AN INVESTIGATION OF THE BIOLOGICAL AND CHEMICAL REACTIVITY OF ALIPHATIC α-SUBSTITUTED NITRO-COMPOUNDS

by

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DEDICATION

In loving memory of my mother and father.

SUMMARY

A range of 2-substituted-2-nitropropanes ($Me_2C(X)NO_2$ with X = I, Br, Cl, NO_2, PO_3Et_2, COMe, CO_2Et, SR, SO_2R, *p*-$NO_2C_6H_4$, *p*-$NO_2C_6H_4N_2$, CN, SCN, and N_3) have been prepared and tested for antimicrobial activity against a representative range of micro-organisms. The structure activity relationship (S.A.R.) indicates antimicrobial activity of $Me_2C(X)NO_2$ in the order of I >SCN, Br >SR, *p*-$NO_2C_6H_4$ >Cl, NO_2 >SO_2R, N_3, CN, PO_3Et_2, COMe, CO_2Et, and *p*-$NO_2C_6H_4N_2$.

Increasing antimicrobial activity correlates well with the increasing ease of abstraction of the α-substituent by thiolate anions (X-philic reactivity towards thiolate) as shown by the chemical studies.

New synthetic procedures have been elaborated for the synthesis of α-thiocyanato and α-azido-nitrocompounds. α -Nitroazides have been shown to undergo $S_{RN}1$ reactions with azide, thiolates, and phenyl sulphinate ion *via* loss of nitrite, rather than loss of azide, from the intermediate radical anions ($R_2C(N_3)NO_2$. The reaction with nitronate-anions proceeded by loss of nitrite from the intermediate radical-anions.

α-Nitrothiocyantes have been shown to undergo $S_{RN}1$ reactions with azide, phenyl sulphinate, nitronates, and some thiolates *via* loss of thiocyanate from the intermediate radical-anions ($R_2C(SCN)NO_2$).

More strongly nucleophilic thiolates such as phenyl thiolate have been shown to react with α-nitrothiocyanates by a non-radical redox mechanism to yield the corresponding disulphides.

The reaction of thiolates with $Me_2C(X)NO_2$(X = CN, COMe, CO_2Et, and PO_3Et_2) has been investigated.

The nature of the radical-anion intermediates for $Me_2C(X)NO_2$(X = Br, Cl, NO_2, SCN, N_3, PO_3Et_2 SO_2R, COMe, CO_2Et, and CN) has been investigated by èlectron spin resonance spectroscopy in collaboration with Professor M.C.R. Symons of Leicester University. They all form stable radical-anions ($Me_2C(X)NO_2$ at 77°K in solid matrices of CD_3OD or methyl THF. E.s.r.

spectroscopy has also been used to show that the direction of dissociation of these radical-anions to radicals and anions correlates with that observed in solution reactions.

The mechanism of oxidation of thiolates to disulphides by α-substituted nitro compounds in protic solvents has been investigated as an *in vitro* model of their biological mode of action.

ACKNOWLEDGEMENTS

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My thanks go to the academic, technical staff, and my colleagues and friends of the organic and microbiology sections for their help and understanding throughout the course of this work.

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Last but not least, my deepest gratitude goes to my brothers and sisters for their moral and financial support, particularly brothers Farid and Adnan whom without their financial support, this work would have been impossible, to all I am indebted.

Except where otherwise stated, the material presented is original and has not been submitted for a degree at this or any other University.

CONTENTS

INTRODUCTION

PART 1

1.1 Antimicrobial Agents

Antimicrobial agents are drugs used to counteract infection and invasion of microorganisms in man. The term "Antimicrobial" describes several groups of particular agents.

Antibiotics are chemical substances produced by living organisms, by semi-synthesis, or by total synthesis. Antibacterial, antiviral, and antifungal drugs are used against bacterial, viral and fungal infections respectively. Antimicrobial agents can be classified as narrow spectrum drugs which act only on a single species or on a limited group of organisms. Examples of such drugs are nystatin, isoniazid, and griseofulvin. At the other extreme are drugs which affect a very wide range of species and are referred to as broad-spectrum agents. Examples of such drugs are tetracyclin and ampicillin.

Antibiotics act in many ways, but principally as follows:-

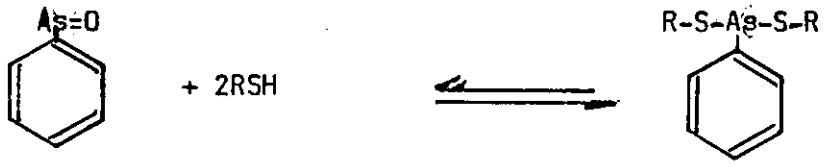
a) Interfere with the synthesis of nucleic acids or proteins, e.g. actinomycin and chloramphenicol.

b) Interfere with mucopeptide synthesis and hence the formation of new bacterial cell wall, e.g. cycloserine, penicillin and cephalothin.

c) By injury to the cytoplasmic membrane, e.g. amphotericin and polymixin[1-4].

Many synthetic compounds have been shown to have a marked effect on the metabolism of microorganisms and are very useful antimicrobial agents. The sulphonamides for instance, (widely used before the discovery of penicillin), affect the folic acid biosynthesis, whilst several

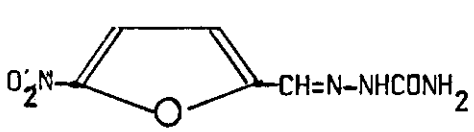
arsenic compounds are known to inhibit certain thiol containing enzymes. They react with the free thiol groups of these enzymes thereby inhibiting their reaction with glutathione[2] (eqn. 1-1).



1-1

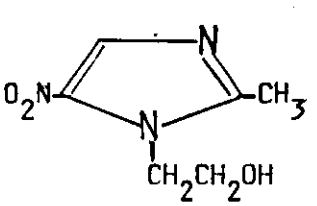
Synthetic nitro compounds are widely used in medicinal applications, especially as antimicrobial agents. Nitrofurazone (5-nitrofurfural semicarbazone, "Furacin" (1)) for example is used topically with great success as a broad spectrum antibacterial[5].

Nitrofuran derivatives appear to inhibit the formation of all types of RNA and DNA, as well as interfering with the conversion of pyruvate to acetyl CoA[5]. While the nitrofuran derivatives have been the most important nitro antibacterial drugs, nitroimidazole derivatives are now of increasing importance and are well-known antiprotozoal drugs. The most troublesome flagellate disease of *temperate* climates, vaginal trichomoniasis, is cured by the oral administration of metronidazole (2). Metronidazole is also used as the drug of choice in treatment of diseases caused by *amoebae*[1,5,6], and is used increasingly against anaerobic infections.



5-Nitrofurfuryl semicarbazone

(1)



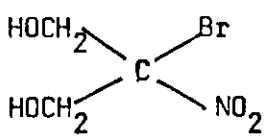
Metronidazole

(2)

Trichloronitromethane (chloropicrin), a synthetic agent, was used as a fumigant for agricultural purposes[5]. Chloropicrin has been reported to act as an oxidizing agent forming disulphide bridges between cysteine residues of reduced haemoglobin (eqn. 1-2)

$$2R\text{-}SH + Cl_3CNO_2 \longrightarrow 2HCl + R\text{-}S\text{-}S\text{-}R + ClC{=}NO_2^- \qquad 1\text{-}2$$

Bronopol (2-bromo-2-nitropropan-1,3-diol (3)) is another synthetic antimicrobial agent that owes its activity to interaction with thiols[7].



2-bromo-2-nitropropan-1,3-diol (3)

PART II

1.2 Bronopol

Bronopol is an α-substituted aliphatic nitrocompound which is active against a wide range of bacteria, including *Ps aeruginosa*, but is less active against yeasts and fungi[7,8].

Bronopol is used as a preservative in suppositories and toiletries, and as an active agent for various formulated products of commercial importance such as cosmetics (e.g. medicated shampoo), pharmaceuticals (e.g. antiseptics, and foam contraceptives), and household products (e.g. liquid soap)[9,10].

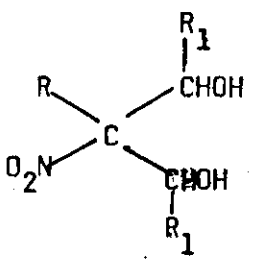
Bronopol is a crystalline powder which is soluble in water and other polar solvents. In aqueous solutions bronopol is stable at low pH, but decomposes at higher pH and higher temperatures. The toxicity of bronopol is very low and it is most active in slightly acidic solutions.

At high pH i.e. (in alkaline media) bronopol degrades and liberates nitrite which can under certain conditions nitrosate available amines that may be present such as diethanolamine to form nitrosamines which may be carcinogenic[11].

Development of bronopol and Structure Activity Relationships (S.A.R.)

In 1961 Zsolnai[12] studied a number of alkyl and aralkyl nitro compounds with potential antifungal properties. It was observed that several α-substituted aliphatic nitro compounds were very active, particularly where the structural feature, $C(Br)NO_2$, was present.

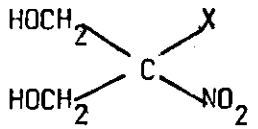
Eckstein *et al*[13] studied the antifungal activity of some 2-nitro-propan-1,3-diol derivatives. They found that the most active compounds were those where the α-substituent was bromine e.g. R=Br and R_1=Me in (4).



(4)

Replacement of bromine by chlorine resulted in compounds with low anti-fungal activity. The most effective anti-fungal compounds has a carbon chain length of 6-7 for the R alkyl group; if R was aryl the activity was retained, especially with an *o,p*-dichloro substituted benzene ring. Once again the most active compound contained the $C(Br)NO_2$ group. Croshaw *et al*[14] obtained similar results at the Boots Company Limited (Nottingham, England).

In the early 1970's Bowman and Stretton[15] studied the properties of derivatives of 2-nitropropan-1,3-diol, i.e. secondary α-halo-nitro, derivatives (5a-d)

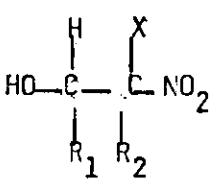


X = I 5a
= Cl b
= F c
= H d

They found that fluoro derivative (5c) and the unsubstituted analogue (5d) were both inactive and that the chloro (5b) was only slightly active. The bromo analogue (3) was very active, as was the iodo analogue (5a). However, the iodo derivative was unstable. The 1,3-diol aided water solubility only, because the 2-nitropropane analogues, 2-bromo and 2-iodo-2-nitropropane were of similar activity as the corresponding 1,3-diol derivatives. 2,2-Dinitropropane and 2-chloro-2-nitropropane were moderately active. Other bromonitro derivatives, e.g. 2-bromo-2-nitrobornane and 2-bromo-2-nitroadamantane were also fairly active. Once again these results confirmed the $C(Br)NO_2$ structural requirement. The minimum inhibition concentration (M.I.C.) values obtained are shown (Table1-1).

Stretton and Manson[16] carried out similar work to that of Bowman and Stretton and obtained similar M.I.C. values for the 2-nitropropane analogues.

In the search for antimicrobial activity Clark *et al*[17] successfully synthesised a series of simple aliphatic nitrocompounds and tested for antimicrobial activity. They studied structure (6) in detail.



