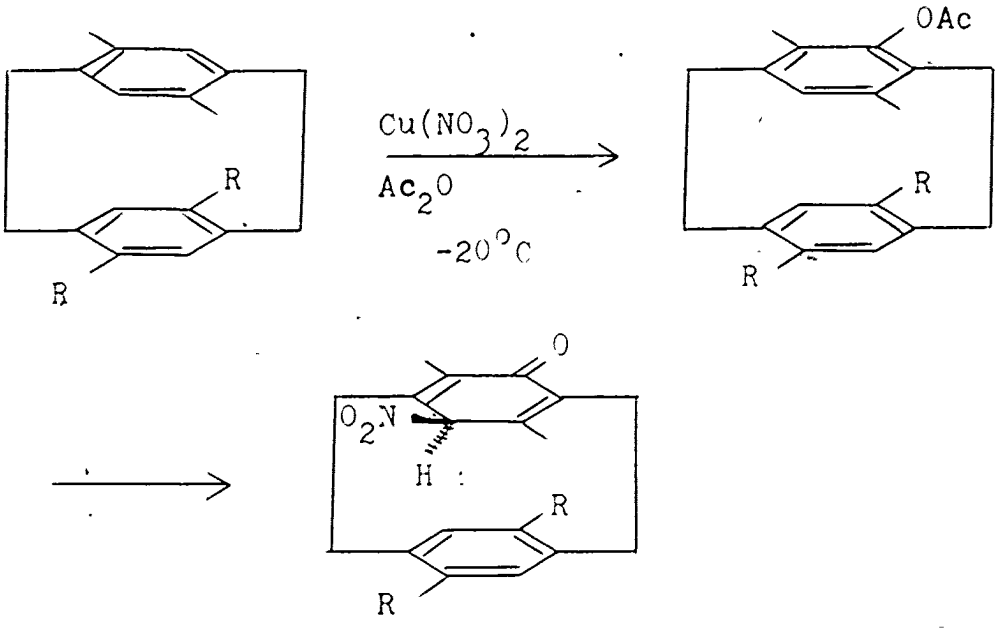
Only products arising from W_4 are shown.

The existence of isotope effect for 1,3,5-tri-*t*-butyl-2-Y-benzenes (Y = Me, NO_2, F) shows that proton loss is rate limiting in the nitration of these compounds. Substituent modification (to give 3-methyl and 5-methyl products), similar to that observed in the *ipso*-Wheland intermediates is observed in the case of 1,3,5-tri-*t*-butyl-2-nitrobenzene. If the proton loss in the Wheland intermediates with a secondary nitro group can be sufficiently slowed down, it is

even possible to trap these intermediates with suitable nucleophiles. Only a few examples of such nucleophilic trapping are known. Reich and Cram[91] reported the isolation of an acetyl nitrate adduct with a secondary nitro group from the nitration of 4-bromo[2.2]paracyclophane. It was not possible to determine whether the adduct was a 1,2 or 1,4 adduct.



The stability of the adduct must be due to the proximate aromatic ring blocking the approach of a base and preventing the abstraction of the proton. Nitration of methyl substituted [2.2]paracyclophanes gave an isolable cyclohexadienone with a secondary nitro group.[92] With the knowledge of *ipso*-nitration chemistry, it can be postulated that the dienone was formed by nitration of the acetate which was also isolated from the reaction mixture.



a) R = H b) R = Me

Effective steric blocking in deprotonation of the dienone by the second aromatic ring must again be responsible for the stability of the dienone.

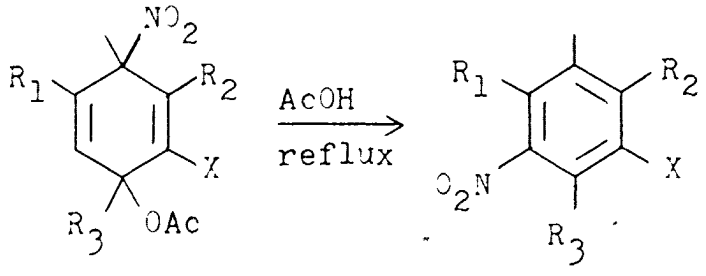
All the above reactions suggest that given the correct steric environment, Wheland intermediates with a secondary nitro group can display as interesting chemistry as the *ipso*-Wheland intermediates.

1.7 *Formal* 1,3 *Rearrangement of the Nitro Group : Unknown Mechanism*

A variety of unconventional products in aromatic nitration have been shown to arise as a consequence of *ipso*-nitration. Mechanisms of reactions leading to most of these products have now been identified or at least proposed. There are rearrangements of *ipso*-adducts, known for some time, that involve a formal 1,3 nitro shift. The mechanism

of these nitro shifts is not known with certainty. These rearrangements take place under relatively mild (neutral or weakly acidic) conditions where loss of acetate leading to the *ipso*-Wheland intermediate is not favorable. In addition there are a set of rearrangements of nitrodienones which occur with unexpected regioselectivity and for which the mechanism is not well established. All these rearrangements are summarized in Scheme 1.7.

Scheme 1.7 Formal 1,3 Shift of the Nitro Group

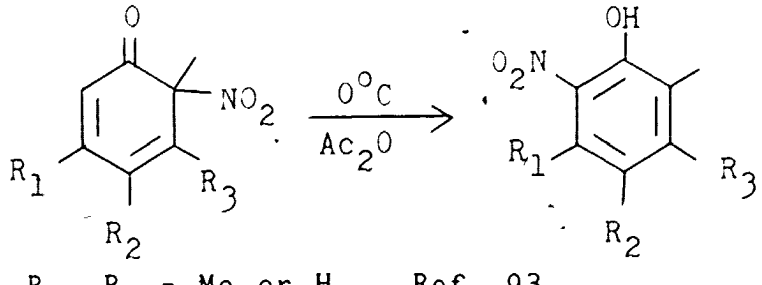


R_1 = Me, R_2 = R_3 = H, X = CN Ref. 61

R_1 = R_3 = H, R_2 = Me, X = CN Ref. 61

R_1 = Me, R_2 = R_3 = H, X = NO_2 Ref. 62

R_1 = R_2 = H, R_3 = Me, X = NO_2 Ref. 63



R_1, R_2, R_3 = Me or H Ref. 93

The major rearrangement product from adducts of dimethylbenzonitriles and nitroxylenes was that from a

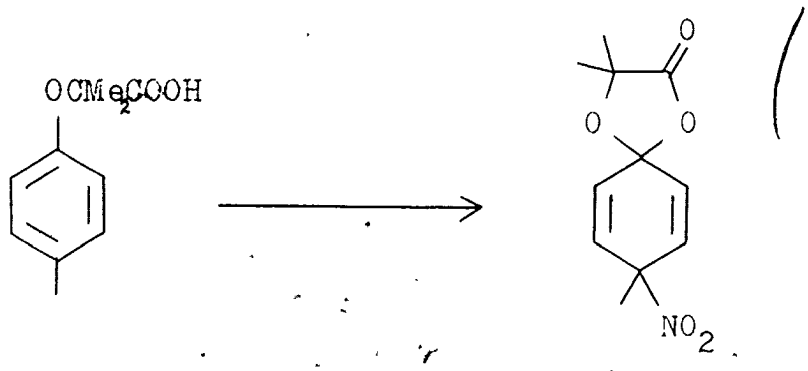
formal 1,3 nitro shift. For dimethylbenzonitrile adducts, the nitro group could not be trapped with mesitylene, so it was not an intermolecular migration. In the case of the 2,3-dimethylbenzonitrile adduct, the nitro group migrated across an unsubstituted position. This formal 1,3 shift cannot be composed of two sequential 1,2 shifts because it has been shown that proton loss at an unsubstituted position is faster than nitro group migrations. The reaction of nitroxylene adducts was also carried out in the presence of hydroquinone as a radical scavenger. Although the amount of the product decreased, the product of the formal 1,3 shift was still formed.

The rearrangement of 6-alkyl-6-nitrocyclohexadienones cannot be a radical-dissociation recombination reaction because the nitro group does not migrate to the 4-position, which has comparable electron density, even when it is unsubstituted. It has been proposed that there is a bonding interaction between the oxygen atom attached to the ring and the migrating nitro group and this interaction leads to the observed regiospecificity.[94] No experimental evidence is known for the proposed bonding interaction.

1.8 *Objectives of the Present Work*

Since 6-alkyl-6-nitrocyclohexa-2,4-dienones are unstable[93] this makes the study of their reactions difficult. It was deemed desirable to prepare a related series of compounds in order to make a thorough

investigation of their reactions and to determine if the regiospecific rearrangement described above occurred in the new series. It might be recalled that 2-methyl-2-(4-methylphenoxy)propanoic acid gave a 1,4 adduct by internal nucleophilic capture of the *ipso*-Wheland intermediate.[72] (cf. Table 1.3)



The 1,4 adduct is in fact a protected 4-methyl-4-nitrocyclohexa-2,5-dienone and such a spiro adduct would seem to be a suitable model compound for study.

Thus the objects of this work are

i) to study the nitration of the analogous substrates with a methyl group *ortho* to the directing ether substituent, viz. 2-methyl-2-(2-methylphenoxy)propanoic acid, (2-methylphenoxy)acetic acid and 2-methyl-2-(2,3,5-trimethylphenoxy)propanoic acid, to see if spirodienes (protected 6-methyl-6-nitrocyclohexa-2,4-dienones) similar to that above can be formed and isolated, and

ii) to investigate aromatization and rearrangement reactions of these dienes.

CHAPTER II

EXPERIMENTAL PROCEDURES

2.1 *Instrumentation*

Melting points are uncorrected and were determined on Buchi SMP-20 melting point apparatus. Infra red spectra, calibrated with polystyrene, were recorded on a Perkin-Elmer 283 spectrometer. Observations were made on potassium bromide discs for solids and on thin films between sodium chloride plates for liquids. Proton nuclear magnetic resonance spectra of solutions in carbon tetrachloride, chloroform-d or methylene chlorode-d_2 were recorded on Perkin Elmer R-12B (60 MHz), Perkin Elmer R-32 (90 MHz), or Bruker WM 250 (250 MHz) spectrometers. Tetramethylsilane was used as internal standard. NMR spectra of nitration reaction mixtures were recorded with the acetic anhydride peak at δ 2.15 as the lock signal. For all other solutions tetramethylsilane (90 MHz) or the solvent deuterium signal (250 MHz) was used as the lock signal. Carbon-13 nuclear magnetic resonance spectra were recorded on Nicolet TT-14 (15.1MHz) or a Bruker WM 250 (62.9 MHz) spectrometer using solutions in chloroform-d with tetramethylsilane as an internal standard. In some cases the cholorform-d peak (δ_C 77.0) was used for calibration. Ultraviolet spectra were recorded on a Beckman DU-8 spectrophotometer generally using methanol as solvent. Mass spectra were recorded on a Perkin Elmer Hitachi RMU-7 spectrometer with 70ev electron

impact ionization or on a Finnigan 3300 GC/MS/CI spectrometer using methane as the carrier gas. Gas chromatography was performed on a Varian Aerograph 2400 or a Varian - 3700 gas chromatograph, using SE 30 or SE 54 glass capillary columns. For high performance liquid chromatography a Varian 5000 liquid chromatography or a Waters Prep LC/System 500 was used. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Vancouver.

2.2 *Reagents*

o-Cresol, *p*-Cresol (both Aldrich Gold Label), 2,3,5-trimethylphenol, 2-methyl-3-nitrophenol, 4-methyl-3-nitrphenol, 2-methyl-4-nitroaniline, 1,1,1-trichloro-2-methylpropan-2-ol, nitroethanol (all Aldrich reagent grade) were used without further purification.

Acetic anhydride was certified ACS from Fisher Trifluoroacetic acid and trifluoroacetic anhydride were Aldrich Gold label (99+%). Fuming nitric acid (Fisher, 300 cm^3) was purified by distilling from urea (10 g) and sulphuric acid (500 cm^3) at 1 mm Hg and stored at -25°C.

Solvents for chromatography including pentane (reagent, Fisher), ether (Fisher) and petroleum ether (reagent, Fisher) were dried over sodium and distilled before use. Solvents for high performance liquid chromatography were water (Baker), isopropanol (Caledon), dichloromethane (Burdick and Jackson), hexane (Burdick and Jackson) and acetonitrile (Baker). Non- deuterated solvents for spectroscopy were certified ACS (Eastman Kodak). Deuterated

solvents used for NMR spectroscopy were chloroform-d (Aldrich Gold Label), methylene chloride-d_2, acetonitrile-d_3, methanol-d_4, pyridine-d_5, acetone-d_6, benzene-d_6 and tetrahydrofuran-d_8 (Merck Sharp and Dohme).

Silica gel (60-200 mesh, Davison commercial grade H), neutral alumina (Brockman Activity I) and alumina (80-200 mesh, Fisher) deactivated with 3% (v/v) distilled water were used for chromatography. Anhydrous magnesium sulphate was used to dry solutions in organic solvents.

The following compounds were prepared by members of Prof. A. Fischer's research group at University of Victoria: [4,6 - $^2H_2$]-*o*-cresol, 2-methyl-2-(4-methylphenoxy)propanoic acid and 4-methyl-4-nitrocyclohexa-2,5-dienone (Dr. G.N. Henderson), (E)- and (Z)-2-cyano-4,5-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (D.L. Fyles), (E)- and (Z)-2-cyano-3,4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (S. Sankararaman), 2-cyano-1,4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (Dr. W.V. Nykodym), (E)-1,4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (T.A. Smyth), (E)-1,4-dimethyl-2,4-dinitrocyclohexa-2,5-dienyl acetate (Dr. L.M. Iyer). Donation of samples of these compounds is gratefully acknowledged.

2.3 *Preparation of Starting Compounds and Authentic Samples*

a. 2-methyl-4-nitrophenol (**9**)[95]

A solution of 2-methyl-4-nitroaniline (11.4 g, 0.076 mol) and sulphuric acid (16.5 cm^3) in water (22.5 cm^3) was

cooled to 0°C and crushed ice (ca. 40g) was added to it. Sodium nitrite (5.2g) dissolved in water (12.5 cm^3) was added dropwise to this slurry maintaining the temperature below 2 °C. The resulting mixture was then stirred at 0 °C for 10 min and added dropwise from a jacketed dropping funnel at 0 °C to a boiling solution of sulphuric acid (50 cm^3) in water (37.5 cm^3) in a 500 cm^3 three necked flask fitted with a condenser. The mixture was refluxed for 10 min after the addition and then poured onto ice. The reaction mixture was extracted with ether and the ethereal solution extracted with 1M sodium hydroxide (5 x 30 cm^3). The alkaline extract was acidified and re-extracted with ether. Washing the ethereal solution with distilled water and brine, followed by drying and evaporation of the solvent gave 2-methyl-4-nitrophenol as dark brown crystals (11.3 g, 98%). Treatment with activated charcoal (0.3g) and recrystallization from methylene chloride-pentane gave yellow crystals (9.8 g), m.p. 94-96 °C (lit.[96] 96 °C).

b. 2-Methyl-6-nitrophenol (**10**)

A nitrating mixture of nitric acid (9.4 g, 0.15 mol) and acetic anhydride (75 cm^3) was prepared by mixing at -78°C, warming to 0 °C, and after 5 min, cooling to -78°C. The nitrating mixture was poured into a slurry of *o*-cresol (10.8g, 0.1 mol) and acetic anhydride (19 cm^3) at -78°C and the resulting mixture warmed to -40°C. After stirring at -40°C for 30 min, the reaction mixture was cooled to -78°C

and poured into a stirred solution of 58% aqueous ammonium hydroxide (130 cm^3) in ether (1000 cm^3) also at -78°C. The ethereal solution was constantly stirred while being allowed to warm to ambient temperature over 1.5 h. The ether layer was decanted, washed with distilled water and brine, dried and the solvent evaporated to give a mixture (14.5 g) of 2-methyl-6-nitrophenol (79 %) and 2-methyl-4-nitrophenol (21 %). The mixture was separated by fractional distillation in a Kugelrohr to give 2-methyl-6-nitrophenol (9.4 g), m.p. 69-70 °C (hexane, lit.[96] 70 °C).

c. 2-Methyl-2-(2-methylphenoxy)propanoic acid (12)[97]

A solution of *o*-cresol (54 g, 0.5 mol) and chloretone (1,1,1-trichloro-2-methylpropan-2-ol)(106.5 g, 1 mol) in acetone (1000 cm^3) was placed in an ice bath and continuously stirred. Powdered sodium hydroxide (160g, 4 mol) was added to this solution in three equal amounts at 2 h intervals. Acetone (250 cm^3), cooled to -20°C, was added to the solution after adding the second and third lot of sodium hydroxide. The reaction mixture was maintained at 0-10 °C during the period of addition. After the addition, the ice-bath was replaced by a water bath at ambient temperature. The reaction mixture was stirred for a further 16 h at ambient temperature. The solvent was removed on a rotavapor at 45°C, the residue dissolved in water, acidified with 1:1 (v/v) hydrochloric acid, extracted with ether (3x500 cm^3) and the ether extract re-extracted with

saturated sodium bicarbonate solution (5x400 cm^3). The bicarbonate extract was acidified with 1:1 hydrochloric acid and extracted with ether (2x500 cm^3). The ethereal extract was dried and the solvent evaporated to give 72.65 g (75%) of the crude product. Crystallization from ether-pentane gave three crops of 2-methyl-2-(2-methylphenoxy)propanoic acid (Total 55.81 g), m.p. 75°C (lit.[98] 75-76°C); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.62 (6H,s, $C(CH_3)_2$), 2.25 (3H,brs, 2-CH_3), 6.82 (1H, dd, J=8.1 Hz, 1Hz,6-H), 6.95 (1H, dt,J=7.5 Hz, 7.4 Hz, 1 Hz, 4-H), 7.06 (1H, ddd, J=8.1 Hz, 7.4 Hz, 1.6 Hz, 5-H) 7.17(1H, dd, J=7.5 Hz, 1.6 Hz, 3-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.7 (2-CH_3), 25.2 ($C(CH_3)_2$), 79.0 ($C(CH_3)_2$), 117.5 (C-6), 122.3 (C-4), 126.3 (C-5), 129.9 (C-2), 131.1 (C-3), 153.3(C-1), 180.6 (COOH).

d. 2-Methyl-2-([4,6-$^2H_2$]-2-methylphenoxypropanoic acid (21)

The preparation followed the same procedure as described above for the acid 12. [4,6-$^2H_2$]-*o*-Cresol (3.3g) gave the acid 21 (2.2g, 38%) as a dark red oil. Crystallization from ether-hexane afforded colourless crystals of 21 (1.7g), m.p. 73 °C; IR (KBr): 3000-2500 (OH), 1698 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.59 (6H, s, $C(CH_3)_2$), 2.22 (3H, s, 2-CH_3), 7.09 (1H, brs, 5-H), 7.17 (1H, brs, 3-H); ^{13}C NMR ($CDCl_3$, 15.1 MHz): δ_C 16.7 (2-CH_3), 25.2 ($C(CH_3)_2$), 79.1 ($C(CH_3)_2$), 117.4 (t, $^1J_{CD}$=22 Hz, C-6), 122.1 (t, $^1J_{CD}$=25 Hz, C-4), 126.2 (C-5), 129.9 (C-2), 131.0 (C-3), 153.3 (C-1), 180.4 (COOH).

e. 2-Methyl-2-(2-methyl-3-nitrophenoxy)propanoic acid (13)

This preparation followed the same procedure as described for 12. 2-Methyl-3-nitrophenol (8) (3.1g) afforded acid 13 in 98% yield (4.7g). Recrystallization from ether-pentane gave pale yellow crystals of 13 (4.1g), m.p. 154°C, IP (KBr): 3000 -2500 (OH), 1710 (C=O), 1520, 1360 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.66 (6H, s, $C(CH_3)_2$), 2.37 (3H, s, 2-CH_3), 7.03 (1H, dd, J= 8.2 Hz, 0.8 Hz, 6-H), 7.21 (1H, t, J= 8.2 Hz, 8.0 Hz, 5-H), 7.47 (1H, dd, J= 8.0 Hz, 4-H); ^{13}C NMR ($CDCl_3$, 15.1 MHz): δ_C 12.4 (2-CH_3), 25.3 ($C(CH_3)_2$), 80.1 ($C(CH_3)_2$). 117.8 (C-4). 121.0 (C-6) 125.2 (C-2), 126.2 (C-5), 151.5 (C-3), 154.4 (C-1), 179.6 (COOH). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.21%, H 5.48%, N 5.86%; found: C 55.29%, H 5.29%, N 5.95%.

f. 2-Methyl-2-(2-methyl-6-nitrophenoxy)propanoic acid (15).

2-Methyl-6-nitrophenol (3.1g) yielded acid 15 (1.1g, 23%) as a red oil, following the same procedure used for acid 12. Unreacted 2-methyl-6-nitrophenol (2g, 65%) was recovered from the reaction mixture. Acid 15 was purified by passing through a MCH-10 (0.4 x 30 cm) reverse-phase column on the Varian 5000 HPLC, using 15% (v/v) aqueous methanol as eluent. A dark red oil was obtained which on drying under vacuum gave equivalent weight 239.2 (calculated for $C_{11}H_{13}NO_5$, 239.1) by titration with sodium hydroxide solution (2 x 10^{-5}M); IR (film): 3000 - 2500 (OH), 1720 (C=O), 1560, 1360 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz):

δ 1.55 (6H, s, $C(CH_3)_2$), 2.37 (3H, s, 2-CH_3), 7.16 (1H, dd, J=8.1 Hz, 7.7 Hz, 4-H), 7.42 (1H, d, J=7.7 Hz, 3-H), 7.57 (1H, d, J=8.1 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 15.1 MHz): δ_C 17.8 (2-CH_3), 24.6 ($C(CH_3)_2$), 83.7 ($C(CH_3)_2$), 121.5 (C-5), 123.2 (C-4), 130.8 (C-2), 136.9 (C-3), 137.5 (C-6), 148.5 (C-1), 178.3 (COOH).

g. 2-Methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid (14).

On using the procedure for acid 1, 2-methyl-4-nitrophenol (9) (6.1g) gave acid 14 (9.0g, 89%). Crystallization from methylene chloride pentane gave pale yellow crystals (8.6g), m.p. 136°C; IR (KBr): 3000 - 2500 (OH), 1703 (C=O), 1498, 1362 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.71 (6H, s, $C(CH_3)_2$), 2.27 (3H, s, 2-CH_3), 6.73 (1H, d, J=8.9 Hz, 6-H), 8.01 (1H, dd, J=8.9 Hz, 3.1 Hz, 5-H), 8.06 (1H, d, J=3.1 Hz, 3-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 16.8 (C-2), 25.4 ($C(CH_3)_2$), 79.6 ($C(CH_3)_2$), 114.6 (C-6), 122.7 (C-5), 126.5 (C-3), 130.2 (C-2), 141.6 (C-4), 159.0 (C-1), 179.4 (COOH). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.21%, H 5.48%, N 5.86%; found: C 55.29%, H 5.55%, N 5.98%.

h. 2-Methyl-2-(4-methyl-3-nitrophenoxy)propanoic acid (16).

4-Methyl-3-nitrophenol (11) (6.1g) afforded acid 16 in 87% yield (8.4g) following the procedure described for 12. Crystallization from ether-pentane gave pale yellow crystals, m.p. 86°C; IR (KBr): 3000 - 2500 (OH), 1712 (C=O), 1525, 1353 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz):

δ 1.61 (6H, s, $C(CH_3)_2$), 2.48 (3H, s, 4-CH_3), 7.10 (1H, dd, J=8.3 Hz, 2.5 Hz, 6-H), 7.25 (1H, d, J=8.3 Hz, 5-H), 7.56 (1H, d, J=2.5 Hz, 2-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 19.6 (4-CH_3), 25.2 ($C(CH_3)_2$), 80.2 ($C(CH_3)_2$), 116.2 C-2), 125.0 (C-6), 127.7 (C-4), 133.3 (C-5), 149.5 (C-3), 153.6 (C-1), 179.1 (COOH). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.21%, H 5.48%, N 5.86%; found : C 55.58%, H 5.74%, N 5.85%.

i. 2-Methyl-2-(2,3,5-trimethylphenoxy)propanoic acid (17)

2,3,5-Trimethylphenol (5) (13.6g) was dissolved in a solution of sodium methoxide (8.1g) in methanol (200 cm^3). The mixture was stirred at ambient temperature for 2 h and the solvent evaporated. The phenoxide was reacted with chloretone following the procedure described for *o*-cresol to give acid **17** (7.8g, 35%). Unreacted phenoxide salt was recovered as 2,3,5-trimethylphenol (6.2g, 46%). The acid **17** on recrystallization from ether-pentane gave colourless crystals (5.2g), m.p. 93°C; IR (KBr): 3000 - 2500 (OH), 1703 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.55 (6H, s, $C(CH_3)_2$), 2.08 (3H, s, 2-CH_3), 2.18 (6H, s, 3-CH_3, 5-CH_3), 6.51 (1H, s, 6-H), 6.67 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 12.2 (2-CH_3), 20.0 (3-CH_3), 21.0 (5-CH_3), 28.1 ($C(CH_3)_2$), 79.6 ($C(CH_3)_2$), 117.0 (C-6), 125.4 (C-4), 125.7 (C-2), 135.0 (C-5), 138.0 (C-3), 152.8 (C-1), 179.3 (COOH); MS: m/e (relative intensity), 222.1316 (10, $M_r(^{12}C_{13}{}^1H_{18}{}^{16}O_3)$, 222.1256), 177 (10), 137 (15), 136 (100),

135(18), 121(65), 91(60), 79(17), 77(30), 65(19), 55(19), 53(16), 51(17).

j. (2-Methylphenoxy)acetic acid[99] (**18**).

A solution of *o*-cresol (54g, 0.5mol) and sodium hydroxide (50g, 1.25 mol) in water (200 cm^3) was added to stirred chloroacetic acid (47.75g, 0.5 mol) in a three-necked 500 cm^3 flask, at 110°C, over 2 h. After the addition, the solution was cooled to 40°C and acidified with 1 M sulphuric acid. The precipitated product was filtered and washed with hexane to remove traces of *o*-cresol. The crude product (68g, 81%) was crystallized from aqueous alcohol to give the colourless crystalline acid **18**, m.p. 151°C (lit.[99] 151-152°C).

k. 2-Methyl-2-(2-methylphenoxy)propanoyl chloride (**61**)

Thionyl chloride (0.875cm^3, 0.012 mol) in anhydrous ether (25cm^3) was added from a dropping funnel to a stirred solution of acid **12** (1.94g, 0.01 mol) and anhydrous pyridine (0.8 cm^3, 0.01 mol) in anhydrous ether (75cm^3) contained in a 250cm^3 three-necked flask fitted with a reflux condenser attached to a mercury bubbler. An argon atmosphere was maintained in the assembly. The mixture was refluxed for 2.5 h, the precipitated pyridinium chloride filtered under argon and the ether distilled off from the filtrate to give the acid chloride **61**. The infra red spectrum of the product (film) showed the disappearance of the absorptions of the acid (3000 - 2500, 1710cm^{-1}) and the appearance of the

characteristic carbonyl absorption (1802, 1778cm^{-1}) due to the acid chloride, ^1H NMR (CCl_4, 90 MHz): δ 1.53 (6H, s, $C(CH_3)_2$), 2.21 (3H, s, 2-CH_3), 6.58-7.15 (4H, m, 3-, 4-, 5-, 6-H).

l. Acetic 2-methyl-2-(2-methylphenoxy)propanoic anhydride (35)

The preparation followed the method described for heptanoic anhydride.[100] A solution containing acid **12** (1.6g, 8.2 mmol), acetyl chloride (1.3cm^3, 18.1 mmol) and pyridine (1.3cm^3, 16.5 mmol) in benzene (10cm^3) was refluxed for 3 h. The pyridinium chloride which had precipitated was filtered under argon and the benzene was removed from the filtrate by distillation to give an oil (1.74g) which contained acid **12** (39%) and the desired mixed anhydride (61%) as analyzed by ^1H NMR. The mixed anhydride had ^1H NMR ($CDCl_3$, 90 MHz): δ 1.52 (6H, s, $C(CH_3)_2$), 2.15 (6H, brs, 2-CH_3, $OCOCH_3$), 6.65-7.15 (4H, m, 3-, 4-, 5-, 6-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 16.6 (2-CH_3), 20.7 ($OCOCH_3$), 24.8 ($C(CH_3)_2$), 79.2 ($C(CH_3)_2$), 116.3 (C-6), 122.2 (C-4), 126.6 (C-5), 129.3 (C-2), 131.1 (C-3), 153.4 (C-1), 169.9 ($OCOCH_3$), 177.7 ($OC(CH_3)_2COO$).

m. 3,3,6-Trimethyl-1,4-dioxaspriro[4,5]deca-6,9-diene-2,8-dione (**112**)

Methylhydroquinone (2.48g, 0.02 mol) was dissolved in deoxygenated acetone (100cm^3) under argon in a 250 cm^3 three-necked flask. Chloretone (1,1,1-trichloro-2-methylpropan-2-ol) (3.25g, 0.02 mol) in acetone (20 cm^3) was

added to the solution followed by powdered sodium hydroxide (4g, 0.1 mol) in three equal portions at two hour intervals. The reaction mixture was worked up as described for the preparation of **12** to give a mixture (3g) of 2-methyl-2-(4-hydroxy-2-methylphenoxy)propanoic acid **113** and 2-methyl-2-(4-hydroxy-3-methylphenoxy)propanoic acid. A solution of ceric ammonium nitrate (14.8g, 27 mmol) in water ($15cm^3$) was added dropwise, over 15 minutes, to the mixture of acids (2g, 9 mmol) in acetonitrile ($15cm^3$).[101] The reaction mixture was stirred at ambient temperature for 30 minutes. Dilution with water ($100cm^3$) and extraction with ether (3 x 50 cm^3) followed by drying and evaporation of the solvent gave a mixture (1.6g) of 3,3,6-trimethyl-1,4-dioxaspiro [4,5]deca-6,9-diene-2-8-dione, (**112**) 3,3,7-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-diene-2,8-dione (**116**) and methyl-*p*-benzoquinone.

Separation of the components of the mixture was achieved by HPLC using a silica column (Si-10, 0.8 x 50cm). The first fraction was a mixture (0.26g) of methyl-*p*-benzoquinone (21%) and (**116**) (79%), ^1H NMR ($CDCl_3$, 90 MHz): δ 1.60 (6H, s, 3-$(CH_3)_2$), 1.94 (3H, brs, 7-CH_3), 6.26 (1H,d, J=10.5Hz, 9-H), 6.45 (1H, m, 6-H), 6.63 (1H, dd, J=10.5Hz, 2.4 Hz, 10-H). The second fraction contained the required dienone **112** (0.14g), m.p. 78°C (ether-pentane); IR (KBr): 1790 (2-C=O), 1680 (8-C=O), 1170 (C-O)cm^{-1}; UV (methanol): 227nm (1178 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.60 (3H,

s, 3-CH_3), 1.62 (3H, s, 3-CH_3), 2.00 (3H, d, J=1.5 Hz, 6-CH_3), 6.17 (1H, m, J=2.1 Hz, 1.5 Hz, 7-H), 6.23 (1H, dd, J=10.1 Hz, 2.1 Hz, 9-H), 6.69 (1H, d, J=10.1 Hz, 10-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 16.5 (6-CH_3), 25.6 (3-CH_3), 26.6 (3-CH_3), 77.4 (C-3), 98.6 (C-5), 129.5 (C-7, C-9), 142.0 (C-10), 151.2 (C-6), 174.5 (C-2), 184.1 (C-8); MS (70ev): m/e (relative intensity), 208.080 (22, $M_r(^{12}C_{11}{}^1H_{12}{}^{16}O_4)$, 208.074), 180(55), 164(78), 149(20), 124(47), 123(48), 122(78), 94(87), 82(55), 78(49), 44(82), 43(100), 39(45). Further elution gave insoluble material (0.04g) which was not further investigated. (Total recovery 61%).

n. Methanol adducts of 4-methyl-4-nitrocyclohexa-2,5-dienone (124)

Sodium methoxide (0.8g) was added to a solution of dienone **124** (2.0g) in methanol (10cm^3) at 0°C. The mixture was stirred at 0°C for one hour and poured into a saturated solution of ammonium chloride. The resulting mixture was extracted with ether, the ethereal solution dried and the solvent evaporated to give a mixture of methoxycyclohexenones, dimethoxycyclohexanones, and 4-methyl-2-nitrophenol (2.2g). The major product *t*-5-methoxy-*r*-4-methyl-4-nitrocyclohex-2-en-1-one * (**126**) was isolated by crystallization from ether-pentane. The mother liquor was concentrated to give 1.37g of residue which was

* *r*-reference substituent, *t*-trans to *r*, *c*-*cis* to *r*

chromatographed on silica gel (40g) using pentane-ether as eluent. Fractions of 30 cm^3 were collected.

The first eight fractions consisted of 2-nitro-*p*-cresol (110mg). Fractions 9 - 12 consisted of *p*-cresol (60mg). Fractions 13 - 17 contained mainly *c*-5-methoxy-*r*-4-methyl-4-nitrocyclohex-2-en-1-one **125** (410 mg), m.p. 71°C (from ether-pentane); IR (KBr): 1685 (C=O), 1550, 1370 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.79 (3H, s, 4-CH_3), 2.47 (1H, dd, J=16.9 Hz, 10.8 Hz, 6-H), 2.95 (1H, dd, J=16.9 Hz, 4.7 Hz, 6-H), 3.41 (3H, s, OCH_3), 4.45 (1H, dd, J=10.8 Hz, 4.7 Hz, 5-H), 6.13 (1H, d, J=10.1 Hz, 2-H), 6.82 (1H, d, J=10.1 Hz, 3-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 18.4 (4-CH_3), 40.0 (C-6), 57.8 (OCH_3), 79.4 (C-5), 90.2 (C-4), 130.4 (C-2), 145.0 (C-3), 194.8 (C-1); MS: m/e (relative intensity); 185 (M^+,2) 139(35), 138 (34), 108(32), 107(55), 79(100), 77(38), 67(22), 59(24), 58(22), 55(25), 53(32), 43(22), 41(35). *Analysis* calculated for $C_8H_{11}NO_4$; C 51.89%, H 5.99%, N 7.57%; found: C 51.59%, H 5.77%, N 7.40%. Fraction 18 consisted of *r*-3,*c*-5-dimethoxy-*c*-4-methyl-*t*-4-nitrocyclohexanone **127** and *r*-3,*t*-5-dimethoxy-*c*-4-methyl-*t*-4-nitrocyclohexanone **128** (110 mg.)

Fractions 19 and 20 contained **128** (310 mg), m.p. 107°C (from ether-pentane); IR (KBr): 1725 (C=O), 1540, 1360 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.76 (3H, s, 4-CH_3), 2.31 (1H, ddd, J=14.9 Hz, 11.0 Hz, 0.7 Hz, *t*-6-H), 2.60 (1H, ddd, J=15.8 Hz, 3.1 Hz, 0.7 Hz, *t*-2-H), 2.78 (1H, ddd,

J=15.8 Hz, 3.5 Hz, 2.3 Hz, C-2-H), 2.96 (1H, ddd, J=14.9 Hz, 6.0 Hz, 2.3 Hz, C-6-H), 3.25 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 4.01 (1H, t, J=3.5 Hz, 3.1 Hz, 3-H), 4.54 (1H, dd, J=11.0 Hz, 6.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 16.9 (4-CH_3), 40.6, 43.1 (C-2, C-6), 57.6, 57.8 (2-OCH_3, 5-OCH_3), 75.5, 82.3 (C-3, C-5), 92.1 (C-4), 203.3 (C-1); MS: m/e (relative intensity), 186 (M-31,2), 171(6), 170(31), 139(54), 138(37), 113(19), 97(22), 85(100), 79(24), 58(48), 55(61), 53(28), 43(31), 41(39), 39(22). *Analysis* calculated for $C_9H_{15}NO_5$: C 49.75%, H 6.96%, N 6.45%; found: C 49.87%, H 6.80%, N 6.46%.

Fractions 21 - 23 consisted of *t*-5-methoxy-*r*-4-methyl-*c*-4-nitrocyclohex-2-en-1-one, **126** (175 mg), m.p. 114-115°C (from ether-pentane); IR (KBr): 1675 (C=0), 1550, 1355 (NO_2)cm^{-1}; UV (methanol): 211 nm (135 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 90 MHz): δ 1.81 (3H, s, 4-CH_3), 2.62 (1H, dd, J=17.5 Hz, 3 Hz, 6-H), 2.97 (1H, dd, J=17.5 Hz, 4 Hz, 6-H), 3.31 (3H, s, OCH_3), 4.20 (1H, m, J=4 Hz, 3 Hz, 2 Hz, 5-H), 6.13 (1H, d, J=10.5 Hz, 2-H), 7.22 (1H, dd, J=10.5 Hz, 2 Hz, 3-H); ^{13}C NMR ($CDCl_3$, 15.1 MHz): δ_C 24.3 (4-CH_3), 38.1 (C-6), 57.8 OCH_3), 81.4 (C-5), 88 (C-4), 129.7 (C-2), 142.5 (C-3), 194.0 (C-1). *Analysis* calculated for $C_8H_{11}NO_4$: C 51.87%, H 5.99%, N 7.57%; found: C 51.83%, H 6.09%, N 7.15%.

Fractions 24 - 26 contained *r*-3,*c*-5-dimethoxy-*t*-4-methyl-*c*-4-nitrocyclohexanone, **129** (60 mg), m.p. 97°C (from ether-pentane); IR (KBr): 1725 (C=0), 1545, 1360 (NO_2)cm^{-1};

^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.85 (3H, s, 4-CH_3), 2.84 (2H, dd, J=14.7 Hz, 5.6 Hz, *c*-2-H, *c*-6-H), 3.08 (2H, dd, J=14.7 Hz, 10.7 Hz, *t*-2-H, *t*-6-H), 3.40 (6H, s, 3-OCH_3, 5-OCH_3), 3.56 (2H, dd, J=10.7 Hz, 5.6 Hz, 3-H, 5-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz); δ_C 21.3 (4-CH_3), 42.4 (C-2, C-6), 58.3 (3-OCH_3, 5-OCH_3), 79.6 (C-3, C-5), 90.5 (C-4), 204.3 (C-1). *Analysis* calculated for $C_9H_{15}NO_5$: C 49.75%, H 6.96%, N 6.45%; found: C 49.88%, H 6.87%, N 6.30%

Fraction 18 was crystallized from methanol when the adduct **128** crystallized. Concentration of the mother liquor and recrystallization from ether-pentane afforded adduct **127** as colourless cyrstals (24 mg), m.p. 125°C; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 1.70 (3H, s, 4-CH_3), 2.34 (2H, dd, J=15.2 Hz, 12.5 Hz, *c*-2-H, *c*-6-H), 2.88 (2H, dd, J=15.2 Hz, 4.7 Hz, *t*-2-H, *t*-6-H), 3.26 (6H, s, 3-OCH_3, 5-OCH_3), 4.06 (2H, dd, J=12.5 Hz, 4.7 Hz, 3-H, 5-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 9.3 (4-CH_3), 43.3 (C-2, C-6), 58.1 (3-OCH_3, 5-OCH_3), 78.8 (C-3, C-5), 95.0 (C-4), 201.9 (C-1). *Analysis* calculated for $C_9H_{15}NO_5$: C 49.75%, H 6.96%, N 6.45%; found: C 49.84%, H 6.96%, N 6.27%.

o. Nitroethylene

Phthalic anhydride (11.1 g), purified by dissolving in chloroform, filtering off the insoluble phthalic acid and evaporating the solvent, was heated in a distillation flask with nitroethanol (4.6 g).[102] The mixture melted at 135 - 145°C. The fraction distilling up to 180°C was collected to

give nitroethylene (2.2 g, 61%), ^{1}H NMR ($CDCl_3$, 90 MHz): δ5.93 (1H, dd, J=7 Hz, 2 Hz, *t*-2-H), 6.68 (1H, dd, J=15 Hz, 2 Hz, *c*-2-H), 7.13 (1H, dd, J=15 Hz, 7 Hz, 1-H).

2.4 *Isolation of cyclohexadiene adducts*

The appropriate amount of nitric acid and acetic anhydride were cooled separately to -78°C. Acetic anhydride was poured into stirred nitric acid. The resulting mixture was warmed to 0°C and after five minutes cooled to the required temperature and used for the nitration of aromatic substrates. In the experiments below only the quantities of nitric acid and acetic anhydride used and the final temperature after following the above procedure are given.

i) Nitration of 2-methyl-2-(2-methylphenoxy)propanoic acid (12)

a) A solution of 12 (29.1 g, 0.15 mol) in acetic anhydride (71cm^3, 0.75 mol), was added from a dropping funnel, over 30 minutes, to a stirred nitrating mixture containing nitric acid (18.9 g, 0.3 mol) and acetic anhydride (71cm^3, 0.75 mol) at -20°C. The reaction mixture was stirred at -20°C for a further 30 minutes and then cooled to -78°C. The NMR spectrum of an aliquot withdrawn into a cold NMR tube showed completion of reaction, the mixture containing 80% aromatic compounds and 20% dienes. The reaction mixture was diluted with cold ether (100 cm^3) and added to stirred ether (1.5 dm^3) at -78°C in a three-

necked flask equipped with an ammonia condenser. Ammonia was condensed into this solution until the temperature which had risen to -51°C, dropped to -60°C (pH 10). Excess ammonia was removed by connecting the flask to a water aspirator and letting the mixture warm to -5°C (pH neutral). The slurry obtained was washed with cold distilled water (3 x 500 cm^3), the ethereal solution dried and the ether evaporated on a rotavapor at 15°C. When the solution was concentrated, the (*E*)- isomer of 3,3,10-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one, **19** precipitated (21 g), m.p. 84°C (from ether-pentane); IR (KBr): 1807 (C=O), 1539,1345 (NO_2), 1180 (C-O)cm^{-1}; UV (methanol): 261 nm (230 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.53 (3H, s, 3-CH_3), 1.58 (3H, s, 3-CH_3), 1.84 (3H, s, 10-CH_3), 5.78 (1H, dt, J=9.6 Hz, 0.9 Hz, 0.8 Hz, 6-H), 6.08 (1H, dd, J=9.9 Hz, 5.4 Hz, 0.9 Hz, 8-H), 6.18 (1H, ddd, J=9.6 Hz, 5.4 Hz, 1.3 Hz 7-H), 6.28 (1H, ddd, J=9.9 Hz, 1.3 Hz, 0.8 Hz, 9-H); ^{13}C NMR ($CDCl_3$, 15.1 MHz): δ_C 20.0 (10-CH_3), 25.0 (3-CH_3), 26.2 (3-CH_3), 77.9 (C-3), 91.7 (C-10), 104.8 (C-8), 122.5 (C-6), 126.9 (C-8), 127.5 (C-7), 129.4 (C-9), 173.8 (C-2). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.21%, H 5.48%, N 5.86%; found: C 55.22%, H 5.34%, N 5.84%.

The mother liquor was evaporated to give a mixture (6g) of **19** and its diastereomer **20** in the ratio 38:62. This mixture could not be separated by fractional crystallizations, chromatography at -40°C on silica or

alumina. The aqueous washings were acidified with 1:1 (v/v) hydrochloric acid and extracted with ether. The ether extract was washed with brine and distilled water, dried and the solvent evaporated to give 2-methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid **14** (10.2 g).

Diene **19** (1.25 g) was dissolved in 10% (v/v) trifluoroacetic acid/chloroform (15 cm^3) at 0°C. The solution was stirred at 0°C for one hour and poured into cold saturated bicarbonate solution. Extraction with ether (3 x 25 cm^3), drying and evaporation of ether gave a mixture of isomers **19** (20%) and **20** (80%). Crystallization from ether-pentane gave a mixture containing 85% of **20**. This mixture (1.1 g) was separated by HPLC on a Varian 5000 LC using a modified phase CN-10 (0.8 x 50 cm) column and hexane-methylene chloride (containing 0.5% isopropanol) as eluent. The first fraction contained 95% of isomer **20**. Recrystallization from methylene chloride-hexane gave pure **20** (520 mg), m.p. 87°C; IR (KBr): 1802 (C=O), 1550, 1370 (NO_2)cm^{-1}; UV (methanol): 257 nm ($\varepsilon 396\ m^2mol^{-1}$); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.35(3H, s, 3-CH_3), 1.44 (3H, s, 3-CH_3), 1.85 (3H, s, 10-CH_3), 5.78 (1H, brd, J=9.7 Hz, 0.9 Hz, 0.7 Hz, 6-H), 6.06 (1H, ddd, J=10 Hz, 5.4 Hz, 0.9 Hz, 8-H), 6.16 (1H, ddd, J=9.7 Hz, 5.4 Hz, 1.2 Hz, 7-H), 6.37 (1H, dm, J=10 Hz, 1.2 Hz, 0.7 Hz, 9-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 20.6 (10-CH_3), 23.8 (3-CH_3), 26.7 (3-CH_3), 77.9 (C-3), 92.0 (C-10), 105.8 (C-5), 121.9 (C-6), 126.3 (C-8), 126.9 (C-7), 128.3 (C-9), 173.8

(C-2). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.2%, H 5.48%, N 5.86%; found: C 55.38 %, H 5.32 %, N 5.75 %.

b) A solution of **12** (0.39 g, 2mmol) in acetic anhydride (1 cm^3) was added dropwise to a nitrating mixture (nitric acid (0.25 g), acetic anhydride (0.9 cm^3)) at -20°C over 10 minutes with stirring. The mixture was stirred for 30 minutes at -20°C. The NMR spectrum of an aliquot withdrawn and placed in a cold NMR tube showed acid **14** (25%) and the diene **19** (75%). The NMR sample was warmed to 0°C and trifluoroacetic acid (0.06 cm^3) was added to it. After 1.5 h the NMR spectrum of the aliquot showed **19** and **20** (78%) and 3,3,10-trimethyl-8,10-dinitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one **30** (22%).

c) A solution of **12** (4.86 g, 0.025 mol) in acetic anhydride (10.6 cm^3) and trifluoroacetic anhydride (3.5 cm^3, 0.025 mol) was added dropwise to a nitrating mixture (nitric acid (3.15 g), acetic anhydride (13 cm^3)) at -20°C, over 15 minutes, with stirring. The mixture was stirred at -20°C for 30 minutes and then at 0°C for one hour. After work-up with liquid ammonia as described earlier, **19** (3.65 g.) was obtained. The aqueous washings, after acidification and extraction with ether, gave a compound (1.15 g) which showed ^1H NMR ($CDCl_3$, 90 MHz): δ 2.67 (3H, s), 8.20 (1H, d, J=10 Hz), 8.54 (1H, dd, J=10 Hz, 2 Hz), 9.44 (1H, d, J=2 Hz). This compound could not be obtained on repeating the experiment and was not identified.