(6)

Table1-1 Minimum inhibitory concentration (M.I.C.) values for a series of halo-nitro compounds

Nitropropane derivatives	*E. Coli*	*S. Aureas*	M.I.C. value ($\mu g/ml^{-1}$)		
			P. Aeruginosa	*N. Crassa*	*A. Niger*
2-Bromo-2-nitropropane-1,3-diol	32	35	15	280	300
2-Chloro-2-nitropropane-1,3-diol	400	480	210	>200	>200
2-Fluoro-2-nitropropane-1,3-diol	40	40	80	300	380
2-Bromo-2-nitropropane	40	40	80	200	380
2,2-Dinitropropane	400	400	280	>200	>200
2-Bromo-2-nitroborane	50	6	80	280	300
2-Bromo-2-nitroadamantane	40	10	80	200	300

Table 2 Minimum inhibitory concentration (M.I.C.) values for a series of halo-nitro compounds

Nitro derivatives	X	R_1	R_2	M.I.C. value ($\mu g/ml^{-1}$)			
				E. Coli	*S. Aureas*	*C. Albican*	*P. Aeruginosa*
1-Bromo-1-nitropropane-2-ol	Br	Me	H	16.6	16.6	16.6	16.6
2-Bromo-2-nitrobutane-1,3-diol	Br	Me	CH_2OH	16.6	16.6	16.6	16.6
2-Bromo-2-nitropropane-1,3-diol	Br	H	CH_2OH	16.6	16.6	50	16.6
1,1-Dibromo-1-nitro-3-methyl-butan-2-ol	Br	$CH(Me)_2$	Br	16.6	16.6	50	5.5

Nonhalogenated nitro-alcohols (X = H, R_1 = R_2 = alkyl) were practically inactive as antimicrobial agents. Inclusion of a bromine (X = Br) increased the activity greatly, while with X = Cl a less active compound was obtained.

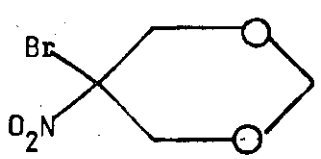
The most active compounds (with M.I.C. values in µg/ml) are shown in Table1-2 .

Similar structure - activity relationships were obtained by Fridman *et al.*[18,19]

Once again the antimicrobial activity of the compounds described is clearly associated with the structural feature, $C(Br)NO_2$.

The potential properties of bronopol as a preservative prompted the search for new analogues of bronopol which would be stable in the full range of pH's and exhibited a broad-spectrum of antimicrobial activity.

In 1971 a compound called bronidox (5-bromo-5-nitro-1,3-dioxan) (7) was patented.[20]



5-bromo-5-nitro-1,3-dioxan (7)

Lappas *et al*[21] studied the structure activity relationships of substituted 5-nitro-1,3-dioxans(8). Each compound was tested for activity against a wide range of bacteria and yeasts. They used a microbiocidal scale, with 1400 being the maximum value (corresponding to the most active compound), to evaluate the antimicrobial activity of the compounds.

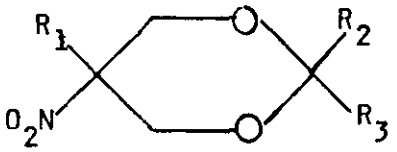
The two most active compounds were:

i) 5-Bromo-2-methyl-5-nitro-1,3-dioxan (8), where

R_1 = Br, R_2 = H, R_3 = CH_3, with microbiocidal index 1375.

ii) 5-Bromo-2-(*p*-hydroxyphenyl)-5-nitro-1,3-dioxan (8) where

R_1 = Br, R_2 = H, R_3 = *p*-HO-C_6H_4-, with microbiocidal index 1375.



(8)

Finally, they noted that under certain conditions with certain derivatives the dioxan ring was cleaved to give a bronopol-like structure which was the effective antimicrobial agent.

Lorenz[22], also working on bronidox, obtained similar results and made the same conclusions.

From these studies on the structure-activity relationship of α-halo substituted nitro compounds, it can be concluded that C(Br) NO_2 is essential for good antimicrobial activity.

Toxicity Studies on Bronopol

Several toxicological studies have been performed to test the suitability of bronopol as a preservative[23-30]. In the original study on bronopol by Croshaw[14], some basic information on the toxicity of bronopol was obtained. The $L.D_{50}$ of bronopol in aqueous solution for mice was 350mg/kg (orally) and 200mg/kg (intraperitonally). The values obtained for mice were 400mg/kg (orally) and 200mg/kg (subcutaneously). In an acute toxicity test, newly weaned albino rats were fed 1/40 and one fourth the $L.D_{50}$ values of bronopol in their diet for 12 weeks. There were no deaths, and similar weight gains were observed as compared to a control group. Food consumption and liver and kidney weights were also similar. When the rats were killed, no histopathological changes were observed in any of the organs examined. A 2% bronopol emulsion was irritant to the skin and to the eye of rabbits after one application.

However, a 0.05% concentration showed no irritation even after application on four successive days. Tests for skin sensitisation gave negative results.

Subsequent studies by Moore *et al*[31,32] on the absorption of bronopol revealed that it was readily absorbed and distributed evenly among various tissues in rats and dogs. Bronopol was also rapidly excreted in the urine and the major metabolite was 2-nitropropane-1,3-diol plus four other polar, but unidentified metabolites.

Further tests were carried-out by Bryce *et al*[9] at the Boots Company to supplement those obtained initially by Croshaw *et al*[10] and obtained similar results to those obtained by Moore *et al*[31,32].

Full toxicity testing on bronidox has not been reported; however, preliminary studies by Lorenz[22] reveal no evidence of sensitisation reactions.

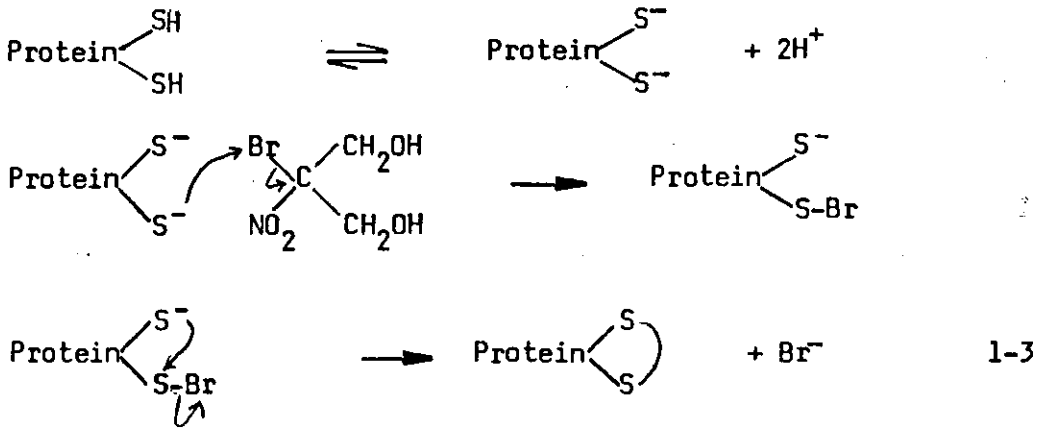
Mode of Action of Bronopol

The mode of action of bronopol and its analogues has been fully investigated in our laboratories in Loughborough.

Stretton and Manson[16] have suggested that the primary mode of action of bronopol is to oxidise sensitive thiols in close proximity, to the corresponding disulphide. The study of bronopol antagonists revealed that sodium thioglycollate and 2-mercaptoethanol prevented the inhibitory action of bronopol. The action of bronopol on rapidly dividing cells and its low activity on non-proliferating cells indicated that the inhibition of some metabolic activity was involved in its mode of action. Since bronopol was antagonised by the addition of thiol containing compounds, it would appear that bronopol affects thiol groups, especially in thiol containing enzymes[16]. Stretton and Manson also showed that loss of enzyme activity, such as that of papain, due to reaction with bronopol

corresponds to loss of free thiol in the enzyme. Bronopol also oxidised cysteine, glutathione, and coenzyme A to the corresponding disulphide in high yield. The *in vitro* mechanism of bronopol is shown (Scheme 1-1).

Scheme 1-1

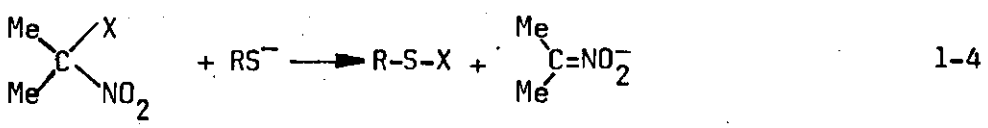


1-3

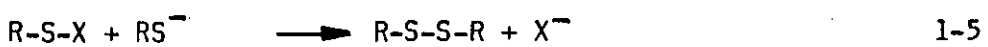
In the proposed mode of action, protein or other thiols are oxidised to the corresponding disulphide and the halonitro compound is reduced to nitro anion and bromide. The nitro anion resulting from bronopol rapidly decomposes.

Study of the reaction of 2-substituted-2-nitropropanes with thiolates by Bowman and Richardson[33-35] has shown that the redox reaction proceeds *via* an ionic reaction. As the M.I.C.'s of bronopol and 2-bromo-2-nitropropane are very similar it is possible that their mechanism of action with thiolates is similar, i.e. depending largely on the $C(Br)NO_2$ function. The proposed *in vitro* mechanism is shown (Scheme 1-2).

Scheme 1-2

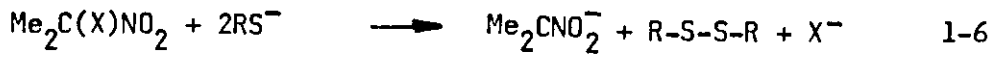


1-4



1-5

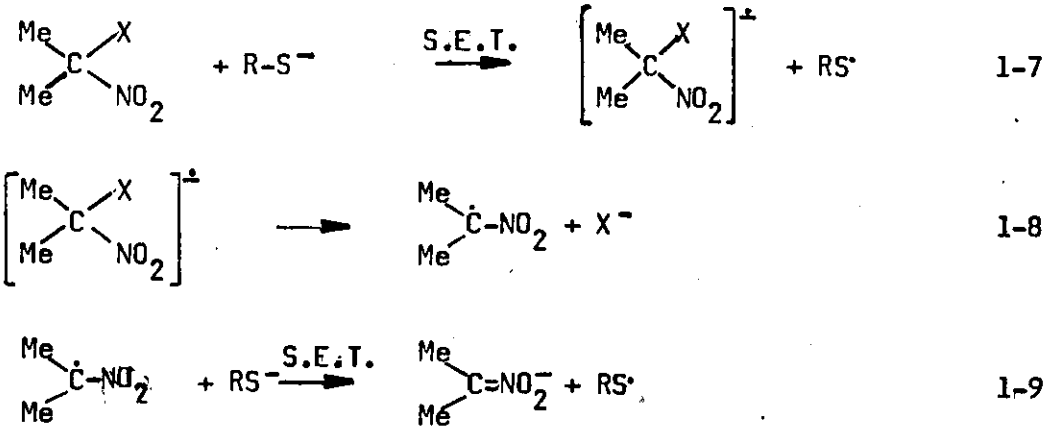
In summary



1-6

The 2-substituent is abstracted by the nucleophilic thiolate to yield a reactive sulphenyl intermediate (R-S-X) which rapidly reacts with further thiolate to yield the disulphide. An alternative single electron transfer (S.E.T.) mechanism suggested by Russell *et al*[36] can be considered (Scheme 1-3), but was shown not to be operative.[33-35]

Scheme 1-3



The above mechanism and others will be discussed further in the succeeding sections.