In an experiment to check whether the unknown compound above was 6-methyl-4,6-dinitrocyclohexa-2,4-dienone (47), 2-methyl-4-nitrophenol (9) (0.153 g) in acetic anhydride (0.47 cm^3) was cooled to -60°C and a nitrating mixture (nitric acid (0.25 g), acetic anhydride (0.47 cm^3) and trifluoroacetic anhydride (0.15 cm^3)) at -78°C was added to it. The reaction mixture was stirred at -60°C for 30 min. An aliquot was withdrawn into a cold NMR tube and its NMR spectrum recorded at -60°C. The reaction mixture contained 2-methyl-4-nitrophenol (59%), 2-methyl-4,6-dinitrophenol (48) (12%) and 6-methyl-4,6-dinitrocyclohexa-2,4-dienone (47) (29%), ^1H NMR (Ac_2O lock, 90 MHz, -60°C): δ 6.34 (1H, d, J=10.5 Hz, 2-H), 7.81 (1H, d, J=2 Hz, 5-H), 7.87 (1H, dd, J=10.5 Hz, 2 Hz, 3-H). On increasing the temperature to -30°C, the intensity of the dienone peaks decreased while that of 2-methyl-4,6-dinitrophenol peaks increased. No other compounds were detected in the reaction mixture.

Another experiment was performed to determine if the unknown product above originated from the 4-nitro acid 14. A solution of 14 (10.48 g) in a mixture of trifluoracetic anhydride (4 cm^3) and trifluoroacetic acid (2.4 cm^3) was maintained at ambient temperature and the reaction was followed by NMR. After 21 days >95% of 14 had reacted to give a single product. The mixture was poured into water, saturated with sodium chloride and extracted with ether. The ether extract on drying and evaporation yielded 6-

methyl-4-nitro-6-((E)-1',1',1'-trifluoro-2'-oxopent-3'-en-4'-yl)cyclohexa-2,4-dienone (46) (0.46 g), m.p. 85°C (from ether-pentane); IR (KBr): 1705 ($COCF_3$), 1600 (ring C=O), 1570, 1345 (NO_2)cm^{-1}; UV (CH_2Cl_2): 303 nm (ε 403 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz): δ 2.29 (3H, s, 4-CH_3), 2.65 (3H, s, 5'-CH_3), 5.38 (1H, s, 3'-H), 7.16 (1H, d, J= 8.9 Hz, 2-H), 8.18 (1H, dd, J= 8.9 Hz, 2.6 Hz, 3-H), 8.24 (1H, d, J= 2.6 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 62.9 M): δ_C 15.9 (6-CH_3), 19.8 (5'-CH_3), 96.6 (C-3'), 116.4 (q, $^1J_{CF}$=292 Hz, C-1'), 122.3 (C-2), 123.5 (C-3), 127.5 (C-5), 132.2 (C-6), 146.4 (C-4), 155.6 (C-4'), 177.9 (C-1), 179.4 (q, $^2J_{CF}$= 33 Hz, C-2'); MS (70 ev): m/e (relative intensity), 289.0567 (17, M_r($^{12}C_{12}{}^1H_{10}{}^{14}N{}^{16}O_4{}^{19}F_3$)289.0564), 272(17), 220(76), 174(100), 146(15), 123(19), 106 (13), 89(31), 78(17), 77(26), 69(39), 67(27), 63(16), 57(18), 55(19), 43(61), 39(41). *Analysis* calculated for $C_{12}H_{10}NO_4F_3$: C 49.82%, H 3.49%, N 4.84%, F 19.71%; found: C 49.63%, H 3.35%, N 4.76%, F 19.47%.

d. A solution of 12 (1.94 g, 0.01 mol) in acetic anhydride (4.4 cm^3) and trifluoroacetic anhydride (1.4 cm^3, 0.01 mol) was added dropwise to a nitrating mixture (nitric acid (1.26 g) acetic anhydride (5 cm^3) at -20°C over 10 minutes with stirring. The mixture was stirred at -20°C for 30 minutes. The NMR spectrum of the reaction mixture showed the presence of acid 14 (17%), diene 19 (35%) and a mixed anyhdride 36 of 2-(3-acetoxy-6-methyl-6-nitrocyclohexa-2,5-dienoxy)-2-methylpropanoic acid (48%). The reaction mixture

was warmed to 0°C and stirred for one hour. All the mixed anhydride **36** was converted to diene **19** (83%) and all of acid **14** was further nitrated to give the dinitrodiene **30** (17%). The reaction mixture was poured into cold saturated sodium bicarbonate and extracted with ether. The ether extract on drying and evaporation of the solvent showed the same amounts of dienes **19** (83%) and **30** (17%) as observed in the reaction mixture.

e) Nitric acid (0.01 cm^3) was injected into a solution of **12** (19 mg, 0.1 mmol) in trifluoroacetic acid (0.1 cm^3) and chloroform-d (0.2 cm^3) at 0°C. The NMR spectrum of the solution after 10 minutes at 0°C showed mononitration and dinitration products, **14** (57%) and **30** (43%) respectively. No diene **19** was observed.

ii) Nitration of 2-methyl-2-([4,6-$^2H_2$]-2-methylphenoxy)propanoic acid (**21**).

A solution of crude **21** (1.2 g. containing 82% **21**) in acetic anhydride (2.5 cm^3) was added dropwise, over 10 minutes, to a nitrating mixture (nitric acid (0.63 g), acetic anhydride (2.2 cm^3)) at -20°C with stirring. The reaction mixture was stirred for additional 30 minutes at -20°C and then cooled to -78°C. Liquid ammonia work-up as described earlier gave (E)-[6,8-$^2H_2$]-3,3,10-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one **23** (0.56 g) from the ether layer. Only one disastereomer could be isolated. It had m.p. 87°C (from ether-pentane): IR (KBr):

1804 (C=O), 1535,1350 (NO_2), 1176 (C-O)cm^{-1}; UV (methanol): 260 nm (ε 383 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 90 MHz): δ 1.55 (3H, s, 3-CH_3), 1.58 (3H, s, 3-CH_3), 1.83 (3H, s, 10-CH_3), 6.17 (1H, brs, 7-H), 6.28 (1H, brs, 9-H); ^{13}C NMR ($CDCl_3$, 15.1 MHz): δ_C 19.9 (10-CH_3), 25.1 (3-CH_3), 26.6 (3-CH_3), 78.0 (C-3), 91.8 (C-10), 105.0 (C-5), 122.4 (t, C-6), 126.2 (t, C-8), 127.6 (C-7), 128.8 (C-9), 173.6 (C-2).

The aqueous washings on acidification and extraction with ether gave 2-methyl-2-([6-$^2H_1$]-2-methyl-4-nitrophenoxy)propanoic acid (0.21 g) which could not be crystallized. It had ^1H NMR ($CDCl_3$, 90 MHz): δ 1.71 (6H, s, $C(CH_3)_2$), 2.28 (3H, s, 2-CH_3), 8.03 (2H, m, 3-H, 5-H).

iii) Nitration of 2-methyl-2-(2-methylphenoxy)propanoyl chloride **61**

2-methyl-2-(2-methylphenoxy)propanoyl chloride (571 mg, 2.5 mmol) in acetonitrile (10 cm^3) was added dropwise, over 15 minutes, to a stirred solution of silver nitrate (680 mg, 4 mmol) in acetonitrile (15 cm^3) at -15°C, contained in a 50 cm^3 flask covered with aluminium foil. The mixture was stirred for another one hour at -15°C, cooled to -40°C and filtered through a cold (-50°C) jacketed funnel under argon. Acetonitrile was removed from the filtrate under vacuum at -20°C, the residue dissolved in carbon tetrachloride and unreacted silver nitrate was filtered off under argon. The product mixture when analyzed by ^1H NMR showed diene **19** (16%), the 6-nitro-acid **4** (8%), the 4-nitro-acid **14** (8%) and

acid **12** (76%).

Control experiments showed that diene **19** (0.1 mmol) did not react with either silver nitrate (0.2 mmol) or 2-methyl-2-(2-methylphenoxy)propanoyl chloride chloride (0.2 mmol) to give any of the aromatic products viz. **12**, **15** and **14** under the reaction conditions.

iv) Nitration of acetic 2-methyl-2-(2-methylphenoxy)propanoic anhydride (35)

A solution of the mixture (100 mg) containing acetic 2-methyl-2-(2-methylphenoxy)propanoic anhydride (35) (61%) in acetic anhydride (0.2 cm^3) was added dropwise, over 10 minutes, to a nitrating mixture (nitric acid (63 mg), acetic anhydride (0.3 cm^3)) at -40°C. The reaction mixture was stirred for 30 minutes at -40°C. An aliquot was withdrawn into a cold NMR tube and the NMR spectrum recorded at 0°C. The reaction mixture analyzed for acid **14** (20%), a mixture of diastereomers of adduct **36** (75%, ^1H NMR (acetic anhydride lock, 90 MHz, 0°C): 5.00 (1H, t, 3-H), 5.80 (1H, t, 2H), 5.95 (1H, dd, 5-H), 6.10 (1H, dd, 6-H) and an unidentified product (5%). One half of the reaction mixture was worked up with aqueous sodium bicarbonate, as described earlier, to give **19** as the only non-aromatic product.

v) Nitration of 2-methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid (14)

a. A solution of acid **14** (2.39 g, 0.01 mol) in acetic anhydride (9.9 cm^3) and trifluoroacetic anhydride (7.2 cm^3,

0.05 mol) was added dropwise, over 20 minutes, to a nitrating mixture (nitric acid (3.15 g), acetic anhydride (9 cm^3)) at -30°C with stirring. The reaction mixture was stirred for 30 minutes at -20°C. At this stage, the NMR spectrum of an aliquot showed that the reaction was complete and that a mixture of 3,3,10-trimethyl-8,10-dinitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one, **30** (41%) and a mixed anhydride **44** of 2-(3-acetoxy-6-methyl-4,6-dinitrocyclohexa-1,4-dienoxy)-2-methylpropanoic acid (59%) was obtained. The reaction mixture was warmed to 0°C and stirred for one hour when the mixed anhydride **44** was completely converted to **30**. Work-up with aqueous sodium bicarbonate as described earlier gave the pure diene **30** (1.26 g, 44% isolated yield). Recrystallization from methylene chloride-pentane gave pale yellow crystals (1.0 g), m.p. 141°C; IR (KBr): 1800 (C=O), 1550,1540,1345 (NO_2), 1175 (C-O)cm^{-1}; UV (methanol): 286 nm (658 $m^2 mol^{-1}$); ^1H NMR ($CDCl_3$, 90 MHz); δ 1.58 (3H, s, 3-CH_3), 1.61 (3H, s, 3-CH_3), 1.94 (3H, s, 10-CH_3), 6.02 (1H, d, J=10.5 Hz, 6-H), 6.78 (1H, dd, J= 10.5 Hz, 1.5 Hz, 7-H), 7.57 (1H, d, J= 1.5 Hz, 9-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 19.2 (10-CH_3), 24.9 (3-CH_3), 26.4 (3-CH_3), 78.1 (C-3), 91.1 (C-10), 103.4 (C-5), 121.3 (C-6), 129.6 (C-7, C-9), 143.9 (C-8), 172.3. (C-2). *Analysis* calculated for $C_{11}H_{12}N_2O_7$: C 46.48%, H 4.26%, N 9.86%; found: C 46.23%, H 4.31%, N 9.65%.

b) In another experiment, a solution of **14** (0.48 g, 2

mmol) in acetic anhydride (5 cm^3) and trifluoroacetic anhydride (1.4 cm^3) was added dropwise, over 10 minutes, to a nitrating mixture (nitric acid (0.63 g), acetic anhydride (4.4 cm^3)) at -20°C with stirring. The reaction mixture was warmed to 0°C and stirred for one hour. Quantitative *ipso* nitration to give **30** was observed.

vi) Nitration of 2-methyl-2-(4-methylphenoxy)propanoic acid (1)

a) A solution of **1** (19.4 g, 0.1 mol) in acetic anhydride (24 cm^3) was added dropwise, over 20 minutes, to a nitrating mixture (nitric acid (12.6 g), acetic anhydride (70 cm^3)) at -40°C with stirring. The reaction mixture was stirred for another 30 minutes at -40°C. The NMR spectrum of an aliquot withdrawn into a cold NMR tube indicated that the reaction was complete. The reaction mixture was added to a solution of sodium bicarbonate (231 g) in water (3.4 dm^3) at 0°C and the resulting mixture stirred for 1.5 h. This solution was extracted with ether. The ethereal solution was washed with water, dried and the solvent evaporated to give 3,3,8-trimethyl-8-nitro-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (12.9 g, 54%), ^1H NMR ($CDCl_3$, 90 MHz): δ 1.54 (6H, s, 3-(CH_3)$_2$), 1.79 (3H, s, 8-CH_3), 6.00 (2H, d, J= 10 Hz, 6-H, 10-H), 6.48 (2H, d, J= 10 Hz, 7-H, 9-H); ^{13}C NMR ($CDCl_3$, 15.1 MHz): δ_C 26.3 (3-CH_3, 3-CH_3, 7-CH_3), 77.5 (C-3), 82.3 (C-8); 97.5 (C-5), 129.1 (C-6, C-10), 131.9 (C-7, C-9), 174.8 (C-2).

The ^{1}H and ^{13}C NMR spectra suggested that a single isomer was present, but the compound did not give a sharp melting point. Addition of the shift reagent tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-d_6-3,5,octanedionato) europium ($Eu(fod)_3$) resolved the ^{1}H NMR spectrum into that of the two diastereomers **52** and **53**. The relative amounts of the diastereomers, **52** (62%) and **53** (38%) were determined by HPLC analysis of the mixture.

The sodium bicarbonate solution above was acidified and extracted with ether. The ether extraction drying and evaporation gave 2-methyl-2-(4-methyl-2-nitrophenoxy)propanoic acid **54** (10.9 g, 46%), m.p. 103-104°C (from ether-pentane); IR (KBr): 1725,1260(COOH), 1530,1350(NO_2)cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 1.65 (6H, s, $C(CH_3)_2$), 2.36 (3H, s, 4-CH_3), 7.05 (1H, d, J= 8.5 Hz, 6-H), 7.31 (1H, dd, J=8.5 Hz, 2 Hz, 5-H), 7.64 (1H, d, J=2 Hz, 3-H); ^{13}C NMR ($CDCl_3$, 15.1 MHz): δ_C 20.4 (4-CH_3), 24.8($C(CH_3)_2$), 81.7 ($C(CH_3)_2$), 121.6 (C-6), 125.5 (C-3), 133.4 (C-4), 137.1 (C-3), 143.1 (C-2), 145.9 (C-1), 179.2 (COOH). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.23%, H 5.48%, N 5.85%; found: C 55.42%, H 5.68%, N 5.80%.

b) Separation of diene diastereomers **52** and **53**

Trial analyses were performed on a Varian 5000 HPLC using methylene chloride/hexane as eluent and on the Waters LC/System 500 using ether-pentane as eluent. The best results were obtained on the Waters 500 instrument using a

1:1 (v/v) mixture of ether-pentane cooled to 0°C. The peaks due to the different diastereomers were separated to the baseline on twice recycling the effluent from the column. Preparative separation was carried out by injecting the diene mixture (200 mg) in ether (10 cm^3) and using a flow rate of 150 cm^3/min. In all 10.65 g of the mixture was injected giving diene **52** (4.85 g) and diene **53** (3.76 g) for a total recovery of 81%.

Diene **52** which was eluted first had m.p. 117°C (ether-pentane); IR (KBr): 1798 (C=O), 1545, 1380 (NO_2)cm^{-1}; UV (methanol): 281 nm (ε 8 m^2mol^{-1}), 220 nm (ε 102 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 90 MHz): δ 1.53 (6H, s, 3-$(CH_3)_2$), 1.77 (3H, s, 8-CH_3), 6.00 (2H, d, J= 10.8 Hz, 6-H, 10-H), 6.44 (2H, d, J= 10.8 Hz, 7-H, 9-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 26.2 (3-$(CH_3)_2$), 26.4 (8-CH_3), 77.4 (C-3), 82.2 (C-8), 97.5 (C-5,) 129.1 (C-6, C-10), 131.9 (C-7, C-9), 174.7 (C=2). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.21%, H 5.48%, N 5.86%; found: C 55.28%, H 5.70, N 5.99%.

Diene **53** which was eluted after **52** had m.p. 108°C (from methylene chloride-pentane); IR (KBr): 1797 (C=O), 1548, 1381 (NO_2)cm^{-1}; UV (methanol) 279 nm (ε 12m^2mol^{-1}), 221 nm (E105 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 90 MHz): 1.53 (6H, s, 3-$(CH_3)_2$), 1.79 (3H, s, 8-CH_3), 6.01 (2H, d, J= 10.8 Hz, 6-H, 10-H), 6.47 (2H, d, J= 10.8 Hz, 7-H, 9-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $_C$ 26.5 (3-$(CH_3)_2$, 8-CH_3), 77.2 (C-3), 82.3 (C-8), 97.3 (C-5), 129.1 (C-6, C-10), 131.8 (C-7, C-9), 174.6

(C-2). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.21%, H 5.48%, N 5.86%; found: C 55.20%, H 5.81%, N 5.87%.

vii) Nitration of 2-methyl-2-(2,3,5-trimethylphenoxy)propanoic acid (17)

a) A solution of 17 (6.66 g, 0.03 mol) in acetic anhydride (14 cm^3) was added dropwise, over 15 minutes, to a nitrating mixture (nitric acid (3.78 g), acetic anhydride (14 cm^3)) at -40°C, with stirring. The reaction mixture was stirred for a further 30 minutes at -40°C and then cooled to -78°C. Liquid ammonia work-up as described earlier gave 3,3,7,9,10-pentamethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one, 27, m.p. 98°C (from ether-pentane); IR (KBr): 1800(C=O), 1535,1368(NO_2)cm^{-1}; UV (methanol): 266nm (ε 681 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.41 (3H, s, 3-CH_3), 1.52 (3H, s, 3-CH_3), 1.75 (3H, s, 10-CH_3), 1.84 (6H, s, 7-CH_3, 9-CH_3), 5.49 (1H, brs, 6-H), 5.77 (1H, brs, 8-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 17.4 (10-CH_3), 18.2 (9-CH_3), 21.1 (7-CH_3), 25.4 (3-CH_3), 26.2 (3-CH_3), 77.8 (C-3), 95.0 (C-10), 106.9 (C-5), 119.8 (C-6), 126.8 (C-8), 135.2 (C-7), 137.8 (C-9), 173.6 (C-2); MS (methane CI): m/e 268 (M+1); (EI, 70ev): m/e (relative intensity), 237 (M-30,8), 177 (14), 151(19), 136(18), 135(100), 123(57), 91(62), 43(52), 41(48), 39(43). *Analysis* calculated for $C_{13}H_{15}NO_5$: C 58.42%, H 6.41%, N 5.24%; found: C 58.51%, H 6.37%, N 5.22%. Only one isomer of the diene was obtained. No aromatic compounds were obtained from the aqueous washings.

b) Trifluoroacetic acid (0.1 mmol) was added to a solution of **17** (0.1 mmol) in chloroform-d (0.3 cm^3) at 0°C. Nitric acid (4 mm^3, 0.1 mmol) was injected into this solution and the NMR spectrum of the solution at 0°C indicated that all of **17** had reacted and that an aromatic derivative had been formed. No other peaks were observed. On work-up with aqueous sodium bicarbonate, 2-methyl-2-(2,3,5-trimethyl-4-nitrophenoxy)propanoic acid **28** was isolated from the aqueous layer (13 mg, 63%), ^1H NMR ($CDCl_3$, 90.0 MHz): δ 1.53 (6H, s, $C(CH_3)_2$), 2.15 (6H, s, 3-$CH_3$5-CH_3), 2.20(3H, s, 2-CH_3), 6.54(1H, s, 6-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 12.8 (2-CH_3), 15.0 (3-CH_3), 17.6 (5-CH_3), 25.3 ($C(CH_3)_2$), 79.9 ($C(CH_3)_2$), 117.1 (C-6), 127.2 (C-2), 127.9 (C-5), 130.0 (C-3), 147.9 (C-4), 153.7 (C-1), 177.8 (COOH).

viii) Nitration of (2-methylphenoxy)acetic acid (**18**).

a) A solution of **18** (8 g, 0.047 mol) in acetic anhydride (175 cm^3) was added dropwise, over one hour, to a nitrating mixture (nitric acid (12.6 g), acetic anhydride (25 cm^3)) at -20°C with stirring. The resulting mixture was stirred for another 30 minutes at -20°C and cooled to -78°C. The NMR spectrum of an aliquot of the reaction mixture showed that all of **12** had reacted to give aromatic derivatives (20%) and a mixture of dienes (80%). Liquid annomia work-up as described earlier afforded a mixture of dienes (6.8 g). The crude product contained a small amount of (2-methyl-4-nitrophenoxy)acetic acid **24** or its derivative. It was

dissolved in ether and stirred with saturated sodium bicarbonate solution for one and a half hours at 0°C. Separation of the layers followed by drying and evaporation of the solvent gave a mixture of dienes (5 g) free from aromatic compounds. The dienes were separated by fractional crystallization from ether-pentane at -20°C. The first product to crystallize was isomer A of 3-carbamoylmethoxy-4-methyl-4-nitrocyclohexa-2,5-dienyl acetate **41A** (300 mg), m.p. 106°C; IR (KBr): 3450 (NH), 1722 (C=O, acetate), 1696 (C=O, amide), 1550,1342 (NO_2)cm^{-1}; UV (methanol): No λ_{max} above 200 nm; ^1H NMR ($CDCl_3$, 250 MHz, -10°C); δ 1.89 (3H, s, 4-CH_3), 2.14 (3H, s, $OCOCH_3$), 4.38 (1H, d, J= 15.4 Hz, OCH_AH_B), 4.42 (1H, d, J= 15.4 Hz, OCH_AH_B), 5.22 (1H, dd, J= 4.0 Hz, 1.1 Hz, 2-H), 5.88 (1H, ddd, J= 4.0 Hz, 3.3 Hz, 1 Hz, 1-H), 6.02 (1H, dd, J= 9.9 Hz, 1.0 Hz, 5-H), 6.16 (1H, ddd, J= 9.9 Hz, 3.3 Hz, 1.1 Hz, 6-H), 6.60 (1H, s, NH), 7.06 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 21.0 (4-CH_3), 23.5 ($OCOCH_3$), 65.4 (C-1), 66.2 (6-OCH_2), 85.9 (C-4), 98.9 (C-2), 128.2, 128.4 (C-5, C-6), 151.5 (C-3), 169.7, 170.5 ($OCOCH_3$, $CONH_2$). *Analysis* calculated for $C_{11}H_{14}N_2O_6$: C 48.87%, H 5.22%, N 10.37%; found: C 48.89%, H 5.42%, N 10.21%.

Adduct **41B** (100 mg) crystallized out after **41A**. It had m.p. 104°C; IR (KBr): 3500 (NH), 1734 (C=O, acetate), 1689 (C=O, amide), 1546,1360 (NO_2)cm^{-1}; UV (methanol): No λ_{max} above 200 nm; ^1H NMR ($CDCl_3$, 250 MHz, -10°C): δ

1.94(3H, s, 4-CH_3), 2.12 (3H, s, $OCOCH_3$), 4.38 (1H, d, J= 15.6Hz, OCH_AH_B), 4.45 (1H, d, J= 15.6 Hz, OCH_AH_B), 5.25 (1H, dd, J= 3.8 Hz, 1.1 Hz, 2-H), 5.98 (1H, ddd, J= 3.8 Hz, 3.3 Hz, 1.2 Hz, 1-H), 6.04 (1H, dd, J=9.8 Hz, 1.2 Hz, 5-H), 6.17 (1H, ddd, J= 9.8 Hz, 3.3 Hz, 1.1 Hz, 6-H), 6.62 (1H, s, NH), 7.05 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 20.9 (4-CH_3), 23.1 ($OCOCH_3$), 65.9 (C-1), 66.2 (OCH_2), 86.2. (C-4), 99.1 (C-2), 128.6, 129.0 (C-5, C-6), 151.4 (C-3), 169.8 , 170.1 ($OCOCH_3$, $CONH_2$). *Analysis* calculated for $C_{11}H_{14}N_2O_6$: C 48.87%, H 5.22%, N 10.37%; found: C 48.65%, H 5.10%, N 10.23%.

A mixture of adducts **41A** and **41B** (1.6 g) crystallized next followed by one isomer of 10-methyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one, **25A** (900 mg), m.p. 74°C; IR (KBr): 1814 (C=0), 1538, 1348 (NO_2), 1222 (C-0) cm^{-1}; UV (methanol): 260 nm (ε 378 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.88 (3H, s, 10-CH_3), 4.48 (1H, d, J= 15.1 Hz, 3-H_A), 4.62 (1H, d, J= 15.1 Hz, 3-H_B), 5.74 (1H, brd, J= 9.7 Hz, 0.8 Hz, 0.7 Hz, 6-H), 6.11 (1H, ddd, J= 10.0 Hz, 5.5 Hz, 0.8 Hz, 8-H), 6.43 (1H, ddd, J= 10.0 Hz, 1.2 Hz, 0.7 Hz, 9-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 21.0 (10-CH_3), 63.6 (C-3), 91.6 (C-10), 108.3 (C-5), 122.4 (C-6), 125.6 (C-8), 128.2 (C-7), 128.8 (C-9) 169.6 (C-2). *Analysis* calculated for $C_9H_9NO_5$: C 51.17%, H 4.30%, N 6.64%; found: C 51.09%, H 4.25%, N 6.55%.

The mother liquor contained a mixture of **25A** and its

diastereomer **25B** which was mixed with the crude product obtained from procedure b) below.

b) Finely powdered (2-methylphenoxy)acetic acid (16.6 g, 0.1m) was added to the nitrating mixture (nitric acid (12.6 g, 0.2 mol), acetic anhydride (94.3 cm^3, 1 mol)) at -50°C in one batch. The reaction mixture was stirred for one and a half hours while allowing it to warm to -20°C. When the solution became clear it was cooled to -78°C and added to a stirred solution of 58% aqueous ammonium hydroxide (200 cm^3) in ether (2 dm^3) at -78°C. Stirring was continued while the mixture was warmed to -10°C. The ether layer was decanted, washed with water, dried and the solvent evaporated to give a mixture of the two diene diastereomers **25A** and **25B** (10.1g). The mother liquor from procedure a) above was mixed with the crude product. Fractional crystallization from ether-pentane first gave **25A** (4.53 g) and then its epimer **25B** (2.6 g) crystallized out. It had m.p. 71°C; IR (KBr): 1810 (C=O), 1540,1348 (NO_2), 1224 (C-O)cm^{-1}; UV (methanol): 257 nm (ε 324 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.88 (3H, s, 10-CH_3), 4.25 (1H, d, J= 15.1 Hz, 3-H_A), 4.35 (1H, d, J= 15.1 Hz, 3-H_B), 5.76 (1H, brdd, J=9.7 Hz, 1.0 Hz, 0.4 Hz, 6-H), 6.12 (1H, ddd, J= 10.0 Hz, 5.5 Hz, 1.0 Hz, 8-H), 6.23 (1H, ddd, J= 9.7 Hz, 5.5 Hz, 1.0 Hz, 7-H), 6.43 (1H, brdd, J= 10.0 Hz, 1.0 Hz, 0.4 Hz, 9-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C64.0(c-3),91.3(C-10),109.1(C-5),122.1(C-6),125.3(C-8), 21.6 (10-CH_3), 127.4 (C-7), 128.0 (C-9), 169.9 (C-2). *Analysis* calculated for $C_9H_9NO_5$: C

51.17%, H 4.30%, N 6.64%; found: C 51.28%, H 4.22%, N 6.56%.

The aqueous washings from procedure a) and b) were mixed together and acidified with 1:1 (v/v) hydrochloric acid. Extraction with ether, followed by drying and evaporation of the solvent gave (2-methyl-4-nitrophenoxy)acetic acid **24** (2.87 g), m.p. 133-135°C (from ether-pentane, lit.[103] 127.7-135.5°C); ^{1}H NMR (CD_3CN, 90 MHz): δ 2.28 (3H, s, 2-CH_3), 4.77 (2H, s, OCH_2), 6.92 (1H, d, J= 8 Hz, 6-H), 8.05 (2H, m, 3-H, 5-H).

c) (2-Methylphenoxy)acetic acid (17 mg, 0.1 mmol) was dissolved in a 5% solution of trifluoroacetic acid in chloroform-d (0.3 cm^3) a 0°C. Nitric acid (0.04 cm^3) was injected into this solution and the reaction was followed by NMR at 0°C. The starting material disappeared and was replaced by 4-nitro and 6-nitro derivatives. No diene was observed. After eight hours the solution was poured into cold saturated sodium bicarbonate solution. The aqueous layer was separated, acidifed and extracted with ether. The ether extract on drying and evaporation gave a mixture (15 mg) of **24** (64%) and (2-methyl-6-nitrophenoxy)acetic acid **26** (36%) identified by comparison of the ^{1}H NMR spectra with those of the authentic compounds.

ix) Nitration of *p*-*t*-butyltoluene (**75**)

p-*t*-Butyltoluene (44.4 g, 0.3 mol) was nitrated according to the procedure of Fischer et al.[56] to give 75 g

of crude product. Crystallization from pentane gave one diastereomer of 1-*t*-butyl-4-methyl-4-nitrocyclohexa-2,5-dienyl acetate **82A** (6 g), m.p. 134°C (lit.[56] m.p. 132-135°C). The remaining mixture was chromatographed on 3% deactivated alumina (1300 g) at -40°C. Elution with 10% ether-pentane gave 4-*t*-butyl-2-nitrotoluene (**76**) (24.6 g) in the first fraction, (Z)-3-*t*-butyl-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate **69** (19.8 g), m.p. 51-52°C (from ether-pentane, lit.[56] m.p. 51-52°C), in the second fraction and **82B**, diastereomer of **82A** in the remaining fractions. It had m.p. 81-83°C (from ether-pentane, lit.[56] m.p. 82-83°C).

2.5 *Shift reagent studies*

The shift reagent $Eu(fod)_3$ was used to determine the relative stereochemistry of the diastereomeric adducts obtained from the nitration of **12** (dienes **19** and **20**) and **1** (dienes **52** and **53**). A solution of the shift reagent (500 mg) in chloroform-d (1 cm^3) was prepared and this was added in increments of 40 mm^3 (20 mg shift reagent) to a solution of the diene (48 mg) in chloroform-d (0.3 cm^3). After each addition the NMR spectrum of the solution was recorded at 0°C. The induced shifts of the various protons were plotted against the corresponding shift of the gem dimethyl group and the slopes of these plots (Table 2.1) were used to assign the relative stereochemistry of the adducts. The shift reagent had almost no effect in the case of dienes **19** and **20** and the relative stereochemistry could not be

assigned. The relative stereochemistry of the dienes 52 and 53 could be assigned on the basis of ^1H NMR shift reagent study. The 8-methyl protons in 53 had experienced twice the induced shift of 52 and 53 was assigned as the trans adduct.

Table 2.1

Relative gradients of various protons in ^1H NMR of 52 and 53

	Gradient relative to 3-$(CH_3)_2$		
Diene	6-H, 10-H	7-H, 9-H	8-CH_3
52	0.55	0.21	0.07
53	0.55	0.21	0.17

A similar induced shift study of the ^{13}C NMR spectra was also performed. The ^{13}C NMR spectra of the diene (300 mg) solution in chloroform-d (1.5 cm^3) was recorded at 0°C after each addition of the solid shift reagent in 50 mg increments. The induced shifts of the carbon atoms were plotted against the corresponding shift of the carbonyl carbon and the slopes of these plots were determined (Table 2.2). Again, the stereochemistry of 19 and 20 could not be assigned on the basis of the relative gradient of the 10-CH_3 group.

Table 2.2

Relative gradients of carbon atoms in the ^1H NMR of **19**, **20**, **52**, and **53** Gradient Relative to C-2

Diene	C-3	C-5	C-6	C-7	C-8	C-9	C-10	3-$(CH_3)_2$	8-CH_3	10-CH_3
19	0.67	0.53	0.14	0.18	0.32	0.27	0.30	0.50,0.52	----	0.23
20	0.57	0.46	0.13	0.16	0.23	0.20	0.25	0.45,0.49	----	0.18
58	0.30	0.31	0.11	0.12	0.05	0.12	0.11	0.35	0.03	----
53	0.35	0.36	0.13	0.14	0.06	0.14	0.13	0.38	0.06	----

However, results from the ^{13}C NMR shift reagent study confirmed the assignment of **52** as the (*Z*)-diastereomer and **53** as the (*E*)-diastereomer as determined by ^1H NMR study.

2.6 *Isomerization reactions of 1,2 adducts*

2.6.1 The general procedure for small scale experiments designed to survey the reaction was as follows. The diene (0.1 mmol) was dissolved in the appropriate solvent (0.3-0.35 cm^3) in a NMR tube and the tube placed in a thermostated bath at the desired temperature. The reaction was followed by observing the NMR spectrum at suitable intervals.

a) (*E*)-3,3,10-Trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**19**) in carbon tetrachloride at ambient temperature gave, after 14 day, its positional isomer 3,3,6-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one

(55) (>95%). The same reaction was complete in nine hours at 50°C. Diene **55** had ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 1.54 (3H, s, 3-CH_3), 1.58 (3H, s, 3-CH_3), 1.85 (3H, m, J= 1.6 Hz, 0.8 Hz, 0.6 Hz, 0.6 Hz, 6-CH_3), 5.30 (1H, ddm, J= 4.9 Hz, 1.1 Hz, 0.6 Hz, 10-H), 5.93 (1H, ddm, J= 9.6 Hz, 4.9 Hz, 1.2 Hz, 0.8 Hz, 9-H), 6.07 (1H, ddm, J= 5.8 Hz, 1.6 Hz, 1.2 Hz, 7-H), 6.30 (1H, ddm, J= 9.6 Hz, 5.8 Hz, 1.1 Hz, 0.6 Hz, 8-H).

b) Diene **19** in chloroform-d after six hours at 50°C gave diene **55** (63%), acid **15** (21%) and unreacted **19** (16%).

c) Diene **19** in acetonitrile-d_3 at ambient temperature gave, after four days the acid **15** (41%), the ester **58** (29%) and unreacted **19** (30%). Traces of **55** were also detected.

d) When tetrahydrofuran-d_8 was used as a solvent diene **19**, at ambient temperature gave after 22 days the acid **15** (50%) and the ester **58** (50%).

e) Diene **19** in benzene-d_6 at ambient temperature gave after eight hours diene **55** (56%), **15** (25%) and unreacted **19** (19%). The reaction was allowed to proceed till subsequent aromatization was complete. The acid **15** (80%) and the ester **58** (20%) were formed.

f) Diene **19** in carbon tetrachloride was isomerized to **55** as in a) above. The reaction was allowed to proceed to completion when the acid **15** (80%) and the ester **58** (20%) were obtained from the aromatization of **55**.

g) Diene **19** in presence of *p*-cresol (0.2 mmol) in carbon

tetrachloride at ambient temperature gave after isomerization and subsequent aromatization the same relative amounts of **15** (80%) and **58** (20%) as in the absence of *p*-cresol. GC/MS analysis showed that less than 1% 4-methyl-2-nitrophenol was present in the reaction mixture.

h) [6,8-$^2H_2$]-3,3,10-Trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**23**) in chloroform-d at ambient temperature gave after three days [8,10-$^2H_2$]-3,3,6-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**56**) (50%) and unreacted **23** (50%). Diene **56** had ^1H NMR ($CDCl_3$, 90 MHz): 1.54 (3H, s, 3-CH_3), 1.59 (3H, s, 3-CH_3), 1.86 (3H, brs, 10-CH_3), 5.94 (1H, brs, 7-H), 6.07 (1H, brs, 9-H).

i) Diene **20** in carbon tetrachloride at 50°C gave after 24 hours its positional isomer (Z)-3,3,6-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**62**) (>95%). The solvent was evaporated and the residue dissolved in methylene chloride-d_2. Diene **62** had ^1H NMR (CD_2Cl_2, 250 MHz): δ 1.50 (3H, s, 3-CH_3); 1.53 (3H, s, 3-CH_3), 1.88 (3H, brs, 6-CH_3), 5.30 (1H, dm, J= 4.6 Hz, 1.2 Hz, 10-H), 5.99 (1H, ddm, J= 9.6 Hz, 4.6 Hz, 1.2 Hz, 9-H), 6.13 (1H, dm, J= 5.8 Hz, 1.2 Hz, 7-H), 6.30 (1H, ddm, J= 9.6 Hz, 5.8 Hz, 1.2 Hz, 8-H). Allylic coupling and other long range couplings with the 6-methyl group could not be determined.

j) 3,3,7,9,10-Pentamethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**27**) in carbon

tetrachloride at 50°C gave after eight hours the diastereomers of 3,3,6,7,9-pentamethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one viz. **66** (64%) and **65** (36%).

k) Diene **27** in carbon tetrachloride at ambient temperature gave after 10 days dienes **66** (46%) and **65** (54%).

l) Diene **27** with *p*-cresol (0.2 mmol) in carbon tetrachloride at 50°C gave after 12 hours dienes **66** (60%) and **65** (40%).

m) Diene **27** with thiophenol (1.5 mmol) in carbon tetrachloride at 50°C gave after 12 hours diene **66** as the only product. Diphenyl disulphide was also formed.

n) (Z)-3-*t*-Butyl-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (**69**) in carbon tetrachloride at 70°C gave after one hour unreacted **69** (34%), its epimer **70** (8%), (Z)-5-*t*-butyl-2-methyl-6-nitrocyclohexa-2,5-dienyl acetate **71** (43%) and its epimer **72** (11%) and 5-*t*-butyl-2-methylphenyl acetate **73** (5%).

o) Diene **69** in carbon tetrachloride at ambient temperature gave after 12 days unreacted **69** (27%), **70** (13%), **71** (33%), **72** (18%) and **73** (9%).

2.6.2 Isolation of isomerization products

a) Diene **19** (300 mg) was dissolved in carbon tetrachloride (3 cm^3) and left at ambient temperature. When 75% isomerization was over the solvent was evaporated by bubbling nitrogen through the solution. Attempts to purify

55 by chromatography of the residue at -50°C were not successful. Diene **55** aromatized to acid **15** on the column. The residue was dissolved in chloroform-d and the ^{13}C NMR spectrum was recorded at 62.9 MHz. The following resonances were assigned to (*E*)-3,3,6-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**55**). δ_C 16.0 (6-CH_3), 25.9 (3-CH_3), 26.5 (3-CH_3), 77.3 (C-3), 87.8 (C-10), 103.4 (C-5), 117.5 (C-9), 124.6 (C-7), 129.3 (C-8), 134.7 (C-6), 173.7 (C-2).

b) (*Z*)-3,3,6-Trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (**62**) was prepared from the diene **20** using the same procedure as above and its ^{13}C NMR spectrum was recorded. Diene **62** had ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 16.5 (6-CH_3), 25.6 (3-$(CH_3)_2$), 78.2 (C-3), 87.8 (C-10), 103.9 (C-5), 117.8 (C-9), 125.4 (C-7), 129.0 (C-8), 134.4 (C-6), 174.0 (C-2).

c) Diene **27** (1 g) was dissolved in carbon tetrachloride (20 cm^3) and heated in a thermostated water bath at 50°C for nine hours. The solvent was evaporated, the residue dissolved in methylene chloride-hexane and the compounds separated by fractional crystallization. The minor isomer **65** of 3,3,6,7,9-pentamethyl-10-nitro-1,4-dioxaspiro[4,5]deca 6,8-dien-2-one crysallized out first (120 mg). It had m.p. 123°C; IR (KBr): 1796 (C=O), 1550,1332 (NO_2)cm^{-1}; UV (methanol): 273 nm (ε 367 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 90 MHz): 1.59 (6H, s, 3-$(CH_3)_2$), 1.76 (3H, s, CH_3), 1.88 (6H, s,

$(CH_3)_2$), 4.86 (1H, brs, 10-H), 5.94 (1H, brs, 8-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 11.7 (6-CH_3), 19.1, 19.9 (7-CH_3, 9-CH_3), 25.4 (3-CH_3), 25.6 (3-CH_3), 78.2 (C-3), 91.9 (C-10), 105.1 (C-5), 124.0, 124.9 (C-7, C-9), 131.3 (C-8), 132.6 (C-6), 174.4 (C-2). *Analysis* calculated for $C_{13}H_{17}NO_5$: C 58.40%, H 6.41%, N 5.24%; found: C 58.37%, H 6.33%, N 5.14%.

The major isomer **66** crystallized in the second crop (496 mg), m.p. 78°C; IR (KBr): 1811 (C=O), 1548,1330 (NO_2)cm^{-1}; UV (methanol): 272 nm (ε 577 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.54 (3H, s, 3-CH_3), 1.58 (3H, s, 3-CH_3), 1.75 (3H, brs, CH_3), 1.88 (3H, d, CH_3), 1.89 (3H, brs, CH_3), 4.95 (1H, s, 10-H), 5.94 (1H, brs, 8-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 11.1 (6-CH_3), 18.7, 19.8 (7-CH_3, 9-CH_3), 26.0 (3-CH_3), 26.7 (3-CH_3), 77.1 (C-3), 91.8 (C-10), 104.8 (C-5), 124.4, 124.5, 131.4 (C-6, C-7, C-9), 130.7 (C-8), 174.0 (C-2); MS (methane CI): m/e 268 (M+1); (EI, 70 ev): m/e (relative intensity), 237 (M-30, 4), 151 (13), 136 (17), 135 (100), 123 (125), 107 (14), 91 (67), 79 (17), 77 (15), 43 (67), 41 (30), 39 (32). *Analysis* calculated for $C_{13}H_{17}NO_5$: C 58.40%, H, 6.41%, N 5.24%; found : C 57.98%, H 6.37%, N 5.24%.

2.6.3 Epimerization of dienes **66** and **65**

a) Diene **65** (0.1 mmol) in carbon tetrachloride (0.3 cm^3) at 70°C gave after 32 hours a mixture of **65** (82%) and **66** (18%) and traces of 2-methyl-2-(2,3,5-trimethyl-6-

nitrophenoxy)propanoic acid **29**. The relative amounts of the isomers remained the same after 48 hours but the amount of the aromatic compound increased.

b) Diene **66** under similar conditions gave a mixture of **65** (33%) and **66** (67%) after 30 hours. After 48 hours **65** (38%) and **66** (42%) were observed along with the acid **29** (20%). The aromatization to **29** was complete before equilibrium between **66** and **65** could be achieved.

2.6.4 Preparation of (*E*)-5-*t*-butyl-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (**72**).

Diene **69** (600 mg) was dissolved in carbon tetrachloride (5 cm^3) and heated in a thermostated water bath at 70°C for one hour. The reaction mixture contained at this stage **69** (33%), its epimer **70** (8%), **71** (43%), **72** (11%) and the aryl acetate **73** (5%). The reaction mixture was chromatographed on silica at -40°C. The compounds were eluted with ether-pentane mixtures. No compound was eluted with pentane, 2% ether-pentane and 5% ether-pentane. Small amounts of the acetate **73** were obtained with 10% ether-pentane. Elution with 15% ether-pentane gave a mixture of dienes **69**, **70** and **71** (430 mg). The desired isomer **72** was eluted with 20% ether-pentane (144 mg). It had m.p. 87°C (from methylene chloride-pentane); IR (KBr): 1750, 1210 ($OCOCH_3$), 1550, 1370 (NO_2)cm^{-1}; UV (methanol): 271 nm (ε 606 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.09 (9H, s, 5-*t*-Bu), 1.84 (3H, d, J= 1.4 Hz, 2-CH_3), 2.09 (3H, s, $OCOCH_3$), 5.23 (1H, d, J= 1.6

Hz, 6-H), 5.66 (1H, d, J= 1.6 Hz, 1-H), 6.06 (1H, dq, J= 6 Hz, 1.4 Hz, 3-H), 6.26 (1H, d, J= 6 Hz, 4-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 20.3 (2-CH_3), 20.7 ($OCOCH_3$), 28.2 ($C(CH_3)_3$), 35.3 ($C(CH_3)_3$), 70.4 (C-1), 82.7 (C-6), 123.8 (C-3), 125.1 (C-4), 129.6 (C-2), 135.6 (C-5), 170.1 ($OCOCH_3$). *Analysis* calculated for $C_{13}H_{19}NO_4$: C 61.63%, H 7.56%, N 5.53%; found: C 61.73%, H 7.67%, N 5.57%. Further elution with a higher proportion of ether gave highly coloured trace impurities.

2.6.5 Preparation of (*E*)-3-*t*-butyl-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (**70**).

A solution of diene **72** (600 mg, 2.37 mmol) and *p*-cresol (384 mg, 3.56 mmol) in carbon tetrachloride (15 cm^3) was heated in a thermostated water bath at 50°C for three hours. The reaction mixture at this stage contained diene **70** (36.5%), unreacted **72** (36.5%) and the acetate **73** (27%). The reaction mixture was chromatographed on silica (110 g) at -40°C. The first five fractions eluted with petroleum ether, 0.5% ether, 1% ether, 1.5% ether and 2% ether had no compound present in them. The sixth fraction eluted with 2.5% ether gave the acetate **73** (147 mg). The seventh fraction eluted with 3% ether contained (*E*)-3-*t*-butyl-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate (**70**) (209 mg). The diene **70** was unstable and isomerized to **72** even at -20°C. It had ^1H NMR ($CDCl_3$, 250 MHz): δ 1.07 (9H, s, $C(CH_3)_3$), 1.67 (3H, s, 6-CH_3), 2.10 (3H, s $OCOCH_3$), 5.48

(1H, dd, J=2.9 Hz, 1.8 Hz, 1-H), 5.94 (1H, d, J= 10.0 Hz, 4-H), 6.23 (1H, dd, J= 10.0 Hz, 1.8 Hz, 3-H), 6.37 (1H, d, J= 2.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 18.0 (6-CH_3), 20.9 (OCOCH_3), 28.2 (3-C(CH_3)$_3$), 33.9 (3-C(CH_3)$_3$), 72.9 (C-1), 90.7 (C-6), 118.0 (C-2), 126.4 (C-4), 127.1 (C-5), 145.0 (C-3), 169.8 (OCOCH$_3$).