PART III

Reactions proceeding by single electron transfer (S.E.T.) and radical-anion intermediates

Single electron transfer (S.E.T.) is the exchange of an electron between two chemical species. No bonds are broken in the process, and no net chemical change takes place except a change in oxidation state (eqn. 1-10).

$$A^{z1} + B^{z2} \rightleftharpoons A^{z1-1} + B^{z2+1} \qquad 1\text{-}10$$

where z_1 = charge on the oxidizing form of species A

z_2 = charge on the reducing form of species B

Electron transfer can be regarded as an act of umpolung (eqn. 1-11)

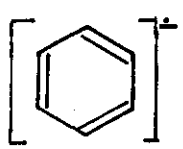
$$\underset{\text{nucleophile}}{R\text{-}E} + \underset{\text{electrophile}}{R\text{-}Nu} \rightleftharpoons \underset{\text{electrophile}}{R\text{-}E^{\dot{+}}} + \underset{\text{nucleophile}}{R\text{-}Nu^{\dot{-}}} \qquad 1\text{-}11$$

The reactions of radical anions, and reactions which involve transient radical anion formation are established as an important part of organic chemistry.[37-46] A radical-ion is a molecule which in addition to having one or more unpaired electrons has a net negative charge (radical anion) or net positive charge (radical cation) (eqns. 1-12, 1-13).

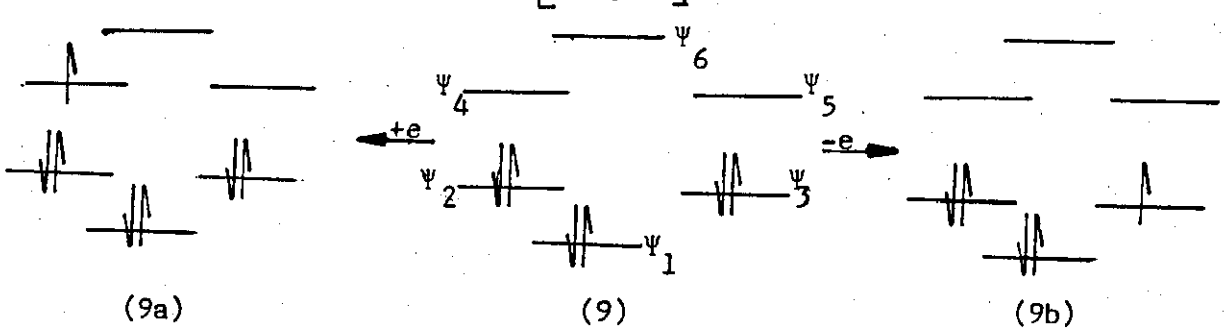
$$M + e \longrightarrow M^{\dot{-}} \quad \text{radical anion} \qquad 1\text{-}12$$

$$M - e \longrightarrow M^{\dot{+}} \quad \text{radical cation} \qquad 1\text{-}13$$

Radical-anions can be subclassified according to the orbitals in which the unpaired electron(s) reside. These orbitals may be σ, Π, or "ρ type" and bonding, antibonding, or nonbonding. By far the largest and most common type of radical anion are the Π-type. The electronic configuration of these radical anions is best exemplified by the molecular orbital (MO) diagram for benzene[40b] (9a).



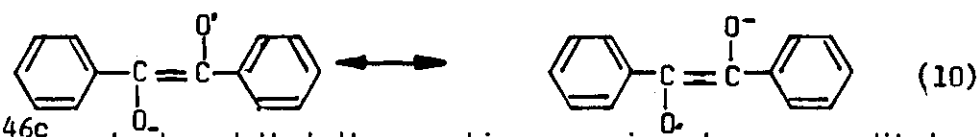
(9a)



(9a) (9) (9b)

Addition of an electron to benzene will give the benzene radical-anion (9a) in which the additional unpaired electron goes into the lowest unoccupied MO, which is Π^* in this case. Similarly, removal of an electron leaves the benzene radical-cation (9b) having an unpaired electron in its highest previously fully occupied MO, which in this case is a Π-bonding orbital.

The first radical-anion was probably observed[46b] as early as 1836, when potassium hydroxide solution was added to benzil producing a deep blue colour which is now attributed to the formation of (10)



(10)

Further[46c] work showed that the reaction was given by many α-diketones. More recently it has been amply demonstrated that radical-anions may be generated in many compounds containing Π-bonds[46d], notably in ketones, azo and nitrocompounds, simple and conjugated olefins, and aromatic compounds. In general the longer the Π-system, the easier is the formation of the radical-anion, due to the resonance stabilisation obtained.

Radical-anions are generally not very stable, although in exceptional cases, e.g. the naphthalene radical-anion, they may be isolated and stored. Atmospheric oxygen readily destroys radical-anions by removing an electron (eqn. 1-14).

$$R^{\dot{-}} + O_2 \longrightarrow R + O_2^{\dot{-}} \qquad 1\text{-}14$$

The importance of single electron transfer (S.E.T.) and radical-anions as intermediates in synthetic processes has received a lot of consideration in the literature[44-46]. The reactions of metal hydrides, for instance, with organic substrates such as ketones, unsaturated hydrocarbons and alkyl halides have been considered to proceed *via* a polar mechanism.[47]

Recently, Ashby and Coworkers[48] and several other researchers[49] demonstrated that metal hydrides do indeed react with aromatic substrates *via* a single electron transfer mechanism[48b], scheme (1-4).

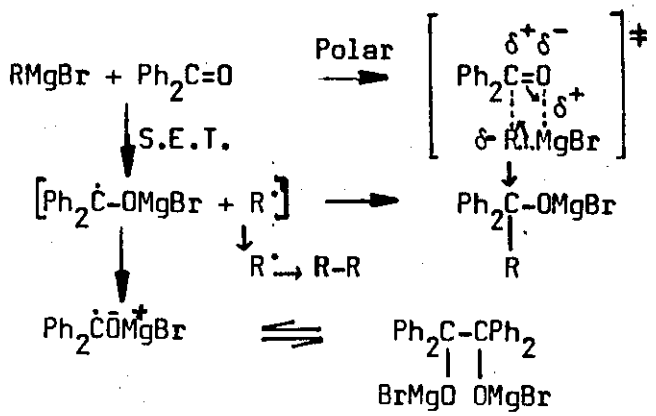
Scheme 1-4

$$Ph_3C\text{-}Br + MH \xrightarrow{S.E.T.} [Ph_3CBr]^{\cdot -} + MH^{\cdot +} \xrightarrow{S.E.T.} \underbrace{[Ph_3C^{\cdot} + Br^- + M\text{-}H^{\cdot +}]}_{\text{solvent cage}}$$

$$[Ph_3C^{\cdot} + Br^- + M\text{-}H^{\cdot +}] \longrightarrow MBr + Ph_3CH \xrightarrow{MH} Ph_3C^-M^+ \xrightarrow{H_2O} Ph_3CH \qquad 1\text{-}15$$
$$\downarrow Ph_3CH$$

Likewise a S.E.T. mechanism has been proposed for certain reactions using Grignard reagents. A more detailed look at this reaction will serve as a good example of comparing polar and S.E.T. mechanism for the same reaction (Scheme 1-5).

Scheme 1-5

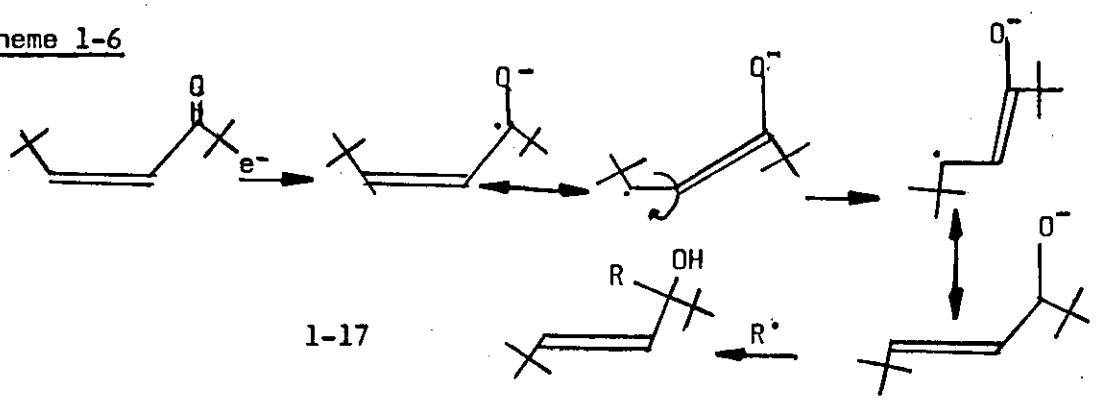


1-16

Ashby and coworkers[45] arguments for the suggested mechanisms for the reaction shown in Scheme (1-5) are that the 1,2-addition product can be formed by either a polar or a S.E.T. mechanistic pathway. If the 1,2-addition product is actually formed *via* a S.E.T. pathway, then evidence might be obtained for the intermediacy of the free radical and radical-anion.

Ashby *et al*[45] have obtained evidence for the S.E.T. mechanism by several methods. Initially, to test for the intermediacy of the ketyl and the radical, they used a *cis*-enone which has the ability to isomerize to the corresponding *trans*-enone if it is reduced to a ketyl. If the *cis*-enone is reduced to the ketyl, it will rapidly isomerize to the *trans*-ketyl which on coupling with alkyl radical will produce the *trans*-1,2-addition product.

Scheme 1-6



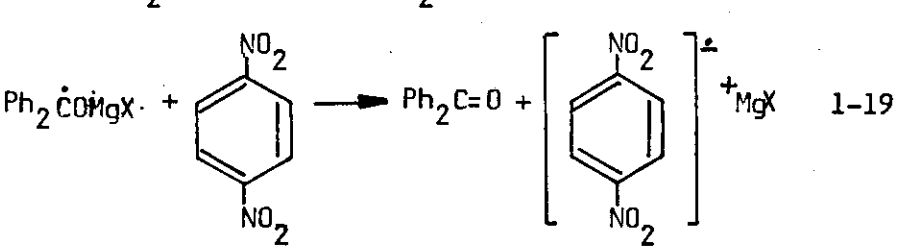
1-17

1,2-addition product

Scheme 1-6 demonstrates that the predominant route for the reaction (even with a ketone that is less easily reduced than benzophenone) was an electron transfer producing a ketyl as an intermediate.

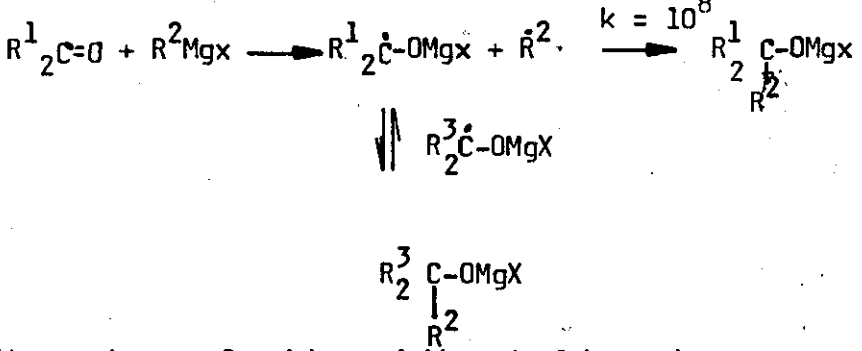
Another means of obtaining evidence for S.E.T. is the trapping of the ketyl and thus inhibiting the formation of 1,2-addition product. p-Dinitrobenzene, which is a strong electron acceptor will capture an electron from the radical-anion, resulting from the mixture of the Grignard reagent and the ketone. The results showed that the Grignard reagent had reacted with the ketone at the same rate in the presence or the absence of p-dinitrobenzene, but that pinacol formation was completely inhibited. (eqn. 1-18, 1-19)

$$RMgX + Ph_2C{=}O \xrightarrow{S.E.T.} Ph_2\dot{C}OMgX + R^{\bullet} \qquad 1\text{-}18$$



1-19

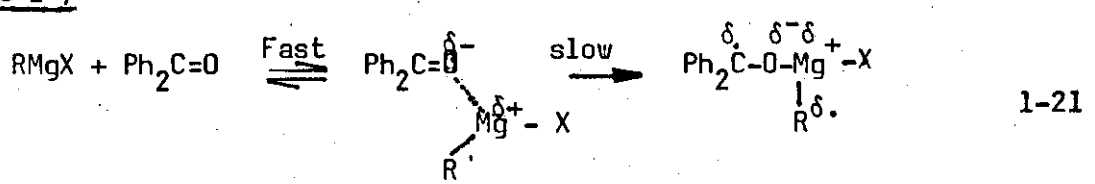
Further evidence for the ketyl intermediate was obtained by use of ketyl cross-over experiments.[50] The cross-over experiment was based on the premise that if a ketyl and a free radical are generated during the reaction, the addition of another ketyl of appropriate reduction potential will cause the formation of another 1,2-addition product corresponding to the added ketyl in addition to the expected product (eqn. 1-20).



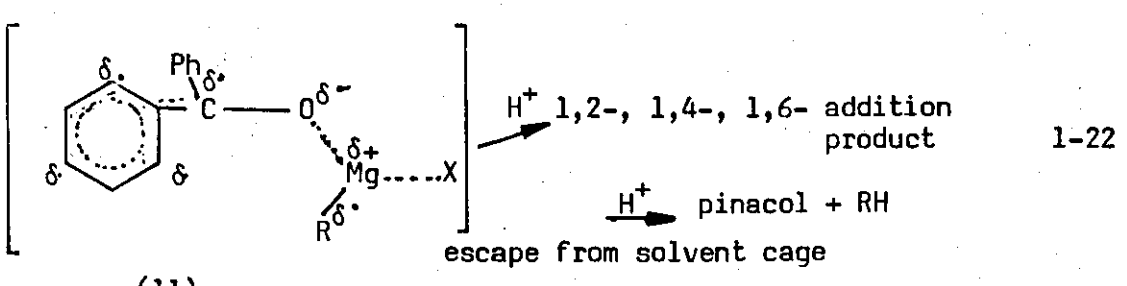
1-20

From these pieces of evidence Ashby *et al* have drawn a general picture to represent the transition state (11) involving alkyl group transfer in the reaction of Grignard reagents with aromatic ketones. In this transition state, electron transfer has already taken place in the prior step so that partial radical character exists at the alkyl group of the Grignard, the carbonyl carbon, and the 2-and 4-positions of the phenyl group. Escape of the radical-anion and the free radical from the solvent cage result in abstraction of hydrogen by the free radical from solvent and dimerization of the radical-anion to form the magnesium salt of the pinacol (their proposed mechanism is shown Scheme 1-7).

Scheme 1-7



1-21



1-22

(11)

They have also presented evidence for the reduction of various metal hydrides with polynuclear hydrocarbons *via* a S.E.T. mechanism as indicated by e.s.r. spectroscopy and visible spectroscopy of the intermediate radical-anions.

Nucleophilic substitution in aromatic systems proceeding by S.E.T. and intermediate radical-anions : $S_{RN}1$ mechanism

One of the most important developments involving S.E.T. and intermediate radical-anions has been the elucidation of the $S_{RN}1$ mechanism. Bunnett[51,52] suggested the terminology $S_{RN}1$ (substitution radical-nucleophilic first order) to describe the reactions which have been shown to proceed *via* intermediate radical anions and radicals rather than Meisenheimer complexes. These reactions are carried-out in liquid ammonia or dipolar aprotic solvents and are dramatically stimulated by solvated electrons, light, or heat. A simple ionic substitution mechanism *via* addition and elimination steps hardly accounts for this stimulation and the following mechanism has been proposed (Scheme 1-8)

Scheme 1-8

$$ArX + \text{electron donor} \longrightarrow [Ar\text{-}X]^{\cdot -} + \text{residue} \qquad 1\text{-}23$$

$$[ArX]^{\cdot -} \longrightarrow Ar^{\cdot} + X^{-} \qquad 1\text{-}24$$

$$Ar^{\cdot} + Y^{-} \longrightarrow [ArY]^{\cdot -} \qquad 1\text{-}25$$

$$[ArY]^{\cdot -} + ArX \longrightarrow [ArX]^{\cdot -} + ArY \qquad 1\text{-}26$$

e.g. X = Cl, Br, I, SPh, F, OPh, SePh.

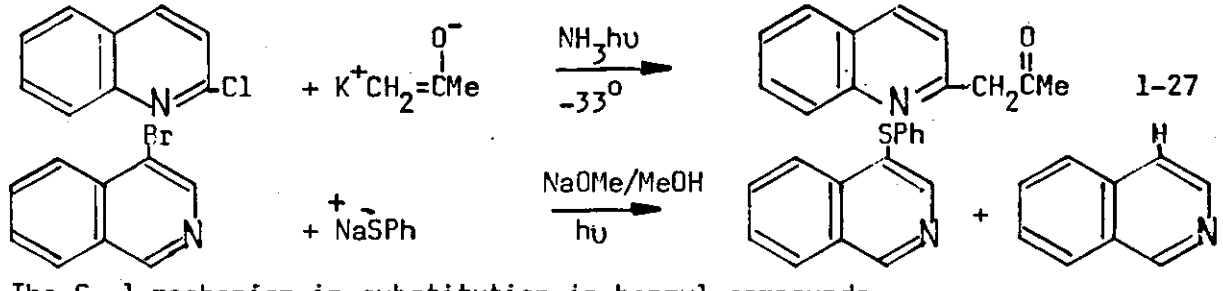
e.g. Y = NH_2, RS , PO_3R_2

Initiation of the chain reaction is effected by electron transfer from a suitable donor to the substrate (eqn. 1-23). The resulting radical-anion expels the nucleofugic group with a pair of electrons to form an aryl radical (eqn. 1-24). Formation of the new carbon-nucleophile bond

is accompanied by attack of the nucleophile on the aryl radical to form a new radical-anion (eqn. 1-25), which then transfers an electron to the neutral starting material thereby completing the chain reaction (eqn. 1-26). This affords the observed substitution product A-Y and another substrate radical-anion, which can re-enter the propagating cycle in eqn. 1-23 .

The overall reaction is analogous to that proposed earlier by Kornblum and Russell for reactions of nucleophiles with certain p-nitrobenzyl halide and 2-halo-2-nitropropanes. However, prior to 1970 this reaction mechanism was unknown in the area of nucleophilic aromatic substitution. Bunnett and co-workers[52] have now shown a wide range of aromatic $S_{RN}1$ reactions with a variety of aryl substrates and anions.

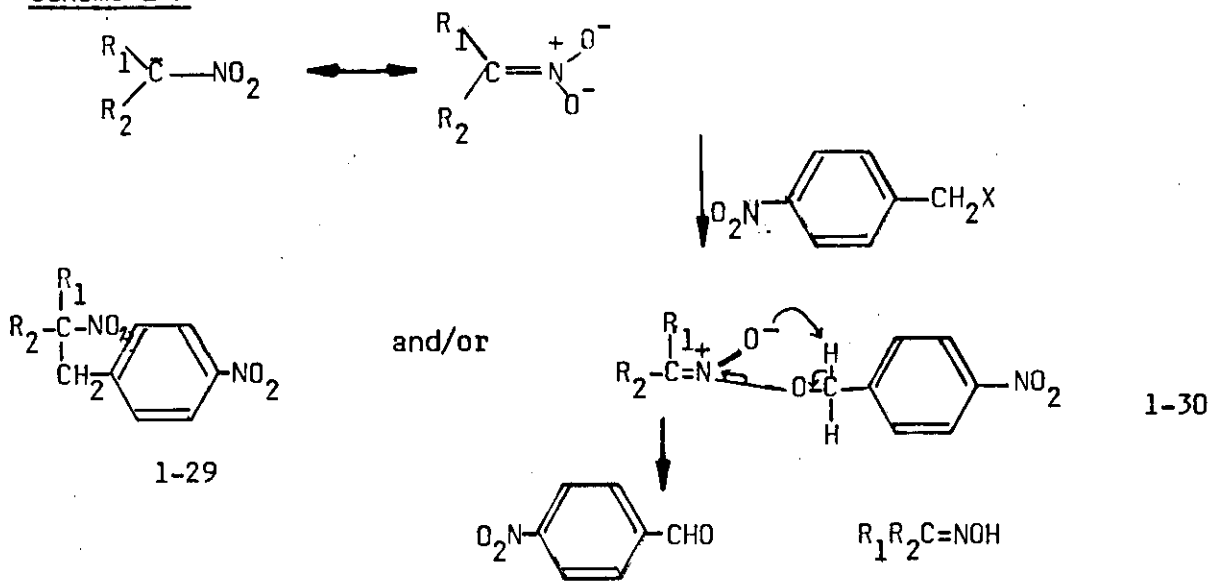
Aromatic substitution reactions proceeding *via* the $S_{RN}1$ mechanism have also been reported by other workers.[53] For example 2-chloroquinoline[54,55] and 4-bromo-iso-quinoline[56] have been substituted with the enolate anion of acetone and sodium thiophenoxide respectively (eqn. 1-27, 1-28).