Further elution with 4% ether gave the starting compound **72** and *p*-cresol (350 mg). Solution with higher concentrations of ether gave *p*-cresol and traces of 4-methyl-2-nitrophenol.

2.6.6 Preparation of (Z)-5-*t*-butyl-2-methyl-6-nitrocyclohexa-2,4-dienyl acetate (**71**).

Diene **69** (684 mg, 2.7 mmol) and *p*-cresol (365 mg, 3.4 mmol) were dissolved in carbon tetrachloride (15 cm^3) and heated in a thermostated water bath at 70°C for one hour. The reaction mixture consisted of diene **69** (22%), diene **71** (60%) and the acetate **73** (18%). The reaction mixture was chromatographed on silica (110 g) at -40°C. Elution with ether gave all the products and traces of *p*-cresol in the first fraction (639 mg). The second fraction (354 mg) contained mainly *p*-cresol and traces of dienes. Rechromatography on silica (80 g) at -40°C gave the acetate **73** on elution with 1 - 2% ether-petroleum ether. Elution with 2,5% ether gave the diene **71** as the major component (70%) along with the acetate **73** (30%) (389 mg). Diene **71** had ^1H NMR ($CDCl_3$, 250 MHz): δ 1.09 (9H, s, C(CH_3)$_3$), 1.80

(3H, brs, 2-CH_3), 2.18 (3H, s, $OCOCH_3$), 5.32 (1H, d, J= 7.5 Hz, 6-H), 5.73 (1H, dd, J= 7.5 Hz, 2.6 Hz, 1-H), 5.90 (1H, dd, J= 5.6 Hz, 2.6 Hz, 3-H), 6.18 (1H, d, J= 5.6 Hz, 4-H); Irradiation at 1.80 sharpened the signals at 5.73 and 5.90. These coupling constants could not be determined; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 17.6 (2-CH_3), 20.8 ($OCOCH_3$), 28.5 (5-$C(CH_3)_3$), 35.8 (5-$C(CH_3)_3$), 72.9 (C-1), 81.9 (C-6), 121.0 (C-3), 124.8 (C-4), 132.6 (C-2), 138.3 (C-5), 170.3 ($OCOCH_3$).

Further elution with 3-5% ether gave fractions containing the diene **69** and *p*-cresol.

2.7 Aromatization of adducts with secondary nitro group

2.7.1 Aromatization of diene **55**

a) Isomerization of **19** (1 g) in chloroform-d (5 cm^3) at 70°C gave after 11 hours diene **55**. This solution of diene **55** was poured into a saturated solution of sodium bicarbonate and stirred overnight at ambient temperature. Extraction with ether, drying and evaporation of ether gave 2-methyl-6-nitrophenyl 2-hydroxy-2-methylpropanoate (200 mg, 20%), m.p. 71-72°C (from ether-pentane); IR (KBr): 3300 (OH), 1770 (C=O), 1530, 1340 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.67 (6H, s, $C(CH_3)_2$), 2.26 (3H, s, 2-CH_3), 7.30 (1H, dd, J= 8.0 Hz, 7.8 Hz, 4-H), 7.55 (1H, dd, J= 7.8 Hz, 0.8 Hz, 3-H), 7.94 (1H, dd, J= 8.0 Hz, 0.8 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 16.2 (2-CH_3), 27.3 ($C(CH_3)_2$), 72.9 ($C(CH_3)_2$), 123.6 (C-5), 126.4 (C-4), 134.1 (C-2), 136.1 (C-

3), 138.1 (C-6) 142.4 (C-1), 174.3 (CO). *Analysis* calculated for $C_{11}H_{13}NO_5$: C 55.21%, H 5.48%, N 5.86%; found: C 55.35%, H 5.37%, N 5.68%. On injection in GC column at 250°C **58** decomposed to give 6-nitro-*o*-cresol which was confirmed by co-injection and GC/MS.

The aqueous layer was acidified with 1:1 (v/v) hydrochloric acid and extracted with ether. Drying and evaporation of the solvent gave acid **15** (780 mg).

b) Diene **19** (0.1 mmol) was isomerized to **55** in carbon tetrachloride as described above. Trifluoroacetic acid (0.1 cm^3) was added to this solution at 0°C and the solution warmed to ambient temperature. The progress of the reaction was monitored by NMR. Diene **55** was quantitatively converted to the acid **15** at ambient temperature after 12 hours.

c) A solution of diene **55** (0.1 mmol) was obtained as above and the solvent evaporated. The residue was dissolved in tetrahydrofuran (0.3 cm^3) and tetracyanoethylene (0.1 mmol) was added to the solution. The reaction was monitored by NMR at ambient temperature. After 24 hours the solvent was evaporated and the residue dissolved in carbon tetrachloride. The insoluble tetracyanoethylene was filtered off. The NMR spectrum of the filtrate showed that **55** had reacted to give the acid **15** (30%) and the ester **58** (70%).

d) Methanol-d_4 (0.1 cm^3) was added to a solution of diene **55** (0.1 mmol) in carbon tetrachloride obtained as above.

The reaction was followed by NMR at ambient temperature. Diene **55** gave after four days the acid **15** (70%) and the ester **58** (30%).

e) Diene **55** (0.1 mmol) was obtained as above and the solvent evaporated. The residue was dissolved in tetrahydrofuran (0.3 cm^3) and the reaction followed by NMR. Diene **55** at ambient temperature gave, after 44 hours, the acid **15** (53%) and the ester **58** (47%).

2.7.2 Aromatization of diene **62**

a) Diene **62** (0.1 mmol) was obtained from a solution of diene **20** in carbon tetrachloride as described above. The solvent was evaporated and the residue was dissolved in tetrahydrofuran (0.3 cm^3). Diene **62** at ambient temperature gave, after 20 hours, the acid **15** as the only product.

b) Diene **62** (0.1 mmol), obtained as above, was dissolved in tetrahydrofuran and tetracyanoethylene (0.1 mmol) was added to the solution. After 24 h at ambient temperature, the solvent was evaporated and the residue dissolved in carbon tetrachloride. Insoluble tetracyanoethylene was filtered off and the NMR spectrum of the filtrate was recorded. The acid **15** was the only product.

2.7.3 Aromatization of dienes **66** and **65**.

a) A solution of diene **66** (19 mg) in ether was added to saturated sodium bicarbonate (1 cm^3) in a separating funnel. The mixture was shaken and the layers separated. The ethereal solution was dried and the solvent evaporated to

give the unreacted **66** (16 mg). The aqueous layer was acidified and extracted with ether. The ether extract on drying and evaporation gave no residue.

b) Diene **66** (19 mg) was dissolved in ether and concentrated sodium hydroxide solution (1 cm^3) was added to it. The mixture was stirred in a reacti-vial at ambient temperature for 30 minutes. Work-up with aqueous sodium bicarbonate as above gave 2-methyl-2-(2,3,5-trimethyl-6-nitrophenoxy)propanoic acid (**29**) (17 mg), m.p. 168°C (from ether-pentane); IR (KBr): 3000-2500 (OH), 1710 (C=O), 1536, 1359 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.49 (6H, s, $C(CH_3)_2$), 2.17 (3H, s, 2-CH_3), 2.22 (3H, s, 3-CH_3), 2.26 (3H, s, 5-CH_3), 6.87 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 13.9 (2-CH_3), 16.9 (3-CH_3), 20.1 (5-CH_3), 24.6 ($C(CH_3)_2$), 83.7 ($C(CH_3)_2$), 127.4 (C-2), 128.4 (C-4), 130.9 (C-5), 140.3 (C-3), 144.2 (C-6), 146.3 (C-1), 175.9 (COOH); MS (Methane CI): m/e 268 (M+1); (EI, 70ev): m/e (relative intensity), 181 (M-87,40), 164 (70), 134 (65), 106 (53), 91 (68), 79 (63), 77 (58), 65 (48), 43 (68), 41 (100), 39 (95).

c) Diene **65** (27 mg) on treating with aqueous sodium hyudroxide as above gave the same product viz. the acid **29** (25 mg).

2.7.4 Aromatization of diene **72**

a) A solution of diene **72** (15 mg) in methanol-d_4 (0.3 cm^3) was heated in a thermostated water bath at 50°C. The reaction was monitored by NMR. Diene **72** gave, after nine

hours, the acetate **73** as the only product. The solvent was evaporated and the ^{1}H NMR spectrum of the residue was recorded in chloroform-d. The identity of **73** was confirmed by comparison with the ^{1}H NMR spectrum of the authentic compound.

b) A solution of **72** (15 mg) in pyridine-d_5 (0.3 cm^3) was heated in a thermostated bath at 50°C. Diene **72** gave, after four hours, the acetate **73** as the sole product.

c) A solution of **72** (15 mg) and N,N-diisopropylethylamine (0.02 cm^3) in methanol-d_4 (0.3 cm^3) at 50°C, in a thermostated water bath, gave after four hours, the aryl acetate **73**.

d) Diene **72** (15 mg) was added to a saturated solution of sodium bicarbonate in 1:1 (v/v) aqueous methanol (2 cm^3). The solution was stirred at ambient temperature for one hour. Extraction with ether, followed by drying and evaporation of the solvent gave all of diene **72** back.

e) Diene **72** (15 mg) was added to 2.5 M sodium hydroxide in 1:1 (v/v) aqueous methanol (2 cm^3). The solution was stirred at ambient temperature for one hour, acidified with 1:1 hydrochloric acid and extracted with ether. The ethereal solution on drying and evaporation of the solvent gave 5-*t*-butyl-2-methylphenol (34%) and 4-*t*-butyl-3-nitrotoluene (66%).

f) Diene **72** (125 mg) was added to 1.25 M sodium hydroxide in methanol (10 cm^3). The solution was stirred at ambient

temperature for one hour and extracted with ether. The ether extract on drying and evaporation gave 5-*t*-butyl-2-methylphenol (8%) and 4-*t*-butyl-3-nitroluene (92%). The residue was dissolved in ether and the ethereal solution repeatedly washed with 2.5 M aqueous sodium hydroxide until the basic layer was colourless. Final washing with water, drying and evaporation of the solvent on rotavapor gave 4-*t*-butyl-3-nitrotoluene (**74**) (75 mg) as a red oil, IR (film): 1544, 1368 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.38 (9H, s, $C(CH_3)_3$), 2.34 (3H, s, 1-CH_3), 7:12 (1H, d, J= 2.0 Hz, 2-H), 7.23 (1H, dd, J= 8.3 Hz, 2.0 Hz, 6-H), 7.42 (1H, d, J= 8.3 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 20.3 (1-CH_3), 30.7 (4-$C(CH_3)_3$), 35.3 (4-$C(CH_3)_3$), 124.2 (C-5), 128.4 (C-2), 131.4 (C-6), 137.1 (C-1), 138.3 (C-4), 151.1 (C-3); MS: m/e (relative intensity), 193.1132 (74, $M_r(^{12}C_{11}{}^1H_{15}{}^{14}N^{16}O_2)$ 193.1103), 178 (100), 164 (36), 149 (71), 133 (33), 115 (35), 105 (50), 91 (58), 77 (32), 65, (26), 43 (54).

2.8 *Isomerization reactions of* 1,4 *adducts*

2.8.1 Small scale reactions, to survey the scope of the reaction were performed by dissolving the diene (0.1 mmol) in the appropriate solvent (0.3 cm^3). The solution was heated in a thermostated water bath at the required temperature and the progress of reaction was followed by NMR.

a) (*E*)-1,4-Dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (**84**) in carbon tetrachloride at 70°C showed no reaction

after five hours.

b) (*E*)-3,4-Dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (**83**), obtained by the nitration of *o*-xylene following the procedure of Ramsay[73], in carbon tetrachloride at 70°C gave, after 15 hours, 3,4-dimethylphenyl acetate (**85**) as the only product. No intermediate was detected.

c) A solution of diene **82A**, obtained from the nitration of *p*-*t*-butyltoluene, in 1:1 (v/v) carbon tetrachloride and chloroform-d did not react over three hours at 70°C.

d) Diene **52** in carbon tetrachloride did not react after 15 days at ambient temperature or after six hours at 70°C.

e) Diene **53** in carbon tetrachloride did not react after 15 days at ambient temperature or after six hours at 70°C.

f) Diene **95** in 1:1 (v/v) carbon tetrachloride and chloroform-d at 70°C gave after 12 hours 2,5-dimethylbenzonitrile (**97**) (ca. 5%) and unreacted **95** (ca. 95%). No intermediate was observed.

g) A solution of diene **96** in 1:1 (v/v) carbon tetrachloride and chloroform-d at 70°C gave after seven hours 2,5-dimethylbenzonitrile (**97**) (ca. 65%) and a mixture of unidentified products (ca. 35%).

h) A solution of diene **92A** in 1:1 (v/v) carbon tetrachloride and chloroform-d at 70°C gave after 12 hours 2,3-dimethylbenzonitrile (ca. 30%), 2,3-dimethyl-5-nitrobenzonitrile (**93**) (ca. 30%), 2-cyano-3,4-dimethyl-6-nitrocyclohexa-2,4-dienyl acetate **94A** (ca. 10%) and

unreacted **92A** (ca. 30%).

i) Diene **92B** under the same conditions as above gave 2,3-dimethylbenzonitrile (ca. 28%), 2,3-dimethyl-5-nitrobenzonitrile (**93**) (ca. 32%), 2-cyano-3,4-dimethyl-6-nitrocyclohexa-2,4-denyl acetate **94B** (ca. 10%) and unreacted **92B** (ca. 30%)

j) Diene **87** in 1:1 (v/v) carbon tetrachloride and chloroform-d, gave after 36 hours at 50°C, 3,4-dimethylbenzonitrile (**89**) (27%), (E)-2-cyano-4,5-dimethyl-6-nitrocyclohexa-2,4-dienyl acetate (**91**) (42%) and unreacted **87**. (31%).

k) Diene **87** in 1:10 (v/v) methanol-d_4 and carbon tetrachloride at 70°C gave after four hours at 70°C, 3,4-dimethylbenzonitrile (**89**) (60%), 3,4-dimethyl-5-nitrobenzonitrile (**90**) (20%) and unidentified products (20%).

l) Diene **86** in carbon tetrachloride gave after 5.5 hours at 78°C, 3,4-dimethylbenzonitrile (**89**) (ca. 50%), and (Z)-2-cyano-4,5-dimethyl-6-nitrocyclohexa-2,4-dienyl acetate **88** (ca. 50%).

m) Diene **86** in 1:10 (v/v) methanol-d_4 and carbon tetrachloride at 70°C gave, after four hours, 3,4-dimethylbenzonitrile (**89**) (51%) and 3,4-dimethyl-5-nitrobenzonitrile (**90**) (49%).

n) A solution of diene **99** in carbon tetrachloride at 70°C gave after 30 hours, 1,4-dimethyl-2-nitrobenzene (**77**) (57%),

1,4-dimethyl-2,6-dinitrobenzene (**101**) (traces) and a mixture (43%) of unreacted **99**, cyclohexadiene **102** and cyclohexenes **100** and **103**.

2.8.2 Preparation of (Z)-2-cyano-4,5-dimethyl-6-nitrocyclohexa-2,4-dienyl acetate (**88**).

Diene **86** (300 mg) was dissolved in carbon tetrachloride and heated in a thermostated water bath at 70°C for nine hours. The solvent was evaporated and the residue dissolved in methylene chloride-hexane. Fractional crystallization gave 3,4-dimethylbenzonitrile (24 mg) from the first crop and **88** (40 mg) from the second crop. Diene **88** had m.p. 103°C; IR (KBr): 2220 (CN), 1755, 1220 ($OCOCH_3$), 1550, 1360 (NO_2)cm^{-1}; UV (cyclohexane): 285 nm (ε 555 m^2mol^{-1}); ^1H NMR ($CDCl_3$, 250 MHz): δ 1.94 (3H, brs), 1.96 (3H, brs), (4-CH_3,5-CH_3), 2.20 (3H, s, $OCOCH_3$), 5.13 (1H, d, J= 8.0 Hz, 6-H), 5.88 (1H, dd, J= 8.0 Hz, 2.6 Hz, 1-H), 6.73 (1H, d, J= 2.6 Hz, 3-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 18.1, 20.5, 20.5 ($OCOCH_3$, 4-CH_3, 5-CH_3), 66.3 (C-1), 85.3 (C-6), 108.5 (C-2), 115.0 (2-CN), 127.4 (C-4), 132.9 (C-5), 143.0 (C-3), 169.7 ($OCOCH_3$). *Analysis* calculated for $C_{11}H_{12}N_2O_4$: C 55.91%, H 5.12%, N 11.86%; found: C 55.90%, H 5.31%, N 11.74%.

2.8.3 Preparation of (*E*)-2-cyano-4,5-dimethyl-6-nitrocyclohexa-2,4-dienyl acetate **91**

A solution of diene **87** (400 mg) in 1:1 (v/v) carbon tetrachloride and chloroform (10 cm^3) was heated at 70°C in a thermostated water bath for seven hours. The solvent was

evaporated and the residue dissolved in methylene chloride-petroleum ether. Diene **91** (50%) could not be crystallized from the mixture. ^{1}H and ^{13}C NMR spectra of the mixture were recorded and the following signals assigned to **91**. It had ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.97 (3H, brs, 4-CH_3), 2.00 (3H, brs, 5-CH_3), 2.14 (3H, s, $OCOCH_3$), 5.12 (1H, brs, 6-H), 6.08 (1H, d, J= 3.1 Hz, 1H), 6.84 (1H, s, 3-H); Irradiation at 1.97 collapsed the signal at 5.12 to a doublet (J= 3.1 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 17.9, 20.3, 20.5 ($OCOCH_3$, 4-CH_3, 5-CH_3), 65.7 (C-1), 88.0 (C-6), 105.9 (C-2), 116.5 (2-CN), 127.3 (C-4), 135.4 (C-5), 145.2 (C-3), 168.7 ($OCOCH_3$).

2.8.4 Characterization of dienes **94A** and **94B** in solution.

Diene **92A** (350 mg) was dissolved in chloroform-d (10 cm^3) and the solution heated at 70°C for six hours. The solution was concentrated to 3 cm^3 on a rotavapor and the ^{13}C NMR spectrum was recorded. In the minor product 2-cyano-3,4-dimethyl-6-nitrocyclohexa-2,4-dienyl acetate **94A** which contributed ca. 10% of the mixture, peaks due to proton-bearing carbon atoms could be assigned. Diene **94A** had ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 17.5, 19.6, 23.9 (3-CH_3, 4-CH_3, $OCOCH_3$), 65.9 (C-1), 82.8 (C-6), 126.3 (C-5).

Similar treatment of diene **92B** gave a mixture containing the epimer of **94A**, **94B** (<10%). It had ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 19.0, 19.5, 22.4, (3-CH_3, 4-CH_3, $OCOCH_3$), 66.2 (C-1), 83.1 (C-6), 125.6 (C-5).

2.8.5 Attempted isomerization of 1,4-dimethyl-2,4-

dinitrocyclohexa-2,5-dienyl acetate (**99**)

A solution of **99** (1 g) in carbon tetrachloride (15 cm^3) was heated at 70°C for 20 hours. On cooling the solution to 0°C, colourless crystals of 4-hydroxy-1,4-dimethyl-2,5,6-trinitrocyclohex-2-enyl acetate (**100**) (16 mg) precipitated. It had m.p. 168°C; IR (KBr): 3500 (OH), 1735, 1235 ($OCOCH_3$), 1565, 1550, 1530, 1370, 1350, 1340 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.66 (3H, s, 4-CH_3), 1.78 (3H, s, 1-CH_3), 2.18 (3H, s, $OCOCH_3$), 5.15 (1H, d, J=12 Hz, 5-H), 6.20 (1H, d, J=12 Hz, 6-H), 6.96 (1H, s, 3-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 21.3 ($OCOCH_3$), 21.8 (1-CH_3), 27.0 (4-CH_3), 68.8 (C-1), 75.0 (C-4), 84.0 (C-6), 87.4 (C-5), 132.8 (C-3), 171.3 ($OCOCH_3$); MS (methane CI): m/e 302 (M-17). The solvent was evaporated from the mother liquor and the residue chromatographed on silica (110 g) at -40°C. Elution with 0-3% ether in petroleum ether gave 1,4-dimethyl-2-nitrobenzene (310 mg, 53%). Elution with 4 - 6% ether in petroleum ether gave 1,4-dimethyl-2,6-dinitrobenzene (159 mg, 21%). Further elution with 8 - 10% ether gave mainly 4-hydroxy-1,4-dimethyl-1-nitrocyclohexa-2,5-dienyl acetate **102** (88 mg). Recrystallization from ether-petroleum ether afforded the pure compound (23 mg). It had m.p. 131°C; IR (KBr): 3390 (OH), 1710, 1260 ($OCOCH_3$), 1525, 1370 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.54 (3H, s, 4-CH_3), 1.69 (3H, s, 1-CH_3), 2.01 (3H, s, $OCOCH_3$), 5.68 (1H, d, J= 9.9 Hz, 6-H), 5.89 (1H, dd, J= 9.9 Hz, 2.1 Hz, 5-H), 7.20 (1H,

d, J= 2.1 Hz, 3-H); MS (Methane CI): m/e 210 (M-17). The next fraction eluted with 12% ether gave mainly 1,4-dimethyl-2,4,5,6-tetranitrocyclohex-2-enyl acetate (**103**) (76 mg). Recrystallization from ether-petroleum ether afforded pale yellow crystals (17 mg), m.p. 146°C; IR (KBr): 1755, 1225 ($OCOCH_3$), 1570 - 1540, 1360 - 1335 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.85 (6H, s, 1-CH_3, 4-CH_3), 2.19 (3H, s, $OCOCH_3$), 5.99 (1H, d, J= 12 Hz, 5-H), 6.20 (1H, d, J=12 Hz, 6-H), 6.98 (1H, s, 3-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C 19.3 (1-CH_3), 20.9 ($OCOCH_3$), 22.9 (4-CH_3) 64.4 (C-1), 82.7 (C-5), 83.5 (C-6), 87.1 (C-4), 127.0 (C-3); MS (Methane CI): m/e 349 (M+1). Further elution with increasing concentration of ether gave the unreacted diene **99** (245 mg, 24.5%).

2.9 *Reactions of 3,3,10-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one*

2.9.1 Reaction with sulphuric acid in aqueous acetone-d_6

Diene **19** (48 mg) was mixed with 0.01M sulphuric acid in 90% aqueous acetone-d_6 (0.4 cm^3) at 0°C and warmed to ambient temperature. The reaction was monitored by NMR. Epimerization of **19** to **20** was observed. Work-up with aqueous sodium bicarbonate, as described earlier, after 15 days gave the ester **58** (8 mg, 17%) from the ether layer. The aqueous layer was acidified and extracted with ether. The ether extract on drying and evaporation gave the acid **15** (40 mg, 83%).

The above reaction was repeated using 0.5M sulphuric

acid in 90% aqueous acetone-d_6 (0.4 cm^3). After work-up as above the ether layer afforded **58** (22 mg, 46%) and the aqueous layer after acidification and extraction with ether gave **15** (25 mg, 54%).

2.9.2 Reaction with sulphuric acid in methanol.

Diene **19** (48 mg) was mixed with 0.01M sulphuric acid in methanol-d_4 (0.4 cm^3) at 0°C and warmed to ambient temperature. The reaction was monitored by NMR. Epimerization of **19** and **20** was observed. The diene aromatized with a half-life of 4 days. Work-up with aqueous sodium bicarbonate after 29 days at ambient temperature gave 2-methyl-6-nitrophenol (30%) and methyl-[$^2H_3$] 2-methyl-2-(2-methyl-6-nitrophenoxy)propanoate **121**-d_3 (70%).

The above experiment was repeated with increasing concentrations of sulphuric acid. Treatment of **19** (48 mg) with 0.05M sulphuric acid in methanol (0.4 cm^3) gave, after 21 days at ambient temperature, 2-methyl-6-nitrophenol (37%) and **121**-d_3 (63%). On reacting **19** (48 mg) with 0.5M sulphuric acid in methanol (0.4 cm^3), the same products viz. 2-methyl-6-nitrophenol (75%) and **121**-d_3 (25%) were obtained after 13 days at ambient temperature.

In one of the control experiments to determine the origin of 2-methyl-6-nitrophenol, 2-methyl-2-(2-methyl-6-nitrophenoxy)propanoic acid **15** (40 mg) in chloroform-d (0.3 cm^3) was reacted with 0.5 M sulphuric acid in methanol (0.1 cm^3). The reaction was followed by NMR at ambient

temperature. After 8.5 hours, the reaction was worked up with aqueous sodium bicarbonate to give methyl 2-methyl-2-(2-methyl-6-nitrophenoxy)propanoate, **121** (38 mg, 90% isolated yield), IR (film): 1735 (C=O), 1540, 1335 (NO_2)cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.49 (6H, s, $C(CH_3)_2$), 2.27 (3H, s, 2-CH_3), 3.76 (3H, s, CO_2CH_3), 7.11 (1H, dd, J= 7.9 Hz, 7.7 Hz, 4-H), 7.37 (1H, brd, J= 7.7 Hz, 3-H), 7.52 (1H, brd, J= 7.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ_C 17.6 (2-CH_3), 24.9 ($C(CH_3)_2$), 52.5 (CO_2CH_3), 83.8 ($C(CH_3)_2$), 122.3 (C-5), 124.3 (C-4), 134.8 (C-3), 126.4 (C-2), 136.3 (C-6), 146.4 (C-1), 173.2 (CO_2CH_3); MS (Methane CI): m/e 254 (M+1); (EI, 70 ev): m/e (relative intensity), 253 (M^+,1), 194 (9), 153 (100), 151 (14), 136 (45), 120 (17), 101 (34), 91 (16), 73 (16), 69 (31), 39 (17).

The methyl ester **121** (30 mg) was reacted with 0.5 M sulphuric acid in methanol-d_4 (0.4 cm^3) in another control experiment. The reaction was monitored by NMR at ambient temperture. No reaction was observed during 33 days. The unreacted **121** was recovered after work-up with aqueous sodium bicarbonate.

In a third control experiment 2-methyl-6-nitrophenyl 2-hydroxy-2-methylpropanoate **58** (25 mg) was treated with 0.5M sulphuric acid in methanol-d_4 (0.4 cm^3). The reaction was monitored by NMR at ambient temperature. The ester **58** trans-esterified to give 2-methyl-6-nitrophenol with a half life of 16 days. Work-up after 33 days gave 2-methyl-6-

nitrophenol (75%) and unreacted 58 (25%).

2.9.3 Reaction with methanesulphonic acid and triflic acid.

a) Methanesulphonic acid (0.01 cm^3) was added to a solution of diene 19 (48 mg) in chloroform-d (0.3 cm^3) at 20°C. The reaction was monitored by NMR at 20°C. After 15 minutes ca. 15% 19 was left unreacted. It epimer 20 (18%), the isomerized diene 55 (ca. 8%), the 4-nitro acid 14 (18%) and the 6-nitro acid 15 (41%) were the other products. As the reaction progressed 19 was the first to disappear from the reaction micture, followed by the dienes 20 and 55 respectively. After two hours at 20°C 15 (75%) and 5 (25%) were the only products observed. The mixture of the acids 15 and 14 (47 mg) could be isolated after aqueous sodium bicarbonate work-up.

b) Diene 19 (48 mg) was reacted with a 1:1 (v/v) mixture of methanesulphonic acid and chloroform-d (0.3 cm^3) at 0°C and the reaction was followed by NMR. Epimerization of 19 to 20 and isomerization to 55 were observed. Work-up with aqueous sodium bicarbonate after two hours at 0°C afforded a mixture (46 mg) of the 6-nitro acid 4 (81%) and the 4-nitro acid 14 (19%).

c) Triflic acid (0.01 cm^3) was injected into a solution of diene 19 (48 mg) in chloroform-d (0.3 cm^3) at 0°C. The NMR spectrum of the solution showed that all the diene had reacted (ca. 5 min) to form aromatic products. Work-up with aqueous sodium bicarbonate afforded a mixture (44 mg) of the

6-nitro acid **15** (75%) and the 4-nitro acid **14** (25%).

d) The above experiment was repeated in the presence of methanol (0.01 cm^3) and the reaction followed by NMR. Epimerization to **20** was observed. After 30 minutes at 0°C the temperature was raised to 20°C. After another 30 minutes the reaction mixture contained **15** (9%), **14** (9%), unreacted **19** (21%) and its epimer **20** (61%).

2.9.4 Reactions with trifluoroacetic acid (TFA).

a) A solution of **19** (600 mg) in TFA (6 cm^3) was stirred at ambient temperature for two hours. Work-up with aqueous sodium bicarbonate gave 3,3,10-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-diene-2,8-dione (**112**) (63 mg, 17%). A mixture of acids (502 mg) was obtained from the aqueous layer and its components were identified by NMR as **15** (23%), **14** (60%) and **12** (ca. 5%).

b) Diene **19** (48 mg) was reacted with 10% (v/v) TFA in chloroform-d (0.3 cm^3) at 0°C. After 25 minutes a mixture containing **19** (20%) and its epimer **20** (80%) was obtained. The relative amounts of the two dienes did not change for another three hours at 0°C after which aromatization commenced.

c) Diene **19** (48 mg) was dissolved in a 1:2 (v/v) mixture of TFA and chloroform-d (0.6 cm^3) at -10°C and the reaction was followed by NMR. An equilibrium mixture of **19** and **20** in the ratio 20:80 was first formed which did not further react till the temperature was raised to 10°C over 30 minutes.

Aromatization commenced at 20°C. Diene **55** was observed as an intermediate and reached a maximum concentration of 19%. After 14 hours at 20°C the reaction was worked up as described above to give **12** (ca. 18%), **15** (39%), **14** (32%) and the spirodienone **112** (ca. 11%).

d) Diene **19** (48 mg) and mesitylene (36 mg) were dissolved in TFA (0.3 cm^3) at 0°C and the solution was warmed to ambient temperature. After one hour the solution was poured into saturated aqueous sodium bicarbonate and 1,4-dimethyl-2-nitrobenzene (42 mg) was added to it as an internal standard. The solution was extracted with ether, the ether extract dried and the solvent evaporated. Analysis by GC indicated the presence of nitromesitylene (13%) in the reaction mixture. The aqueous layer on acidification and extraction with ether, followed by drying and evaporation of the solvent gave **12** (25%), **15** (36%) and **14** (25%).

e) Diene **19** (48 mg) was reacted with 100% TFA at -15°C. After 45 minutes the reaction mixture contained acid **14** (ca. 12%) and dienes **19**, **20** (48%) and **55** (26%), along with acid **15**. The reaction mixture was warmed to ambient temperature. Work-up after 24 hours gave acids **12** (ca. 13%), **15** (38%), **14** (38%) and the spirodienone **112** (ca. 11%).

The above reaction was repeated and the temperature maintained at -15°C. The dienes **20** and **55** were observed in the reaction mixture first. The acid **14** could be detected

next and the peaks due to acid **15** increased as the concentration of **55** decreased. The dienone **112** could be detected when the intensity of the overlapping diene peaks decreased. Work-up after four days at -15°C gave **12** (ca. 12%), **15** (51%), **14** (25%) and **112** (ca. 12%).

f) Diene **19** was dissolved in a 1:1 (v/v) mixture of methanol-d_4 and TFA (0.4 cm^3) at -10°C and the reaction followed by NMR. No aromatization reactions occurred at -10°C, 0°C or +10°C. Isomerization to **55** began at +10°C. The concentration of **55** reached 40% after six hours at +10°C. The temperature was increased to ambient temperature. Work-up after three days at ambient temperature gave **15** (52%) and **20** (48%) and traces of 2-methyl-6-nitrophenol (**10**).

g) Diene **19** (48 mg) was dissolved in a 1:3 (v/v) mixture of methanol-d_4 and TFA (0.4 cm^3) at -10°C and the reaction followed by NMR. After 20 minutes at 0°C an equlibrium mixture containing **19** (22%) and **20** (78%) was obtained. There was no further change in the mixture after two hours at 0°C. On warming to ambient temperature the dienes slowly aromatized. Work-up after three days at ambient temperature gave 2-methyl-6-nitrophenol (**10**) (17%), **15** (26%), **20** (57%) and traces of **19**.

The same experiment was repeated with the temperature being maintained at 0°C. The equilibrium mixture of **19** (20%) and **20** (80%) obtained after 20 minutes did not change

even after three days. Only trace aromatic products were observed.

h) Diene **19** (48 mg) was dissolved in a 9:1 (v/v) mixture of TFA and methanol-d_4 (0.3 cm^3) at 0°C and reaction monitored by NMR. A mixture of **19** (35%) and **20** (65%) was observed after 10 minutes. Diene **19** reacted completely to give **20** (35%), **55** (30%) and a mixture of aromatic compounds (35%). The solvent was evaporated after five hours at 0°C to give traces of **20**, diene **55** (32%), **12** (12%) **15** (24%) and **14** (32%).

2.9.5 Miscellaneous reactions

a) Tetracyanoethylene (26 mg) was added to a solution of **19** (48 mg) in tetrahydrofuran-d_8 (0.4 cm^3) and the reaction monitored by NMR at ambient temperature. After 15 days the ester **58** (72%), the acid **15** (18%) and some unidentified compound (ca. 10%) were observed in the reaction mixture. The products were separated from tetracyanoethylene by HPLC on a silica column (Si-10, 0.8 x 50 cm) using methylene chloride-hexane as eluent. Tetracyanoethylene (20 mg) was eluted in the first fraction, the ester **58** (16 mg) in the second fraction and unidentified compounds in the third fraction.

b) Nitroethylene (0.011 cm^3) was added to a solution of **19** (48 mg) in chloroform-d and the reaction monitored by NMR. No reaction was observed after 24 hours at ambient temperature. The same reaction was repeated using benzene-

d_6 as solvent. No reaction was observed after 24 hours at ambient temperature.

c) A reacti-vial containing a solution of **19** (50 mg) in 70% aqueous methanol (2.8 cm^3) was placed in an ultrasonic bath at 45°C for 2.5 hours. The solution was saturated with sodium chloride, extracted with ether, dried and the solvent evaporated to yield **15** (43%) and unreacted **19** (57%).

d) Boron trifluoride gas was bubbled through a solution of **19** (24 mg) in chloroform-d (0.5 cm^3) at -60°C for two minutes. Chloroform-d (0.2 cm^3) cooled to -60°C was added to replenish the evaporated solvent. The NMR spectrum recorded at -40°C (ca. 10 minutes after bubbling of boron trifluoride was stopped) showed that all of the diene had reacted. Work-up with aqueous sodium bicarbonate at 0°C afforded a mixture (21 mg) of aromatic compounds which was analyzed by ^1H NMR (250 MHz). The mixture consisted of **14** (31%) **15** (54%), 2-methyl-2-(2-methyl-3-nitrophenoxy)propanoic acid **13** (7%) and **12** (8%). The nitro derivatives **13**, **15**, and **14** decomposed to the corresponding phenols on injection into a GC column. Presence of **13** was confirmed by co-injection with 2-methyl-3-nitrophenol (**8**).

2.10 *Aromatization reactions of* 10-*methyl*-10-*nitro*-1,4-*dioxaspiro*[4,5]*deca*-6,8-*dien*-2-*one* (25)

2.10.1 Pyrolysis

a) A solution of **25A** (17 mg) in a 1:1 (v/v) mixture of carbon tetrachloride and chloroform-d (0.35 cm^3) was heated

at 50°C for 12 hours. Aqueous sodium bicarbonate work-up yielded (2-methyl-6-nitrophenoxy)acetic acid **26** (16 mg), m.p. 129-130°C (lit.[104] 129°C) as the sole product.

b) A solution of **25A** (17 mg) in tetrahydrofuran (0.35 cm^3) was heated at 50°C for 14 hours. Work-up as above gave the 6-nitro acid **26** (17 mg) as the only product.

Similar reaction of the epimer **25B** (17 mg) in tetrahydrofuran (0.3 cm^3) gave the same product **26** in quantitative yield.

2.10.2 Reactions with trifluoroacetic acid (TFA)

Except as otherwise specified all the reactions were performed on a mixture containing **25A** (65%) and **25B** (35%).

a) Diene **25A** (15 mg) was dissolved in a 1% (v/v) mixture of TFA in chloroform-d (0.4 cm^3) at 0°C. The reaction was followed by NMR at 0°C. The diene **25A** epimerized to **25B** to give an equilibrium mixture of **25A** and **25B** (31:69) after 14 hours at 0°C. The same concentrations were observed after 24 hours.

Diene **25B** under similar conditions gave the same equilibrium concentrations of **25A** and **25B** above, after 24 hours at 0°C. The relative concentrations did not change till 60 hours at 0°C when aromatization commenced.

c) Diene **25** (17 mg) was dissolved in a 25% (v/v) mixture of TFA in chloroform-d at 0°C. After 15 minutes the NMR spectrum of the mixture showed formation of an equilibrium mixture of **25A** and **25B**. Work-up after 24 hours at 0°C gave

the 6-nitro acid **26** as the only product.

d) The concentration of TFA was increased to 10% in another experiment performed at -20°C. The equilibrium concentrations of **25A** and **25B** were achieved after 10 minutes at -20°C. Work-up after three hours at -20°C gave **26** (16 mg) as the sole product.

e) When the concentration of TFA was increased to 25%, diene **25** started to aromatize at 0°C. Aromatization was complete in 30 minutes when the reaction mixture was warmed to 0°C. Work-up with aqueous sodium bicarbonate gave a mixture of aromatic acids (17 mg). Analysis by ^{1}H NMR showed that the mixture consisted of **18** (5%), the 4-nitro acid **24** (15%) and the 6-nitro acid **26** (80%).

f) A same product mixture as above was obtained when the above experiment was repeated with neat TFA.

2.10.3 Reaction with sulphuric acid.

a) Diene **25** (17 mg) was dissolved in 0.1M sulphuric acid in methanol (0.3 cm^3) at 0°C. The reaction was monitored by NMR. No reaction occurred over three hours at 0°C. The reaction mixture was warmed to ambient temperture at which temperature aromatization occurred with a half-life of one hour. After 18 hours the reaction mixture was worked-up with aqueous sodium bicarbonate to give 2-methyl-6-nitrophenol as the only product.

In a control experiment the 6-nitro acid **26** (21 mg) was reacted with 0.1M sulphuric acid in methanol (0.5 cm^3) at

ambient temperature for 24 hours. Work-up as above gave methyl (2-methyl-6-nitrophenoxy)acetate (**122**) (21 mg) as the only product.

b) Diene **25** (12 mg) was dissolved in 0.1M sulphuric acid in 90% aqueous acetone (0.3 cm^3) at 0°C and the reaction monitored by NMR. No reaction occurred at 0°C. The solution was warmed to ambient temperature when aromatization occured with a half-life of 11 hours. Work-up with aqueous sodium bicarbonate after 48 hours gave 2-methyl-6-nitrophenol as the only product.

In a control experiment the acid **26** reacted under similar conditions to give 2-methyl-6-nitrophenol (8%) and the unreacted **26** (92%).

2.10.4 Reaction with boron trifluride.

Diene **25** (17 mg) was dissolved in chloroform-d (0.6 cm^3) and cooled to -60°C. Boron trifluoride gas was bubbled through the solution for two minutes and the solution was warmed to -40°C. The reaction was followed by NMR. Aromatization was complete after 40 minutes. Work-up with aqueous sodium bicarbonate gave the acid **26** (15 mg) as the only product.

2.11 *Reactions of* (Z)-3,3,8-*trimethyl*-8-*nitro*-1,4-*dioxa*-*spiro*[4,5]*deca*-6,9-*dien*-2-*one* (**52**)

2.11.1 Solvolysis

a) A solution of diene **52** (48 mg) in 1:1 (v/v) aqueous methanol (2 cm^3) was stirred in a reacti-vial at 60°C for 30

minutes. The solution was saturated with sodium chloride and extracted with ether. The ethereal solution was dried and the solvent was evaporated to give 4-methyl-2-nitrophenol (51) (18%) and unreacted 52 (82%).

When the solution of 52 was stirred at 60°C for four hours in another experiment 4-methyl-2-nitrophenol (51) (80%) and *p*-cresol (20%) were obtained on work-up as above.

b) Diene 52 (48 mg) and tris(hydroxymethyl)aminomethane (26 mg, 1.1 equivalent) were dissolved in 1:1 aqueous methanol (4 cm^3). The solution was stirred at 60°C for four hours. Work-up as above gave 4-methyl-2-nitrophenol (51) (80%) and *p*-cresol (20%).

c) Diene 52 (48 mg) and urea (60 mg, 5 equivalent) were dissolved in 1:1 aqueous methanol (4 cm^3) stirred at 60°C for four hours. Work-up as above gave 4-methyl-2-nitrophenol (51) (66%), *p*-cresol (14%) and unreacted 52 (20%).

2.11.2 Reactions with trifluoroacetic acid (TFA)

a) Diene 52 (48 mg) was dissolved in a 1:1 (v/v) mixture of TFA and chloroform-d at 0°C. The reaction was monitored by NMR. Aromatization at 0°C was very slow. The reaction mixture was warmed to ambient temperature. After 24 hours the solvent was evaporated and the residue was dissolved in chloroform-d. ^1H NMR spectrum of the product indicated the presence of 4-methyl-2-nitrophenol (51) (20%) and 2-methyl-2-(4-methyl-2-nitrophenoxy)propanoic acid 54 (70%). *p*-

Cresol and the acid 1 were also formed.

b) Diene 52 (48 mg) was dissolved in a 3:1 (v/v) mixture of TFA and chloroform-d (0.3 cm^3) at 0°C and the mixture warmed to ambient temperature. The reaction was monitored by NMR. Work-up as above after seven hours gave 4-methyl-2-nitrophenol (51) (20%), the acid 54 (75%) and traces of *p*-cresol and 1.

c) Diene 52 (48 mg) was dissolved in neat TFA (0.3 cm^3) at 0°C and the reaction was monitored by NMR. After eight hours at 0°C the reaction mixture was worked up with aqueous sodium bicarbonate. The non-acidic ether layer gave 4-methyl-2-nitrophenol (51) (20%). The aqueous layer on acidification, extraction with ether, drying and evaporation of the solvent afforded the acids 1 (14%) and 54 (66%).

d) A mixture of 52 (24 mg, 0.1 mmol) and 1,3,5-trimethoxybenzene (17 mg, 0.1 mmol) was dissolved in neat TFA (0.3 cm^3) at 0°C and the reaction was followed by NMR. After nine hours at 0°C the reaction was worked up with aqueous sodium bicarbonate. Both the acidic and the non-acidic fractions of the products were complex mixtures. The presence of 1,3,5-trimethoxy-2-nitrobenzene in the non-acidic fraction was detected by gas chromatography. Co-injection of an authentic sample confirmed that 1,3,5-trimethoxy-2-nitrobenzene was present. The acidic fraction contained 54 (30%) and 1 (70%) (relative amounts).

e) A solution of 52 (48 mg) and mesitylene (36 mg) in neat

TFA (0.3 cm^3) was prepared at 0°C and then warmed to ambient temperature. After one hour the reaction mixture was poured into an excess of saturated sodium bicarbonate solution. 1,4-dimethyl-2-nitrobenzene (**77**) (36 mg) was added as an internal standard. The resulting mixture was extracted with ether. The ether extract was dried and the solvent was evaporated. Analysis of the residue by GC indicated the presence of nitromesitylene (9%). The aqueous solution was acidified and extracted with ether to give, after drying and evaporation of the solvent acids **1** (36%) and **54** (55%).

f) Diene **52** (48 mg) was dissolved in a 1:1 (v/v) mixture of TFA and methanol-d_4 (0.3 cm^3) at 0°C. After 24 hours at 0°C conversion of **52** to 4-methyl-4-nitrocyclohexa-2,5-dienone (**124**) was complete. After another two days at 0°C the dienone **124** aromatized to give 4-methyl-2-nitrophenol (**51**) (95%) and *p*-cresol (5%).

g) Diene **52** (48 mg) was dissolved in a 3:1 (v/v) mixture of TFA and methanol-d_4 at 0°C. Conversion of **52** to dienone **124** was complete in 105 minutes at 0°C. After 24 hours at 0°C 4-methyl-2-nitrophenol (**51**) was obtained as the sole product.

h) Diene **52** (48 mg) was dissolved in 95:5 (v/v) mixture of TFA and methanol at 0°C. After four hours at 0°C, **52** reacted to give 4-methyl-2-nitrophenol (**51**) (72%) and the acid **54** (28%) on aqueous sodium bicarbonate work up.

In another experiment with a 99:1 (v/v) mixture of TFA

and methanol, **52** (48 mg) reacted over four hours at 0°C to give 4-methyl-2-nitrophenol (**51**) (52%) and **54** (48%).

i) Diene **52** (48 mg) was dissolved in a 1:1 (v/v) mixture of TFA and trifluoroacetic anhydride (0.3 cm^3) at 0°C. The reaction was monitored by NMR. Diene **52** aromatized to acid **54**. Before reaction of **52** was complete, **54** started to decompose to 4-methyl-2-nitrophenol (**51**). After 28 hours at 0°C, aromatization of **52** to **54** and subsequent decomposition of **54** to **51** (ca. 95%) was complete. Some unidentified product (ca. 5%) was also formed.

2.11.3 Reactions with strong protic and Lewis acids.

a) Diene **52** (48 mg) was dissolved in methanesulphonic acid (0.3 cm^3) at 0°C and the solution warmed to 10°C. ^1H NMR of the solution showed that aromatization of **52** was complete after 15 minutes. Work-up with aqueous sodium bicarbonate afforded 4-methyl-2-nitrophenol (**51**) (20%), **1** (16%), **54** (56%) and 2-methyl-2-(4-methyl-3-nitrophenoxy)propanoic acid **16** (8%).

b) Diene **52** (48 mg) was dissolved in triflic acid (0.3 cm^3) at 0°C. By the time first NMR spectrum of the solution could be recorded (ca. 10 minutes) the reaction of **52** was complete. Work-up as above gave 4-methyl-2-nitrophenol (**51**) (15%) and a mixture of **1** (15%), **54** (63%) and the 3-nitro acid **16** (7%).

c) Diene **52** (48 mg) was dissolved in chloroform-d (0.3 cm^3) and the solution was cooled to -40°C. Boron

trifluoride gas was bubbled through the solution for two minutes. Chloroform-d was replenished and the reaction monitored by NMR. No reaction ocurred over 10 minutes at -40°C. On raising the temperature to -30°C, the reaction of **52** was complete in 30 minutes. After the usual aqueous sodium bicarbonate work up a product mixture consisting of **1** (19%), **54** (62%) and **16** (19%) was obtained.

2.11.4 Reactions with sulphuric acid

a) Diene **52** (48 mg) was reacted with 0.5M sulphuric acid in 90% aqueous acetone-d_6 (0.3 cm^3) at 0°C. The reaction was monitored by NMR. The diene aromatized through the intermediate formation of the dienone **124**. After 18 hours at 0°C, the mixture was warmed to ambient temperature. The reaction was complete after 10 hours at ambient temperature. Usual bicarbonate work-up afforded 4-methyl-2-nitrophenol (**51**) (77%) and *p*-cresol (23%).

b) Diene **52** (48 mg) was dissolved in 0.5M sulphuric acid in methanol-d_4 (0.3 cm^3) at 0°C. After three hours at 0°C, conversion of **52** to the dienone **124** was complete. Usual bicarbonate work-up after 10 hours at ambient temperature gave 4-methyl-2-nitrophenol (**51**) (89%) and *p*-cresol (11%).

2.11.5 Reactions with sodium methoxide

Various ratios of diene **52** to sodium methoxide were tried at different temperatures and for different periods. All the reactions were worked up by pouring the reaction mixture into saturated aqueous ammonium chloride at 0°C and

extracting with ether. The ether extract was dried and the solvent evaporated. The NMR spectrum of the residue was recorded at 0°C in chloroform-d.

a) Diene **52** (48 mg, 0.2 mmol) was dissolved in methanol-d_4 (3 cm^3) at 0°C and sodium methoxide (12 mg, 0.22 mmol) was added to it. The mixture was stirred at 0°C for five minutes to give, after work up, dienone **124** (31%), t-5-methoxy-*r*-4-nitrocyclochex-2-en-1-one, **126** (59%) and 4-methyl-2-nitrophenol (**51**) (5%).

b) Diene **52** (48 mg, 0.2 mmol) and sodium methoxide (32 mg, 0.6 mmol) in methanol (3 cm^3) at -20°C for 30 minutes gave after work up dienone **124** (60%) and the cyclohexenone **126** (40%).

c) Diene **52** (48 mg, 0.2 mmol) was reacted with sodium methoxide (54 mg, 1 mmol) in methanol (3 cm^3) at 0°C for one hour. The products obtained were analyzed by HPLC. The mixture consisted of *p*-cresol (6%), cyclohexenone **126** (40%), its C-5 epimer **125** (21%) and *r*-3,*t*-5-dimethoxy-*c*-4-methyl-*t*-4-nitrocyclohexanone **128** (33%).

d) The above experiment was repeated and the reaction worked up after seven hours at 0°C. The products consisted of **125** (13%), **126** (67%), **128** (15%) and *r*-3,*c*-5-dimethoxy-*c*-4-methyl-*t*-4-nitrocyclohexanone **127** (5%) (analyzed by HPLC).

2.11.6 Reactions with other bases

a) Diene **52** (48 mg) was dissolved in acetonitrile (3 cm^3) at 0°C. Powdered potassium hydroxide (22 mg, 2 equivalents)

and 18-crown-6 (58 mg, 1.1 equivalent) was added to this solution and the mixture stirred in a reacti-vial at 0°C for eight hours. Work up with aqueous ammonium chloride as described above gave 4-methyl-2-nitrophenol (51) (36%) and *p*-cresol (64%).

b) Diene 52 (48 mg) was dissolved in acetonitrile (1.5 cm^3) at 0°C. Potassium hydroxide (22 mg) was dissolved in water (1 cm^3) and the solution added to the acetonitrile solution. The mixture was stirred at 0°C for one hour. Work-up as above gave dienone **16** (50%) and unreacted **52** (50%).

c) Diene **52** (48 mg) was dissolved in 0.25 M sodium hydroxide in 50% aqueous acetonitrile (3 cm^3) at 0°C and the solution stirred at 0°C for nine hours. The major products after work-up were **124** and isomers of 5-hydroxy-4-methyl-4-nitrocyclohex-2-en-1-one (**130**), identified by comparison with the ^1H NMR spectra of **125** and **126**. The products were not isolated or characterized.

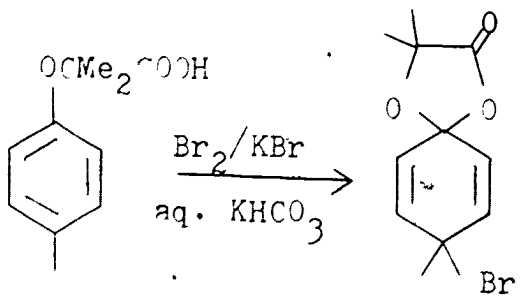
d) N,N-Diisopropylethylamine (0.3 cm^3) was added to a solution of **52** (48 mg) in 50% aqueous acetonitrile (8 cm^3) at 0°C. The mixture was stirred at 0°C for eight hours to give after work up dienone **124** (25%), *p*-cresol (26%) and 4-methyl-2-nitrophenol (49%).

CHAPTER III

RESULTS AND DISCUSSION

3.1 *Formation of 2-aryloxy-2-methylpropanoic acids*

2-Aryloxy-2-methylpropanoic acids have been known from the beginning of the century.[98] In 1969 Corey et al first described their use in trapping *ipso*-Wheland intermediates with the carboxyl group acting as an internal nucleophile.[97] They brominated 2-methyl-2-(4-methylphenoxy)propanoic acid (1) with bromine in aqueous potassium bicarbonate to form 8-bromo-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one

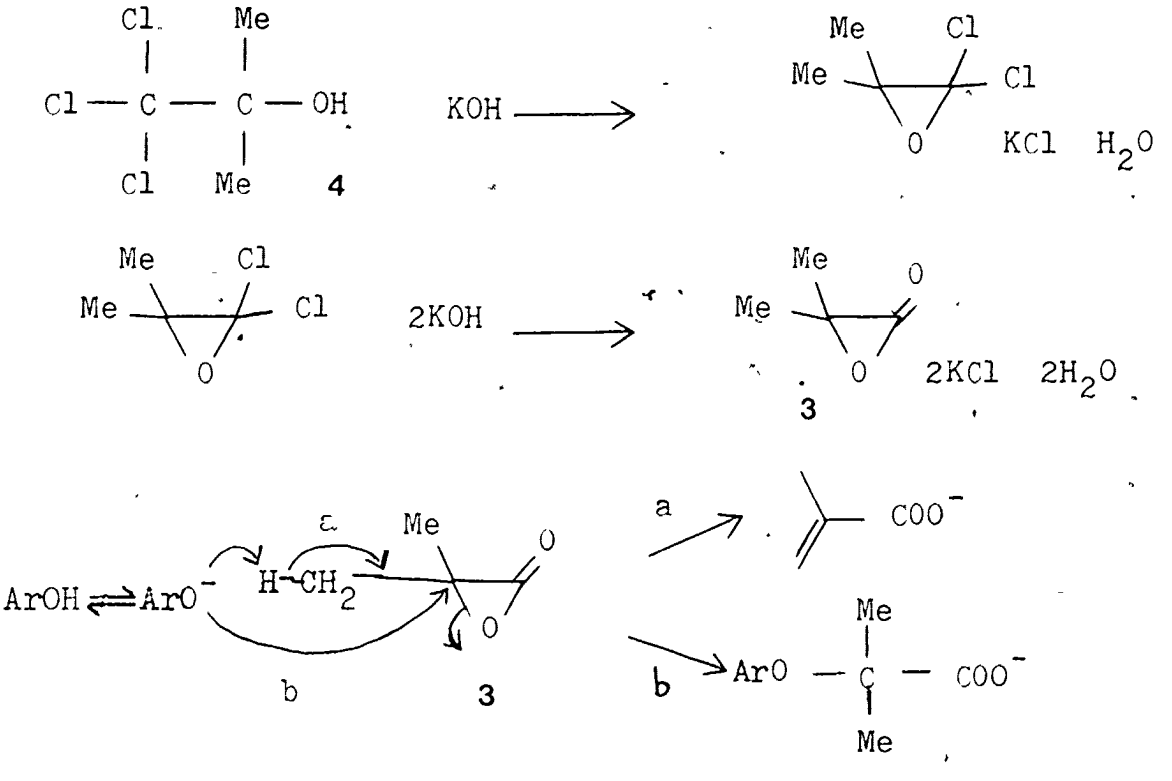


1 2

(2). A number of these acids were prepared either as substrates for nitration or for identification of products during the course of this work. Weizmann et al.[105] suggested the intermediacy of an α-lactone in the synthesis of 2-alkoxy-2-methylpropanoic acid. Dimethyl oxirinanone (3) and other dialkyl α-lactones have now been isolated at 77. K[106] and the bistrifluoromethyl oxirinanone has been shown to be stable at room temperature.[107] The formation of 2-aryloxy-2-methylpropanoic acid from 1,1,1-trichloro-2-methylpropan-2-ol (4) (chloretone) and appropriately

substituted phenols can be explained by a mechanism similar to that proposed by Weizmann[105] and is shown in Scheme 3.1--

Scheme 3.1 Formation of 2-aryloxy-2-methylpropanoic acid



In pathway b) (Scheme 3.1) the attack of the nucleophile on 3 is shown on the alkyl carbon instead of the carbonyl carbon. This is in accordance with the direction of attack of a soft base like phenoxide on small ring lactones.[108] It is also in accordance with the direction of polarization (carbon positive, oxygen negative) of the carbon-oxygen single bond in α -lactones, as shown by the requirement for strong electron-withdrawing groups to stabilize the molecule at room temperature.[107] As can be seen from Scheme 3.1, there is a competing reaction, namely, abstraction of proton

leading to methacrylic acid. Methacrylic acid was formed in the reactions investigated in the present work but was pumped off while drying the worked-up product under reduced pressure. No quantitative data were obtained on the yield of methacrylic acid versus that of 2-aryloxy-2-methylpropanoic acid. However the yield of the 2-aryloxy-2-methylpropanoic acid varied from 23% to 98% (Table 3.1) and appeared to be lower for phenols, substituted at both the *ortho* positions presumably reflecting steric hindrance. In the case of 2,3,5-trimethylphenol (5) very poor yields of the corresponding acid were obtained and it was necessary to preform the phenoxide salt by preliminary reaction with sodium methoxide in methanol to obtain a modest 35% yield.

Table 3.1

Yields of 2-aryloxy-2-methylpropanoic acids

ArOH	Yield	$ArOCMe_2COOH$
o-cresol (6)	75%	12
p-cresol (7)	92%[a]	1
2-methyl-3-nitrophenol (8)	98%	13
2-methyl-4-nitrophenol (9)	89%	14
2-methyl-6-nitrophenol (10)	23%	15
4-methyl-3-nitrophenol (11)	87%	16
2,3,5-trimethylphenol (5)	35%	17

a. Yield from Ref. 1

3.2 *Nitration of 2-methylphenoxy and 2-methylaryloxy acids*, 12, 14, 17, and 18

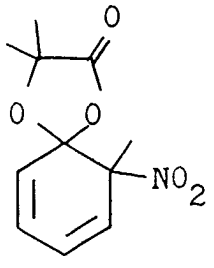
3.2.1 Nitration of 2-methyl-2-(2-methylphenoxy)propanoic acid **12** in acetic anhydride gave 20% of an aromatic product which was an acid and 80% of non-acidic, non-aromatic compounds. The aromatic acid product was separated from the non-aromatic neutral products by extraction into base during the work-up and was recovered after acidification of the basic extract. It was shown to be 2-methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid **14** identical to the authentic sample prepared from 2-methyl-4-nitrophenol (**9**) and chloretone (**4**). None of the 6-nitro isomer (**15**) was detected in the product. The non-acidic component was made up of two compounds in the proportion 85:15 as determined by NMR. The major compound **19** was isolated by crystallization. ^{1}H NMR showed that there were four protons in the region 5.5-6.5. There was a methyl group at δ 1.84 and the *gem*-dimethyl groups resonated at δ 1.53 and 1.58. ^{13}C NMR showed that there were four proton-bearing sp^2 carbon atoms and two fully substituted sp^3 carbon atoms in addition to the carbon bearing the *gem*-dimethyl groups. The ultraviolet spectrum of the compound showed it to be a conjugated diene (λ_{max} = 261 nm). The presence of the nitro group was confirmed by the infra red spectrum. All these facts were consistent with the 1,2 adduct structure of **19**. The minor neutral product **20** was clearly an isomer of **19**, as shown by

the ^{1}H and ^{13}C NMR spectra. Compound **20** was not isolated from the reaction product but was obtained when **19** was reacted with 10% trifluoroacetic acid in chloroform. A mixture containing **19** and **20** in 20:80 ratio was obtained and **20** was isolated by HPLC. The spectral characteristics of **20** are in accordance with it being the epimer of **19**.

Attempts to assign the relative stereochemistry of **19** and **20** by shift reagent studies were not successful. Tentative assignment of the stereochemistry was made on the basis of the reactivity of the two dienes and will be discussed later. In order to assign the ^{1}H and ^{13}C NMR shifts of **19** and **20**, 2-methyl-2-([4,6-$^{2}H_{2}$]-2-methylphenoxy)propanoic acid **21** was nitrated in acetic anhydride to give its 4-nitro substituted product **22** (20%) and a mixture of dienes (80%). Only the major isomer **23**, the deuterated analog of **19**, could be isolated. The NMR spectrum of **23** exhibited only two peaks in the diene region for H_7 and H_9. The chemical shifts of the vinylic protons in **19**, **20** and **23** are shown in Table 3.2.

Table 3.2

Chemical Shifts of vinyl protons in the dienes **19**, **20** and **23**



Diene	Chemical shift of			
	H_6	H_7	H_8	H_9
19	5.78 dt	6.18 ddd	6.08 ddd	6.28 ddd
20	5.78 bd	6.16 ddd	6.06 ddd	6.37 dm
23	--	6.17 brs	--	6.28 brs

In **19** the proton at δ 5.78 has a large coupling constant of 9.6 Hz and two small coupling constants of 0.9 Hz and 0.8 Hz. Similarly the proton at δ 6.28 has a large coupling constant of 9.9 Hz and two small coupling constants of 1.3 Hz and 0.8 Hz. Thus these two protons are at the ends of the diene system. It follows that in **23** the downfield proton at δ 6.28 must therefore be H_9 and the proton at δ 6.17 must be H_7. In **19** the protons at δ 6.18 and δ 6.08 are coupled to each other by a coupling constant 5.4 Hz, consistent with the protons being attached at the carbons of the central single bond of the diene system, with the downfield proton being H_7 as shown by the corresponding shift being present in the spectrum of **23**. The diene coupling pattern and the chemical shifts which can be unambiguously assigned to H_7 and H_9 in the deuterated analog **23** enabled assignment of all the protons in **19** and by analogy in **20**.

Nitration of (2-methylphenoxy)acetic acid **18** in acetic

anhydride was carried out by adding powdered crystals of the acid to the nitrating mixture at -50°C and gave 20% of (2-methyl-4-nitrophenoxy)acetic acid (24) and 80% of a mixture of diastereomers of 10-methyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one (25A and 25B). The acid (24) had the appropriate ^{1}H NMR for a 1,2,4-trisubstituted benzene and its melting point was the same as the literature value. None of the 6-nitro isomer (26) was formed. The non-acidic compounds were separated by fractional crystallization. The UV spectra showed that they were conjugated dienes. Their ^{1}H NMR spectra were similar to that of 19. Further the side chain methylene group which gave a sharp singlet in the ^{1}H NMR spectrum of 18 now showed an AB pattern (J = 15.1Hz). This suggested that the methylene protons were in different magnetic environments, consistent with the closure of the side chain to the lactone ring. These two dienes were assigned structures 25A and 25B. It was shown that these compounds were epimers by obtaining a same equilibrium mixture of 25A and 25B on treating them separately with 1% (v/v) trifluoroacetic acid in chloroform-d at 0°C.

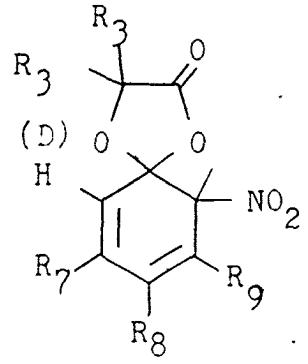
When 2-methyl-2-(2,3,5-trimethylphenoxy)propanoic acid 17 was nitrated only one product was obtained. This was neutral and non-aromatic. The ultra-violet spectrum showed the presence of a conjugated diene chromophore and the infra-red spectrum showed the presence of a nitro group.

The ^{1}H NMR spectrum was consistent with the product being the 7,9-dimethyl derivative of **19**. It was therefore assigned the structure **27**. Neither the diastereomer of **27** nor the 4-nitro and 6-nitro products (**28** and **29** respectively) were detected in the product.

When the 2-methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid **14** was nitrated in a mixture of trifluoroacetic anhydride and acetic anhydride at 0°C and the reaction mixture stirred at 0°C for 1 h, a single non-aromatic neutral product was formed which was assigned the structure **30** on the basis of spectral data (^{1}H NMR, ^{13}C NMR, IR and UV). No 2-methyl-2-(2-methyl-4,6-dinitrophenoxy)propanoic acid (**31**) was formed. The ^{13}C NMR shifts of 1,2 adducts obtained from the nitration of acids **12**, **21**, **14**, **17** and **18** are compared in Table 3.3. The similarity in the structures of these adducts is clearly reflected in their ^{13}C NMR spectra.

Table 3.3

^{13}C NMR shift of conjugated spirodienes



25A $R_3 = R_7 = R_8 = R_9 = H$

25B $R_3 = R_7 = R_8 = R_9 = H$

19 $R_3 = Me, R_7 = R_8 = R_9 = H$

20 $R_3 = Me, R_7 = R_8 = R_9 = H$

23 $R_3 = Me, R_7 = R_9 = H, R_8 = D$

30 $R_3 = Me, R_7 = R_9 = H, R_8 = NO_2$

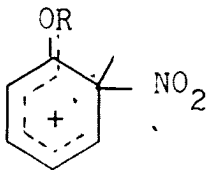
27 $R_3 = R_7 = R_9 = Me, R_8 = H$

Chemical Shift (δ_C) of	Adduct 25A	25B	19	20	23	30	27
C-2	169.6	169.9	173.8	173.8	173.6	172.3	173.6
C-3	63.6	64.0	77.9	77.9	78.0	78.1	77.8
C-5	108.3	109.1	104.8	105.8	105.0	103.4	106.9
C-6	122.4	122.1	122.5	121.9	122.4(t)	121.3	119.8
C-7*	128.2	127.4	127.5	126.9	127.6	129.6	135.2
C-8	125.6	125.3	126.9	126.3	126.2(t)	143.9	126.0
C-9*	128.8	128.0	129.4	128.3	128.8	129.6	137.8
C-10	91.6	91.3	91.7	92.0	91.8	91.1	95.0
10-CH_3	21.0	21.6	20.0	20.6	19.9	19.2	17.4
R_3	--	--	25.0	23.8	25.1	24.9	25.4
R_3	--	--	26.2	26.7	26.6	26.4	26.2
R_7	--	--	--	--	--	--	21.1
R_9	--	--	--	--	--	--	18.2

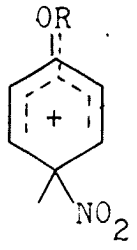
* Assignments could be interchanged

The striking features of the nitration of the 2-methylphenoxy and 2-methylaryloxy acids are that i) extensive *ipso*-attack occurs and ii) no 6-nitro derivatives are formed. With respect to the first point the extent of *ipso*-attack, which is at a position *ortho* to the oxygen substituent, is from 80 to 100%. Attack at the *para*-position is barely competitive. Attack at the other *ortho*-position, the unsubstituted *ortho*-position, does not occur at all. Alkoxy substituents are *ortho-para* directing, a result of the strong stabilization of the transition state for electrophilic substitution by the lone pair of the electrons on the oxygen (resonance effect). Thus nitration of the 2-methylphenoxy acids could be expected to lead to *ortho*- and *para*-nitro derivatives, including products from attack at the *ortho* position *ipso* to the methyl group. Nitration of aromatic ethers in acetic anhydride gives high (1/2 *o*)/*p* ratios (anisole : 1.3:1), the ratio increasing with increasing length of the side chain and with decreasing temperature.[109] The high yields of the *ipso*-nitro versus *para*-nitro product accords with the observed ratio but the absence of 6-nitro derivative is anomalous. The three Wheland intermediates in the nitration of 2-methylphenoxy acids, which are stabilized by delocalization of the positive charge onto the oxygen through conjugation of the lone pair electrons with the positive center, are W_2, W_4 and

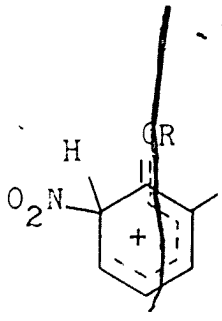
W_6 below



W_2



W_4



W_6

The other three possible Wheland intermediates (W_1, W_3 and W_5) do not have the lone pair conjugated with the positive center and would be of higher energy. The intermediates W_4 and W_6 will lead to aromatic nitro compounds by deprotonation. The *ipso*-intermediates W_2 can be trapped by the side chain carboxyl group attacking at C-1 to give a 1,2 adduct.

To understand the absence of any product arising from W_6, models of the intermediates W_2 and W_6 were made. In both the cases the ether side-chain must adopt a conformation which avoids hindrance with the incoming nitronium ion, i.e. the side chain must be twisted towards the *ortho*-position which is not attacked by the nitronium ion. The consequent non-bonding interactions of the side-chain and the substituent at this *ortho*-position are more severe for W_6, where there is an *o*-methyl substituent, than is W_2 where there is only an *o*-hydrogen. This must be responsible for raising the energy of the transition state leading to W_6 above the energy of the transition state

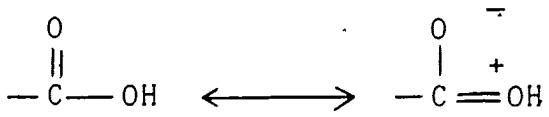
leading to W_2. The difference in the energies of the two transition states seems to be enough to exclude formation of W_6 in favour of W_2 in all the compounds studied.

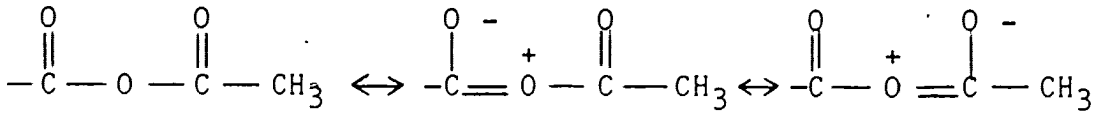
2-Methylanisole (32) can be considered as a model compound to estimate the extent of nitration at C-4 in 12 and 18. In 56% sulphuric acid where all of the *ipso*-Wheland intermediate is expected to be trapped by water and therefore not contribute to the indirect formation of 4-nitroproduct, 32 gives 23% 2-methyl-4-nitroanisole (33).[46] In comparison both 12 and 18 give 20% of the 4-nitro product. In the case of 17 the yield of 4-nitro product would be expected to be reduced by the steric hindrance of the two adjacent methyl groups. An estimate of this effect can be obtained from the nitration of *m*-xylene (34) for which the ratio of 2- to 4- substitution is 15:85.[110] Thus the 20% of 4- nitration which occurs in 12 and 18 would be expected to be reduced by ca. 1/6 to 4% in 17. In fact no 4-nitro product was observed.

3.2.2 Formation of 1,4 adducts

During the course of nitration of 12 at -20°C a one proton signal at δ 5.0 was observed in the ^{1}H NMR spectrum of the reaction mixture. This signal slowly disappeared when the reaction mixture was warmed to and maintained at 0°C. When trifluoroacetic acid was added to the reaction mixture in which the signal at δ 5.0 was present the signal disappeared. The signal at δ 5.0 was thought to be due to

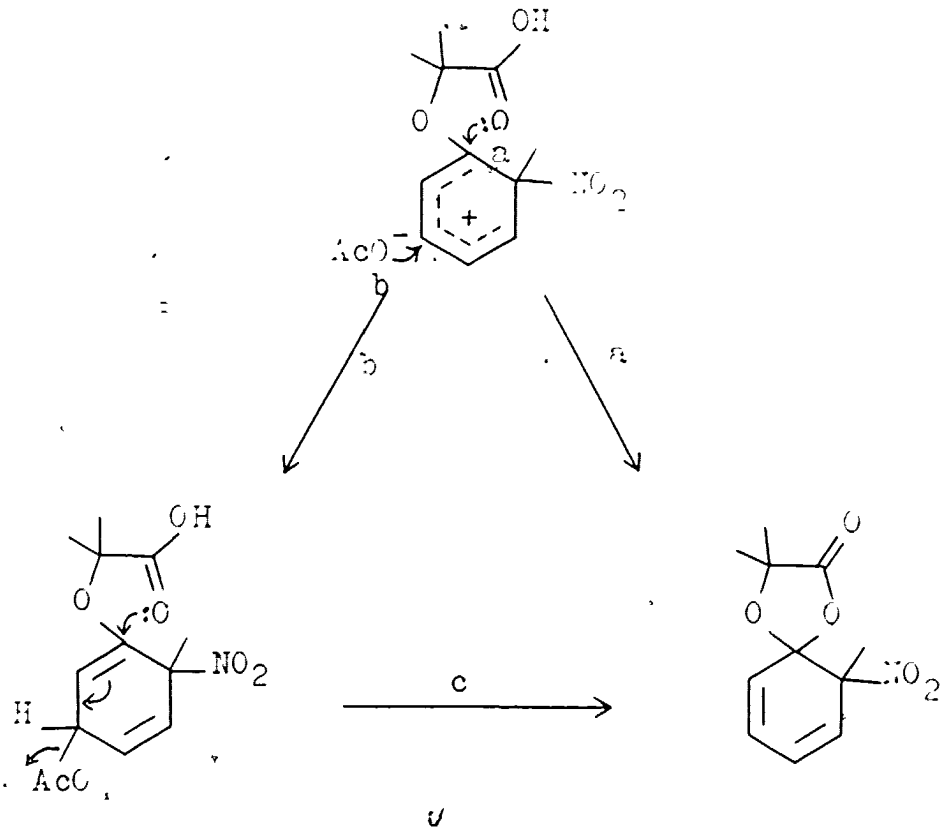
the proton conjugated with the oxygen substituent in the side-chain in a 1,4-adduct formed by addition of acetate to the C-5 position in the Wheland intermediate W_2 (p.130). Such a proton should resonate at higher field than other vinylic protons. Attempts to increase the amount of this product by varying reaction temperature between 0°C and -40°C, varying the concentration of nitric acid from 0.9 equivalents to 2 equivalents and varying the sequence of mixing the reagents gave inconsistent results. The signal at δ 5 did not occur or occurred with different and inexplicable intensities in each experiment. However, when the reaction was performed in a mixture of acetic anhydride and trifluoroacetic anhydride, the signal at δ 5 occurred consistently although its intensity varied in repeated experiments. It seems likely that on mixing **12** and acetic anhydride the mixed anhydride (35) of **12** and acetic acid was formed to an extent which varied from experiment to experiment. Nitration of the mixed anhydride (35) leads to the 1,4-adduct **36** since acetic acid from the solution can compete with the weakened internal nucleophile for the Wheland intermediate, the carboxylic acid being a better nucleophile than the anhydride. The nucleophilicity of the carboxyl group can be attributed to the contribution of a dipolar resonance form.



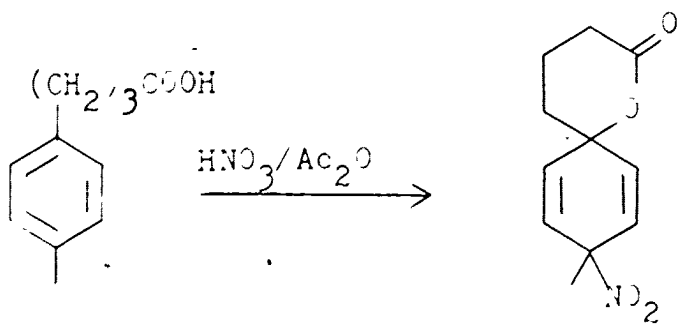


When the hydrogen is substituted by the electron-withdrawing acetyl group in the mixed anhydride, the electron-density on the carbonyl group is reduced. This should result in a decrease in the nucleophilicity of the carbonyl group. The rate of pathway a) and/or pathway c) (Scheme 3.2) will be slowed down and enable the observation of the 1,4 adduct.

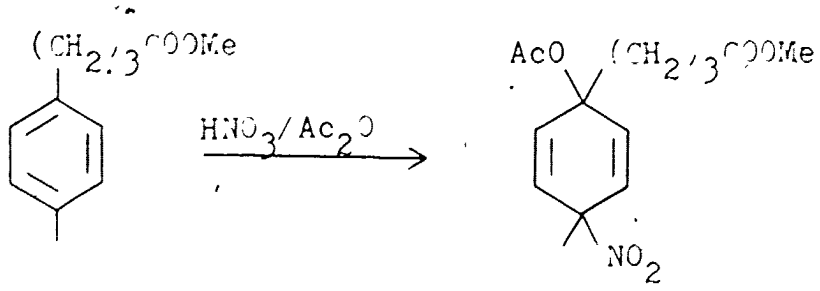
Scheme 3.2 Formation of 1,4- and 1,2-adducts



Nitration of 4-(*p*-tolyl)butyric acid (37), where the carboxyl group can act as an internal nucleophile gave the 1,4 adduct (38) with a spiro-lactone ring. But when the nucleophilicity of the carboxyl group was decreased by using methyl 4-(*p*-tolyl)butyrate (39) as the substrate, no lactone formation was observed. Only 40 the 1,4 adduct formed from the capture by acetate, an external nucleophile was observed.[71]



37 38

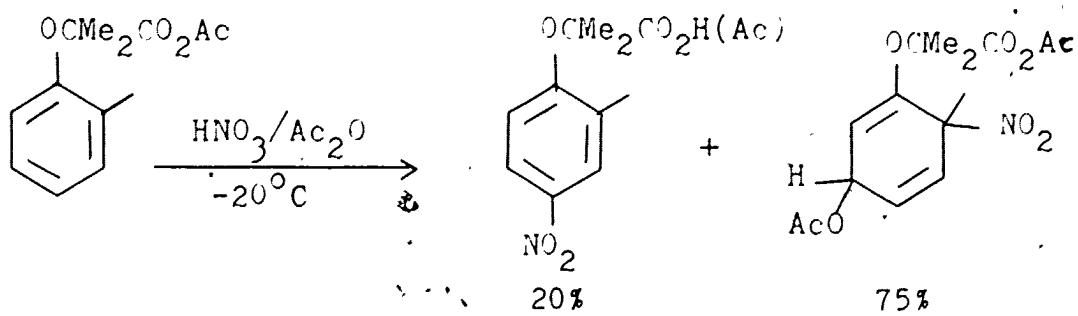


39 40

Trifluoroacetic acid is know to induce rapid mixed anhydride formation.[111] The consistent appearance of the signal at δ 5 when nitration of 12 was performed in the presence of trifluoroacetic anhydride can be attributed to consistent formation of the mixed anhydride. The variation

of the intensity of the signal at δ 5 can be attributed to the variation in the amount of mixed anhydride (35) present in the reaction mixture since the conditions for the formation of 35 were not standardized. Another factor which would contribute to the variation of the amount of the 1,4 adduct is the fact that trifluoroacetic acid can cause acid catalyzed loss of acetate to reform W_2 which would eventually close to the spirodiene (19).

To test the hypothesis, that the intermediate formation of 35 leads to a 1,4 adduct, acetic 2-methyl-2-(2-methylphenoxy)propanoic anhydride (35) was made by treating 12 with acetyl chloride. A mixture of 12 (39%) and the mixed anhydride (35) (61%) was obtained which was nitrated without separating the components. A mixture of diastereomers of 1,4 adduct 36 with one proton signal at 5.50 was indeed observed. No 1,2 adduct was formed although some might have been expected because 12 (39%) was present in the substrate. However, increasing the anhydride concentration did increase the amount of 36 formed.

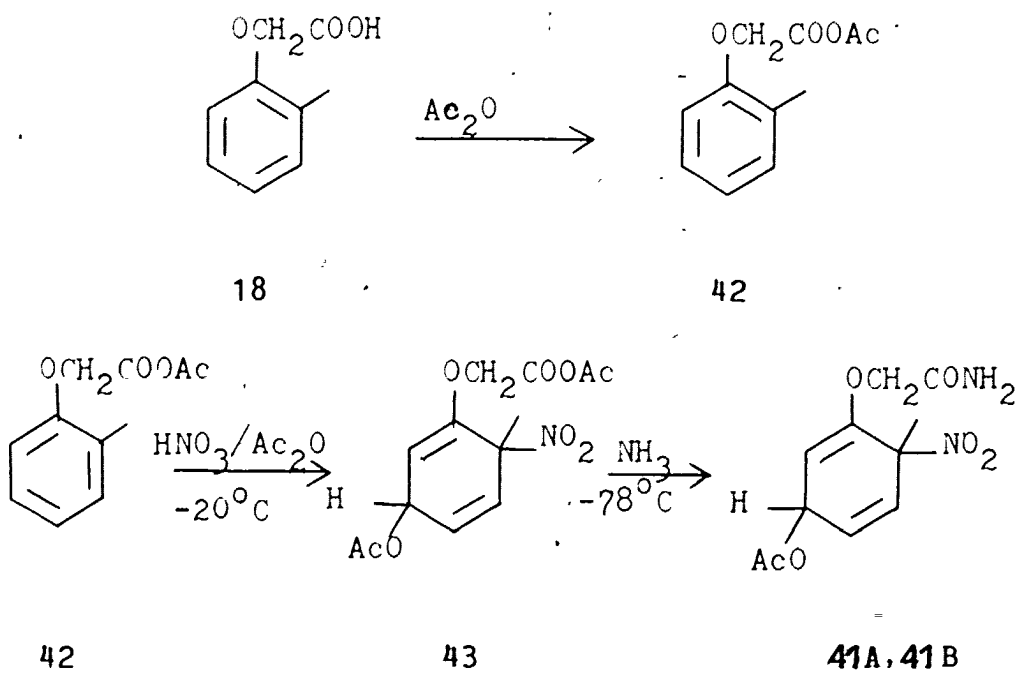


35 36

Further evidence for mixed anhydride formation was obtained in the nitration of (2-methylphenoxy)acetic acid **18**. The acid **18** is slightly soluble in acetic anhydride. Instead of adding the solid compound to the nitrating mixture as described earlier, **18** was first dissolved in acetic anhydride (40 equivalents) by heating and then added to the nitrating mixture. A complex mixture of non-aromatic products (80%) was obtained along with the 4-nitro product (20%). The 1,2 adducts **25A** and **25B** were present to the extent of 60% of the non-acidic products. The remaining 40% was made up of two compounds, **41A** and **41B** which could be separated by fractional crystallization. The NMR spectrum of each compound exhibited a one proton signal at δ 5.2 highfield to three other protons between δ 5.7-6.3. There were two methyl signals, one of which could be assigned to the ring methyl group (δ 1.89) and the other was assigned to an acetate methyl group (δ 2.14). A singlet at δ 4.4 was observed when the spectra were recorded at ambient temperature. This was assigned to the side chain methylene protons and indicated that free rotation of the side chain was possible. The UV spectrum did not show the conjugated diene chromophore. The IR spectrum and the ^{13}C NMR spectrum indicated the presence of two carbonyl groups. The IR spectrum also showed absorption at 3300 cm^{-1} and the ^{1}H NMR spectrum had a broad peak at δ 6.7 which resolved into two broad singlets integrating for one proton each when the

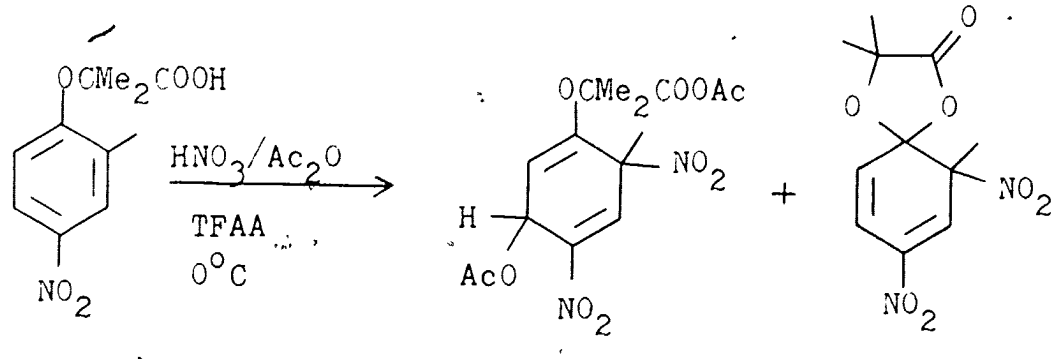
sample was cooled to 0°C. These were assigned to a NH_2 group. The presence of two carbonyl groups suggested that the side chain $-OCH_2COOH$ in **18** was converted to $-OCH_2CONH_2$ in the product. The two products were assigned the diastereomeric structures **41A** and **41B**. Their formation must have occurred during work-up with liquid ammonia and can be best explained by the intermediacy of the mixed anhydrides **42** and **43** (Scheme 3.3). Mixed anhydride formation was favoured under the nitration conditions because of the large excess of acetic anhydride used and the heat employed to dissolve the substrate.

Scheme 3.3 Formation of 1,4-adduct via mixed anhydrides



Nitration of 2-methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid (**14**) in trifluoroacetic

anhydride-acetic anhydride at 0°C also appeared to give the expected 1,4-adduct **44** with ^{1}H NMR absorptions at δ 5.25, 6.58 and 7.45 as well as the spiro diene **30** with peaks at 6.02, 6.78 and 7.57. The first set of absorptions disappeared on standing and the spiro peaks due to **30** were enhanced, probably as a result of acid-catalyzed loss of acetate and spiro ring closure. The NMR assignments are supported by the absence of the 10 Hz coupling of the adjacent vinyl protons in the 1,4 adduct. Here again formation of the 1,4 adduct can be attributed to the intermediate formation of **45**, a mixed anhydride of the acid **14** and acetic acid, under the conditions used.

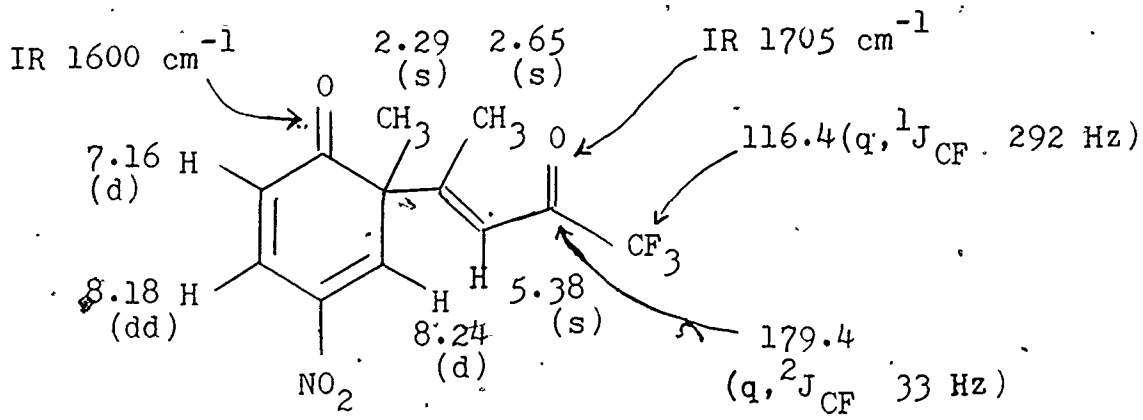


14		**44**	**30**
	30 min	41%	59%
	1 h	--	100%

3.2.3 Problems from dinitration

In one experiment when trifluoroacetic acid was added to the nitration mixture from acid **12** and the mixture then warmed to 0°C, the signal at δ 5.0, due to the 1,4 adduct

36, disappeared. At the same time signals due to the aromatic product **14** also disappeared, giving rise to signals assigned to the dinitrodiene **30**. When this reaction mixture was worked up with liquid ammonia, the aqueous washings contained a compound which exhibited ^{1}H NMR : δ 2.67 (3H, s), 8.20 (1H, d, J = 10 Hz), 8.54 (1H, dd, J = 10 Hz, 2 Hz), 9.44 (1H, d, J = 2 Hz). This compound could not be identified. In an attempt to elucidate its structure the acid **14** was treated with a mixture of trifluoroacetic acid and trifluoroacetic anhydride. A single product **46** which analyzed (mass spectrum and elemental analysis) for $C_{12}H_{10}NO_4F_3$ was obtained after 21 days at ambient temperature. Its ^{13}C NMR showed the presence of a $-COCF_3$ group which could be identified by one and two bond coupling with fluorine in the proton decoupled spectrum. The UV spectrum showed the presence of a conjugated dienone. The IR and ^{13}C NMR spectra showed the presence of two carbonyl groups. ^{1}H NMR showed that there was a trisubstituted double bond with a methyl group trans to the proton at the unsubstituted position (no allylic coupling). Another sharp methyl signal indicated the presence of a methyl group attached to a quaternary carbon. All the spectral data could be explained by the structure below.



The product **46** obtained is not the product with low field proton signals, obtained from the nitration reaction mixture.

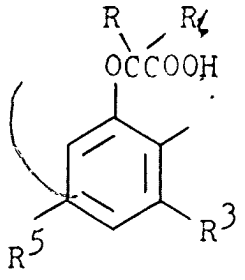
Nitration of 2-methyl-4-nitrophenol (**9**) was carried out in acetic anhydride. 6-Methyl-4,6-dinitrocyclohexa-2,4-dienone (**47**) and 2-methyl,4,6-dinitrophenol (**48**) were obtained. However the dienone **47** did not prove to be unknown product either.

3.2.4 Nitration of acids **12**, **17** and **18** in trifluoroacetic acid/chloroform-d.

Acids **12**, **17** and **18** were nitrated in trifluoroacetic acid/chloroform-d to determine the product ratios under these conditions. The results are summarized and are compared with the results of nitration in acetic anhydride in Table 3.4.

Table 3.4

Products from nitration of 2-methylphenoxy- and 2,3,5-trimethylphenoxy- acids.



12 R = Me, $R^3 = R^5 = H$

17 $R = R^3 = R^5 = Me$

18 $R = R^3 = R^5 = H$

	Products in acetic anhydride				Products in TFA/$CDCl_3$ at 0°C			
	Expected		Observed					
	4-	2-,6-	4-	2-	%TFA	4-	6-	other
12	23%	77%	20%	80%	33	57%	--	43%(30)
17	4%	96%	---	100%	25	100%	--	-----
18	23%	77%	20%	80%	25	60%	40%	-----

The striking feature of the results is that in the presence of trifluoroacetic acid nitration occurs largely or completely at the 4-position. It is likely that nitration also occurs at the *ipso*-position but that the ring does not close to form the spirodiene under the conditions and instead W_2 ejects the nitronium ion to reform the original substrate which has a further opportunity for nitration at the 4-position.

However nitration of **18** in trifluoroacetic acid and

chloroform gave 40% of the 6-nitro product **26**. This means the steric effect, which prevents nitration at the 6-position, is more effective when there is a *gem*-dimethyl group rather than a methylene group in the side chain. The fact that **18** is not nitrated at the 6-position in acetic anhydride, whereas it is nitrated at the 6-position in trifluroracetic acid and chloroform is attributed to a greater extent of solvation of the carboxylic acid side chain in acetic anhydride, thus raising the effective size of the side chain and making hindrance of more importance in this solvent. In the cases of **12** and **17** the *gem*-dimethyl group in the side chain results in the buttressing effect with the 2-methyl substituent being of significance, independent of the extent of solvation of the side chain and 6-nitration does not occur in either solvent.

3.3 *Nitration of 2-methyl-2-(4-methylphenoxy)propanoic acid*(1)

Nitration of 4-methylanisole (**49**) can be used as a model to estimate the product ratio in **1**. At low acidities where the *ipso*-Wheland intermediate is trapped quantitatively by water, **49** gives ca. 60% 4-methyl-2-nitroanisole (**50**).[46] The remaining 40% being 4-methyl-2-nitrophenol (**51**) resulting from *ipso*-attack. When **1** was nitrated a mixture of diastereomers **52** and **53** (46%) and 2-methyl-2-(4-methyl-2-nitrophenoxy)propanoic acid **54** (54%) was obtained. (cf. Ref. 37, 47% yield of adducts). The

acid **54** was identified by its ^{1}H and ^{13}C NMR spectra. The presence of two diastereomers in the adduct mixture was detected by its melting behaviour and further by addition of shift reagent which separated the superimposed peaks of the two diastereomers in the ^{1}H NMR spectrum. The adducts were separated by HPLC. Both the adducts had UV absorption maximum at 220 nm and thus the non-conjugated diene structure was assigned to them. The relative stereochemistry of the two adducts was assigned by shift reagent studies. Differential effect of the added shift reagent on the 8-methyl group enabled assignment of the relative stereochemistry. The relative gradient for C-8 and 8-H in adduct **52**, which was eluted first, was half the corresponding relative gradient in adduct **53**. This indicated that the 8-methyl group was further from the complexing site, the carbonyl group, in **52** than in **53**. Thus **52** was assigned as the (*Z*)- isomer and **53** was assigned as the (*E*)- isomer.