The $S_{RN}1$ mechanism in substitution in benzyl compounds 1-28

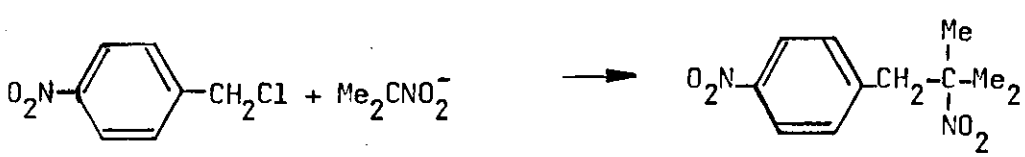
The first example of S.E.T. and radical-anion intermediates in aliphatic substitution was discovered during an investigation of the reaction of p-nitro-benzyl halides with the sodium salt of 2-nitropropane[57,59] (Scheme 1-9).

Scheme 1-9



1-29 and/or 1-30

The salt of 2-nitropropane (12) is an ambident anion, and its reaction with an alkyl halide can lead to alkylation on carbon or oxygen. The latter route is normally predominant[60,61] (eqn. 1-30). In fact C-alkylation only occurs when *p*- or *o*-nitrobenzyl halides are reacted with the salt. In all other cases O-alkylation occurs by an S_N2 mechanism, giving the corresponding ketones or aldehyde *via* the nitronic ester. When *p*-nitrobenzyl chloride was reacted with the sodium salt of 2-nitropropane an 83-95% yield of the C-alkylated product was obtained (eqn. 1-31).

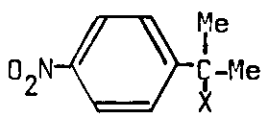


1-31

o-Nitrobenzyl chloride gave a 46% yield of the carbon alkylate in the same reaction, but *m*-nitrobenzyl chloride reacted to give O-alkylation. It was also found that the ratio of C-to O-alkylation occuring in the reaction of the salt of 2-nitropropane with a series of α-substituted ρ-nitrobenzyls depended on the nature of the α-substituent. The poorer the leaving group the more C-alkylate was formed.

The rate of reaction when carbon-alkylation predominated was at least 100 times that when oxygen-alkylation predominated. In view of these results it was suggested that O-alkylation proceeded *via* an S_N2 mechanism but since the rate of C-alkylation was largely unaffected by the nature of the leaving group a direct ionic displacement was unlikely for this type of reaction. Consequently, an alternative mechanism ($S_{RN}1$) was assigned.

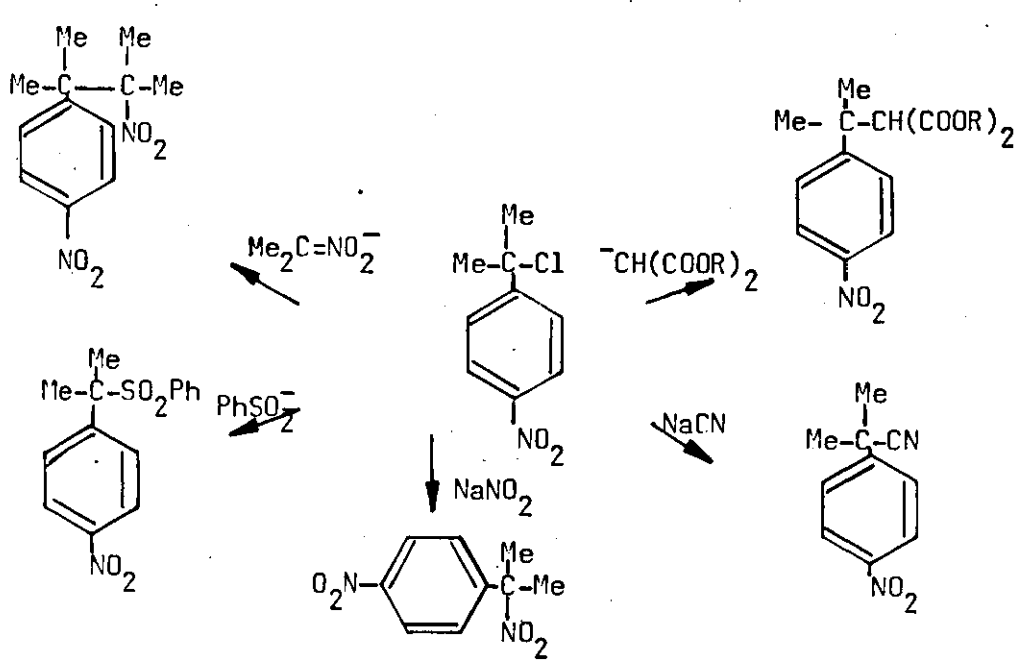
More support for a chain mechanism ($S_{RN}1$) was provided by studies of the reaction of the α-substituted *p*-nitrocumyl system (13) with anions.[62]



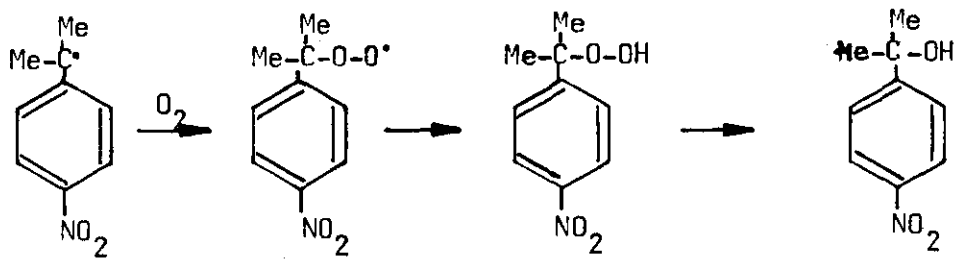
(13)

Since in this system substitution must occur at a tertiary carbon center, S_N2 type attack is not possible. Kornblum and co-workers[63,64] have studied the system intensively, and found that *p*-nitrocumyl chloride reacted relatively rapidly with a variety of nucleophiles at room temperature in dipolar aprotic solvents to give high yields of the substituted products (Scheme 1-10).

Scheme 1-10



The mechanism of *p*-nitrocumyl compounds with anions has been studied extensively. The reactions are inhibited by molecular oxygen.[64] Oxygen scavenges the intermediate, presumably, the p-nitrocumyl radical (14), giving the peroxy radical. The latter is converted to the hydroperoxide by hydrogen abstraction from the solvent and finally to the corresponding alcohol (eqn. 1-32).

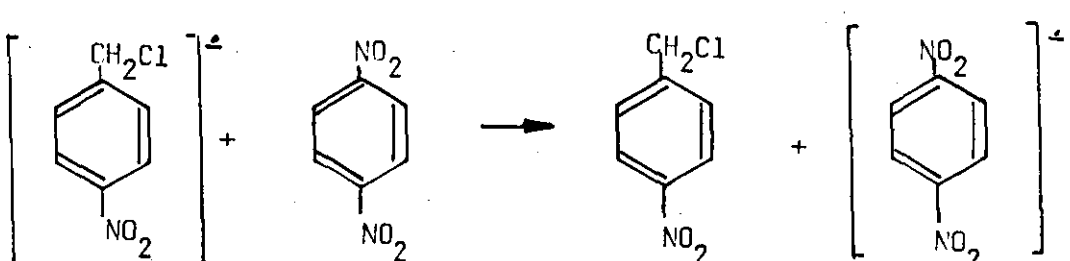


1-32

(14)

Also, very small amounts of oxygen inhibit the reaction of *p*-nitrocumyls. For example the reaction of *p*-nitrocumyl chloride with sodium benzene sulphinate is normally complete in two hours under nitrogen giving a 95% yield of the sulphone, but the presence of only 1 mol % of oxygen causes the reaction to proceed only 1% to completion in the same period. These results suggest that the reactions are chain processes, with a small amount of oxygen being able to intercept a chain carrying radical, presumably the *p*-nitrocumyl radical (14).

The inhibition of the reactions of substituted *p*-nitrocumyl compounds with anions by *p*-dinitrobenzene (*p*-DNB) in low concentration has also been observed. The *p*-DNB readily accepts an electron and can participate in electron transfer reactions with intermediates of the substitution process. Kornblum[43] suggested that *p*-DNB causes the inhibition by accepting an electron from the intermediate radical anion (15) and thus interrupting the chain sequence (eqn. 1-33).

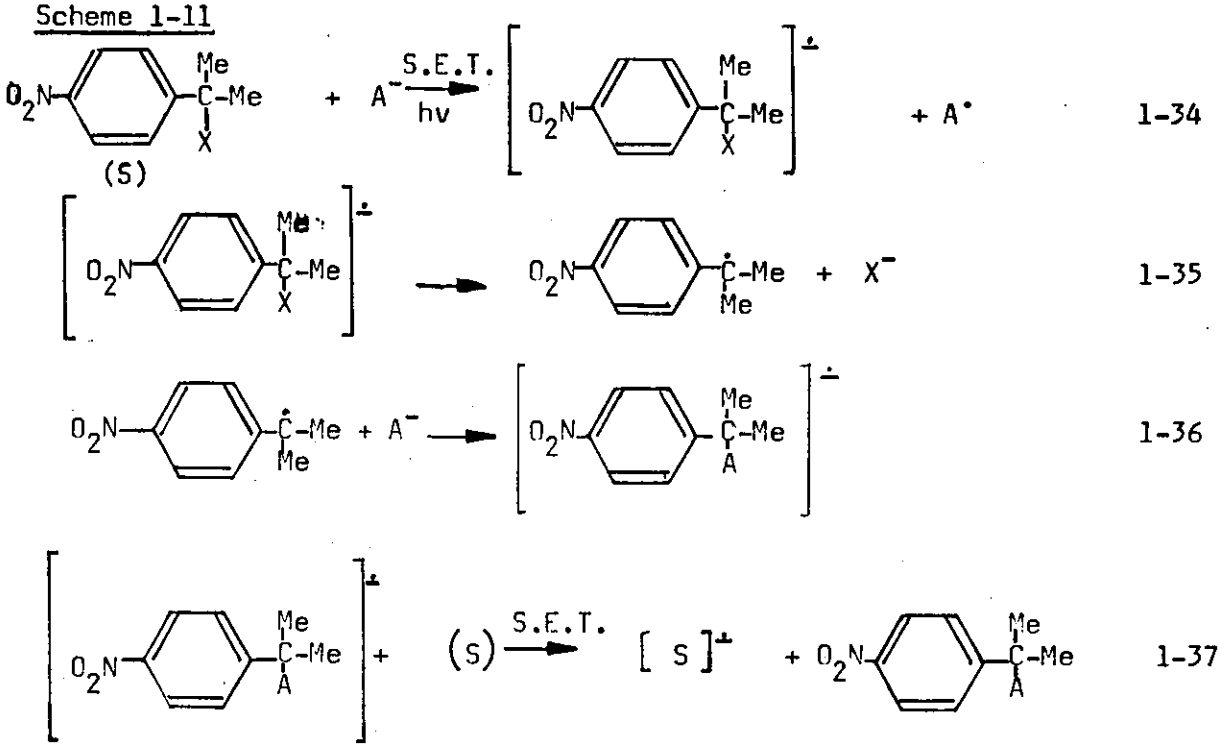


1-33

Di-(tert-butyl) nitroxide also inhibits the reactions of p-nitrocumyl chloride with anions. The compound is a known free radical scavenger, and the presence of 5 mol % in the reaction caused almost total inhibition of the reaction. In the absence of di-(tert-butyl) nitroxide the reaction was 90% complete in the same time. This result again suggests that radicals are chain carriers in these reactions.