3.4 *Isomerization reactions of* 1,2 *adducts*

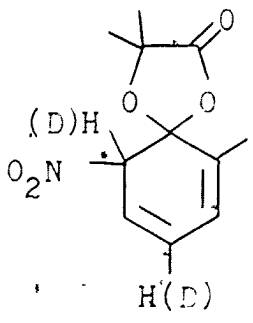
3.4.1 Isomerization of 3,3,10-trimethyl-10-nitro-1,4-dioxasprio[4.5]deca-6,8-dien-2-one (**19**)

Diene **19** in carbon tetrachloride at 50°C isomerized over 9h to give a new compound. This new compound (**55**) had ^{1}H NMR spectrum which showed the presence of a methyl group (δ 1.85) attached to a vinyl carbon, and a *gem*-dimethyl group (δ 1.54, 1.58). The signal at δ 1.85 was broadened

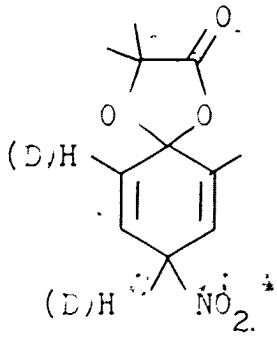
by allylic coupling. The region between δ 5-6.5 had signals of four protons. There were three vinylic protons at δ 5.93, 6.07 and 6.30 which showed as multiplets, and there was another multiplet centered at δ 5.30 which was assigned to a deshielded allylic proton. The proton decoupled ^{13}C NMR spectrum of the new compound showed three proton-bearing sp^2 carbon atoms and another fully substituted sp^2 carbon atom. There was another signal at δ_C 87.8 which split into a doublet in the gated decoupled ^{13}C spectrum. This was assigned to a sp^3 carbon atom bearing a secondary nitro group. In the ^1H NMR spectrum of the compound on irradiating the methyl signal at δ 1.85, all the vinylic proton signals and the allylic proton signal sharpened, indicating that the methyl group was coupled to these protons by allylic and long range couplings. This same compound was obtained from **19** in 63% yield when heated in chloroform-d at 50°C for 6h, or in 80% yield when the chloroform-d solution was left at ambient temperature for 12 days.

When **23**, the deuterated analog of **19** was dissolved in chloroform-d, it gave over 3 days at ambient temperature a new compound **56** which had proton signals at δ 1.54, 1.59, 1.86, 5.94, 6.07 in the ^1H NMR spectrum. There was no proton signal at δ 5.30, indicating that in the compound obtained from **19**, this signal was due to the proton originally at the 6- or 8- position of **19**. Thus on the

basis of ^{1}H and ^{13} NMR spectra of the new compound from **19** and the ^{1}H NMR spectrum of its deuterated analog from **23** two structures can be proposed for it --



55



57

When this compound was treated with sodium bicarbonate solution **15**(80%) and **58**(20%) were obtained. These were separated by extraction of the neutral **58** from the basic solution which retained the acid **15**. The acid **15** was identified by comparison of its ^{1}H NMR spectrum with that of an authentic sample. The neutral product was found to be a tri-substituted aromatic compound. Its ^{1}H NMR spectrum showed an ABC pattern of three adjacent protons. The gem-dimethyl group on the side chain was still present in the molecule (^{1}H and ^{13}C NMR). The IR spectrum showed that the compound was an alcohol and that an ester function and a nitro group were present. The compound decomposed to 2-methyl-6-nitrophenol (**10**) on injecting into a GC column. The presence of **10** was confirmed by coinjection and GC/MS. Elemental analysis gave the empirical formula $C_{11}H_{13}NO_5$ suggesting that the compound was a structural isomer of acid

15. Based on this information, the neutral compound was assigned the structure 58.

Since the nitro group was *ortho* to the side chain in the aromatic products the new diene was assigned the conjugated diene structure 55. When 55 was treated with trifluoroacetic acid in chloroform-d again only the 6-nitro product, namely 15 (100%) was formed.

Isomerization of 19 to 55 was observed in other solvents. The results are summarized in Table 3.5.

Table 3.5

Yields of Products of isomerization of 19

Solvent	Temperature	Half life	Maximum amount of 55 observed	Products after complete aromatization	
				15	58
$CDCl_3$	50°C	2.8h	80%	80%	20%
CCl_4	ambient	4 days	>95%	80%	20%
CD_3CN	ambient	3 days	traces	59%	41%
C_6D_6	ambient	3 days	56%	80%	20%
THF-d_8	ambient	3 days	---	50%	50%
Pyridine-d_6	50°C	3h	---	92%	8%

The rate of disappearance of 19 did not vary much with change in solvent but was greatly increased on increasing the temperature. In all cases 15 (and 58) were the only aromatic product(s). The relative amount of 58 on complete

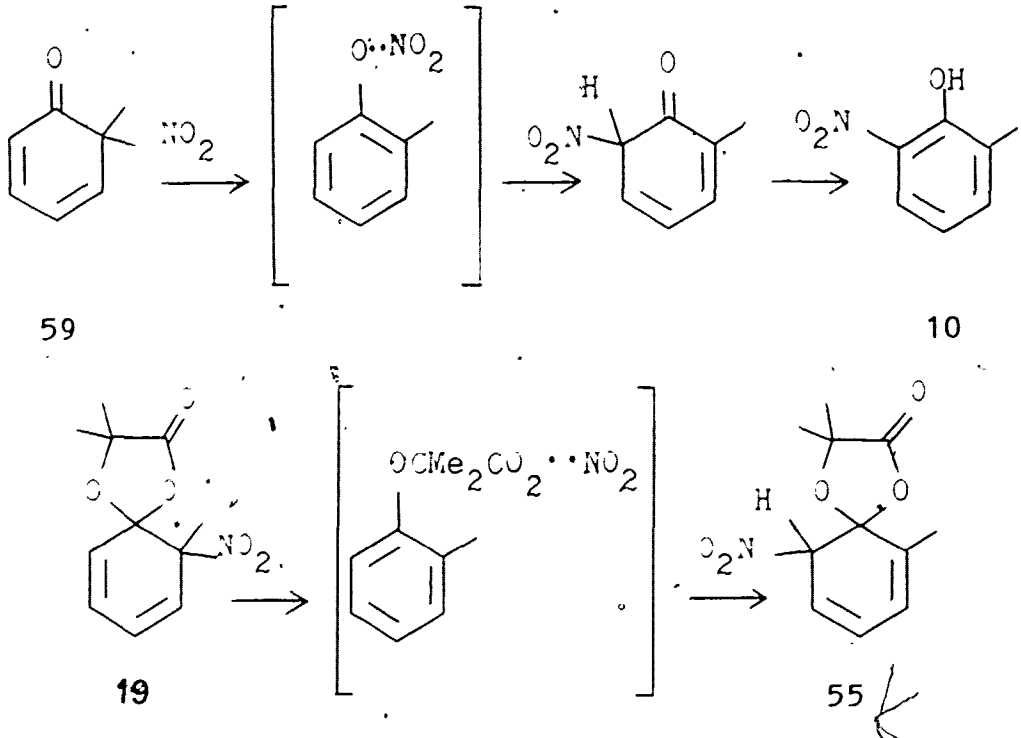
aromatization increased with the basicity of the solvent on going from carbon tetrachloride to tetrahydrofuran, but in pyridine the amount of 58 decreased to 8%. The maximum amount of 55 detected in the solution decreased with increasing basicity of the solvent. Only traces of 55 were observed in acetonitrile-d_3 while no 55 was observed in tetrahydrofuran or pyridine-d_5.

Since the rate of the reaction did not vary with the solvent, and the isomerization occurred under essentially neutral conditions, charged species as intermediates are unlikely. Other possible reaction pathways are homolytic dissociation-recombination or a concerted nitro group shift.

3.4.2 Trapping experiments

The isomerization of 6-methyl-6-nitrocyclohexa-2,4-dienone (59) is formally very similar to the new rearrangement reaction of 19. A mechanism similar to that which has been proposed for the rearrangement of 59[94] can be considered for the isomerization of 19 to 15 (Scheme 3.5).

Scheme 3.4 Possible mechanism for isomerization of **19** and **59**



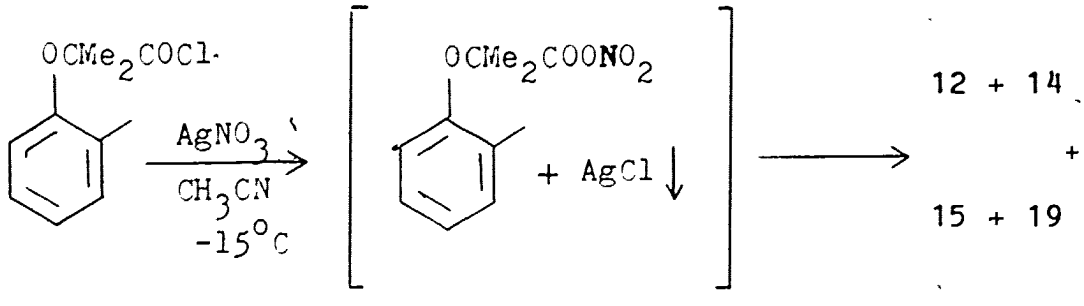
59 **10**

19 **55**

If the mechanism shown in Scheme 3.5 is followed, some leakage of the nitrogen dioxide radical from the caged radical pair is possible. The isomerization of **19** was performed in the presence of p-cresol as a radical trapping agent. When the isomerization to **55** and subsequent aromatization was complete and the reaction mixture was analyzed by GC less than 1% 4-methyl-2-nitrophenol (**51**) was detected. Thus if the radical pair is an intermediate in the rearrangement, it must be a caged radical pair and possibly even a tight radical pair in which case it can be represented as the nitrate ester **60** of **12**. To determine if such an ester could be an intermediate, it was generated *in situ* from the acid chloride **61** and silver nitrate in acetonitrile at -15°C (Scheme 3.5). Since **55** is not stable

in acetonitrile, if it were formed, 15 and/or 58 were expected to be the observed product(s). Moreover, if 60 is an intermediate some 19 can be expected from the reverse isomerization reaction. However no 2-methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid (14) should be formed because the rearrangement is regiospecific. When the products from the nitrate ester generated *in situ* were examined, 15 (8%), 14 (8%), 19 (16%) and 12 (76%) were obtained. The formation of 14 ruled out the nitrate ester 60 as an intermediate but a caged radical pair cannot be still ruled out by this experiment.

Scheme 3.5 Formation and Reaction of 60



61 60

If such a radical pair exists, the products obtained should be non-stereospecific. Both 19 and 20 should give the same product(s) because the same radical pair would be formed from both isomers.

If the radical pair is not an intermediate, the other possibility is a concerted nitro shift, in which case the rearrangement will be stereospecific, namely 19 should form

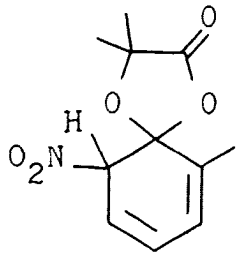
only one isomer (55) and 20 should form the diastereomer 62. Isomerization of 20 was studied to determine the stereochemistry of the reaction.

3.4.3 Rearrangement product from 20

When 20 was heated in carbon tetrachloride at 50°C for 24h, a diene different from 55 was obtained. The ^{1}H NMR spectrum differed from that of 55 in the chemical shifts of the methyl groups and the coupling constant between the protons at C-9 and C-10. No trace of the diastereomer 62 was found in the spectrum of 55 and vice versa. The NMR data for the two dienes are summarized in Table 3.6.

The trapping experiment showed that the homolytic mechanism, if it contributed to isomerization was responsible for less than 1% of the reaction. Isomerization of the diastereomers showed that the isomerization was stereospecific. These results suggest that the isomerization is a concerted reaction, namely a [1,5] sigmatropic shift of the nitro group.

Table 3.6



55 - (*E*)-diastereomer

62 - (*Z*)-diastereomer

^{1}H NMR (250 MHz) data for 3,3,6-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-ones

Diene	3-CH_3	6-CH_3	7-H	8-H	9-H	10-H	$^3J_{9,10}$ (Hz)
55	1.54, 1.58	1.85	6.07	6.30	5.93	5.30	4.9
62	1.50, 1.53	1.88	6.13	6.30	5.99	5.30	4.6

^{13}C NMR data for 3,3,6-trimethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-ones

Diene	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	3-CH_3	6-CH_3
55	173.7	77.3	103.4	134.7	124.6	129.3	117.5	87.8	25.9, 26.5	16.0
62	174.0	78.2	103.9	134.4	125.4	129.0	117.8	87.8	25.6	16.5

Further evidence for the different stereochemistry of the dienes **55** and **62** was obtained in the aromatization of these dienes in tetrahydrofuran, a solvent more basic than carbon tetrachloride. Diene **55** in tetrahydrofuran gave the 6-nitro acid **15**(50%) and the 2-methyl-6-nitrophenyl ester **58**(50%) on aromatization. On the other hand **62**, on aromatization in tetrahydrofuran, afforded acid **15** as the only product. When the aromatization was carried out in the

presence of 1.1 equivalents of tetracyanoethylene (TCNE) in tetrahydrofuran, **55** gave **15**(30%) and **58**(70%). Under the same condition **62** again aromatized to **15** quantitatively. The different product ratio in these above reactions clearly indicated that the relative orientation of the substituents in **55** and **62** was different.

These aromatization reactions can be considered as 1,2 elimination reactions with the solvent acting as a base. The α-carbon atom (C-5 of **55** and **62**) has the two functional groups in the spirolactone ring attached to it and both of them can act as a leaving group under suitable condition. The β-carbon (C-10 of **55** and **62**) bears a secondary nitro group and therefore the β-hydrogen atom (10-H of **55** and **62**) is acidic.

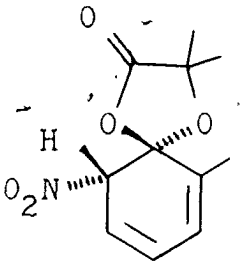
The transition state of elimination reactions is affected by various factors,[112] some of which are indicated below. Substrates having a β-nitro group usually undergo elimination by the E_{1cB} pathway. If the product of an elimination reaction is aromatic, the carbon nucleofuge bond breaking becomes competitive with carbon hydrogen bond breaking or the transition state of the reaction becomes more E_2-like. With E_{1cB}-like transition states, *syn* elimination becomes more facile, while with the transition state having more E_2, character high *anti*/*syn* product ratios are obtained. The nucleofuge also affects the transition state: a poor nucleofuge shifts it toward the E_{1cB} end of

the spectrum while a good nucleofuge shifts it towards the E_2 end of the spectrum. In six-membered rings, *anti* elimination is favoured so the nucleofugicity of the group *trans* to the β-hydrogen affects the reaction most.

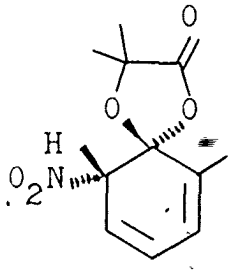
Both 55 and 62 have a β-nitro group. If they undergo elimination by the E_{1cB} pathway both the dienes would give the same cyclohexadienyl anion as an intermediate and would be expected to give the same product(s). Since the two dienes give different product ratios, the E_{1cB} mechanism is not involved. Both the dienes give aromatic products and thus their transition states are expected to be more E_2-like. Thus the transition state for the elimination of 55 or 62 must be intermediate between the E_2 and E_{1cb} transition states. If two products are formed, there would be a transition state for each. Considering the groups at the α-carbon, $-OCOCMe_2O^-$ is a poor nucleofuge while $-OCMe_2COO^-$ is a much better nucleofuge.

When the alkoxide is *trans* to the β-hydrogen, the transition state for *anti* elimination will be more E_{1cB}-like than is the case when the carboxylate is in this position. Also because of the activation by the β-nitro group, *syn* elimination would also become favoured. Given the poor nucleofugicity of the alkoxide as compared to the carboxylate, the normally minor *syn* elimination would become competitive with the normally favoured *anti* elimination and products from both the *syn* and *anti* elimination would be

expected. If the carboxylate is trans to the β-hydrogen the transition state will become more E_2-like and a high *anti/syn* ratio would be expected. Diene **55** gave two products which can arise by competing *syn* and *anti* elimination while **62** gave only product reflecting high preference for one mode of elimination over the other. Thus **55** can be assigned the (*E*)-configuration where the alkoxide is trans to the β-hydrogen and **62** can similarly be assigned the (*Z*)-configuration.



55



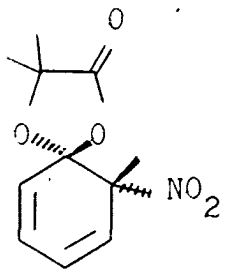
62

The product ratio obtained in the presence of TCNE also corroborates the above configurational assignment. TCNE has a low-energy vacant orbital and it can therefore act as a weak Lewis acid. In the transition state for the formation of **58**, the developing negative charge is localized on the alkoxy oxygen and this transition state would be stabilized by complexation. The transition state for the formation of **15** has the developing negative charge delocalized over the carboxyl group and stabilization by complexation with TCNE

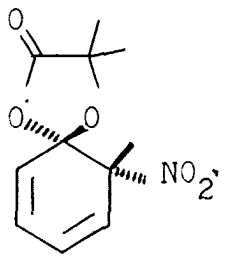
would be less than that for the formation of **58**. Thus if the formation of **15** and **58** are competing reactions, aromatization in the presence of TCNE should increase the amount of **58**. In **55** where the alkoxy group is assigned *trans* to the β-hydrogen, complexation would increase the anti elimination product **58** over the *syn* elimination product **15**. Such an increase is indeed observed, as the amount of **58** increases from 50% to 70% in the presence of TCNE. When the carboxy group is *trans* to the β-hydrogen as assigned in **62**, complexation with the alkoxy group would decrease the *anti/syn* ratio. The fact that no **58** is obtained from **62** in the presence of TCNE suggests that even on stabilization of the transition state by TCNE, the transition state for the formation of **58**, is still higher in energy than the transition state for the *anti* elimination of the carboxy group to give **15**.

When **55** was treated with pyridine, a base stronger than tetrahydrofuran, the amount of **58** obtained decreased from 50% to 8%. With increasing base strength, the transition state for elimination becomes more E_{1cB}-like[112] or formation of the cyclohexadienyl carbonion is almost complete in the transition state. In this case, the product ratio would be determined by the nucleofugicity of the competing groups. Thus in **55** loss of the carboxy group would be favoured, leading to higher amount of **15**(92%) and a corresponding decrease in the amount of **58**(8%) in the product.

Once the relative stereochemistry of **55** and **62** is assigned, it can be used to assign the relative stereochemistry of **19** and **20** which could not be assigned by any other means. Since the isomerization of **19**(**20**) to **55**(**62**) is shown to be stereospecific, **19** can be assigned the (*E*)-configuration and **20** can be assigned as the (*Z*)-diastereomer.

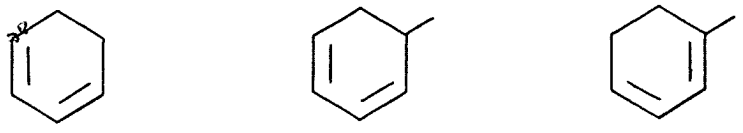


19



20

The stereospecific rearrangement of **19**(**20**) to **55**(**62**) occurs very readily even at ambient temperature. The reaction goes in the direction **19** to **55** because **55** is more stable than **19**. *Ab initio* calculations[113] on substituted cyclohexadienes show that 1-methylcyclohexadiene (**63**) is more stable than 5-methylcyclohexadiene (**64**). Since only relative energies are considered, the spirolactone and the nitro group can be neglected for comparison purposes.

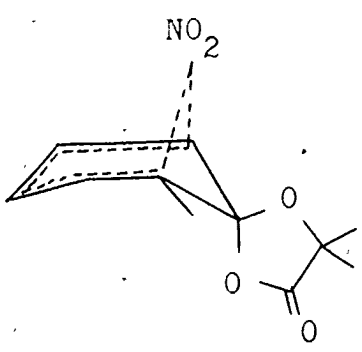


64 63

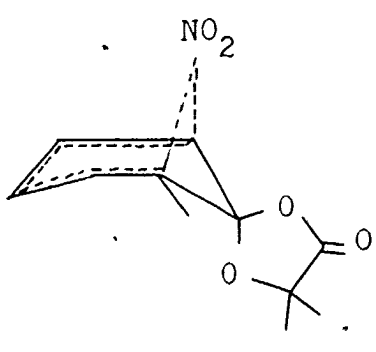
Relative Energy 0 kJmol^{-1} -12.0 kJmol^{-1} 4.6 kJmol^{-1}

Gain in stabilization energy 4.6-(-12.0) = 16.6 kJmol^{-1}.

Diene **19** is less stable than **20** as it is the minor component in the mixture equilibrated in the presence of trifluoroacetic acid. Since the rearrangement is a single step process and the reaction is exothermic, it should have low activation energy, leading to facile rearrangement if steric factors are not considered. The transition states for the rearrangement of **19** and **20** can be shown as --



T.S. for **19**



T.S. for **20**

The only difference in the transition states is in the stereochemistry of the sp^3 center which is not involved in the pericyclic transition state. The transition states for the rearrangement are close in energy. The rate constants

for the isomerization of **19** and **20** in carbon tetrachloride at 50°C can be calculated from the changes in concentration (obtained from integration of the NMR spectra) of the unreacted diene as the reaction progressed. The rate constants are --

$$k \text{ (for } \mathbf{19}) = 6.87 \times 10^{-5} s^{-1}$$

$$k \text{ (for } \mathbf{20}) = 2.44 \times 10^{-5} s^{-1}$$

The activation energy difference (calculated from the rate constants for isomerization of **19** and **20**) is -2.8 $kJmol^{-1}$ and when combined with the energy difference of the reactants (calculated from equilibrium concentrations of **19**(20%) and **20**(80%) at 0°C), 3.2 $kJmol^{-1}$, this gives an energy difference between the transition states of 0.4 $kJmol^{-1}$ with the transition state for **19** being slightly higher in energy.

3.4.4 Isomerization of 3,3,7,9,10-pentamethyl-10-nitro-1,4-dioxaspiro[4,5]deca-6,8-dien-2-one(**27**).

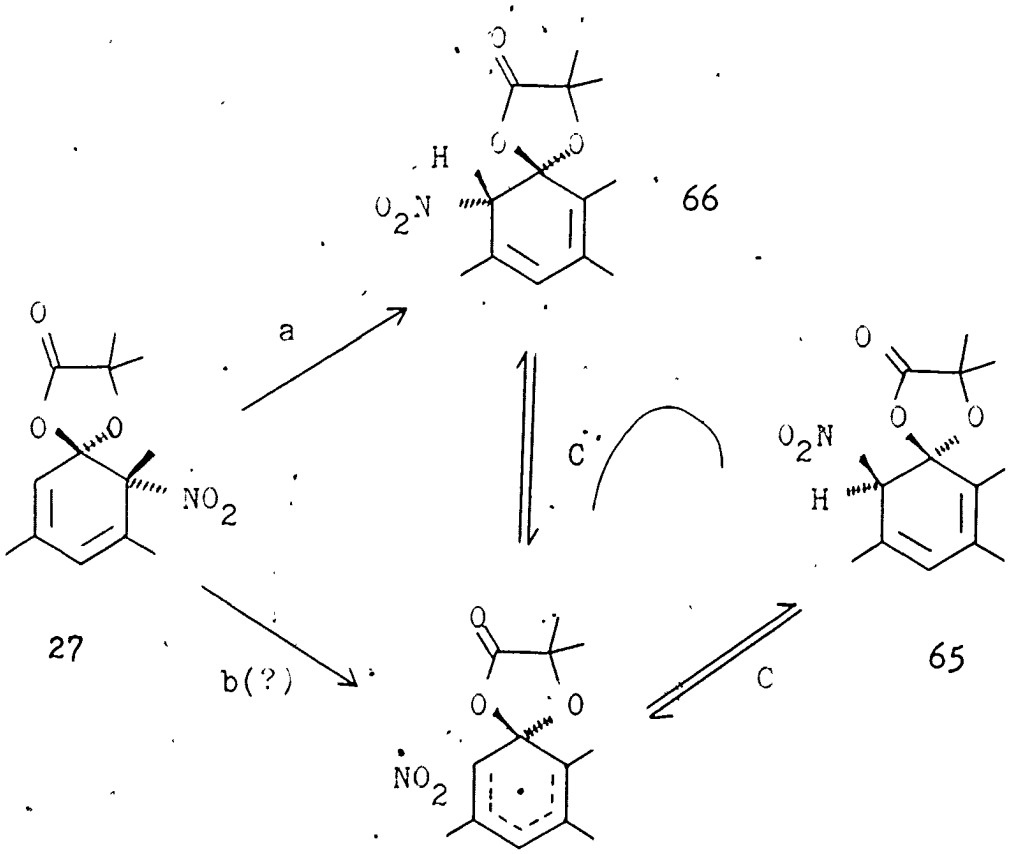
Dienes **55** and **62** were obtained in essentially quantitative yields under suitable conditions, but could not be obtained crystalline. Diene **65** (36%) however could be obtained pure (as minor component) when **27** was heated in carbon tetrachloride at 50 °C for 8h and the product mixture was fractionally crystallized from methylene chloride-hexane. The major component of the mixture, diene **66** (64%) was obtained by recrystallization of the mother liquor. No other compound was present. When the rearrangement was

performed at ambient temperature, the same products **65** (54%) and **66** (46%) were obtained after 10 days. But now **65** was the major product. The structures **66** and **65**, epimeric at C-10, were assigned to these dienes. The UV spectra of both **66** (λ_{max} 273 nm) and **65** (λ_{max} 272 nm) showed that they were conjugated dienes. The ^{1}H and ^{13}C NMR spectra of **66** and **65** were in accord with their being the 7,9-dimethyl derivatives of **55** and **62**. ^{13}C NMR spectra of both the dienes showed the presence of a sp^3 carbon bearing a secondary nitro group at δ_C 91.9 for **66** and δ_C 91.8 for **65**. Both the dienes when treated with sodium hydroxide gave the same product, 2-methyl-2-(2,3,5-trimethyl-6-nitrophenoxy)propanoic acid **29**. When **65** was heated in carbon tetrachloride at 70°C an equilibrium mixture of **66** (18%) and **65** (82%) was obtained after 32h, which did not change on further heating to 48h. After that the relative amounts of the dienes did not change but the amount of **29** started to increase. On the other hand, when **66** was heated, **65** was found but aromatization commenced before equilibrium was reached. This further confirmed that **66** and **65** were epimers.

Formation of **66** and **65** from **27** was not in accordance with the concerted mechanism proposed for the rearrangement of **19** (page 150) and expected for the rearrangement of **27** also. Epimerization of **66** and **65** under the conditions under which isomerization of **27** occurred suggested that the rearrangement of **27** may be occurring by a homolytic

dissociation-recombination. To resolve these complications, rearrangement of **27** was carried out in the presence of radical trapping agents. When rearranged in presence of p-cresol, no significant change occurred in the relative amounts of **66** (60%) and **65** (40%) obtained. But when **27** was allowed to rearrange in the presence of thiophenol, a more effective radical trap than *p*-cresol, formation of **65** was completely suppressed and only **66** was formed. Thus isomerization of **27** is a concerted process, which is overshadowed by radical epimerization of the product (Scheme 3.6).

Scheme 3.6 Pathways in the isomerization of **27**



The trapping experiments show that **27** and **66** have the same stereochemistry. The major diastereomer **19** obtained from the nitration of **12** has the (*E*)-configuration as discussed above. Diene **27** which was obtained as the sole product in the nitration of **17** is therefore assigned the (*E*)-configuration by analogy to **19**.

The evidence points to processes a and c (Scheme 3.6) operating in the rearrangement. However, process b may also occur. The two closely related spirodienes **19**(**20**) and **27** displayed a delicate balance between concerted and homolytic processes in their rearrangement reactions. The spirodienes **25A** and **25B** when heated in carbon tetrachloride or tetrahydrofuran solution gave regiospecifically the 6-nitro acid **26**, suggesting that a similar [1,5] nitro shift occurs but the intermediate diene (**67**) is not stable enough to be detectable. The dinitrospirodiene **30** rearranged in chloroform-d at ambient temperature to give 2-methyl-2-(2-methyl-4,6-dinitrophenoxy)propanoic acid (**31**) in one experiment, indicative of a [1,5] nitro shift. Here again the intermediate diene (**68**) could not be observed.

It was therefore decided to study another known 1,2 adduct **69**[56], to see if it rearranged and to see if the study of such rearrangement could shed any more light on the competing processes involved in the rearrangement of the spirodienes.

3.4.5 Rearrangement of 3-*t*-butyl-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate **69**

When **69** was heated in carbon tetrachloride at 70°C for 1h a mixture of four dienes **69**, **70**, **71** and **72** and 5-*t*-butyl-2-methylphenyl acetate **73** was obtained. A mixture of the same compounds was formed from **69** after 12 days on standing a solution in carbon tetrachloride at ambient temperature. One of the dienes (**72**) could be isolated from the reaction mixture by chromatography on silica at -40°C. When **72** was heated in carbon tetrachloride a mixture of the same five compounds was formed. Dienes **69** and **72** were also heated in the presence of *p*-cresol as a radical trapping agent. Only three compounds **69**, **71** and **73** were observed in the reaction mixture from **69**, while the three compounds **70**, **71** and **73** were observed in the reaction mixture from **72**. The results are summarized in Table 3.7.

Table 3.7

Products from thermolysis of 3-*t*-butyl-6-methyl-6-nitrocyclohexa-2,4-dienyl acetate **69** and its isomer **72** in CCl_4

Starting compounds	Reaction conditions	**69**	**70**	**71**	**72**	**73**
69	70°C, 1h	33%	8%	43%	11%	5%
69	amb. temp. 12 days	27%	13%	33%	18%	9%
69	70°C, 1h 1.25 eq. *p*-cresol	22%	---	60%	---	18%
72	50°C, 2h	12%	25%	9%	45%	9%
72	50°C, 3h 1.5 eq. *p*-cresol	---	36.5%	---	36.5%	27%

Dienes **69** and **72** rearranged in the presence of *p*-cresol to give a mixture of compounds. Diene **71** and **70** could be separated by chromatography on silica at -40°C. On isolation, **70** slowly reverted back to **72** even at -20°C. Although **71** could not be obtained completely free from the acetate **73** its ^1H and ^{13}C NMR spectra could be determined.

Since like **69**, the ^1H NMR spectrum of **70** showed two vinylic protons coupled to each other by a coupling constant of 10 Hz (-CH=CH-) **70** was assigned to be the diastereomer of **69**.

In the ^1H NMR spectra of **71** and **72** there was a broad methyl signal which was coupled to a vinylic proton. There

was no large coupling between the vinylic protons, thus these protons must be attached to the central carbon atoms of the diene system. The gated decoupled ^{13}C NMR spectra of **71** and **72** had doublets at δ_C 81.9 and 82.7 respectively indicating the presence of a secondary nitro group. The ^{13}C NMR spectra also confirmed that only two of the carbon atoms of the diene system had an attached proton. The UV spectrum of **72** (λ_{max} 271 nm) showed it to be a conjugated diene. The ^1H NMR of **71** showed a large coupling of 7.5 Hz between the two allylic protons so these had to be attached to adjacent carbon atoms. Thus the epimeric structures **71** and **72** were assigned to the two conjugated dienes.

An interesting feature in the ^1H and ^{13}C NMR spectra of **71** and **72** is that 6-H, the proton *ipso* to the nitro group, is highfield to 1-H, the proton *ipso* to the acetate, but C-6 is downfield of C-1 in the ^{13}C NMR spectrum. These assignments were confirmed for **72** by selective decoupling of the high field proton (5.23 ppm) whereupon the downfield carbon signal (82.7 ppm) collapsed to a singlet. Correspondingly when the downfield proton (5.66 ppm) was irradiated, the upfield carbon signal (70.4 ppm) collapsed to a singlet.

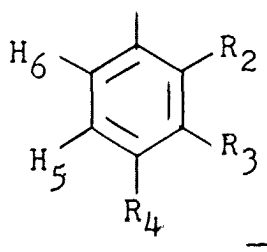
That the nitro group was adjacent to the *t*-butyl group was further proved by treating **72** with sodium hydroxide in methanol to give 4-t-butyl-3-nitrotoluene (**74**). It is clear that the rearrangement observed in the spirodienes also

occurs in the conjugated diene derived from *p*-*t*-butyltoluene (**75**).

When **72** was treated with 1.25 M sodium hydroxide in methanol, 4-*t*-butyl-3-nitrotoluene **74** was obtained as the major product (92%). 4-*t*-Butyl-3-nitrotoluene (**74**) is a strained molecule and there is only one report where it was detected by GC in the direct nitration of **75** in very low yield (ca. 5%).[114] In 4-*t*-butyl-2-nitrotoluene (**76**), the proton *ortho* to the nitro group is the most deshielded proton in the ^{1}H NMR spectrum.[56] In **72**, where the nitro group is forced out of the plane of the benzene ring by the *t*-butyl group, the proton *ortho* to the nitro group is the most shielded proton.

Table 3.8

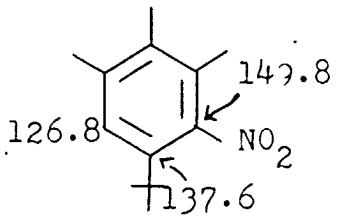
Chemical shifts of aromatic protons in 1,4-dialkyl-2-nitrobenzenes



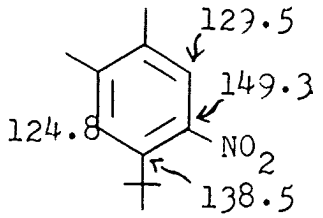
74	R_2 = H	R_3 = NO_2	R_4 = t-Bu
76	R_2 = NO_2	R_3 = H	R_4 = t-Bu
77	R_2 = NO_2	R_3 = H	R_4 = Me

Compound	R_2	R_3	H_5	H_6
74	7.12	----	7.42	7.23
76	----	7.96	7.40	7.24
77	----	7.67	7.22	7.10

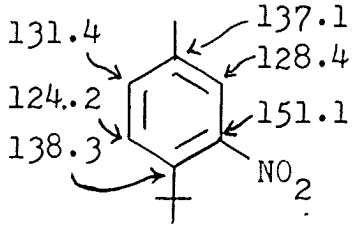
The structure of **74** was further confirmed by comparing its ^{13}C NMR spectrum with the ^{13}C spectra of 1-*t*-butyl-4,5-dimethyl-2-nitrobenzene (**78**)[115] and 1-*t*-butyl-3,4,5-trimethyl-2-nitrobenzene (**79**)[77] This also enabled assignment of all the chemical shifts in the ^{13}C spectrum of **48**.



79



78



74

Elimination of acetic acid from diene **72** on treatment with base would be expected to be very facile. However, while this reaction was observed when the base was sodium hydroxide in methanol, it was not observed when the bases N,N-diisopropylethylamine in methanol, or neat pyridine were used. Instead, solvolysis of the nitro group occurred leading to elimination of nitrous acid and formation of the acetate **73**. When sodium hydroxide in 1:1 (v/v) aqueous methanol was used **74** (66%) and 5-*t*-butyl-2-methylphenol (**80**) (34%) were formed. Even in the reaction brought about by sodium hydroxide in methanol 8% of **80** was formed. The reason that elimination of acetic acid occurs very

reluctantly in 72 is because the transition state for removal of the proton ∝ to the nitro group (in either an E_1 or E_2 pathway) is not stabilized by delocalization of the developing negative charge into the nitro group since such delocalization would require coplanarity of the nitro group and the diene systems. This is prevented by the adjacent *t*-butyl substituent.

3.4.7 Relative stereochemistry of 69, 70, 71 and 72

Previously only 69 was obtained by direct nitration of 75[56] and its stereochemistry was not known. Trapping experiments show that 69 and 71 and 70 and 72 have the same respective relative stereochemistries. The relative stereochemistry of all of the dienes was determined from the coupling pattern in their NMR spectra and the above stereochemical relationships. Bartoli et al.[116] have shown that in 2-alkyl-4-methoxy-1-nitro-1,2-dihydronaphthalenes (81) there is a definite relationship between the stereochemistry at C-1 and C-2 and the coupling constant between 1-H and 2-H (Table 3.9).

Table 3.9

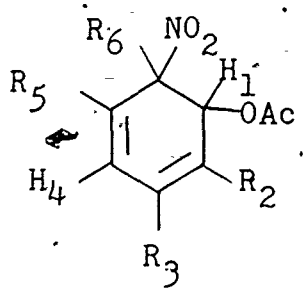
$J_{1,2}$ values of *cis* and *trans* 2-alkyl-4-methoxy-1-nitro-1,2-dihydronaphthalenes (81)[116]

2-Alkyl Group	Stereochemistry	$J_{1,2}$(Hz)
CH_3	cis	6.0
	trans	4.2
$PhCH_2CH_2$	cis	5.7
	trans	2.7
$PhCH_2$	cis	5.3
	trans	2.4

In all of the cases the coupling constant was larger for the *cis* stereochemistry than for the *trans*. 1,2-Dihydronaphthalenes have $J_{1e,2e}$ = 2 Hz, $J_{1a,2e} = J_{1e,2a}$ = 6.4-7.2 Hz as reported by Katritzky.[117] Katritzky has also shown that in 1,2-dihydronaphthalenes, a substituent at either the 1- or the 2-position prefers to occupy an axial position. In a *trans* 1,2-disubstituted-1,2-dihydronaphthalene this leads to small coupling constant for the 1-H and 2-H interaction since both of the protons occupy the equatorial position. In **71** the coupling constant between the two allylic protons is 7.5 Hz while in **72** the coupling constant is 1.6 Hz. Therefore the nitro and acetate have to be *cis* in **71** and *trans* in **72**.

Table 3.10

Chemical shifts for vinylic and allylic protons and vicinal coupling constants in dienes from 4-*t*-butyltoluene (**75**)

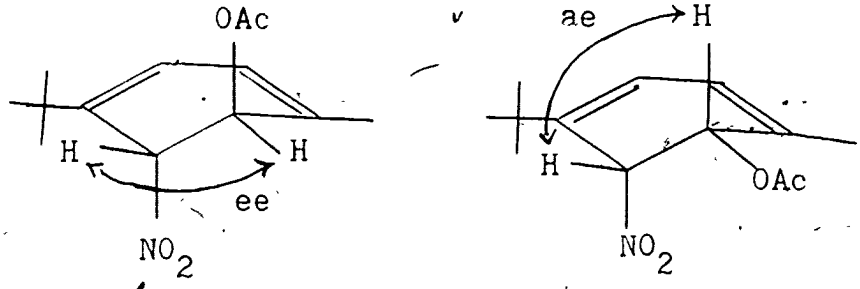


69, **70** $R_2 = R_5 = H$, $R_3 = t\text{-Bu}$, $R_6 = Me$

71, **72** $R_2 = Me$, $R_3 = R_6 = H$, $R_5 = t\text{-Bu}$

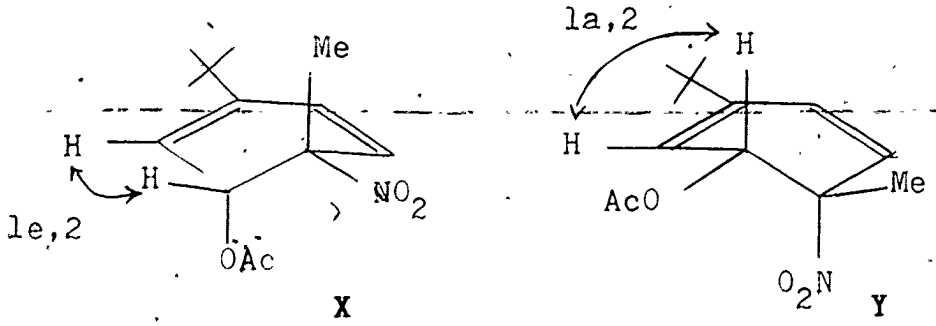
Diene	Chemical Shift (ppm)						Coupling Constant (Hz)			
	H_1	R_2	R_3	H_4	R_5	R_6	J_{12}	J_{16}	J_{45}	J_{34}
69	5.53	5.74	--	6.24	6.38	--	5.6	---	10.3	---
70	5.48	6.37	--	5.94	6.23	--	2.9	---	10.0	---
71	5.73	--	5.90	6.18	--	5.32	---	7.5	---	5.6
72	5.66	--	6.06	6.26	--	5.23	---	1.6	---	6.0

Preferred conformations of **71** and **72**



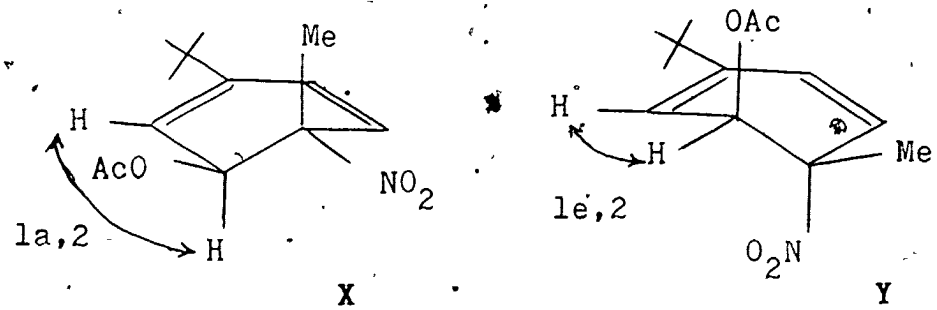
71 **72**

Conformations of **69**



X **Y**

Conformations of **70**

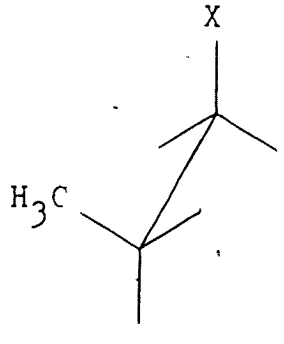


X **Y**

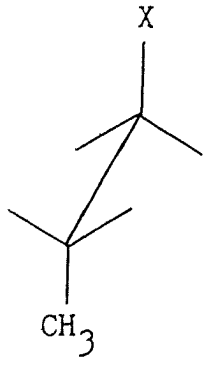
The $J_{2e,3}$ as reported by Katritzky[117] and Bartoli[116] for 1,2 dihydronaphthalene itself is 6.6 Hz, while $J_{2a,3}$ is 2-3 Hz. Since **69** and **71** are stereochemically related **69** should have the same *cis* relationship of the nitro and acetate as proposed for **71**. The observed $J_{1,2}$ for **69**, analogous to

J_{23} in 1,2-dihydronaphthalenes, is 5.6 Hz which is close to the value of 6.6 Hz. This indicates that **69** has a 1eH-2H coupling , i.e. the conformation **69X** of **69** is preferred. This is consistent with a preference for the maximum number of axial substituents in such systems (cf. ref. 30). On the other hand, coupling between the same two protons in **70** is 2.9 Hz which indicates 1aH - 2H coupling. It follows that in **70** the conformation **70X** is preferred. This is not in accord with the preference for the maximum number of axial substituents but may reflect a stabilizing interaction between the vicinal acetate and nitro group.

Further evidence for the assigned conformation of **69** is provided by the γ *-gauche* effect in ^{13}C NMR.[118] When there



γ *-gauche*



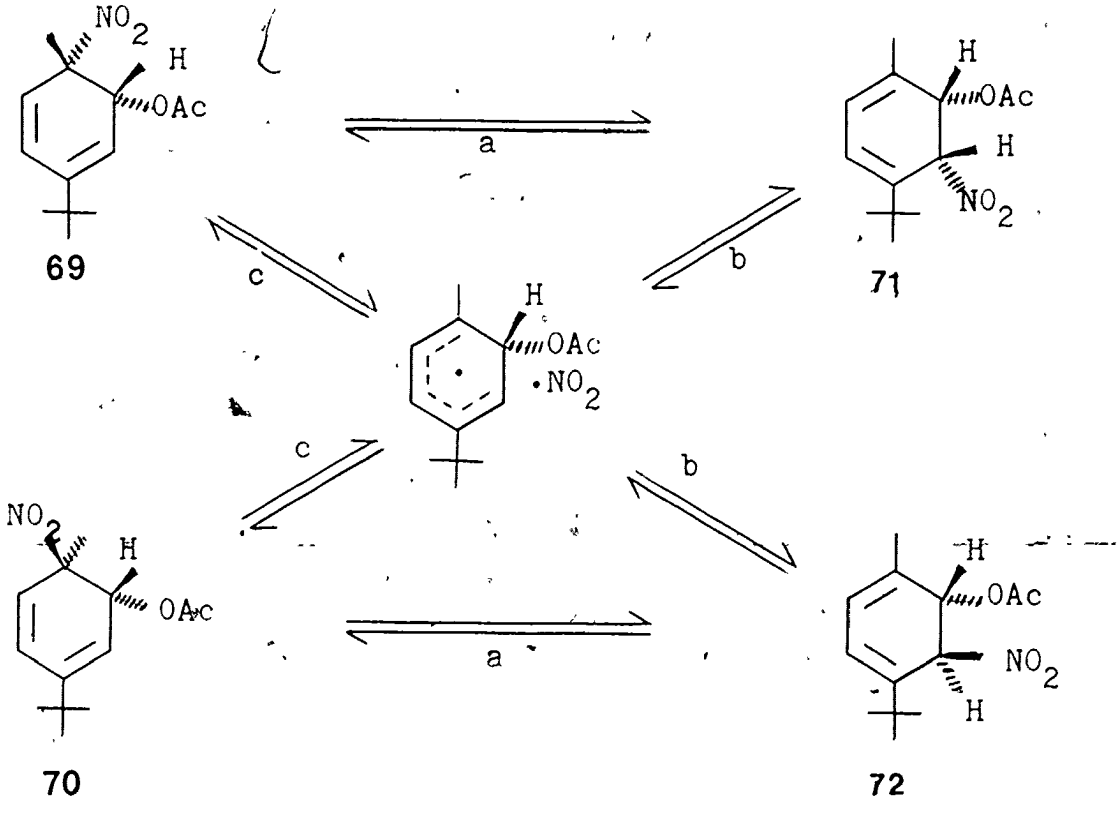
γ *-anti*

is a heteroatom substituent in the γ -position relative to the carbon atom being observed, it can be in the *gauche* or *anti* conformation. The chemical shift of the carbon atom is affected by the position of the heteroatom in the γ - position. When the hetero atom is in the *gauche*

conformation, the carbon atom resonates at higher field than when it is in the anti conformation. This is known as the γ-gauche effect. In **69X** the acetate and methyl are antiperiplanar while in **70** the groups are *gauche*. The γ-*gauche* effect of the electronegative substituent results in an upfield shift of 6 ppm for the 6-methyl group in **70** as compared with **69**. The alternative conformation **69Y** of **69** has the methyl and acetate groups *gauche* and the γ-*gauche* effect would be the same for **69** and **70**. i.e. the ^{13}C shifts of the 6-methyl group would then be identical.

The stereochemistry of the dienes **69**, **70**, **71** and **72** assigned on the basis of the arguments elaborated above is shown in Scheme 3.7 which also shows the pathways for interconversion.

Scheme 3.7 Isomerization and Epimerization Pathways of **69**, **70**, **71** and **72**



The existence of the sigmatropic pathway from **69** to **71** and from **70** to **72** is demonstrated by the trapping experiments which suppress the radical epimerization reaction(s). There must be at least one radical epimerization sequence, either b or c (Scheme 3.7), and the observations do not allow a choice between these processes to be made.

i) **69** $\overset{a}{\rightleftharpoons}$ **71** $\overset{b}{\rightleftharpoons}$ **72** $\overset{a}{\rightleftharpoons}$ **70**

ii) **71** $\overset{a}{\rightleftharpoons}$ **69** $\overset{c}{\rightleftharpoons}$ **70** $\overset{a}{\rightleftharpoons}$ **72**

Either of the sequences (i) or (ii) would explain the epimerization observations, but the existence of both the

sequences cannot be ruled out.

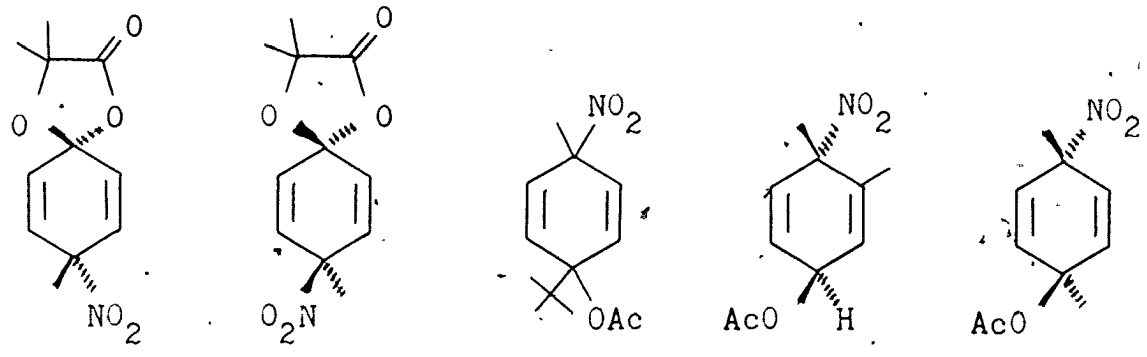
From the identification of **69** as the (*Z*)-isomer it follows that the addition of acetyl nitrate to 4-*t*-butyltoluene (**75**) is a *cis* addition. As discussed in the introduction (p. 15) Ridd[38] has suggested that in nitration in acetic anhydride, the nitronium ion is generated within the encounter pair from the substrate and protonated acetyl nitrate. It follows that when the Wheland intermediate is formed by addition of the nitronium ion *ipso* to the methyl group in **75**, an acetic acid molecule, from the protonated acetyl nitrate which has lost the nitronium ion, is appropriately located to add to the 2-position from the same face of the molecule as the nitronium ion. This would account for the stereoselective *cis* addition. On the other hand, nitration of **12** gives predominantly the (*E*)-isomer **19** because the acetic acid molecule prevents side-chain attack from the same face of the molecule as the nitronium ion.

3.5 *Isomerization of* 1,4 *adducts*

3.5.1 Attempted isomerization of adducts from alkylbenzenes

All the 1,2 adducts studied showed a [1,5] nitro group rearrangement, at least a part of which was concerted. A concerted [1,3] nitro shift is also possible. Some 1,4 acetyl nitrate adducts were therefore investigated. Dienes **52** and **53**, and dienes obtained from 4-*t*-butyltoluene, *o*-xylene and *p*-xylene (**82A**, **83** and **84** respectively) did not undergo rearrangement on heating in chloroform-d or carbon

tetrachloride-chloroform-d mixtures at 70°C for periods varying from 3h to 15h. The dienes studied are shown below --



52 53 82A 83 84

No reaction occurred for 52, 53, 82A and 84. The adduct 83 from *o*-xylene aromatized to 3,4-dimethylphenyl acetate (85).

3.5.2 Isomerization of adducts from dimethylbenzonitriles

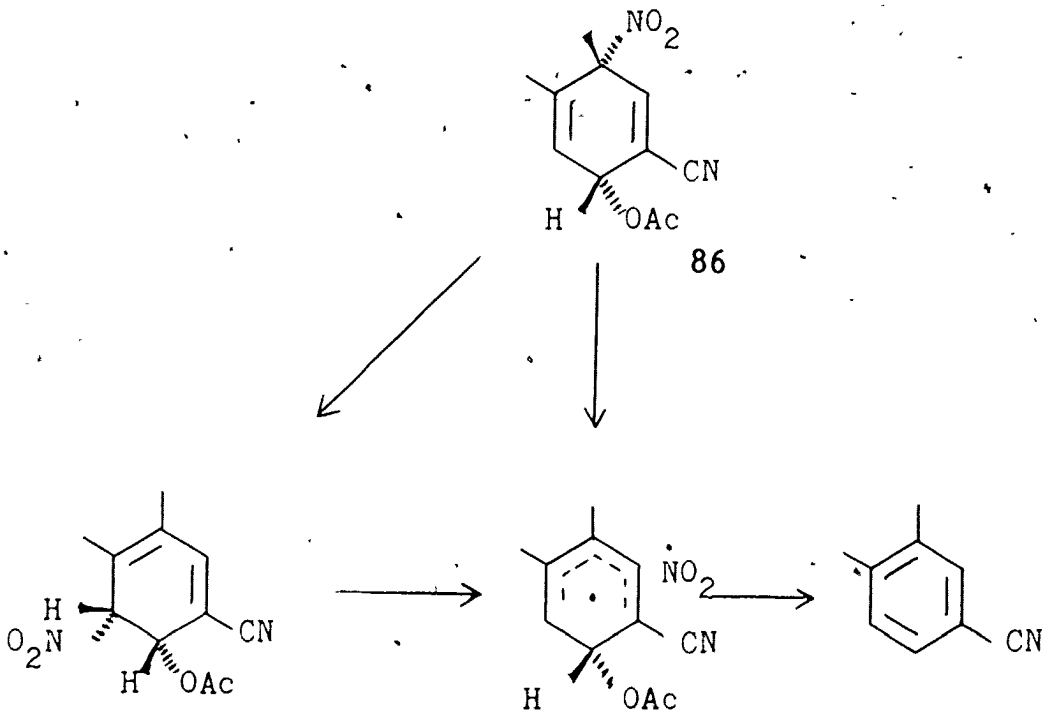
a) Isomerization of (*E*)- and (*Z*)-2-cyano-4,5-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (87 and 86 respectively)

When 86 was heated in carbon tetrachloride at 70°C for 9h, a new diene 88 (50%) was observed in the NMR mixture together with 3,4-dimethylbenzonitrile (89) (ca. 50%). The crystalline 88 was isolated and its structure assigned on the basis of the following spectral data. The UV spectrum showed a conjugated diene chromophore (λ_{max} 285 nm). The IR spectrum indicated the presence of a conjugated nitrile (2220 cm^{-1}) and nitro and carbonyl groups. The ^1H NMR spectrum showed the presence of one vinylic proton and two allylic protons. The gated decoupled ^{13}C NMR spectrum

showed presence of a carbon bearing a secondary nitro group (δ_C 85.3 doublet). The vicinal coupling constant between the two allylic protons was 8 Hz, indicating that one proton was axial and one equatorial and therefore a *cis* relationship of the substituent groups. Only one isomer of the compound was obtained.

When **86** was heated in 10% (v/v) methanol-d_4 and carbon tetrachloride no **88** was obtained. The only products were 3,4-dimethyl-5-nitrobenzonitrile **90** (49%) and 3,4-dimethyl benzonitrile **89** (51%). The nitroderivative **90** must have been formed by the methanol catalyzed loss of acetic acid from **88** as the latter was formed. In a separate experiment dissolution of **88** in neat methanol at ambient temperature gave **90** instantly. A solution of **88** on heating in carbon tetrachloride gave **89** as the only product. The rearranged product **88** aromatizes presumably by elimination of nitro and acetoxy radicals under the reaction conditions. Thus the extent of concerted and homolytic rearrangement cannot be determined in this case. A mechanism accounting for known facts is shown in Scheme 3.8.

Scheme 3.8 Isomerization and Aromatization Pathways of 86 and 88



Though there may be a homolytic component in the reaction, only one diastereomer, viz. the (Z)-isomer **88** was obtained. Fischer and Greig reported that **86** gives **89** and **90** on refluxing in mesitylene or in acetic acid. The formation of **90** must have involved isomerization of **86** to **88** and subsequent elimination of acetic acid.

A solution of **87** in 1:1 (v/v) carbon tetrachloride and chloroform-d gave a new compound **91** in 50% yield after 7h at 70°C. The other compound was again **89**. All attempts to crystallize any of these failed. The structure of **91** was

assigned by analysis of the ^{1}H and ^{13}C NMR spectra of the mixture. The ^{1}H NMR spectrum showed the presence of three methyl groups indicating that the acetate was still present in the diene **91** along with the two ring methyl substituents. There were also two allylic protons and one vinylic proton. The vicinal coupling constant between the two allylic protons was 3.1 Hz. The ^{13}C NMR spectrum showed the presence of a sp^3 carbon bearing a secondary nitro group (δ_C 87). When **87** was heated in 10% methanol-carbon tetrachloride no diene was formed but 3,4-dimethyl-5-nitrobenzonitrile was observed in the reaction mixture (ca. 20%). Thus the structure **91**, the diastereomer of **88**, was proposed for the new diene. The NMR spectra of **91** and **88** are compared in Table 3.11.

Table 3.11

^{1}H NMR data for 2-cyano-4,5-dimethyl-6-nitrocyclohexa-2,4-dienyl acetates **88** and **91**

	Chemical Shifts (ppm)					Coupling Constants (Hz)	
Diene	1-H	3-H	6-H	$OCOCH_3$	4-CH_3, 5-CH_3	J_{16}	J_{13}
88	6.08	6.84	5.12	2.14	1.97, 2.00	8.0	2.6
91	5.88	6.73	5.13	2.20	1.94, 1.96	3.1	---

The isomerizations of **87** and **86** to **91** and **88** respectively are both stereospecific. These must be predominantly concerted rearrangements, presumably involving

a [1,3] sigmatropic shift of the nitro group.

Diene **86** has been shown to have the (Z)-configuration[119] and a [1,3] sigmatropic shift would give the isomer **88** with the same stereochemistry, consistent with the argument based on the H_1-H_6 coupling constant. Similarly **91** formed from the (*E*)-isomer **87** must be the (*E*)-isomer and here again the assignment is supported by the H_1-H_6 coupling constant, having the value appropriate for the diequatorial arrangement of the hydrogen atoms. The *trans* substituents adopt the preferred diaxial conformation. This argument lends confidence to the assignment of the stereochemistry of the adduct **71** and **72** in the 4-*t*-butyltoluene series, which is based on the coupling constant evidence.

b) Attempted isomerization of adducts from 2,3-dimethylbenzonitrile and 2,5-dimethylbenzonitrile.

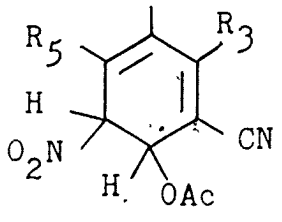
Adducts **92A** and **92B** obtained from 2,3-dimethylbenzonitrile were each heated in chloroform-d at 70°C for 6h. The ^{13}C NMR spectra of the reaction mixtures indicated the presence in each of an sp^3 carbon atom with a secondary nitro group. In the gated decoupled spectra, the peak attributed to this carbon atom (C-6) was split into a doublet. The solutions were heated for a further 12h at 70°C and the ^1H NMR spectra of the mixtures were recorded. However, the spectra were complex, reflecting the formation of several compounds and the peaks could not be conclusively assigned to any new rearranged dienes.

In a separate experiment **92A** gave 2,3-dimethyl-5-nitrobenzonitrile (**93**) (30%) after 12h at 70°C and **92B** similarly gave the same nitroderivative **93** (32%) under the same conditions. This evidence for [1,3] nitro migration and the ^{13}C NMR spectra discussed above indicated the intermediacy of rearranged dienes in the reaction mixture. The maximum amount that appeared to be present at any one time was ca. 10%. The peaks due to the rearranged dienes **94A** (from **92A**) and **94B** (from **92B**) could be assigned in the ^{13}C NMR spectra by comparison with the ^{13}C NMR spectra of **88** and **91** (Table 3.12).

Diene **95** from 2,5-dimethylbenzonitrile (**97**) did not react after heating at 70°C for 12h. Its regioisomer **96** after 7h at 70°C, gave **97** (ca. 65%) and unidentified products (ca. 35%). The ^{13}C NMR spectrum of the reaction mixture from **96** had peaks between δ_C 80-90 possibly due to sp^3 carbon atoms with a secondary nitro group but the presence of **98** could not be shown conclusively.

Table 3.12

^{13}C NMR spectra of 2-cyano-3,4-dimethyl- and 2-cyano-4,5-dimethyl-6-nitrocyclohexa-2,4-dienyl acetates



94A, 94B $R_3 = CH_3$, $R_5 = H$

91, 88 $R_3 = H$, $R_5 = CH_3$

Diene	Chemical Shift (δ_C) C-1	C-2	C-3	C-4	C-5	C-6	R_3/R_5	4-CH_3	$OCOCH_3$
94A	65.9	*a*	*a*	*a*	126.3	82.8	(17.5,	19.6,	23.9)
94B	66.2	*a*	*a*	*a*	125.6	83.1	(19.0,	19.5,	22.4)
91	66.0	105.9	145.2	127.3	135.4	87.0	(17.9,	20.3,	20.5)
88	66.3	108.5	143.0	127.4	132.9	85.3	(18.1,	20.5,	20.5)

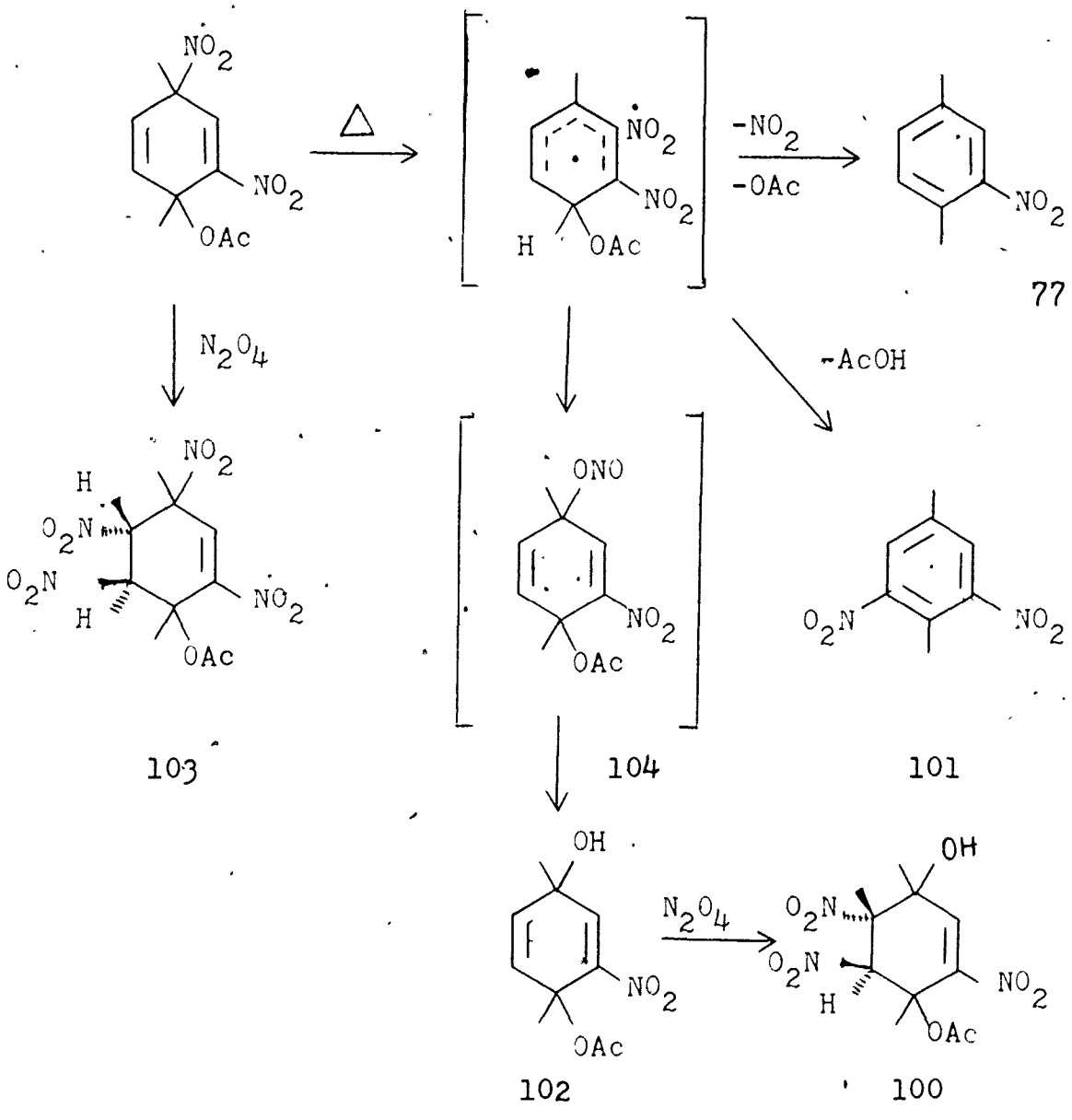
a. could not be assigned.

3.5.3 Rearrangement of the adduct from 1,4-dimethyl-2-nitrobenzene (**77**)

On heating a solution of the diene **99** in carbon tetrachloride at 70°C for 20h followed by cooling to 0°C, colourless crystals (1%) were obtained. This compound was assigned the structure **100** on the basis of the IR spectrum of which indicated presence of an alcohol (3500 cm^{-1}), an acetate (1735, 1235 cm^{-1} and nitro group(s) (broad intense absorptions at 1565-1530 and 1370-1340 cm^{-1}). The ^{13}C NMR spectrum indicated the presence of one double bond and two

sp^3 carbon atoms each bearing a secondary nitro group (δ_C 84.0, 87.4). The ^1H NMR spectrum showed one vinylic proton conjugated with a nitro group (δ 6.96) and two protons with a vicinal coupling constant of 12 Hz. The methane chemical ionization mass spectrum had a peak at m/e 302. Since the compound was an alcohol, this peak was assigned to the M-17 fragment. The M-59 peak (loss of acetate) was also present. Four more compounds were obtained from the reaction mixture on column chromatography at -40°C. The first two compounds were known aromatic compounds **77** (53%) and 1,4-dimethyl-2,6-dinitrobenzene (**101**) (21%). The compound eluted next was a 1,4 diene **102** (^1H and ^{13}C NMR). The IR spectrum showed it to be an alcohol (3390 cm^{-1}) and acetate (1710, 1260 cm^{-1}) and nitro (1525, 1370 cm^{-1}) groups were also present. The methane chemical ionization mass spectrum had a peak at m/e 210 and since the compound was an alcohol the peak was assigned to a M-17 fragment. The next compound eluted from the column was a cyclohexene with its ^1H and ^{13}C NMR spectra similar to that of **100**. The IR spectrum showed the presence of acetate and nitro groups. The chemical ionization mass spectrum showed the M+1 peak at m/e 349. The compound was assigned the tetranitrocyclohexene structure **103**. The adduct **103** is formed from **99** while **100** and **102** can be shown to arise from **104** as in Scheme 3.9.

Scheme 3.9 Products Obtained from Pyrolysis of 99



3.6 *Factors affecting the viability of sigmatropic nitro shift*

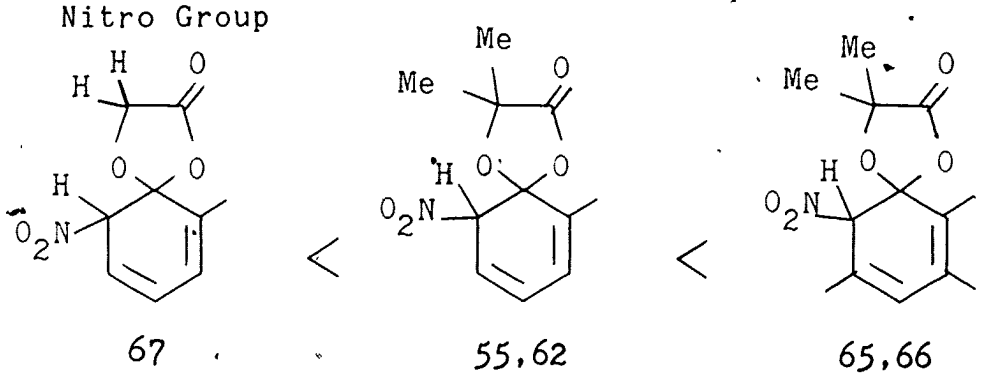
The isomerization reactions of the 1,2 and 1,4 adducts revealed various aspects of the balance between rearrangement by a concerted process and by a homolytic process. In both 1,2 and 1,4 adducts, the homolytic process appears to involve a cyclohexadienyl intermediate. Both

[1,5] and [1,3] sigmatropic shifts of the nitro group have been demonstrated in the present work. Although both [1,3] and [1,5] shifts are symmetry allowed and they might potentially occur in the same (conjugated diene) system, competitive shifts are not observed. One factor favouring the [1,5] shift is that this preserves the conjugated diene system in the product, while the [1,3] shift would result in the conjugated diene being converted into a 1,4 diene.

It is to be noted that the only 1,4 diene systems which exhibit the sigmatropic rearrangement are those which have a conjugatively electron-withdrawing group (C≡N) attached to a vinyl carbon which is at the terminus of the conjugated system in the product.

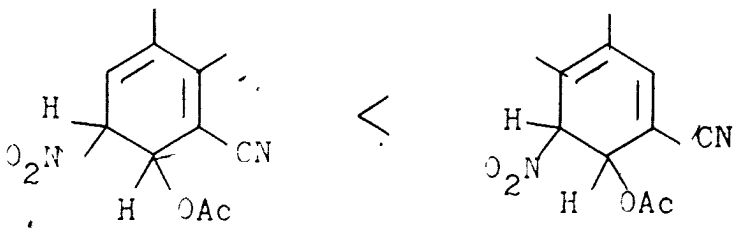
Even though rearrangement occurred, detection of isomerized dienes was possible only if the dienes were relatively stable. The stability of the dienes seemed to increase with increasing crowding around the secondary nitro group, thus obstructing the loss of a proton from the diene. This is evident from the two series of adducts in Scheme 3.10.

Scheme 3.10 Stability of Conjugated Dienes with a Secondary Nitro Group



67 < 55,62 < 65,66

stability →



94 < 88,91

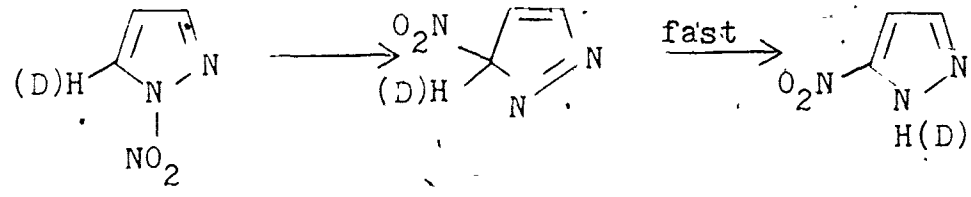
Diene **67** was not observed. Only the aromatic compound **26**, resulting from loss of proton from **67** was observed. Diastereomers **55**, **62** were obtained in >95% yield but could not be crystallized. They aromatized on standing in solution. Diastereomers **65** and **66** with the secondary nitro group flanked by substituents on both sides were the most stable dienes in the series. A similar trend was observed in the dimethylbenzonitrile series. Dienes **94** with an unsubstituted position adjacent to the nitro group aromatized readily and could not be observed in greater than

10% concentration in the reaction mixture. Dienes **88**, **91** with substituents on both sides of the nitro group were much more stable and one of them (**88**) could be crystallized.

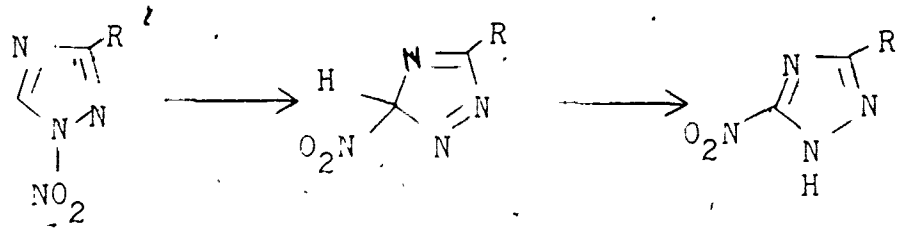
3.7 *Sigmatropic rearrangements in related systems*

Support for the proposal that sigmatropic rearrangements occur in the systems studied in the present work is provided by earlier observations of sigmatropic rearrangements in related systems. There are reports of nitro group migrations in N-nitropyrazoles (**105**)[120] and N-nitro-1,2,4-triazoles (**106**).[121,122] Isotope labelling in N-nitropyrazoles has shown that there is no primary isotope effect so hydrogen migration is not the rate determining step in these rearrangements. (Scheme 3.11)

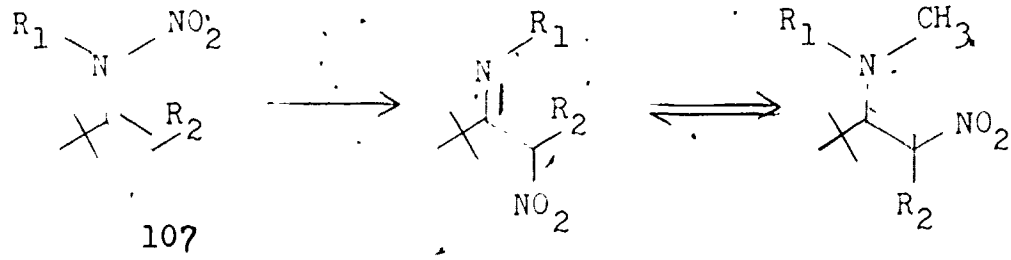
Scheme 3.11 Sigmatropic Nitro Shifts



105



106



107

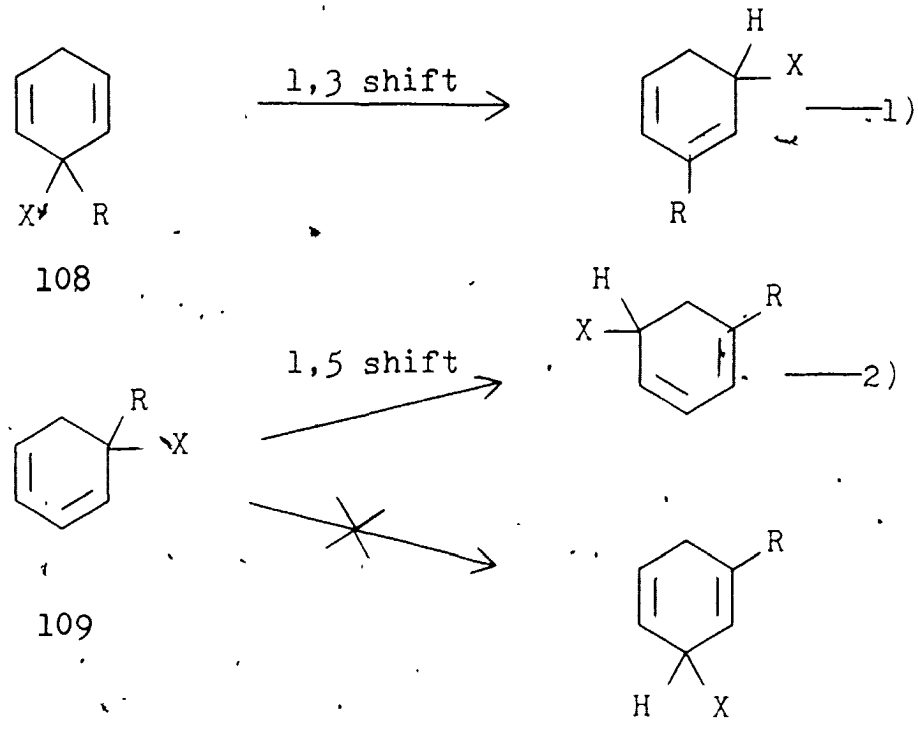
R_1= H, R_2 = n-C_3H_7 R_1 = H, R_2 = n-C_3H_7 R_1= CH_3, R_2 = H
R_1 = CH_3 R_2 = n-C_3H_7 R_1 = CH_3 R_2 = n-C_3H_7
R_1 = CH_3 R_2 = H

Scheme 3.11 also shows a [1,3] NO_2 rearrangement from N-Nitroenamines (**107**) to α-nitro imines.[128] According to the orbital symmetry rules, in cyclic systems the thermal rearrangement has to be suprafacial for the migration framework and antarafacial (in [1,3] shift) or suprafacial [1,5] for the nitrogroup.[124]

In 1,4-cyclohexadienes (**108**) only the [1,3] nitro shift

is possible while frontier orbital theory[125] suggests that the [1,5] shift will be favoured over a [1,3] shift in 1,3-cyclohexadiene (**109**) (Scheme 3.12).

Scheme 3.12. Sigmatropic Shifts in [1,3] and [1,5] Cyclohexadienes



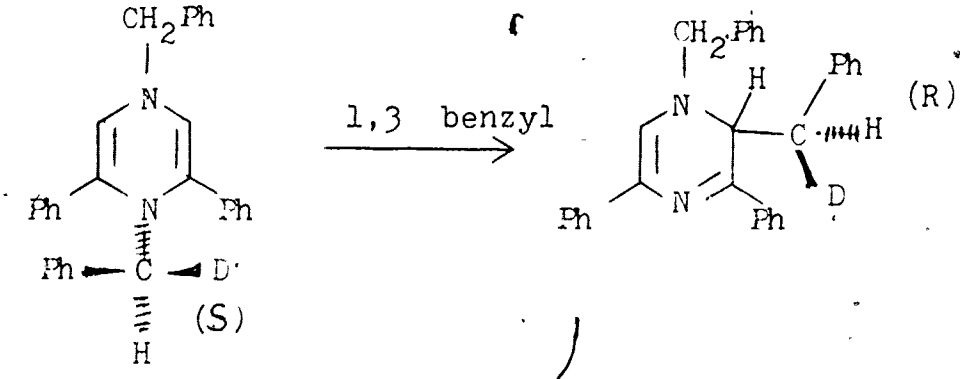
108

109

Rearrangements in 1,4-cyclohexadienes **108** (Scheme 3.12) are not known. A related rearrangement is known in 1,4-dialkyl-1,4-dihydropyrazines.[126,127] In the case of chiral 1,4-dibenzyl-1,4-dihydropyrazine (**110**) the rearrangement to **111** occurred with inversion of configuration at the migrating group as expected (Scheme 3.13). There was a competing radical dissociation-recombination reaction (12±6%) which could be suppressed by addition of butane

thiol as a radical scavenger.[127]

Scheme 3.13 [1,3] Benzyl Shift with Inversion



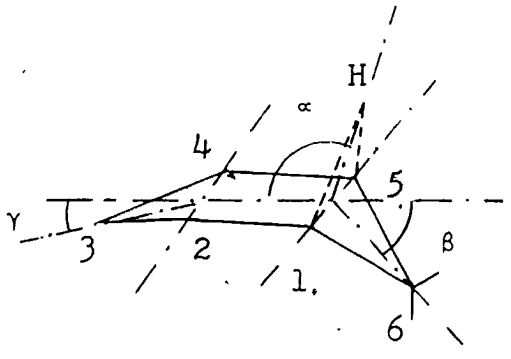
110 111

Rearrangements of conjugated cyclohexadienes have been studied in more detail : Schiess et al.[128,129] have shown that 1-methyl-1-X-cyclohexa-2,4-dienes (**109**, R = Me) undergo 1,5 rearrangement by two pathways. When X = Me or Ph the rearrangement occurs by successive ring opening, hydrogen shift and ring closure. For X = $COOCH_3$, 15% of the reaction follows the above path and the rest occurs by [1,5] sigmatropic shift. When X = CHO, $COCH_3$, COPh the rearrangement is exclusively a [1,5] sigmatropic shift.[129] They have also shown for X = $COOCH_3$, that the rearrangement does not occur by two successive [1,3] shifts.[129]

Simple Hückel calculations indicate that both [1,3] and [1,5] sigmatropic shifts should be accelerated by a polar migrating group.[130] No information is available for [1,3] shifts but [1,5] shift of a formyl group in 1-methyl-1-formylcyclohexa-2,4-diene occurs in 1h at 188°C.[128] So the

more polar nitro group should in principle undergo rearrangement below 190°C.

Finally the effect of the carbon atom which remains sp^3 throughout the [1,5] sigmatropic shift in conjugated cyclohexadiene should be considered. INDO calculations of [1,5] H shift in cylcohexadiene show the following transition state.[131]



$\alpha = 100.6^{\circ}$

$\beta = 65.5^{\circ}$

$\gamma = 5.0^{\circ}$

The transition state shows that carbon atoms C_1 through C_5 (as numbered in the diagram) are approximately in a plane while the migrating hydrogen and C_6 are on the opposite sides of that plane. It is also evident that the migrating group has to be pseudo-axial in the reactant and product. Substituents on C_1-C_5 will destroy the symmetry and the migrating group may not remain equidistant from C_1 and C_5 in the transition state. If C_6 is substituted the migrating group will have steric interactions with the pseudo-equatorial substituent at C-6. Thus the size of the migrating group and the pseudo-equatorial C-6 substituent will influence the ease of reaching the transition state and

thus the rate of the reaction. But the pseudoequatorial C-6 substituent is not in a position to completely block the rearrangement. The [1,5] nitro shift observed in nitrodienones may also involve a sigmatropic rearrangement. This could account for the regiospecificity observed for the reaction and commented upon in the introduction.

3.8 *Aromatization reactions of* 3,3,10-*trimethyl*-10-*nitro*-1,4-*dioxaspiro*[4,5]*deca*-6,8-*dien*-2-*one* (19)

3.8.1 Reactions with neat acids and with acids in aprotic solvents

a) The reaction of diene **19** with trifluoroacetic acid (TFA) in chloroform-d (Table 3.13) occurred by initial epimerization which could be followed by NMR. Diene **20** was the more stable diastereomer and an equilibrium mixture of **19** and **20** was formed, containing 80% of **20**. On prolonged reaction and/or at higher concentrations of TFA and/or at higher temperatures, the epimerization was followed by further reactions of dienes **19** and **20**. The rearrangement of diene **19(20)** to **55**(and **62**) occurred and **55**(and/or **62**) could be detected in reaction mixtures. This rearrangement appears to be acid-catalyzed because the rearranged diene was formed much more rapidly in the acidic solutions (26% in 45 min. at -15°C in neat TFA (Table 3.13); cf. $t_{1/2}$ 4 days at ambient temperature in CCl_4). Formation of the 2-methyl-2-(2-methyl-4-nitrophenoxy)propanoic acid (**14**) and 3,3,6-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-diene-2,8-dione (**112**)

occurred concurrently with the rearrangement. The rearranged dienes **55**(and/or **62**) gradually aromatized to form 2-methyl-2-(2-methyl-6-nitrophenoxy)propanoic acid (**15**).

Reaction of diene **19** with methanesulfonic acid in chloroform (Table 3.13) followed a similar pattern to that exhibited in trifluoroacetic acid viz. initial rapid epimerization to a mixture of **19** and **20** was followed by the rearrangement of **19**(**20**) to **55**(**62**) which was concurrent with the formation of the 4-nitro acid **14**. The rearranged diene **55**(**62**) rearomatized to the 6-nitro acid **15**.

Table 3.13

Products from reaction of **19** with neat acids or with acids in aprotic solvent.

Concentration of acid (in $CDCl_3$)	Reaction Conditions	12	15	14	112	19	20	55/62
10% TFA	30 min., 0°C	---	---	---	---	20%	80%	--
	24 h, 0°C	---	---	8%	---	9%	62%	21%
	4 days, 0°C	8%	21%	25%	---	--	27%	7%
33% TFA	14 h, ambient	18%[a]	39%	32%	11%[a]	--	---	--
100% TFA	45 min., -15°C	--	---	12%[a]	---	14%[a]	48%	26%
	4 days, -15°C	12%[a]	51%	25%	12%[a]	--	---	--
	1 h, ambient	11%[a]	17%[a]	55%	17%[a]	--	---	--
3% $MeSO_3H$	2 h, 20°C	--	75%	25%	---	--	---	--
50% $MeSO_3H$	2 h, 0°C	--	81%	19%	---	--	---	--
3% CF_3SO_3H	ca.5 min., 0°C	--	75%	25%	---	--	---	--

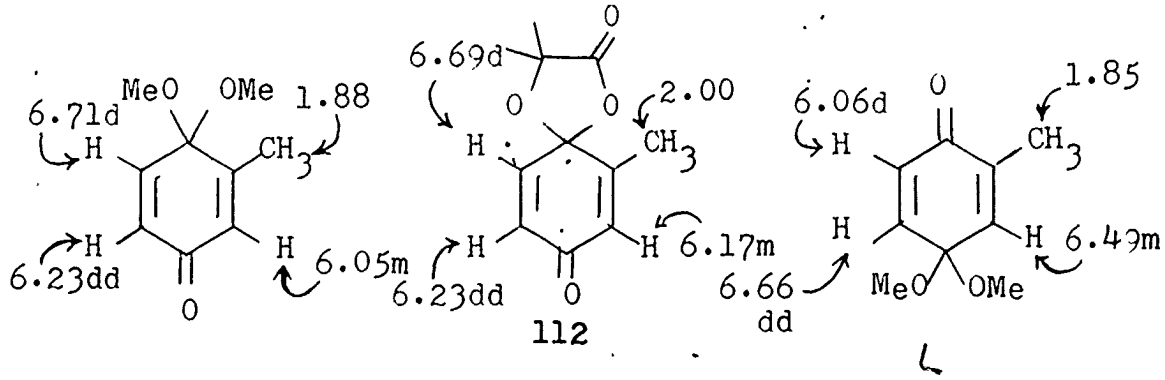
a. ±3%

No significant change in the product distribution occurred when 50% (v/v) methanesulfonic acid was used instead of 3% (v/v) solution. In the case of the triflic acid catalyzed reaction, the reaction was so rapid that the intermediate steps of epimerization and rearrangement could not be followed. A notable difference between the strong acid catalyzed reaction and the reaction in trifluoroacetic acid is the absence of both the dienone product **112** and the acid

12 in the strong acid reactions.

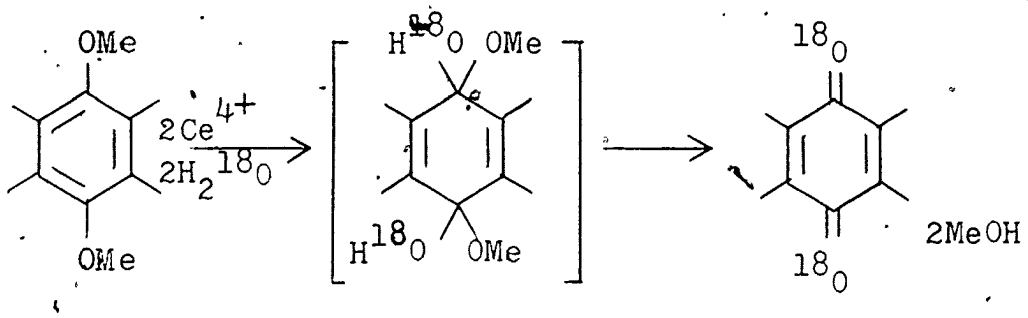
b) Structure of dienone 112

The dienone 112 was isolated as a non-acidic product from the neutralized reaction mixture of 19 and trifluoroacetic acid in a yield of 15±5%. The structure 112 was based on the following spectral data. The IR spectrum of the compound showed two carbonyl groups. One of the carbonyl groups (1680 cm^{-1}) was conjugated with a double bond(s). No nitro group was present in the compound (no absorptions at 1560, 1350 cm^{-1}). The molecular formula was determined as $C_{11}H_{12}O_4$ based on exact mass (Obs. 208.080 M_r $^{12}C_{11}$ $^{1}H_{12}$ $^{16}O_4$ 208.074). The UV absorption maximum at 227 nm (1178 m^2mol^{-1}) suggested an α,β - α' β' unsaturated ketone. The ^1H NMR spectrum of the compound showed that the gem-dimethyl group in 22 was still present, but the signal of the methyl group on the six membered ring was now broadened by allylic coupling. Comparison of the NMR spectrum with the spectra of two regioisomeric quinone monoketals[132] finally confirmed the assignment of structure 112 to this compound

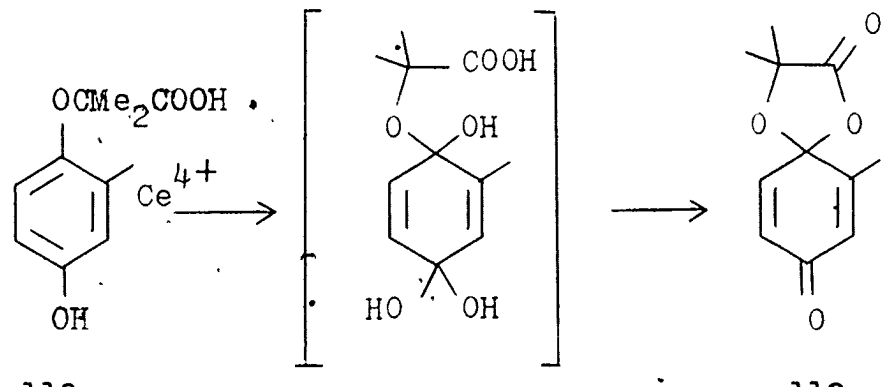


112

Compound 112 was prepared by an alternate route to confirm its structure. Ceric ammonium nitrate is known to oxidize hydroquinone dimethyl ethers to quinones via intermediate quinone bis hemiketals.[133]



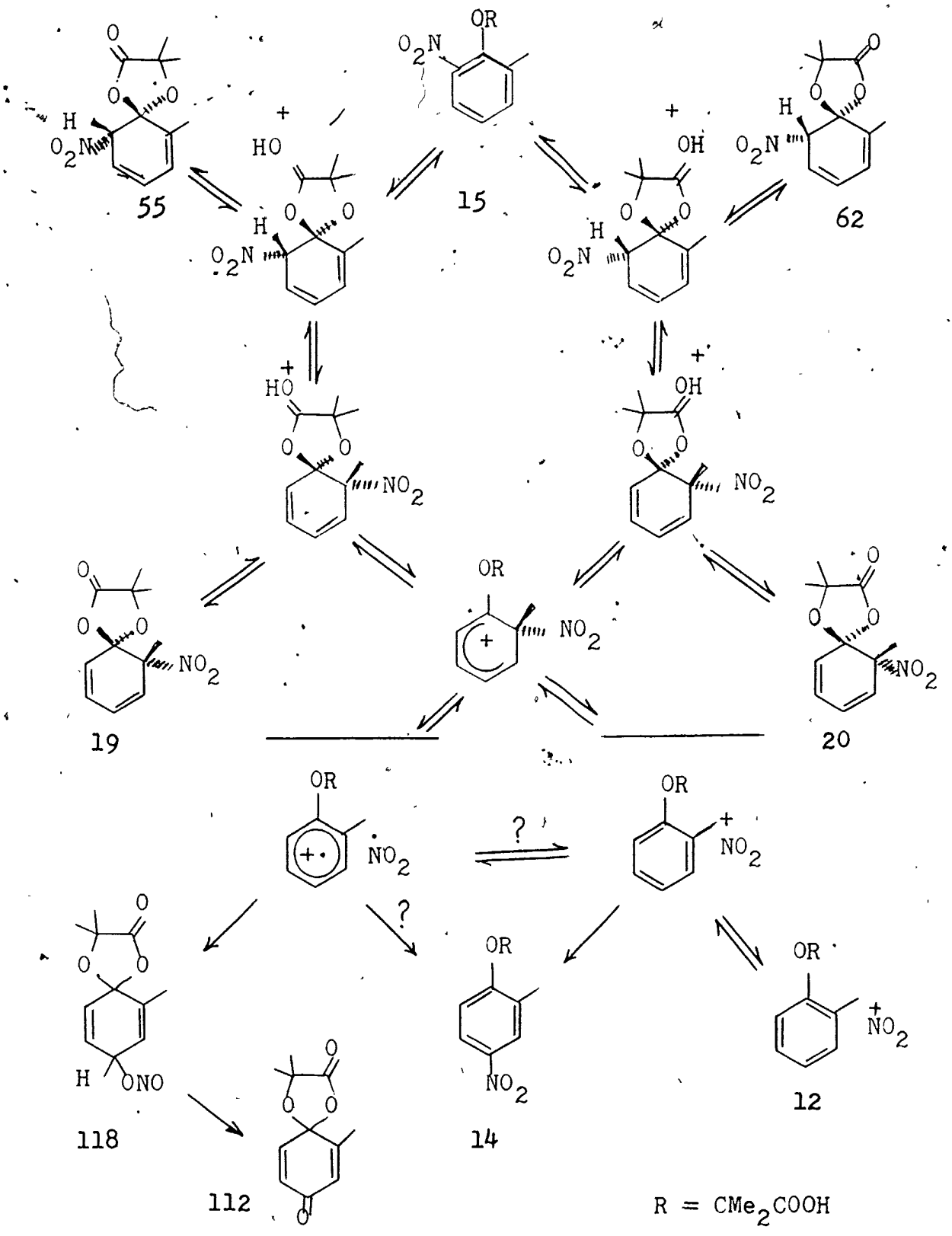
It was thought that if 2-methyl-2-(4-hydroxy-2-methylphenoxy)propanoic (113) acid was treated with ceric ammonium nitrate some of the intermediate could form 112.