Attempts to detect the radical-anion of *p*-nitrocumyl chloride by e.s.r. spectroscopy have failed.[36b] This failure is attributed to the rapid expulsionof the chloride anion before the radical-anion can reach a high enough concentration to give an e.s.r. signal i.e. the intermediate radical-anions are not very stable and have a short lifetime. In view of these studies, the sequence of (Scheme 1-11) was suggested as the mechanism for the reaction of α-substituted *p* -nitrocumyl compounds with anions.

Scheme 1-11



The sequence in the scheme 1-11 closely resembles that proposed by Bunnett for $S_{RN}1$ aromatic substitution. The same mechanism was also rationalised by Kornblum[39] and Russell[40] for substitution in

aliphatic α-substituted nitro-compounds.

Substitution in aliphatic systems

The participation of purely aliphatic systems in $S_{RN}1$ reactions has also been observed. Reactions of the salt of 2-nitropropane with 2-halo-2-nitropropanes were described as early as 1939[65] (eqn. 1-38).

$$Me_2C{=}N\overset{\cdot}{O}_2^- + Me_2C(X)NO_2 \longrightarrow Me_2(NO_2)C(NO_2)Me_2 \qquad 1\text{-}38$$

X. = Cl, Br, I.(16)

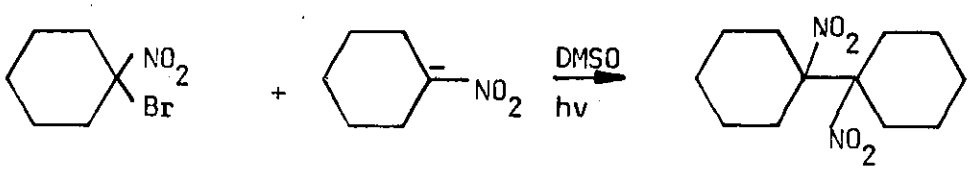
The reaction of the sodium salt of 2-nitropropane with 2-chloro-2-nitropropane, 2-bromo-2-nitropropane and 2-iodo-2-nitropropane in refluxing ethanol were found to give 29 and 43% yields, respectively, of 2,3-dimethyl-2,3-dinitrobutane (16).

Van Tamelen and Van Zyl[66] have described the displacement of the halogen atom of 2-halo-2-nitropropane by diethylethylmalonate (eqn. 1-39).

$$Me_2C(X)NO_2 + EtC^-(CO_2Et)_2 \xrightarrow{Et_2O} Me\text{-}\underset{NO_2}{\overset{Me}{C}}\text{—}\underset{CO_2Et}{\overset{Et}{C}}\text{—}CO_2Et \qquad 1\text{-}39$$

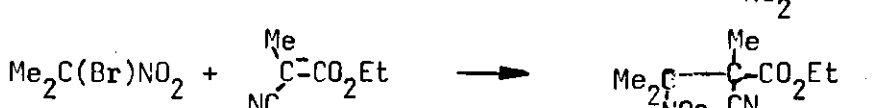
68%

Kornblum and co-workers[67,68] reported in 1970 similar reactions using dipolar aprotic solvents. They found that the transformations took place rapidly under mild conditions (eqns. 1-40, 1-41).



1-40

89%



1-41

More recent investigations[69] have confirmed and extended these studies. Catalysis by light and inhibition by catalytic of p-DNB, di-(tert-butyl) nitroxide, and molecular oxygen have been observed in reactions using a variety of anions and α-substituted nitro-aliphatic compounds. The proposed mechanism is given in Scheme 1-12.

Scheme 1-12

$$R_2C(X)NO_2^- + A^- \xrightarrow{S.E.T} [R_2C(X)NO_2]^{\cdot -} + A^{\cdot} \qquad 1\text{-}42$$

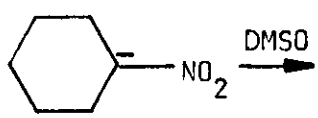
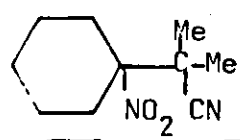
$$[R_2C(X)NO_2]^{\cdot -} \longrightarrow R_2\dot{C}NO_2 + X^- \qquad 1\text{-}43$$

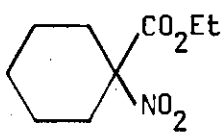
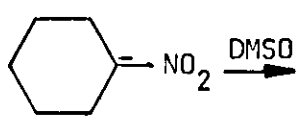
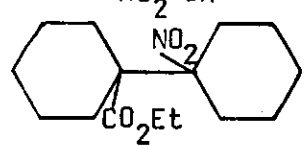
$$R_2\dot{C}NO_2 + A^- \longrightarrow [R_2C(A)NO_2]^{\cdot -} \qquad 1\text{-}44$$

$$[R_2C(A)NO_2]^{\cdot -} + R_2C(X)NO_2 \longrightarrow R_2C(A)NO_2 + [R_2C(X)NO_2]^{\cdot -} \qquad 1\text{-}45$$

where X = SO_2Ph, NO_2, I, Cl, Br, SR[33-35] and R = alkyl, A = SO_2Ar, nitronate, $Me_2C(CO_2Et)_2$.

Other α-substituted nitroaliphatics react with anions to yield a product which is formally the result of direct displacement of the nitro group[71] (eqn. 1-46, 1-47).

$Me_2C(CN)NO_2$ +  DMSO  + NO_2 1-46

 +  DMSO  + NO_2 1-47

These reactions are again subject to catalysis by light and to inhibition by catalytic concentrations of a variety of radical scavengers and strong electron acceptors. The proposed mechanism is given in Scheme 1-13.

$$R_2C(X)NO_2 + A^- \xrightarrow{S.E.T} [R_2C(X)NO_2]^{\cdot -} + A^{\cdot} \qquad 1\text{-}48$$

$$[R_2C(X)NO_2]^{\cdot -} \longrightarrow R_2\dot{C}X + NO_2^- \qquad 1\text{-}49$$

$$R_2\dot{C}X + A^- \longrightarrow [R_2C(A)X]^{\cdot -} \qquad 1\text{-}50$$

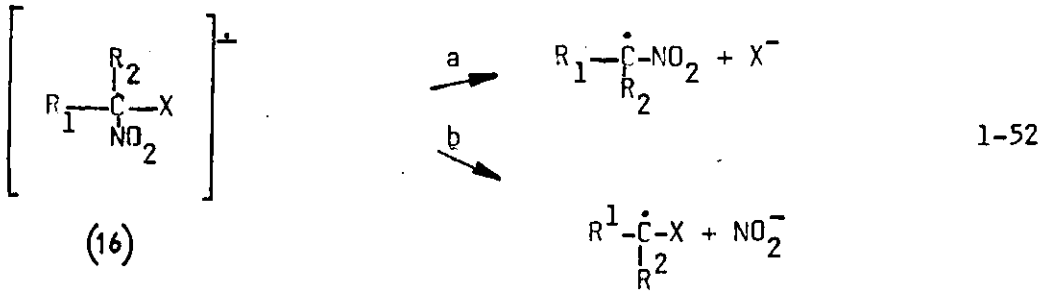
$$[R_2C(A)X]^{\cdot -} + R_2C(X)NO_2 \longrightarrow [R_2C(X)NO_2]^{\cdot -} + R_2C(A)X \qquad 1\text{-}51$$

where X = - COOR, -COR, - NO_2, - CN, and R.

R = alkyl

and A = $Me_2C{=}NO_2$, $PhSO_2$, $EtC(CO_2Et)_2$.

Schemes 1-12 and 1-13 differ only in the way in which the intermediate radical-anion (16) dissociates (eqn 1-52).



(16) 1-52

They also demonstrate that nitro compounds differ in their reactivity for undergoing radical-anion substitution. It is therefore necessary to enquire why some α-substituted nitro-compounds react by loss of the α-substituent and some by loss of nitrite, as well as why 2,2-dinitropropane reacts easily with loss of nitrite but not α-cyano, α-keto, and α-ethoxycarbonyl nitro-compounds. Kornblum[69] in his answer to the above question bases his argument on the following considerations: a chain reaction involving radical-anions is most likely to be observed when minimal energy is needed for the formation of the intermediate radical-anions. It is known that one electron reduction of a nitro group is brought about relatively easily[69] i.e. nitro radical-anions are comparatively easy to produce, because they are relatively stable. It is therefore not surprising that the chain sequences of eqns. (1-42)-(1-44), which only invoke nitro radical-anion formation, are feasible processes. With, for example, α-nitro esters, the reaction with a nucleophile would involve the sequence of eqns. (1-48)-(1-51). Preliminary studies[69] revealed that there is little or no reaction with α-nitro esters. Kornblum's suggestion is that the radical-anion ($[R_2C(CO_2Et)A]^{\cdot-}$) is of relatively high energy and, therefore, the chain process is rendered essentially inoperative. This theory is supported by ready reaction of these compounds with a nitro anion as the nucleophile i.e. a nitro group to stabilise the radical-anion $[Me_2C(CO_2Et)C(NO_2)Me_2]^{\cdot-}$. In summary, when a radical and an anion combine two possibilities for

localization of the odd electron exist eqns. (1-53 and 1-54).

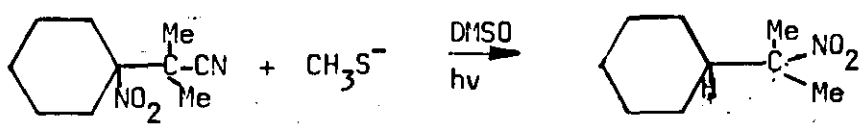
$$R^{\cdot} + A^{\cdot -} \longrightarrow R - A^{\cdot -} \qquad 1\text{-}53$$

and/or

$$R^{\cdot} + A^{\cdot -} \longrightarrow {}^{\cdot -}R - A \qquad 1\text{-}54$$

This means that localization into the nitro-alkyl or nitro-phenyl moiety (eqn. 1-54) is most important i.e. the radical-anions shown in eqn. (1-44) correspond to that of eqn. (1-54); on the other hand, in reaction of α-nitro esters with nitro-paraffin salts the radical-anion shown in (eqn. 1-50) corresponds to that of eqn. (1-53).

Finally, in 1978 the replacement of a nitro group by hydrogen, was reported[72]. This reaction takes place at room temperature when the nitro compound is treated with the sodium salt of methyl mercaptan, eqn. (1-55)-(1-56).



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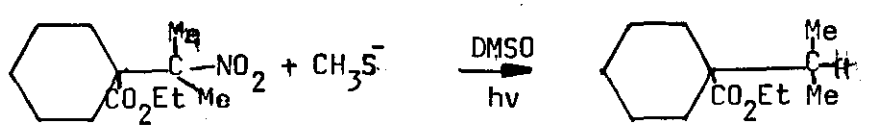


1-56

These transformation exhibit the characteristics of electron transfer chain substitution reactions. The mechanism[72,73] is illustrated in Scheme (1-14).