113 112

Methylhydroquinone (114) was treated with chloretone (4) and base in acetone to give a mixture of 113 and its regioisomer (115). The mixture was treated with ceric ammonium nitrate to give a mixture of 112, its regioisomer 116 and methylbenzoquinone (117). The protected quinone 112 was separated from other compounds by HPLC. The ^{1}H NMR and ^{13}C NMR of 112 obtained from two different routes were identical.

Scheme 3.14 Products from Reaction of 19 with Acids



c) Mechanism for the formation of the products of reactions of **19** with acids.

The pathways shown in Scheme 3.14 can account for the formation of the products cited above. Protonation is shown on the carbonyl group in Scheme 3.14. Another potential site of protonation is the diene system. Dienes can be protonated to give allyl cations. This alternative was ruled out on the basis of pK_a values of the two protonated species. The pK_a of the unsubstituted cyclohexenyl cation (protonated cyclohexadiene) can be estimated to be -10.4.[134] The protonated carbonyl of an ester has pK_a of -7.[135] Thus the carbonyl group is at least a thousand times more basic than the diene and must be the predominant site of protonation.

The protonated diene can open the lactone ring to give the *ipso*-Wheland intermediate. Ring closure and deprotonation would result in the observed epimerization. The [1,5] sigmatropic shift of the nitro group to give protonated **55(62)** appears to be another (slower) reaction of the protonated **19(20)**. The only other examples known of acid catalysis in sigmatropic shifts are those of the Claisen rearrangement and the [1,5] shift of the benzylic group. Svanholm and Parker[136] showed that the rate of Claisen rearrangement of alkyl phenyl ethers in TFA, was enhanced by ca. 10^5. Miller[137] has also shown that 6-alkyl-6-benzylcyclohexa-2,4-dienones undergo a [1,5] sigmatropic

shift of the benzyl group under acid catalyzed conditions.

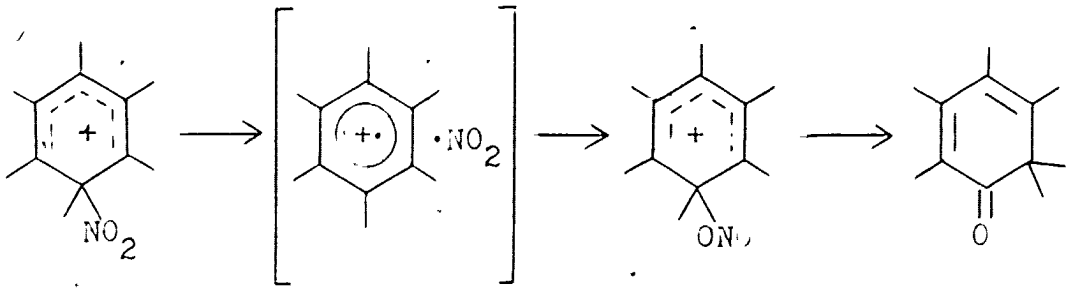
Formation of **14** is likely to involve a process of denitration of the Wheland intermediate to form the encounter pair consisting of acid **12** and the nitronium ion. These can react to form the 4-nitro derivative **14**. This pathway would parallel that for the acid-catalyzed rearrangement of dienone to *o*-nitrophenols as shown by Coombes[84]. An additional pathway to **14** is the homolytic cleavage of the Wheland intermediate to form nitrogen dioxide and the radical cation of **12**.

Once the radical-radical cation pair is formed by homolysis, the nitrogen dioxide can combine at the *ipso*-, 4- and 6-positions. The steric effect which hindered electrophilic attack would also hinder the combination of the radicals at the 6-position. Combination at the *ipso*-position, if it occurs through the nitrogen center of the NO_2 radical, cannot be detected. Combination through the oxygen center is also possible but no products derived from such a combination were detected. Recombination can also occur at the 4-position, either through nitrogen to give the Wheland intermediate for 4-nitration or through oxygen leading to 3,3,6-trimethyl-8-nitrito-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (**118**) which could be readily oxidized to the observed spirodienone, **112**.

Evidence for combination of nitrogen dioxide through the

oxygen center was obtained by Detsina *et al.*[138] They showed that the ^{18}O-labelled 1,2,3,4,5,6-hexamethyl-6-nitrocyclohexa-2,4-dienyl cation (**119**), obtained by nitration of hexamethylbenzene with ^{18}O-labelled sodium nitrate in fluorosulphonic acid rearranged at 0°C to give a dienone product **120**, where the oxygen, attached to the ring in the product was entirely from the nitro group in the cyclohexadienyl cation. Complete retention of the ^{18}O-label was observed (Scheme 3.15).

Scheme 3.15 Pathway for the Oxidation of **119** to **120**



119 **120**

Oxidation of nitrites and nitrates is postulated to explain the formation of side chain oxidation products during nitration of highly substituted alkylbenzenes.[40,139] Benzyl nitrate was shown to give benzaldehyde and nitrous oxide by autodecomposition.[140] Similar formation of the nitrite ester by combination of the radical cation and nitrogen dioxide through oxygen and subsequent oxidation of the cyclohexadienyl nitrite would lead to **112**.

Support for the dissociation recombination pathway(s) is

provided by the formation of 12, which suggests that some leakage of the NO_2^+ or NO_2 species can occur. Further support is provided by the fact that it is possible to trap some of the escaped nitro species with mesitylene when the reaction with trifluoroacetic acid is carried out in the presence of mesitylene.

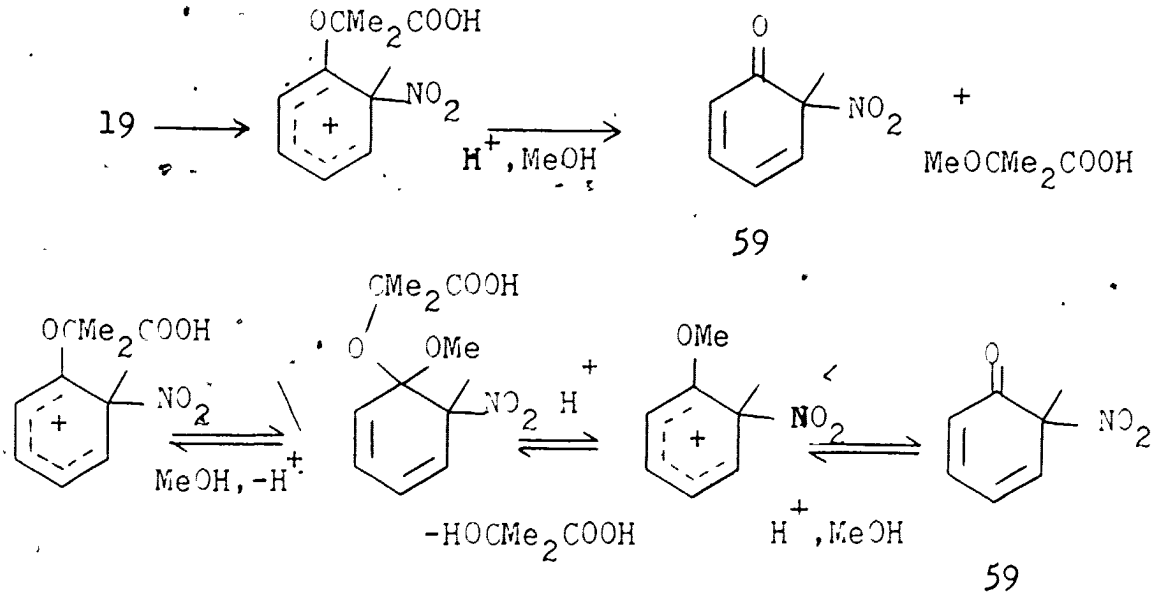
The ratio of acids 15 to 14 obtained varied with temperature. This is not surprising since the products were obtained by quite different processes. It will be recalled that nitration of 12 in chloroform in the presence of trifluoroacetic acid gave only 14 and its further nitration product 30. This indicates that none of 15 formed in the acid catalyzed rearrangements of 19 can be obtained by a pathway involving dissociation of nitronium ion and renitration.

3.8.2 Reactions with acids in methanol

Reaction of diene 19 with TFA in methanol also resulted in the initial epimerization to form the 19/20 mixture (Table 3.14). Subsequently the 6-nitro acid 15 was formed. The rearranged diene 55(62) was not observed in the mixture containing 50% and 75% TFA but was observed in mixtures containing 90% TFA. The acids 12 and 14 were not formed at the lower acid concentration but were formed in 90% TFA. On the other hand 2-methyl-6-nitrophenol (10) was formed at the lower acid concentration but was absent in 90% TFA. In separate experiments it was demonstrated that 2-methyl-2-(2-

methyl-6-nitrophenoxy)propanoic acid 15 was not cleaved by 75% trifluoroacetic acid in methanol and that the nitrocresol 10 would not have been formed from this product. At the lower acid concentration (higher methanol concentration) the methanol apparently causes the rapid conversion of 55 to 15. Methanol could be expected to be effective at deprotonating the conjugate acid of 55 by removing the proton *ipso* to the nitro group. In 90% TFA this process is slowed down because the methanol is effectively completely protonated, or at least hydrogen bonded to the TFA, and is not available to act as a base. Hence under this condition, the reaction is similar to that in neat TFA and 55 is observed. Again at the lower acid concentration, the methanol can stabilize the transition state for cleavage of the side chain in the Wheland intermediate formed by protonation and ring opening.

Scheme 3.16 Possible Pathways from 19 to 59



An alternative pathway which involves a similar ether cleavage in the Wheland intermediate is also possible (Scheme 3.16). Both pathways involve initial protonation of the lactone and its unimolecular opening to the carbonium ion. The same protonation and ring-opening sequence has been demonstrated by Salomaa et al.[141] for acidic hydrolysis of 2-substituted-1,3-dioxolan-4-ones.

The product nitrodienone 59 is independently known to rearrange rapidly to give 10 which is observed in the products under these conditions[93]. Since the methanol is effectively completely bonded to the TFA in 90% TFA, the cleavage of the side-chain is suppressed at this concentration and it is superseded by the denitration-renitration process leading to the 4-nitro acid 14 and 12 (through leakage of the nitro species). The reaction in 90%

TFA parallels the reaction in 100% TFA in all respects

Table 3.14

Products from reactions of **19** with acids in methanol

Concentration of acid (in methanol)	Reaction Conditions	12	15	14	19	20	55/62	121	10
50% TFA	3 days, ambient	--	52%	--	--	48%[a]	--	--	traces
75% TFA	20 min., 0°C	--	--	--	20%	80%	--	--	------
	3 days, 0°C	--	--	--	20%	80%	--	--	------
	3 days, ambient	--	26%	--	--	57%[a]	--	--	17%
90% TFA	10 min., 0°C	--	--	--	35%	65%	--	--	------
	5 h, 0°C	12%	24%	32%	--	--	32%	--	------
3% triflic acid[b]	30 min., ambient	-	9%	9%	21%	61%	--	--	------
0.01M H_2SO_4	4 days[c], ambient	--	--	--	--	--	--	70%	30%
0.05M H_2SO_4	4 days[c], ambient	--	--	--	--	--	--	63%	37%
0.5M H_2SO_4	2 days[c], ambient	--	--	--	--	--	--	25%	75%

a. Yield of **19** and **20**
b. in chloroform-d containing 3% methanol.
c. Half-life

except for the absence of the spirodienone **112**. Less 2-methyl-6-nitrophenol (**10**) is formed in 50% TFA than in 75% TFA. This suggests that in the competition between rearrangement of the protonated **19**(**20**) to **55**(**62**) and the ring opening and cleavage of the Wheland intermediate to the dienone, the latter process is favoured at the higher acid

concentration.

Reaction of **19** with sulphuric acid in methanol was similar to the reactions with 50% and 75% TFA in methanol. Formation of **10** and methyl 2-methyl-2-(2-methyl-6-nitrophenoxy)propanoate (**121**) occurred (Table 3.14). The latter compound is most likely formed by esterification of the corresponding acid **15** (which is the product obtained in TFA catalyzed reactions). It was demonstrated that the acid **15** esterified rapidly when treated with sulphuric acid in methanol to give the ester **121**. As in the reactions with TFA in methanol, higher acid concentrations led to an increase in the amount of the nitrocresol formed and a corresponding decrease in the amount of the ester **121**, and the same explanation as that proposed in the TFA case is proposed for this.

The reaction of **19** with 3% (v/v) triflic acid in chloroform containing 3% (v/v) methanol (Table 3.14) showed the marked effect of methanol on the course of the reaction (c.f. Table 3.13). Both the rearrangement and the denitration pathways were slowed down and the reaction barely proceeded beyond the epimerization stage over the time that it was observed.

3.8.3 Reactions of **19** with sulphuric acid in 1:9(v/v) water and acetone-d_6

When **19** was treated with sulphuric acid in aqueous acetone, initial epimerization was observed, but the

relative amounts of **19** and **20** could not be determined. Further reaction gave two aromatic products which were identified as the 6-nitro acid **15** and the 2-methyl-6-nitrophenol ester **58**. With 0.01M sulphuric acid **15** (83%) and **58** (17%) were obtained. With more concentrated acid (0.5M), the ratio of the amounts of **15** and **58** changed to 54:46. Formation of 6-nitro, substituted products suggests that initial epimerization is followed by isomerization to **55(62)** which aromatizes to the observed products. As in the case of reactions carried out in methanol, products arising from dissociation-recombination pathway(s) were not observed. Moreover, unlike the reactions in methanol, the side-chain cleavage (formation of **10**) did not occur. In relatively non-polar solvent, the concentration of the Wheland intermediate would be reduced and thus its cleavage to the dienone is not probable. The dissociation recombination pathway of the Wheland intermediate leading to **14** and possibly **12**, obviously requires much more strongly acidic conditions and much higher concentration of the Wheland intermediate than even the side-chain cleavage.

Since **55(62)** is not observed in the reaction mixture, deprotonation of **55(62)** must be a fast reaction. Hence the half-life of the reaction with 0.01M sulphuric acid (2 days) must be the half-life for the [1,5] sigmatropic nitro shift. This half-life is comparable to the half-life for isomerization (3 days) in neutral solvents. It is

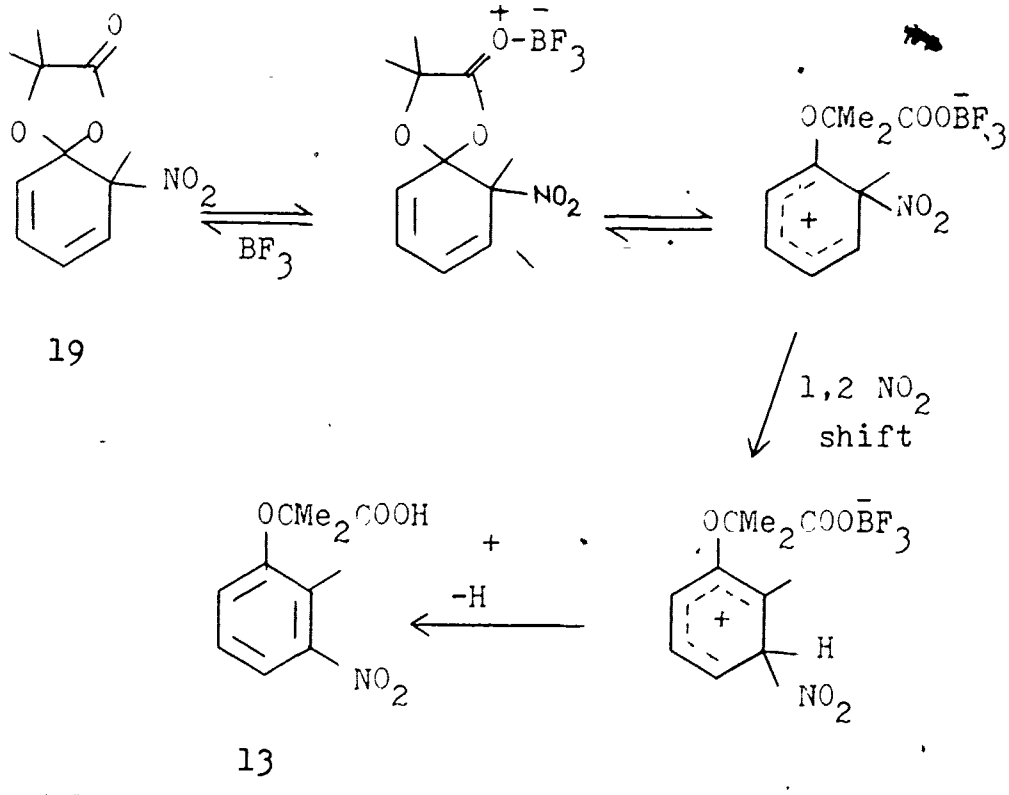
interesting to note that acid catalysis of [1,5] shift which was observed in neat TFA is not observed in protic solvents. A likely explanation is that the solvent competes effectively for the acid i.e. the solvent exerts a levelling effect on the acid and the concentration of the conjugate acid of **19** is much lower than in aprotic solvents.

3.8.4 Reaction with boron trifluoride

Attempts were made to bring about the 1,2 shift of the nitro group in diene **19** (c.f. p 19) by reaction with a variety of acids in both hydroxylic and aprotic solvents. In all cases products of a formal 1,3 nitro shift either by denitration-renitration, or by a [1,5] sigmatropic rearrangement, were obtained but no [1,2] shift product was observed. With an oxygen substituent on the aromatic ring, the [1,2] nitro shift leading to products with the nitro group *meta* to the oxygen substituent is an high energy process. Thus the absence of such products is not surprising. Boron trifluoride gas was bubbled for 2 minutes through a chloroform-d solution of **19** at -60°C. The product of a [1,2] shift, **13** (7%) was observed by ^{1}H NMR (250M Hz) and **15** (54%), **14** (31%) and **12** (8%) were observed as well. The compounds were identified by the chemical shift of the gem-dimethyl group on the side chain and confirmed by GC. Formation of **13** suggests that the boron trifluoride adduct of the lactone is a higher energy intermediate than the protonated lactone. This will make it less selective than

the protonated form and thus give some product of [1,2] nitro shift.

Scheme 3.17 [1,2] Nitro Shift in the Reaction of **19** with BF_3



19

13

3.8.5 Attempted solvolysis in aqueous methanol

In 70% aqueous methanol at 45°C, **19** gave **15** (43%) and unreacted **19** (57%) after 2.5h. Thus the [1,5] nitro shift followed by ring opening was the only reaction and no solvolysis occurred. No epimerization occurred under these conditions, demonstrating that the reaction requires acid catalysis.

3.8.6 Attempted cycloaddition with tetracyanoethylene and nitroethylene

Since **19** is a conjugated diene, cycloaddition with reactive dienophiles was attempted. Nitroethylene did not react with **19** after 24 h at ambient temperature. With tetracyanoethylene in tetrahydrofuran-d_8 some reaction of **19** was observed after 24 h. The reaction mixture was left at ambient temperature for 15 days and the acid **15** (18%) and the ester **58** (72%) along with some unidentified compounds, were observed. Since **55** gives a comparable amount of **58** (70%) in the presence of tetracyanoethylene, the reaction of **19** clearly involves an isomerization of **19** to **55** and subsequent aromatization.

3.9 *Aromatization of* 10-*methyl*-10-*nitro*-1,4-*dioxaspiro*[4,5]*deca*-6,8-*dien*-2-*one* (25)

3.9.1 Products from reactions with trifluoroacetic acid and with trifluoroacetic acid in chloroform-d

a) Epimerization

Diastereomers **25A** and **25B** could be equilibrated by reacting each of the adducts with 1% (v/v) TFA in chloroform-d at 0°C. The epimerization was slow under these conditions. The equilibrium mixture (**25A** -31%, **25B** -69%) was obtained from **25A** after 14 h while starting from **25B** it took 24 h to reach the same equilibrium mixture. At higher concentrations of TFA, epimerization was faster but aromatization began to compete. Diene **25** aromatized more

rapidly than **19** which could be epimerized with 10% TFA in chloroform-d without complications. The only difference between **19** and **25** is the *gem*-dimethyl group. This *gem*-dimethyl group must be responsible for the change in stability towards aromatization in going from **19** to **25**.

b) Aromatization

Aromatic products from reactions of **25** with TFA are shown in Table 3.15. At low concentrations of TFA the only observable processes occurring were epimerization and [1,5] nitro shift of the conjugate acid of **25**. Only **26** was observed as the final product. The isomerized diene **67** (analog of **55**) was not observed during any of the reactions although it must have been formed as an intermediate. It will be recalled that **67** was not observed in the thermal isomerization reactions (p. 185), the ring opening process leading to **26** presumably being faster than the rearrangement step. The same situation pertains in acid.

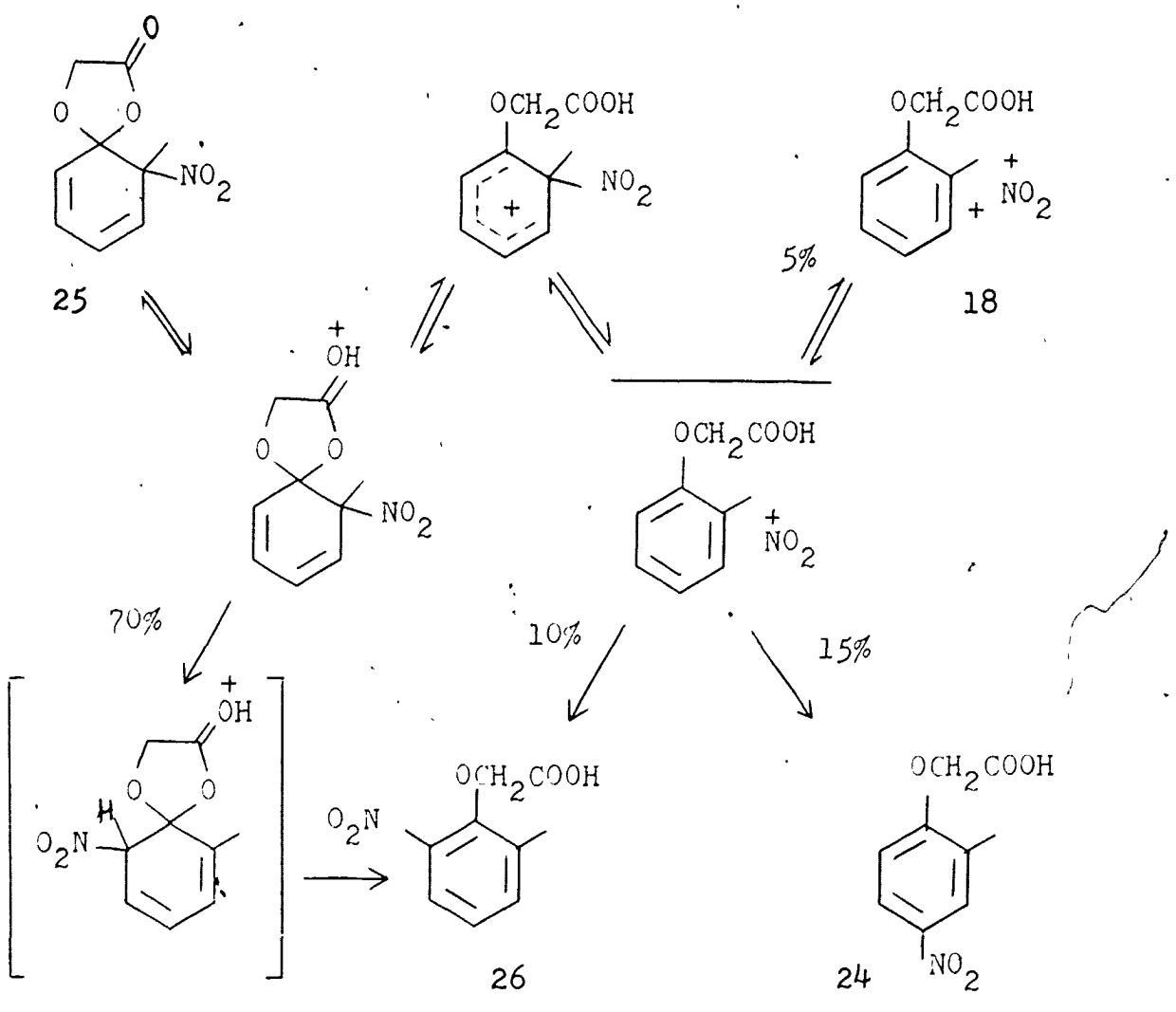
Table 3.15

Aromatics Products from reaction of **25** with TFA

Reaction conditions	**18**	**24**	**26**
5% TFA/$CDCl_3$, 24 h, 0°C	--	--	100%
10% TFA/$CDCl_3$, 3 h, -20°C	--	--	100%
25% TFA/$CDCl_3$, amb. temp.	5%	15%	80%
100% TFA, amb. temp.	5%	15%	80%

At higher concentrations of the acid (25%), the [1,5] nitro shift is still the major pathway of reaction but denitration and renitration leading to **18** and **24**, respectively, also occur. Further increase in the acid concentration, up to 100% TFA, does not affect the product ratio. A complication in this case is that **18** is nitrated at both the 4- and 6-positions in TFA. So whenever **24** is formed in the reaction mixture some **26** must also be formed from the same renitration path. Note that nitration of **18** in TFA-chloroform-d leads to 6-nitro (**26**) as well as 4-nitro (**24**) products and the ratio of **24**:**26** is 60:40. The mechanism can be shown as depicted in Scheme 3.18.

Scheme 3.18 Pathways for Aromatization of **25** under Acidic Conditions



Numbers above the arrows indicate % product formed by that route in > 25% TFA.

3.9.2 Reactions with sulphuric acid

Diene **25** reacted with 0.1M sulphuric acid in methanol or with 0.1M sulphuric acid in 90% aqueous acetone at ambient temperature to give the nitrocresol **10** as the only product in both cases. The corresponding acid **26**, when treated with

sulphuric acid in methanol under the same conditions, gave methyl (2-methyl-6-nitrophenoxy)acetate (122) as the only product. With sulphuric acid in aqueous acetone under the same conditions 10 (8%) and unreacted 26 (92%) were obtained. Thus the 10 is not a secondary product formed from 26 under the reaction conditions. It must be formed by dealkylation of some intermediate formed from 25.

3.9.3 Reaction with boron trifluoride

The aromatization of 25 was complete in 40 min at -40°C with boron trifluoride. The only product was 26. No denitration-renitration or [1,2] nitro shift occurred.

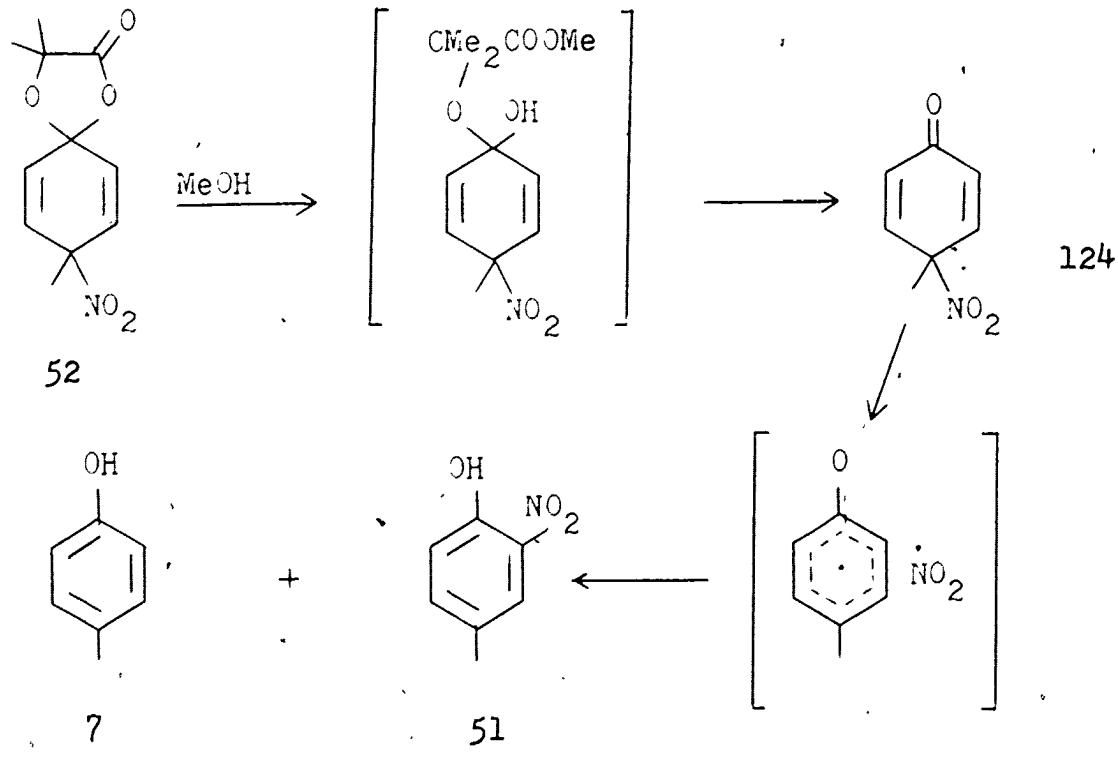
3.10 *Reactions of* 3,3,8-*trimethyl*-8-*nitro*-1,4-*dioxaspiro*[4,5]*deca*-6,9-*dien*-2-*one* (52)

3.10.1 Attempted solvolysis of 52

When 52 was heated in aqueous methanol at 60°C, the nitrocresol 51 (18%) and unreacted 52 (82%) were obtained after 30 min. When the reaction was carried out for 4 h, 51 (80%) and *p*-cresol (20%) were obtained. The reaction was repeated in presence of tris(hydroxymethyl)aminomethane (123) and in the presence of urea but the same relative amounts of the two cresols were obtained. The nitrous acid traps eliminated any possibility of solvolysis of nitro group and subsequent nitrous acid catalyzed hydrolysis of the lactone. Thus lactone hydrolysis leading to the dienone 124, followed by thermal homolysis of the C-NO_2 bond and

recombination at the *ortho*-position, is the route leading to the products (Scheme 3.19). Myhre[85] has shown that 4-methyl-4-nitrocyclohexa-2,5-dienone (124) aromatizes by a radical path under neutral conditions.

Scheme 3.19 Hydrolysis and Subsequent Aromatization of 52

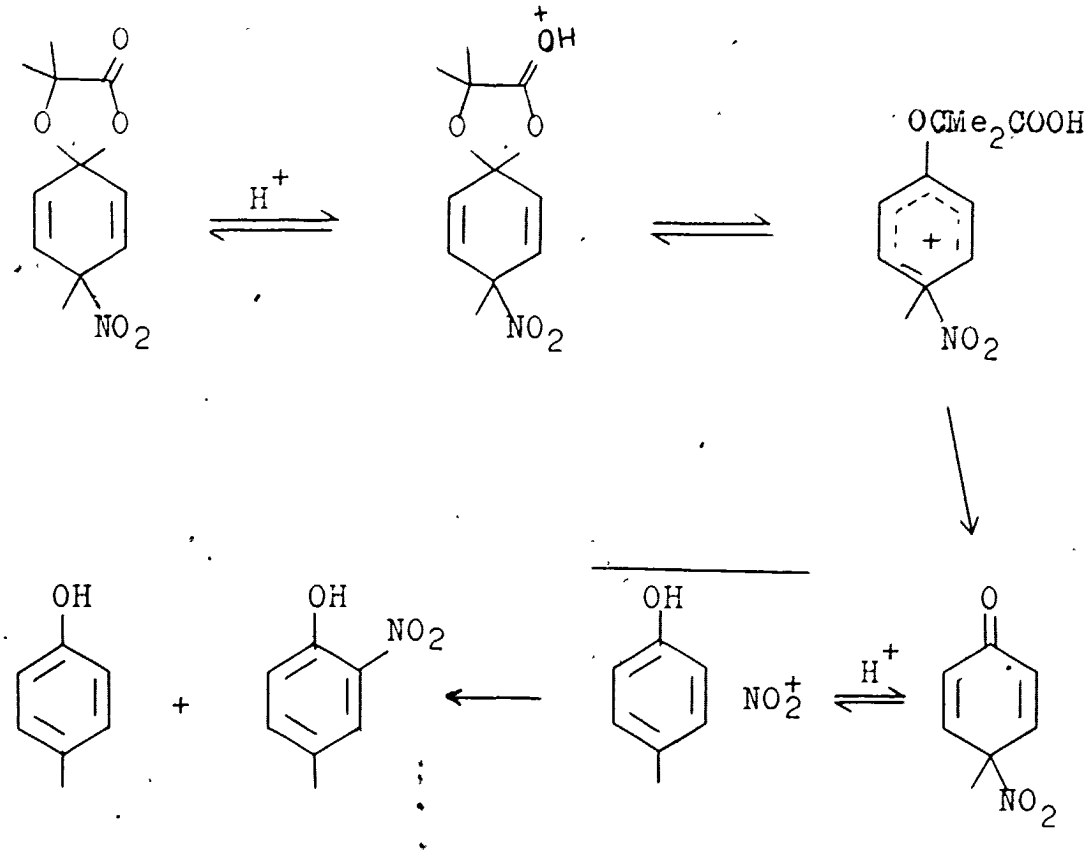


3.10.2 Reaction of diene 52 with acids in non-hydroxylic solvents

Reaction of diene 52 in 50% (v/v) trifluoroacetic acid in chloroform-d gave 51 (20%), 7, 2-methyl-2-(4-methylphenoxy)propanoic acid, (1) and 2-methyl-2-(4-methyl-2-nitrophenoxy)propanoic acid, (54) (70%). Comparable results were obtained in 75% TFA and in 100% TFA and the only noteworthy change which occurred when the strong acids,

methanesulfonic acid and triflic acid, were used to induce the aromatization of 52 was that a small amount of 2-methyl-2-(4-methyl-3-nitrophenoxy)propanoic acid 16 was also formed. The cresols 7 and 51 are formed presumably via protonation, ring opening to the Wheland intermediate and side chain cleavage to form the dienone (112) which is known to aromatize to 7 and 51 under neutral or weakly acidic conditions. (Under more strongly acidic conditions, renitration of 7 occurs and only 51 is formed from the dienone).

Scheme 3.20 Formation of Cresols from 52 under Acidic Conditions



In the above sequence a unimolecular cleavage of the side chain in the Wheland intermediate is proposed. This would explain the approximately constant fraction of the nitrocresol formed under a wide range of acidic conditions (Table 3.16). The other products **1** and **54** also arise by a unimolecular reaction of the same intermediate to form the encounter pair of **1** and the nitronium ion which i) renitrate to give **54** or ii) dissociate to give free **1** and nitronium ion.

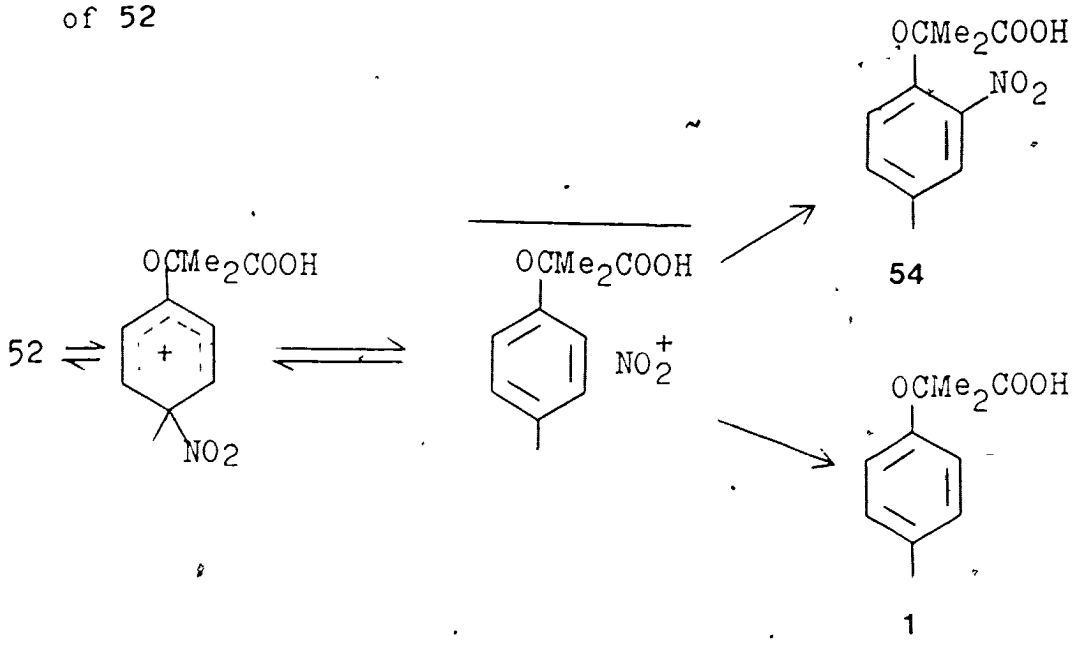
Table 3.16

Products from reaction of 52 with acids in non-hydroxylic solvents

Reaction Conditions	51	7	1	54	16	other
50% TFA/$CDCl_3$, 24 h, amb. temp.	20%	ca.5%	ca.5%	70%	--	---
75% TFA/$CDCl_3$, 7 h, amb. temp.	20%	traces	traces	75%	--	---
100% TFA, 8 h, 0°C	20%	----	14%	66%	--	---
CH_3SO_3H(neat), 15 min., 10°C	20%	----	16%	56%	8%	---
CF_3SO_3H(neat), ca. 10 min., 0°C	15%	----	15%	63%	7%	---
50% TFA/$(CF_3CO)_2O$, 28h, 0°C	100%[a]	----	---	---	--	---
100% TFA/trimethoxybenzene, 9 h, 0°C	---	----	70%[b]	30%[b]	--	*c*
100% TFA/mesitylene 1 h, amb. temp.	---	----	36%	55%	--	9%[d]

a. formed by intermediate formation of 54
b. relative amounts
c. nitrotrimethoxybenzene detected by GC
d. nitromesitylene

Scheme 3.21 Denitration-Renitration Pathway in the Reaction of 52



Some of the nitro acid 54 must be formed by renitration of the acid 1 following escape of the nitronium ion from the encounter pair, since, when the reaction of 52 in 100% TFA was carried out in the presence of mesitylene (or trimethoxybenzene) the amount of 1 was increased substantially while that of 54 was decreased and some nitromesitylene (or nitrotrimethoxybenzene) was formed. However only a portion of the escaped nitronium ion could be trapped in the experiments and the reactions must be more complex than has been proposed.

It has been observed earlier that the [1,2] nitro shift in the oxygen-substituted nitrocyclohexadienyl cation is not a favoured process although this is a predominant pathway of reaction in other substituted nitrocyclohexadienyl cations. The oxygen substituent stabilizes the cation with the charge

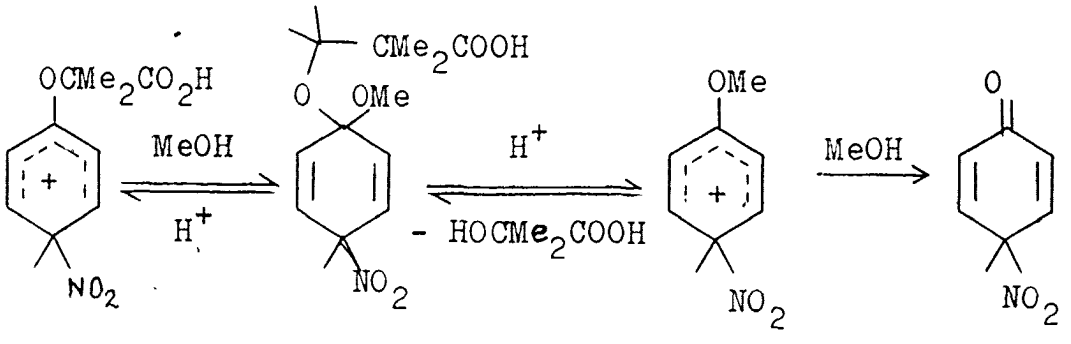
conjugated with the oxygen lone pair. The cation from the [1,2] shift process is not similarly stabilized and thus there is a considerable barrier to the process in the system containing the ether substituent. However the incursion of the [1,2] shift process can be detected in the reaction catalyzed by strong acids.

When 52 was reacted with a mixture of trifluoroacetic acid and trifluoroacetic anhydride, the acid 54 was formed as the initial product, which subsequently slowly cleaved at the side-chain to form the nitrocresol 51.

3.10.3 Reaction of 52 with acids in protic solvents

At lower concentrations of TFA, 52 was quantitatively converted to the dienone 124, which could be observed in the reaction mixture and which then aromatized to 51. In 50% TFA, *p*-cresol (5%) was also detected. At very high concentration of the acid, the amount of 51 decreased while that of 7 increased (Table 3.17). Even with only 1% methanol 52% 51 was formed and only 48% of 54 was obtained. The route to 54 is presumably similar to that described for reaetions in non-hydroxylic solvents : unimolecular dissociation of the Wheland intermediate into the encounter pair and renitration. However there must be an additional pathway to the dienone since this is formed to much greater extent than in the non-hydroxylic solvents and is formed as the major product even when only 1% methanol is present. Such a pathway has been suggested for the 2-methylphenoxy

series : capture of the Wheland intermediate by methanol, leading eventually to the dienone.



Evidently the unimolecular fission of the nitronium ion in the Wheland intermediate from the 4-methylphenoxy series is less competitive with methanol capture of the intermediate than is the case in the 2-methylphenoxy series.

Table 3.17

Products from reaction of **52** with acids in methanol at 0°C

Acid Concentration	Reaction Time	**124**	**51**	**7**	**54**
50% TFA,	24 h	100%	---	---	---
	3 days	----	95%	5%	---
75% TFA,	105 min	100%	---	---	---
	24 h	----	100%	---	---
95% TFA,	4 h	----	72%	---	28%
99% TFA,	4 h	----	52%	---	48%
0.5M H_2SO_4,	3 h	100%	---	---	---
	a	----	89%	11%	---

a. at ambient temperature

Reaction of **52** with sulphuric acid in methanol was similar to the reaction with TFA in methanol. First the dienone **124** was obtained and subsequently **7** and **51**. Reaction of **52** with aqueous sulphuric acid in acetone was also similar. The dienone **124** was formed and it aromatized to **7** and **51**.

3.10.4 Reaction of **52** with boron trifluoride

The nitro group in the *ipso*-Wheland intermediate obtained from **52** underwent [1,2] migration in methanesulphonic acid and triflic acid to give the 3-nitro derivative **16** (7-8%). If the argument made earlier were in fact correct, the boron trifluoride adduct of **52** would be less selective than the conjugate acid of **52** and give more of **16**. When a solution of diene **52** in chloroform was treated with boron trifluoride gas, aromatization to give **16** (19%), the product of [1,2] nitro shift was observed along with **1** (19%) and **54** (62%). Observation of **13** in the reaction of **19** with boron trifluoride need not be surprising in this light.

3.10.5 Reactions of **52** with bases

Diene **52**, with acids, gave the dienone **124** very readily. To test whether the lactone was hydrolyzed in bases as well, **52** was treated with sodium methoxide in methanol. With 3 equivalents of sodium methoxide at -20°C, dienone **124** (60%) and a monomethoxy adduct **126** (40%) were formed after 30 minutes. With 1.1 equivalents of methoxide at 0°C, **124** (31%), **126** (59%) and **51** (5%) were obtained after 5 min from

52. When 5 equivalents of methoxide was used at 0°C p-cresol (1%), monomethoxy adducts **125** (21%) and **126** (40%) and the dimethoxy adduct **128** (33%) were obtained after 1 h at 0°C. After 7 h at 0°C, with 5 equivalents of methoxide **125** (13%), **126** (67%), **127** (5%) and **128** (15%) were obtained.

The dienone **124** was independently reacted with methanol and five addition compounds were obtained. These were separated by column chromatography and by fractional crystallization. There were two monomethoxy adducts (**125** and **126**) and three dimethoxy adducts (**127**, **128** and **129**). The monomethoxy adducts were shown to contain a conjugated carbonyl group by ^{13}C NMR (194.8 and 194.0 ppm for **125** and **126** respectively) and IR (1685 cm^{-1} and 1675 cm^{-1} for **125** and **126** respectively) spectroscopy. The methoxy group was identified by its characteristic ^{13}C and ^{1}H chemical shifts. The presence of a nitro group was confirmed by IR and that of a methyl group *ipso* to the nitro group was indicated by ^{13}C and ^{1}H NMR. The ^{1}H NMR spectrum also indicated the presence of a double bond with two vinylic protons having a vicinal coupling constant of ca. 10 Hz (10.8 Hz in **125** and 10.5 Hz in **126**). The ^{1}H NMR also indicated a methylene group with magnetically non-equivalent protons coupled by a geminal coupling constant of ca. 17 Hz (16.9 Hz in **125** and 17.5 Hz in **126**). The chemical shift of the methylene protons suggested that they were adjacent to the carbonyl group. The spectral data suggested that **125** and **126** were

formed by 1,4-addition of one equivalent of methanol to the dienone **124** and thus they were assigned as diastereomers of 5-methoxy-4-methyl-4-nitrocyclohex-2-enone.

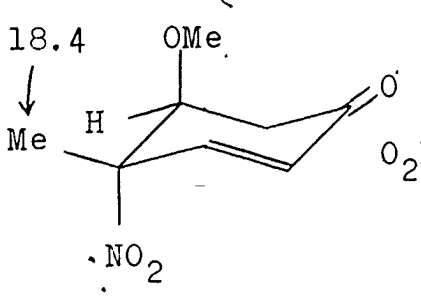
The three dimethoxy adducts were shown to contain a non-conjugated carbonyl group as indicated by a downfield shift (relative to **125** and **126**) in the carbonyl carbon signal (201.9, 203.3, 204.3 ppm in **127**, **128** and **129** respectively). The ^{1}H NMR indicated that no vinylic hydrogen atoms were present and the ^{13}C NMR confirmed that no carbon-carbon double bond was present in any of the adducts. The ^{1}H and ^{13}C NMR further suggested that the two methoxy groups were equivalent in **127** and **129** while in **128** two methoxy carbon resonances and two methoxy proton resonances were observed indicative of a non-symmetrical molecule. Each of the adducts had two pairs of geminally coupled protons, the two pairs being equivalent in **127** and **129** and non-equivalent in **128**. The chemical shifts suggested that both the pairs of methylene protons were adjacent to the carbonyl group. Thus the three adducts **127**, **128** and **129** were assigned as diastereomers of 3,5-dimethyl-4-methyl-4-nitrocyclohexanone, obtained by 1,4 addition of two equivalents of methanol to **124**. The relative stereochemistry of the adducts was determined by using the γ-*gauche* effect described on page 171. In the case of the monomethoxy adducts **125** and **126**, the methoxy group can be *cis* or *trans* to the methyl group. When it is *cis* to the methyl group, the two groups will always be

gauche to each other. When it is *trans* to the methyl group the two groups will be *anti* to each other in the preferred conformation. Thus the methyl carbon in the adduct where the methyl and the methoxy groups are *cis* should resonate at a higher field than in the adduct where the two groups are *trans*.

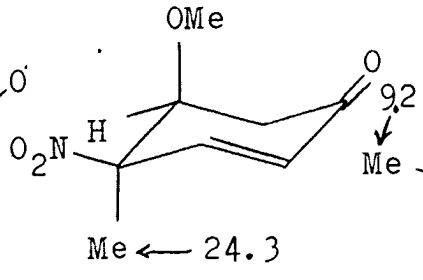
The asymmetrical dimethoxy adduct **128** will have one of the methoxy groups *trans* to the methyl group and the other one will be *cis*. Following the same reasoning as for the monomethoxy adducts, in the symmetrical dimethoxy adducts **127** and **129**, the methyl group in the adduct where both the methoxy groups are *cis* to the methyl group will resonate at a higher field than in the adduct where the two methoxy groups are *trans* to it. The relative stereochemistry of all the adducts could be assigned on the basis of the above reasoning and is shown in Table 3.18. The difference between the methyl carbon shift in **127** and **129** is twice the corresponding difference in **125** and **126**. This would be expected since the substituent effects on ^{13}C chemical shifts are generally additive.

Table 3.18

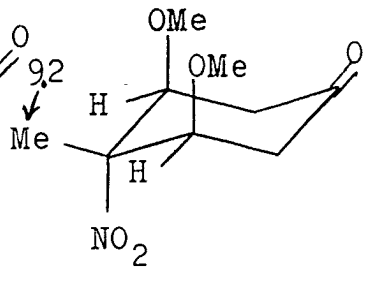
Relative stereochemistry of methoxy adducts



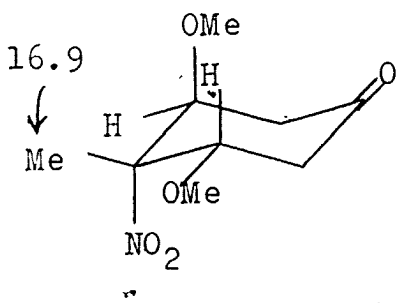
gauche
125



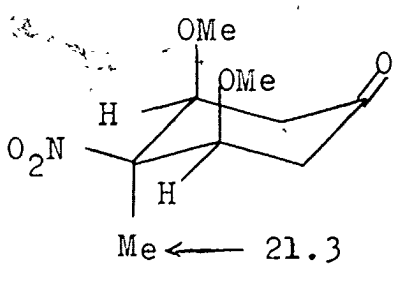
anti
126



gauche-gauche
127

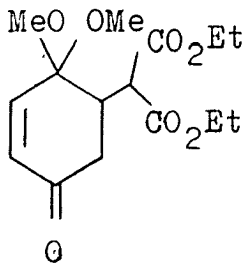


gauche-anti
128

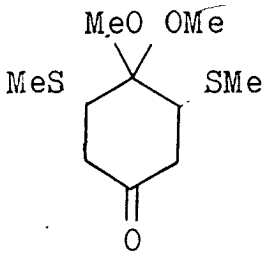


anti-anti
129

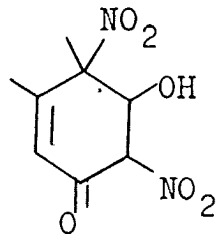
Such 1,4 addition to cyclohexadienones generally leads to aromatic products[22], but some adducts similar to the methoxy adducts above (125-129) have been isolated and are shown below.



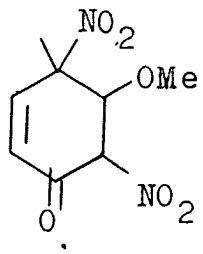
Ref. 142a



Ref. 142b



Ref. 142c



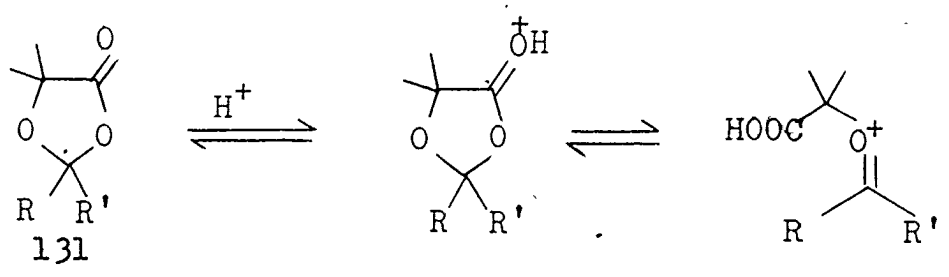
Ref. 62

Other bases which were reacted with 52 were potassium hydroxide, sodium hydroxide and N,N-diisopropylethylamine. When treated with potassium hydroxide in acetonitrile at 0°C, 52 gave 124 (50%) and unreacted 52 (50%) after 1 h. When the reaction was carried out in the presence of 18-crown-6, 51 (36%) and 7 (64%) were obtained after 8 h at 0°C. Dienone 124 and the isomers of 5-hydroxy-4-methyl-4-nitrocyclohex-2-enone (130) were obtained by the reaction of 52 with sodium hydroxide in 50% aqueous acetonitrile. The structure of the hydroxy compound was assigned by comparing the ^{1}H NMR spectrum with those of the corresponding methoxy adducts. The compound was not isolated or characterized. Treatment of 52 with N,N-diisopropylethylamine in 50% aqueous acetonitrile gave 124 and 51.

3.11 *Comparison of aromatization reactions of* 19, 52 and 25

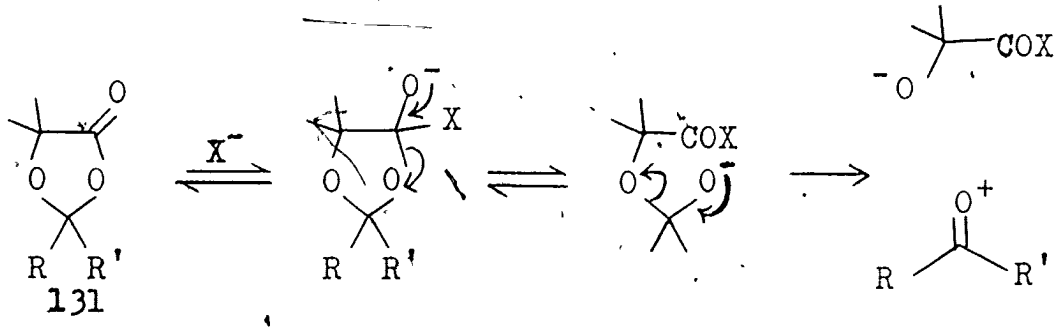
The lactone ring, which is a common feature of 19, 52 and 25 is a substituted 1,3-dioxolan-4-one (131). Thus it can be looked upon as both a ketal and a cyclic ester. In 2-substituted-1,3-dioxolan-4-ones, the ring exhibits

reactions, under acidic conditions, which are due to the ketal function.[141] A unimolecular cleavage of the conjugate acid of the ring occurs in the presence of acids, which is equivalent to alkyl-oxygen cleavage of the ester function.



131

Ketals are insensitive to bases, and under these conditions, the ring exhibits the reactions of an ester. Ester hydrolysis by acyl-oxygen cleavage to give a hemiketal intermediate occurs. Since the hemiketal is extremely sensitive to base, it undergoes further hydrolysis to give a carbonyl compound.

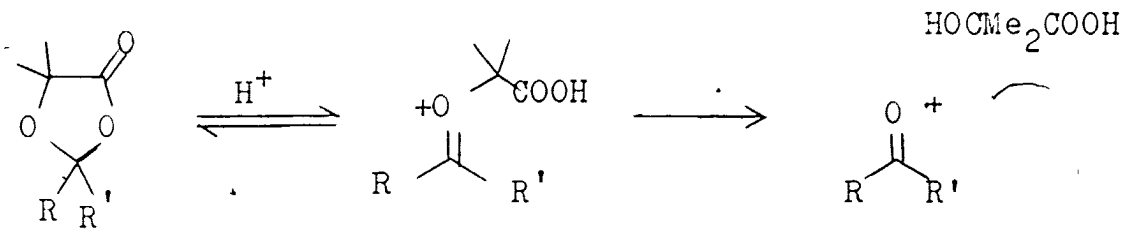


131

Under basic conditions, 52 was hydrolyzed to the corresponding carbonyl compound, the dienone **124**. Hence the lactone ring does behave as an ester under these conditions. Attempts to demonstrate a similar reaction for **19** were not conclusive probably due to the unstable nature of 6-methyl-6-nitrocyclohexa-2,4-dienone (**59**) (whereas **124** is stable up to 0°C **59** decomposes above -40°C). The base catalyzed

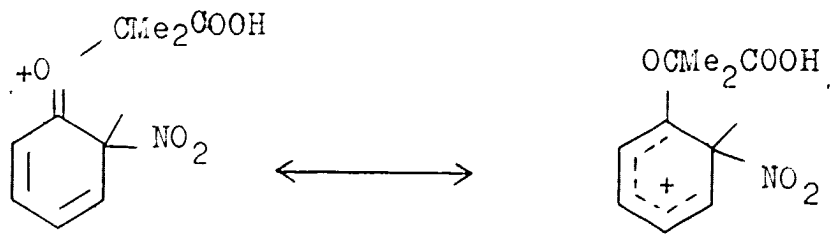
hydrolysis of the spirodienes has been used as a preparative method to synthesize 4,4-dimethylcyclohexadienone from 8-bromo-3,3,8-trimethyl-1,4-dioxaspiro[4,5]deca-6,9-dien-2-one (2), involving displacement of bromide by $LiMe_2Cu$ and subsequent hydrolysis.[143]

Under acidic conditions when R and/or R' are alkyl groups, the ring opening step is followed by dealkylation to give a ketone or an aldehyde.

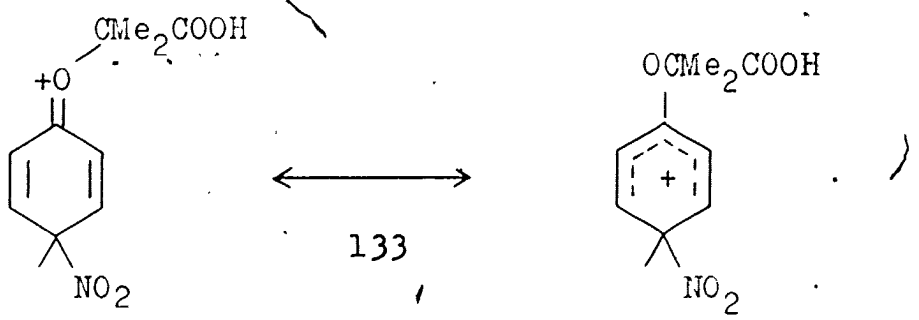


131

In the compounds studied R and R' form a cyclohexadiene ring which can delocalize the positive charge on oxygen.



132



133

Comparison of the acid catalyzed reactions of **19**, **52** and **25** under similar conditions show that

i) diene **52** has a marked preference for cleavage of the side-chain to give the nitrocresol **51** as a significant product and, in hydroxylic solvents as the major product.

ii) the reaction of dienes **19** and **25** are complicated by competition between [1,5] sigmatropic shift of the nitro group and the denitration-renitration process to give the 4-nitro derivative. Side-chain cleavage was, at most, a minor reaction of **19** while **25** underwent side chain cleavage only in hydroxylic solvents and then quantitatively. The sigmatropic rearrangement was relatively more important in the case of **25** than in the case of **19**, since at low acidities **25** gave only the 6-nitro acid **26**, the product from the rearrangement process, whereas **19** gave both the 4-nitro acid **14**, the denitration-renitration product, as well as the 6-nitro acid **15**. Even at high acidities the 4-nitro acid **24** was a minor product from **25** whereas the analogous **14** was the major product from **19**.

The preference for the rearrangement process in **25** may be attributed to the absence of the gem-dimethyl group on the lactone ring which may inhibit, to some degree, the rearrangement process in **19**. The formation of denitration-renitration products **14** and **54** from **19** and **52** respectively may be attributed to the delocalization of the positive charge into the cyclohexadiene moiety of the ring-opened

oxonium ion intermediates (132 and 133 respectively). This should impart some Wheland intermediate character to the intermediate which then undergoes cleavage of the nitro group as nitronium ion. It appears from the above discussion that i) the gem-dimethyl group decreases the reactivity towards isomerization, ii) the spirocyclohexadiene moiety modifies the reactivity of the 1,3-dioxolan-4-one ring in acid catalyzed reactions and iii) the intermediate **132** derived from **19** which has two adjacent fully substituted, sp^3 carbon atoms, has a greater tendency to undergo denitration-renitration reactions than the intermediate **133** formed from **52** which has the fully substituted sp^3 carbon atoms separated by a double bond.

3.12 *Conclusions*

This dissertation describes the nitration of substituted *o*-methylphenoxyalkanoic acids. These substrates undergo *ipso*-attack by the nitronium ion at the methyl substituted *o*-position to give conjugated spirodienes.

This is the first report in which adducts are formed by *ipso*-nitration *ortho* to the directing substitutent group. This work also extends significantly the number of conjugated diene adducts known.

The conjugated spirodienes undergo a novel thermal isomerization by a [1,5] sigmatropic shift of the nitro group to give conjugated dienes with a secondary nitro group. This is the first time that such derivatives have

been isolated. The concerted [1,5] shift is accompanied by a radical epimerization reaction which can be suppressed by radical scavengers. The non-conjugated diene adducts studied generally do not undergo nitro group rearrangement under thermal conditions. The only exception found in this study is that of 1,4-adducts with a nitrile group conjugated with the diene system in the product. Such adducts undergo a stereospecific [1,3] nitro shift. The resultant dienes with a secondary nitro group have also been isolated. The nitro group rearrangements studied involve a carbon to carbon nitro shift which has been observed for the first time. Previously reported sigmatropic nitro shifts are from nitrogen to carbon terminus.

Acid catalysis of the sigmatropic nitro shift in the conjugated spirodienes is observed in the presence of trifluoroacetic acid or stronger acids only in non-hydroxylic solvents. Examples of acid-catalyzed sigmatropic shifts are in fact rare. The conjugated spirodienes also undergo epimerization and a 1,3 extramolecular nitro shift by denitration-renitration sequence. The denitration product can be isolated and the escaped nitronium ion can be trapped. This is the first example where the nitronium ion ejected from *ipso*-adducts has been trapped. Whereas 1,3 nitro shifts in *ipso*-adducts obtained from aromatic ethers are common under acidic conditions, the 1,2 nitro shifts in the spirodienes under Lewis acid conditions to give *m*-

nitroaromatic ethers are observed in this work for the first time.

The acid-catalyzed denitration-renitration sequence can be suppressed under appropriate acidic conditions for the conjugated dienes studied, when regiospecific formation of 6-nitroaromatic products is observed. For the non-conjugated spirodiene studied, the denitration-renitration sequence can be suppressed to give quantitative dealkylation to 4-methyl-4-nitrocyclohexa-2,5-dienone. This dienone can also be obtained from the diene under basic conditions and the mono- and bis- adducts of the dienone with methanol have been isolated and characterized.

3.13 *Possible directions for further research*

The rearrangement and aromatization reactions of the spirodienes and other conjugated acetyl nitrate adducts have raised several points which are worth further investigation. The present work incorporates mainly product studies while more kinetic studies would help in quantifying the results and allow a better understanding of the various competing processes in both the rearrangement (concerted and radical processes) and aromatization (acid-catalyzed sigmatropic shift, epimerization, denitration, etc.) reactions. A few suggestions for future work are made below.

Kinetic studies :

i) Rearrangement of ^{15}N-labelled **19** can be studied to measure the isotope effect on the [1,5] sigmatropic nitro

shift which should be present in a concerted reaction. This would confirm the proposed sigmatropic nature of the rearrangement. On the other hand if there is a caged-radical pair involved, the ^{15}N-labelled diene may exhibit CIDNP effects in the ^{15}N NMR.

ii) Comparison of rates of aromatization of the isomerized diene **55** and its deuterated analog **56** in tetrahydrofuran may reveal the relationships between the routes leading to **15** and **58** with the possibility of observing even some isotope effect.

Mechanistic studies :

i) Diene **52** gave 20% **16**, the product of [1,2] nitro shift, on reaction with boron trifluoride. Such a high proportion of *m*-nitro derivative of aromatic ethers in an electrophilic process is exceptional. It is worth investigating any possible relationship between the Lewis acid strength and/or the length of the alkyl chain in the aryl alkyl ether and the [1,2] nitro shift, since there are not many routes to *m*-nitroaromatic ethers.

ii) Dienes **19** and **52** could nitrate mesitylene in neat trifluoroacetic acid. This is similar to transfer nitrations reported by Olah.[88] Olah's studies showed that nitration of toluene with 9-nitroanthracene gave predominantly the *p*-nitro isomer indicating that the nitrating species may be the conjugate acid of 9-nitroanthracene instead of a free nitronium ion. Similar

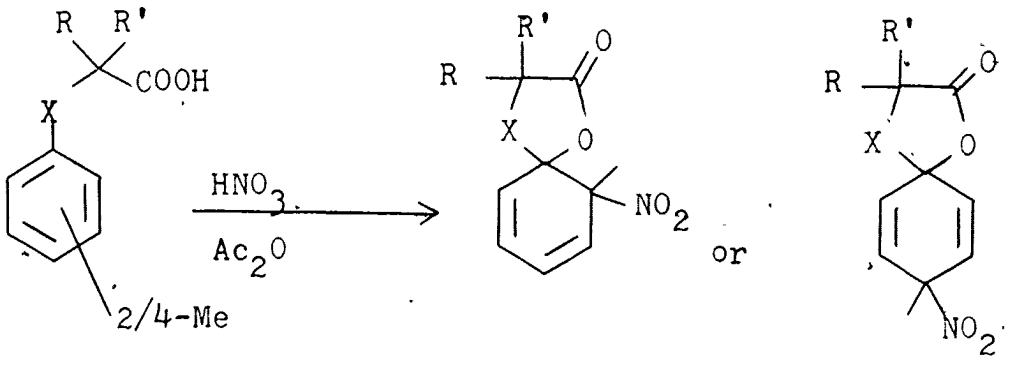
distinction of the nitrating species may be possible in the present case if a suitable substrate is used.

iii) ESR studies and radical traps may be used to confirm the proposed radical dissociation recombination mechanism for the formation of **112** from **19**. Dienes similar to **19** can be studied to see if this reaction is a general case.

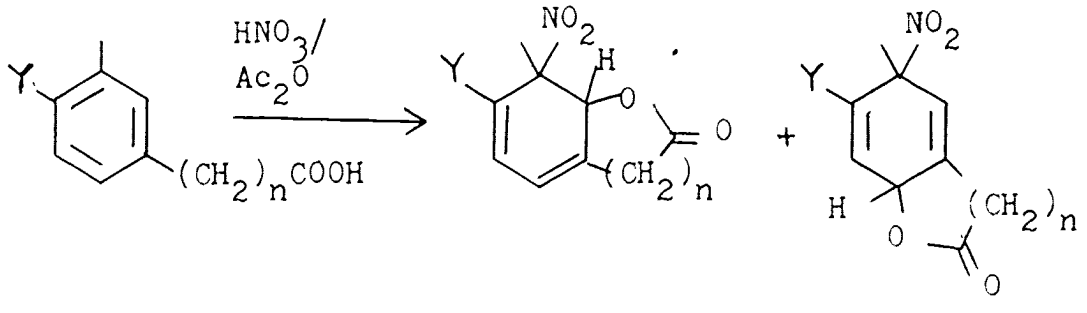
Product studies :

i) The carbonyl group in the lactone ring of the spirodienes played a major role in the acid and base catalyzed reactions of the diene. If the carbonyl group can be reduced to give a lactol or even a cyclic ketal, the reactivity of the diene may be markedly affected and may display new routes to aromatic products.

ii) The heteroatom in the side chain may be varied or the side-chain may be so substituted on the ring to give fused lactones.



R,R'=H,Me X= NMe, S, SO, SO_2, etc.



n = 1,2 Y = Cl, Br, F etc.

iii) The [1,5] sigmatropic nitro shift has given access to 2-(2-methyl-6-nitroaryloxy)-2-methylpropanoic acids and 4-*t*-butyl-3-nitrotoluene which are not obtained by direct nitration. The rearrangement reaction has potential to become a general route to specifically substituted nitroaromatics and its scope needs to be investigated.

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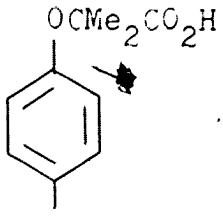
Appendix I : Key to Numbered Structures



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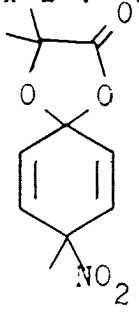

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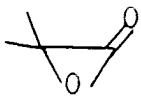

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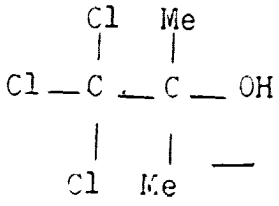

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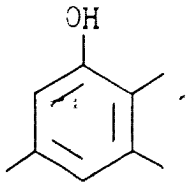

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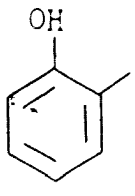

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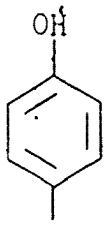

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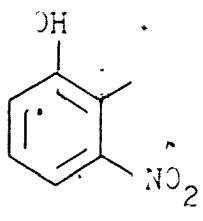

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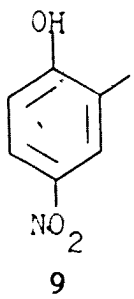

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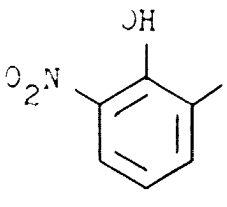

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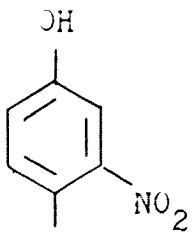

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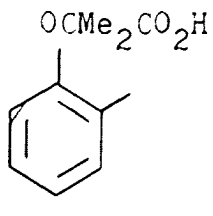

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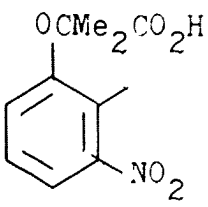

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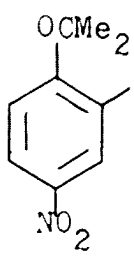

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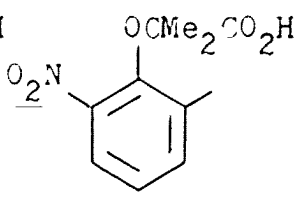

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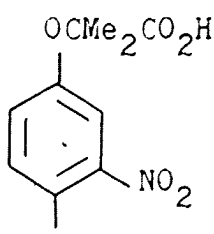

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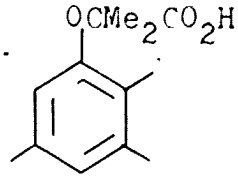

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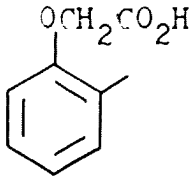

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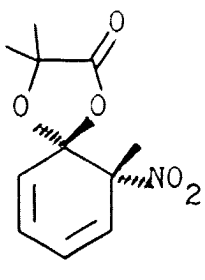

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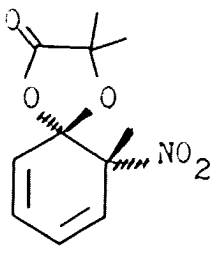

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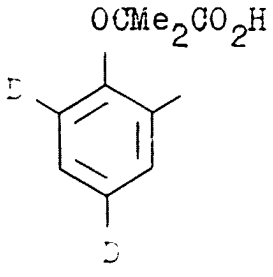

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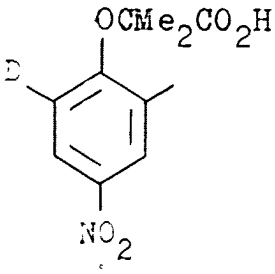

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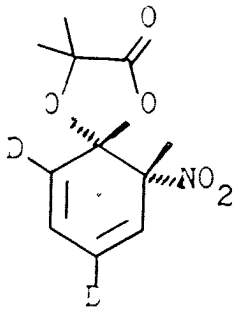

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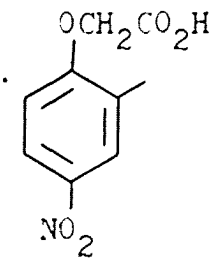

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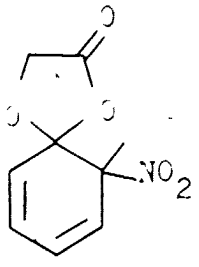

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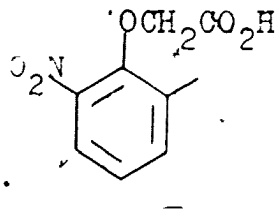

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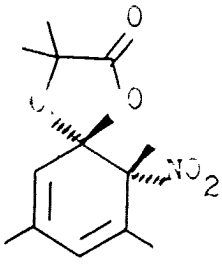

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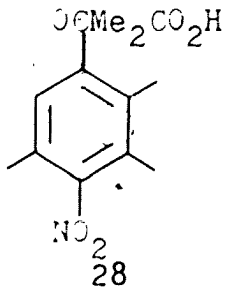

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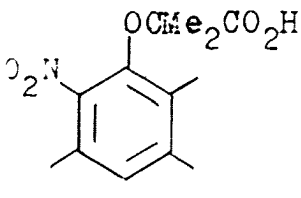

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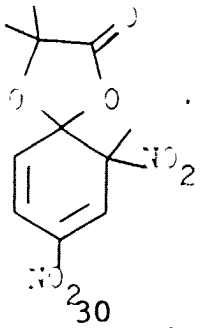

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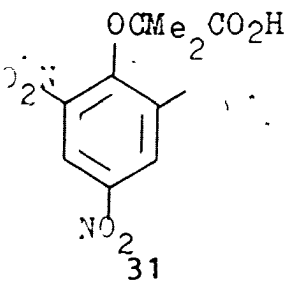

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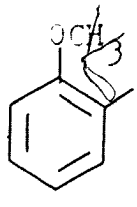

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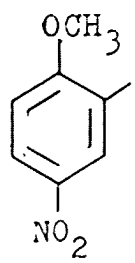

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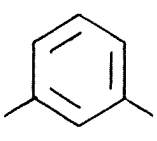

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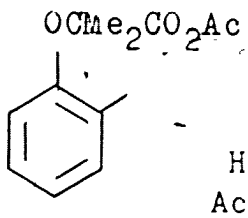

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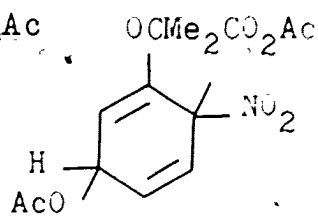

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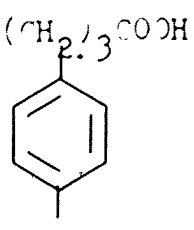

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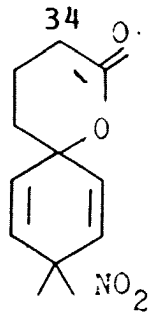

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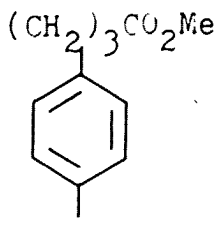

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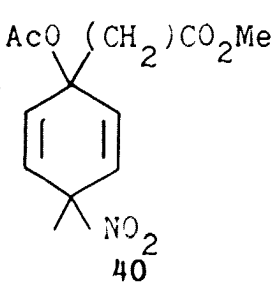

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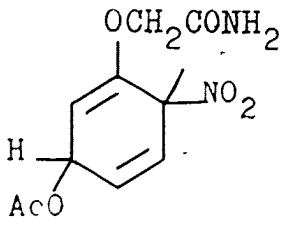

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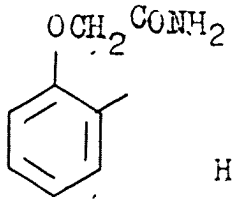

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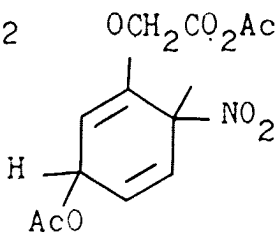

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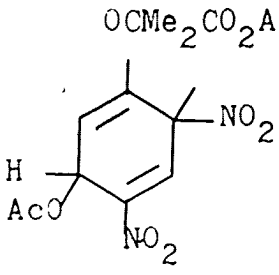

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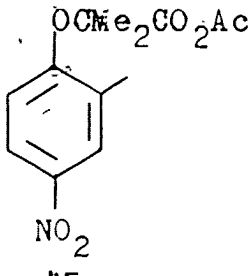

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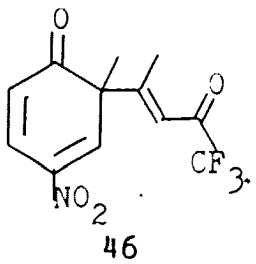

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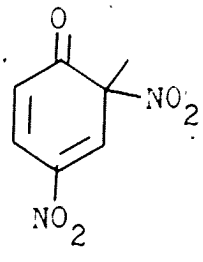

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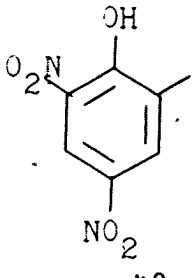

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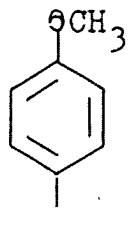

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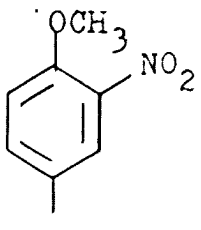

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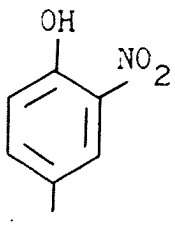

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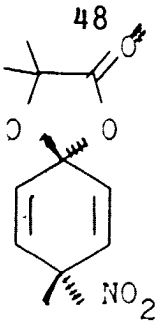

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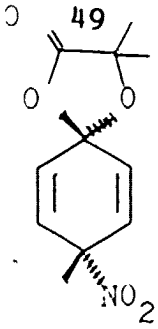

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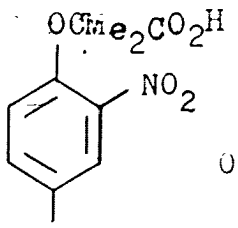

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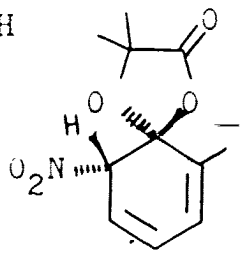

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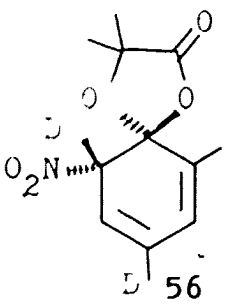

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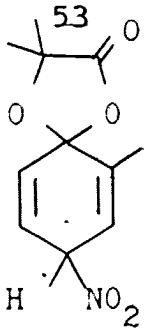

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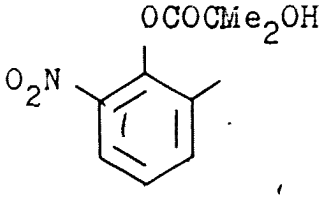

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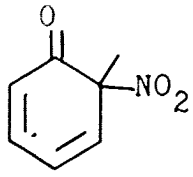

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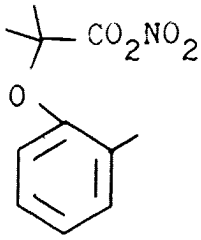

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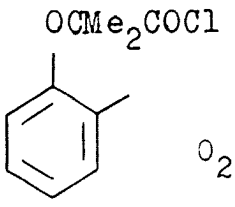

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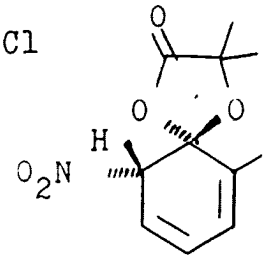

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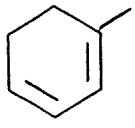

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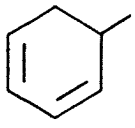

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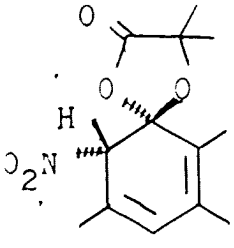

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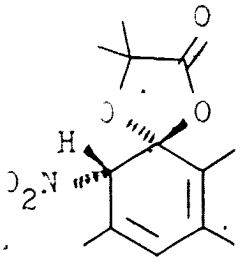

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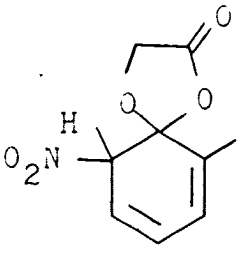

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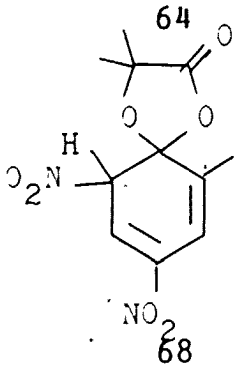

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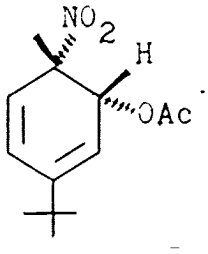

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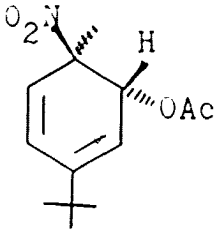

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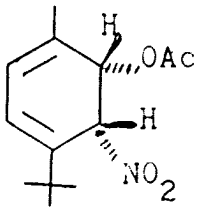

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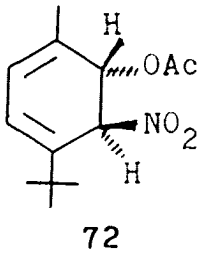

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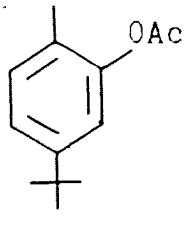

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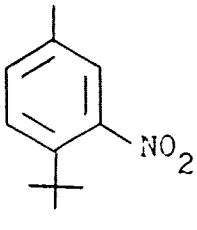

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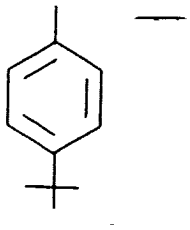

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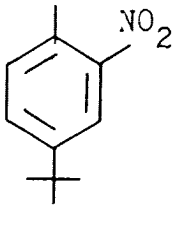

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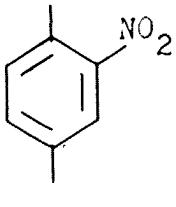

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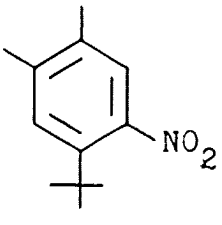

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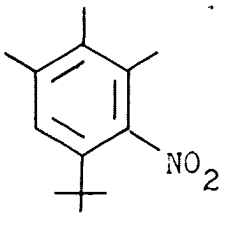

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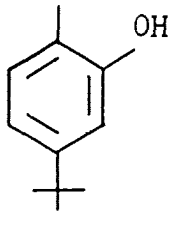

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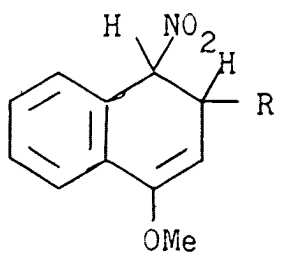

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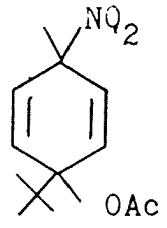

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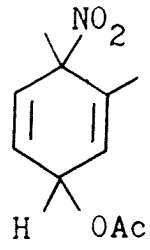

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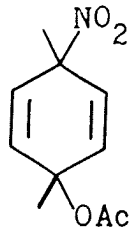

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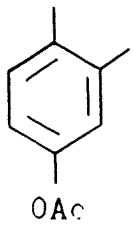

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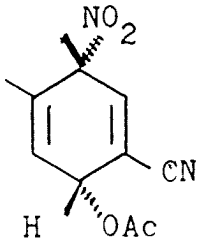

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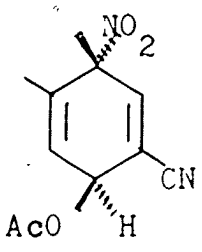

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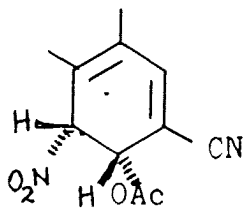

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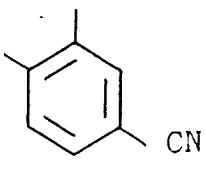

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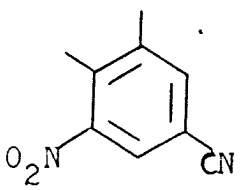

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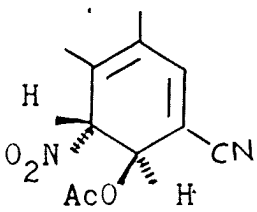

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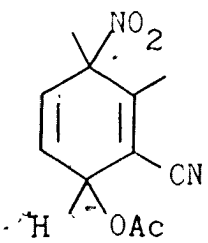

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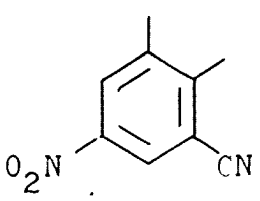

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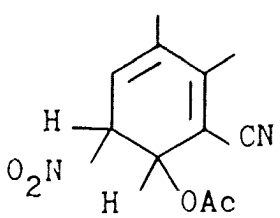

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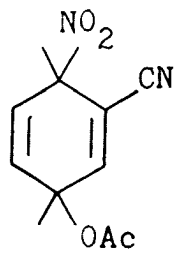

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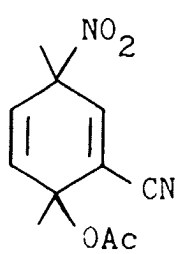

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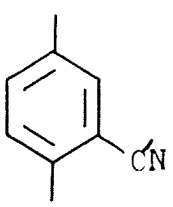

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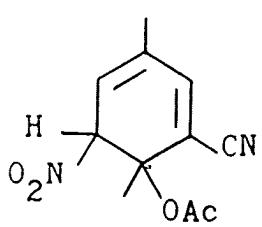

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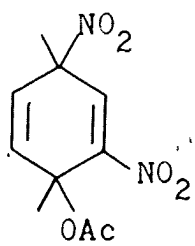

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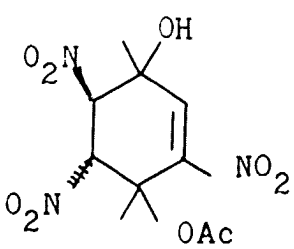

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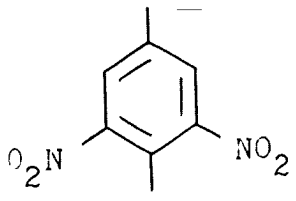

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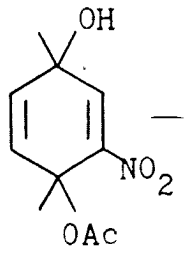

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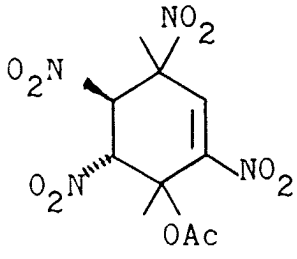

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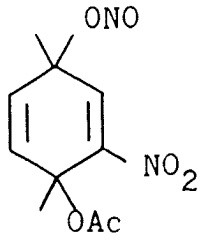

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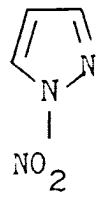

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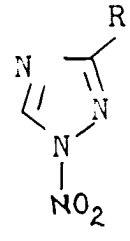

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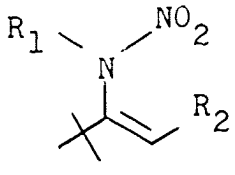

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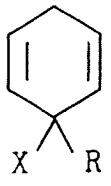

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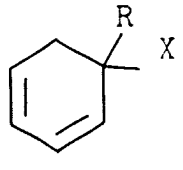

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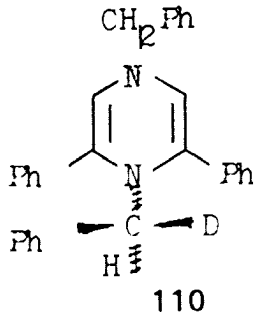

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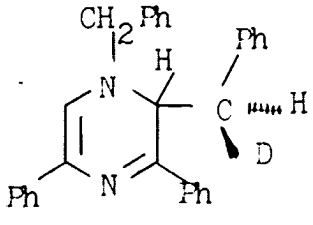

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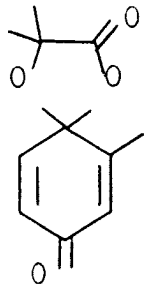

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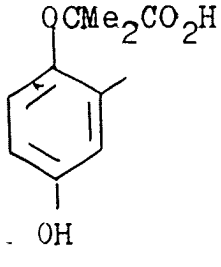

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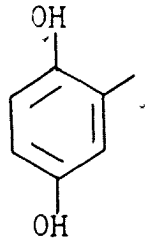

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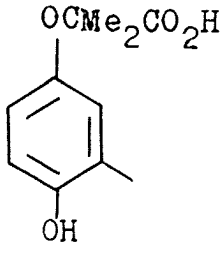

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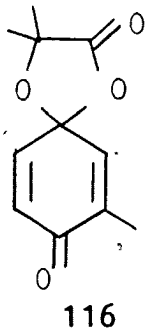

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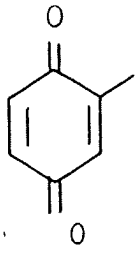

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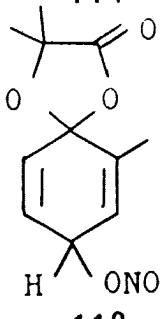

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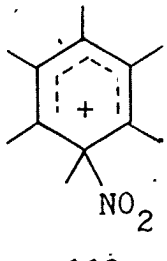

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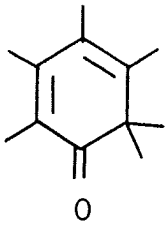

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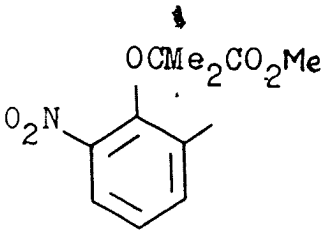

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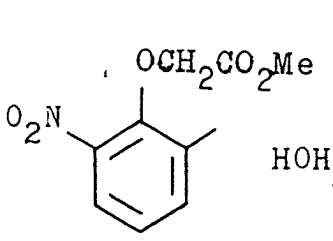

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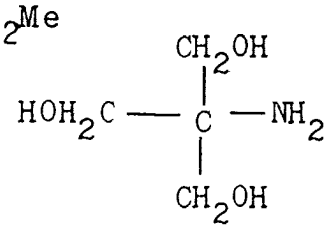

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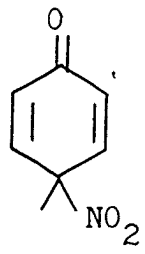

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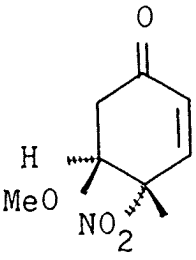

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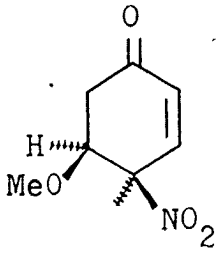

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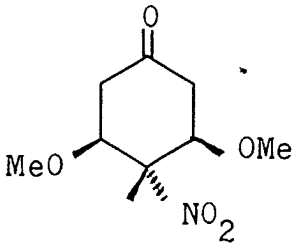

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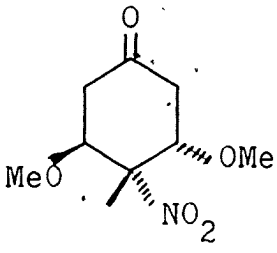

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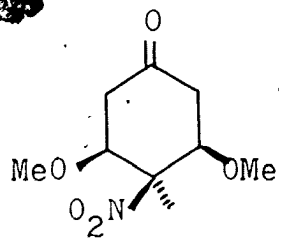

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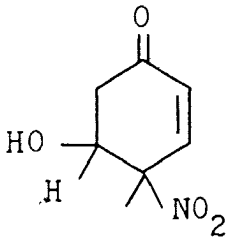

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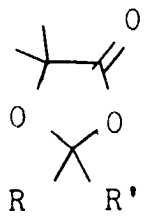

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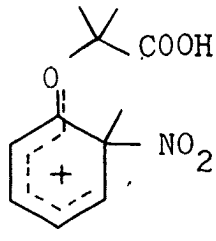

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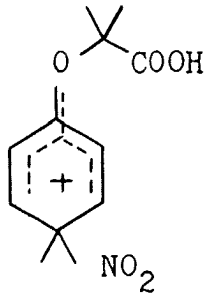

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Abasaheb Garware College, Pune, India	1976 to 1979
University of Victoria, B.C.	1980 to 1983

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University of Victoria Special Graduate Fellowship	1980-81
University of Victoria Graduate Fellowship	1981-82
Lewis J. Clark Memorial Fellowship	1982-83

Publications:

Sigmatropic Rearrangements of Adducts from *ipso*-Nitration: Formation of Adducts containing a Secondary Nitro Group. Girish S. Bapat, Alfred Fischer, George N. Henderson and Sumit Raymahasay, J. Chem. Soc., Chem. Comm., 119(1983).

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