Scheme 1-14

$$R_3C\text{-}NO_2 + CH_3S^- \xrightarrow{S.E.T.} R_3C\text{-}NO_2^{\cdot -} + CH_3S^{\cdot} \qquad 1\text{-}57$$

$$R_3C\text{-}NO_2^{\cdot -} \longrightarrow R_3C^{\cdot} + NO_2^- \qquad 1\text{-}58$$

$$R_3C^{\cdot} + H_3C\text{-}S^- \longrightarrow R_3C\text{-}H + H_2C^{\cdot}\text{-}S^- \qquad 1\text{-}59$$

$$[CH_2S]^{\cdot -} + R_3C\text{-}NO_2 \xrightarrow{S.E.T.} H_2C{=}S + [R_3CNO_2]^{\cdot -} \qquad 1\text{-}60$$

Other reactions of nucleophiles with α-substituted nitro-compounds will be further elaborated, where relevant, in the discussion section.

PART IV

The reaction of thiolate anions with α-substituted nitro-compounds

The antimicrobial mode of action of α-substituted nitro-compounds implicates their reactivity with thiolate anions (Part I). The reaction of thiolate anions with aliphatic α-substituted nitro-compounds is therefore of some importance but has, in general, been poorly investigated.

Zeldrin and Shechter[74] have reported that the reaction of n-butane thiolate with 1,1,1,-trinitroethane in hot ethanol leads to the formation of the corresponding disulphide (71%) and the anion of 1,1-dinitroethane (42%) eqn. (1-61).

$$MeC(NO_2)_3 + BuS^- \longrightarrow BuSSBu + Me\bar{C}(NO_2)_2 \qquad 1\text{-}61$$

The authors suggested an ionic mechanism for the reaction, (Scheme 1-15)

Scheme 1-15

$$MeC(NO_2)_3 + \overset{+}{K}BuS^- \longrightarrow Me\bar{C}(NO_2)_2\overset{+}{K} + BuSNO_2 \qquad 1\text{-}62$$

$$BuSNO_2 + \overset{+}{K}BuS^- \longrightarrow BuSSBu + K\,NO_2 \qquad 1\text{-}63$$

Russell and Danen[36b] offered an alternative mechanism, which invokes the intermediacy of the 1,1,1,-trinitroethane radical-anion, (Scheme 1-16).

Scheme 1-16

$$CH_3C(NO_2)_3 + BuS^- \xrightarrow{S.E.T.} BuS^{\cdot} + [CH_3C(NO_2)_3]^{\pm} \qquad 1\text{-}64$$

$$[CH_3C(NO_2)_3]^{\pm} \longrightarrow CH_3\bar{C}(NO_2)_2 + {}^{\cdot}NO_2 \qquad 1\text{-}65a$$

or

$$\longrightarrow CH_3\dot{C}(NO_2)_2 + NO_2^- \qquad 1\text{-}65b$$

$$CH_3\dot{C}(NO_2)_2 + BuS^- \longrightarrow CH_3\bar{C}(NO_2)_2 + BuS^{\cdot} \qquad 1\text{-}66$$

$$2\ BuS^{\cdot} \longrightarrow BuSSBu \qquad 1\text{-}67$$

Sokolovsky *et al*[75] reported that the oxidation of protein thiol and peptides such as glutathione (17) with tetranitromethane (18) resulted primarily in disulphide formation Scheme (1-17), or to an acidic derivative (RSO_2H).

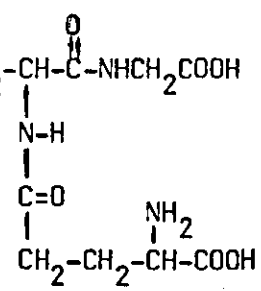
Scheme 1-17

$$RSH + C(NO_2)_4 \longrightarrow RSNO_2 + C(NO_2)_3^- + H^+ \qquad 1\text{-}68$$

(17) (18)

$$RSH + RSNO_2 \longrightarrow RSSR + NO_2^- + H^+ \qquad 1\text{-}69$$

For glutathione R =



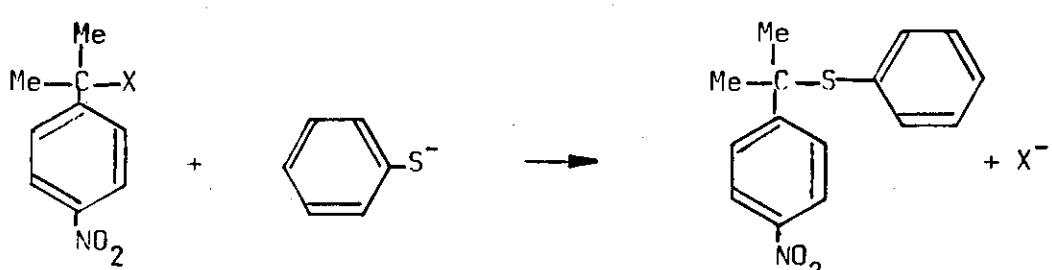
The acidic derivative was identified as a sulphinic acid by chromatographic and electrophoresis analysis, and by its conversion into a sulphonic acid on oxidation with iodine (Scheme 1-18).

Scheme 1-18

$$RSNO_2 + H_2O \longrightarrow RSOH + NO_2^- + H^+ \qquad 1\text{-}70$$

$$RSOH + \tfrac{1}{2}O_2 \longrightarrow RSO_2H \qquad 1\text{-}71$$

Substitution of α-substituents in aliphatic nitro-compounds by thiolates has been shown by Kornblum *et al*[63-64]. They demonstrated that the reactions of phenyl thiolate with α, *p*-dinitrocumene and *p*-nitrocumyl chloride gave the substitution product in high yield under mild conditions by an $S_{RN}1$ mechanism (eqn. 1-72).

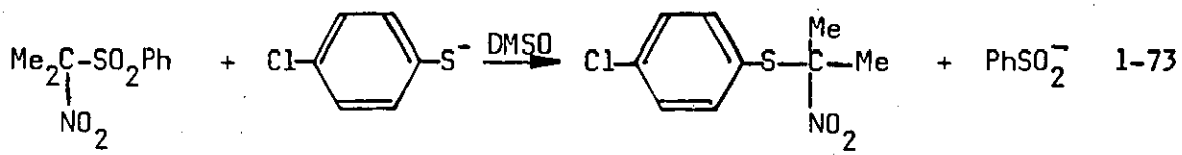


1-72

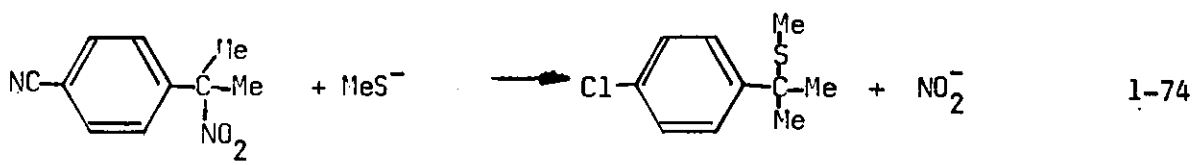
X = Cl, NO_2

Likewise, the reaction of p-chlorophenylthiolate with α-nitrosulphones[76] and the reaction of methane thiolate with 2-(p-cyanophenyl)-2-nitropropane[43] (Scheme 1-19) gave the corresponding substituted products by an $S_{RN}1$ mechanism.

Scheme 1-19



1-73

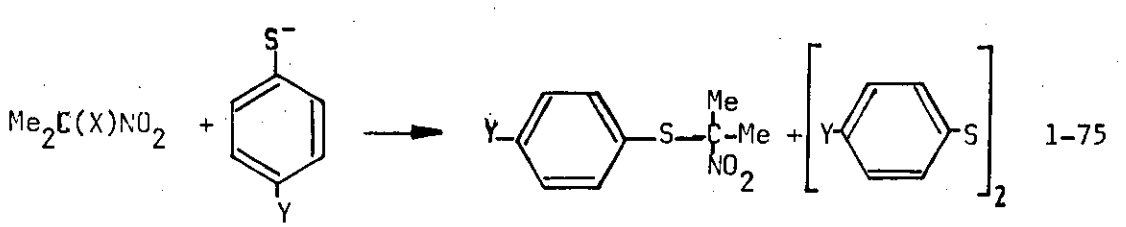


1-74

The $S_{RN}1$ mechanism has also been shown to operate in the reactions of a range of α-substituted nitro-compounds with a variety of thiolates[77].

Recently, Bowman and Richardson[33-35] studied the reactions of aliphatic α-substituted nitro compounds with various thiolates. They found that thiolates derived from the more acidic thiols reacted to give α-nitrosulphides by an $S_{RN}1$ mechanism, but that thiolates derived from the less acidic thiols (more nucleophilic thiolates) were oxidised to disulphides (Table 1-3 and Scheme 1-20).

Scheme 1-20



1-75

where X = Br, Cl, I, NO_2, SO_2Ph.

Y = H, CH_3, Cl, NO_2.

Table 1-3

$$Me_2C(X)NO_2 + RS \longrightarrow Me_2C(SR)NO_2 + RSSR \qquad 1\text{-}75$$

R	X, reaction conditions	% yield α-nitrosulphide	% yield disulphide
2-Benzothiazolyl	Br (DMF, 2h)	89	-
4-Nitrophenyl	Br (DMF, 2h)	83	-
2-Nitrophenyl	I (30 min); Cl(5h); NO_2(24h)	0; 34; 55	98; 14; 9
4-Chlorophenyl	I; Br(2h); Cl; SO_2Ph; NO_2(18h)	0; 0; 35; 59; 69	75; 70; 32, 0; -
Phenyl	Br (MeOH, 5 min); (DMF 2h) Cl; NO_2	-	96; 87
	(16h); SO_2Ph	-	52; 92; 48
Benzyl	Br; Cl; NO_2; SO_2Ph	-	80; 86; 87; 58

The substitution reactions of thiolates with various substrates (aromatic[77], benzylic[43,69], and aliphatic [34,35,76]) have been shown to proceed by an $S_{RN}1$ mechanism (Scheme 1-21).

Scheme 1-21

$$R_2C(X)NO_2 + RS^- \xrightarrow[h\nu]{S.E.T.} [R_2C(X)NO_2]^{\cdot -} + RS^- \qquad 1\text{-}76$$

$$[R_2C(X)NO_2]^{\cdot -} \longrightarrow R_2\dot{C}NO_2 + X^- \qquad 1\text{-}77$$

$$R_2\dot{C}NO_2 + RS^- \longrightarrow [R_2C(SR)NO_2]^{\cdot -} \qquad 1\text{-}78$$

$$[R_2C(SR)NO_2]^{\cdot -} + R_2C(X)NO_2 \xrightarrow{S.E.T.} R_2C(SR)NO_2 + [R_2C(X)NO_2]^{\cdot -} \qquad 1\text{-}79$$

Russell[36,37] has proposed a non-chain radical oxidative dimerisation mechanism for the oxidation of thiolates by trinitroethane (Scheme 1-16). This mechanism could be extended to cover the oxidation of thiolates by 2- substituted-2-nitropropanes (Scheme 1-22).

Scheme 1-22

$$Me_2C(X)NO_2 + RS^- \xrightarrow{S.E.T.} [Me_2C(X)NO_2]^{\cdot -} + RS^{\cdot} \qquad 1\text{-}80$$

$$[Me_2C(X)NO_2]^{\cdot -} \longrightarrow Me_2\dot{C}NO_2 + X^- \qquad 1\text{-}81$$

$$Me_2\dot{C}NO_2 + RS^- \longrightarrow Me_2CNO_2^- + RS^{\cdot} \qquad 1\text{-}82$$

$$2RS^{\cdot} \longrightarrow RSSR \qquad 1\text{-}83$$

Thus, the difference in reactivity of different thiolates could be explained by Schemes 1-21 and 1-22, i.e. the intermediate nitropropyl radical either adds to thiolate (Scheme 1-22) to yield α-nitrosulphide or undergoes electron transfer (Scheme 1-22) with thiolate to yield disulphide. Thiolates of the less acidic thiols are more easily oxidised and electron transfer (eqn. 1-82) could therefore predominate giving disulphide and the thiolates from the less nucleophilic thiolate could undergo addition giving α-nitrosulphides. However, Bowman and Richardson[33-35] attempted to trap possible thiyl radical intermediates during the oxidation of phenyl thiolate with 2-bromo-2-nitropropane using norbornadiene, but were unsuccessful. Diphenyl disulphide was the only isolatable product

and no trace of norbornadiene-thioether adducts could be detected. They also provided other evidence against a radical mechanism for the redox-reaction. Their argument was that, if the competition is as shown in Scheme 1-21 and 1-22, then the product obtained should be independent of the nature of the α-substituent, since both processes have a common intermediate, the 2-nitropropyl radical. Their results demonstrated that for thiolates of intermediate reactivity e.g. 4-chlorophenyl and 2-nitrophenyl thiolate the nature of the α-substituent does determine the route of reaction; i.e. the reaction between the thiolate and the α-substituted nitropropane is the point of divergence between the paths to form either α-nitrosulphide or disulphide, not the reaction with the 2-nitropropyl radical.

Furthermore, sulphenyl halides are well known reactive species which react rapidly with thiolates to form disulphide. In order to trap the sulphenyl intermediate they reacted triphenylmethyl thiolate with 2-chloro-2-nitropropane in methanol (eqn. 1-84). The sterically hindered triphenylmethyl-sulphenyl chloride (19) was isolated and no disulphide detected. The disulphide should have been formed if thiyl radicals were intermediates. The equivalent reaction with

$$Ph_3CS^- + Me_2C(Cl)NO_2 \longrightarrow \underset{(19)}{Ph_3CSCl} + Me_2CNO_2^- \qquad 1\text{-}84$$

2-bromo-2-nitropropane was also attempted, but gave unreliable results due to the instability of the intermediate sulphenyl bromide. In light of these pieces of evidence Bowman and Richardson[33-35] suggested that the oxidation is best explained by an ionic mechanism involving nucleophilic attack by the thiolate anion on the α-substituent (Scheme 1-23 and eqn. 1-85) and subsequent reaction of a second thiolate molecule with the sulphenyl intermediate (eqn. 1-86). Thus the distribution

Scheme 1-23

$$RS\overset{\curvearrowright}{}X\overset{\curvearrowright}{}CMe_2NO_2 \longrightarrow R\text{-}S\text{-}X + Me_2CNO_2^- \qquad 1\text{-}85$$

$$RS^- + RSX \longrightarrow RSSR + X^- \qquad 1\text{-}86$$

of product depends on competition between a S_N2 mechanism and the $S_{RN}1$ one. This proposal is able to account for their results shown in Table 1-3; the more nucleophilic the thiolate and the easier the abstraction of the 2-substituent ($I>Br>Cl>NO_2>SO_2Ph$), the more disulphide formation is favoured, and vice versa. Finally, they obtained evidence for the competition between the $S_{RN}1$ (Scheme 1-21) and S_N2 (Scheme 1-23) routes by trapping the radical and radical-anions involved in the $S_{RN}1$ mechanism, e.g. they carried out the reaction of 2-nitrophenylthiolate with 2-bromo-2-nitropropane under O_2, in the presence of p-DNB, or with the exclusion of light and showed that the yield of disulphide was substantially increased at the expense of the α-nitrosulphide. These pieces of evidence support the Bowman and Richardson mechanism and show that the non-chain oxidative dimerisation *via* intermediate radical and radical-anions proposed by Russell[36,37] was unlikely. Summary of the mechanisms proposed by Bowman and Richardson is shown in Scheme 1-24.

Scheme 1-24

$$Me_2C(X)NO_2 + RS^- \xrightarrow{S_{RN}1} Me_2C(SR)NO_2 + X^- \qquad 1\text{-}87$$

$$Me_2C(X)NO_2 + RS^- \xrightarrow{S_N2} R\text{-}S\text{-}X + Me_2\dot{C}NO_2 \qquad 1\text{-}89$$

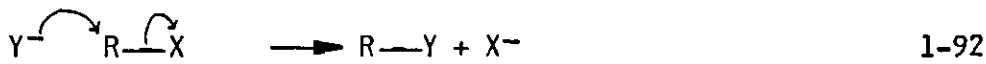
$$R\text{-}S\text{-}X + RS^- \xrightarrow{S_N2} R\text{-}S\text{-}S\text{-}R + X^- \qquad 1\text{-}90$$

$$Me_2\dot{C}NO_2 + Me_2C(X)NO_2 \xrightarrow{S_{RN}1} Me_2C(NO_2)C(NO_2)Me_2 \qquad 1\text{-}91$$

Their conclusion was that certain thiolates undergo oxidative dimerisation with α-substituted nitro compounds by an ionic mechanism *via* a reactive sulphenyl intermediate (R-S-X) to yield disulphide. They have suggested that these reactions are dependent on the nature of the α-substituent and the nucleophilicity of the thiolate.

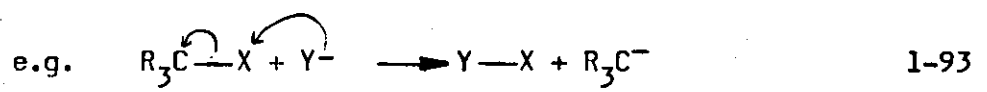
X-Philic reactions

In S_N2 nucleophilic substitution the attacking reagent (the nucleophile) brings an electron pair to the carbon atom of the substrate, using this electron pair to form the new bond, and the leaving group (nucleofuge) comes away with an electron pair (eqn. 1-92)



1-92

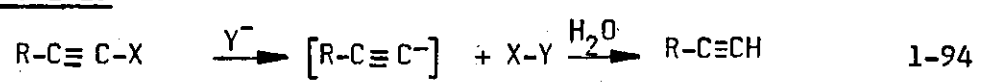
Recently, a new type of nucleophilic substitution called "X-philic" has been subjected to intensive review in literature[78]. In simple terms X-philic reactions are S_N2 nucleophilic substitutions at (X) with the carbon atom playing the role of the leaving group (eqn. 1-93).



1-93

X-philic reactions occur with the release of a carbanion. Certain structural features favour this incipient carbanion and will facilitate the X-philic reactions. Accordingly, a general tendency toward reactions of X-philic type must increase in the series $C_{sp}3<C_{sp}2<C_{sp}$. A typical example is the reaction of halo acetylenes with nucleophiles[79,80] (Scheme 1-25).

Scheme 1-25

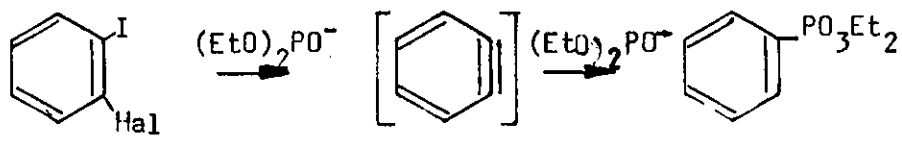


1-94

where R = Ar, Het.

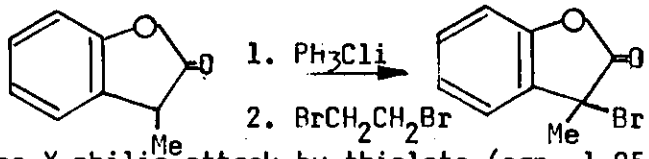
Y = OAlk, SR, NH_2, Ph_3C.

Aryl halides are a second class that may be involved in reactions with attack by nucleophile on halogen[81,82]. For example, the reaction of dihalobenzene with diethylphosphonate eqn. 1-95.



1-95

In light of the previous examples, the net result of an X-philic reaction is the transfer of a "positive" (X) moiety from a carbon atom of the substrate to the nucleophile with the formation of a carbanion. These reactions can be very useful from a synthetic point of view, e.g. "X-ation" (halogenation, cyanation)[83] of the nucleophilic moiety and the generation of a carbanion (eqn. 1-96).



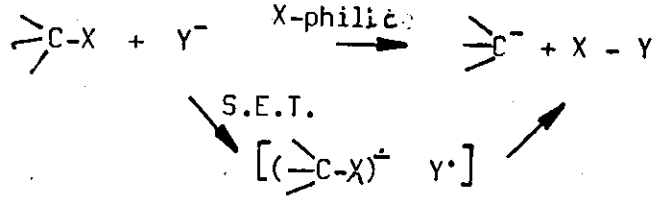
1-96

The X-philic attack by thiolate (eqn. 1-85) anion on the α-substituent of α-substituted nitro-compounds is a good example of an X-philic reaction.

The assignment of the X-philic mechanism is dependent on the structures of the initial and final compounds. For examples, the X-philic route has been supported by the isolation of the product due to the transfer of a "positive" halogen moiety, e.g. bromonitrile[84] (eqn. 1-97).

$$(C_6F_5)_2CHBr + CN^- \longrightarrow BrCN + (C_6F_5)_2\bar{C}H \qquad 1\text{-}97$$

In most reports the real mechanism is not well understood. Alternatively single electron transfer (S.E.T.) which is discussed in (Part IV) can be considered, i.e.



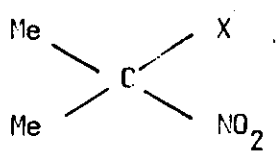
DISCUSSION

2.1

Interest in the chemistry of α-substituted nitro-alkanes is due to their biological activity and chemical reactivity, which has been discussed in the introduction.

The objectives of the project were:

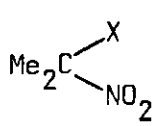
a) To synthesize 2-substituted-2-nitropropane derivatives with potential antimicrobial activity. The synthesis of the following representative compounds was planned;



with X = Cl, Br, I, COMe, CO_2Et, NO_2, CN, $P(OEt)_2$, SCN, p-NO_2, C_6H_4, SO_2-Ph, SO_2Me, SPh.

b) To determine the antimicrobial activity of the prepared compounds (Minimum Inhibition Concentration, M.I.C.), and thereby to determine the structure-activity relationship (S.A.R.) of the α-substituent.

c) To investigate the chemistry of the previously unstudied compounds such as:



where X = SCN, N_3, PO_3Et_2

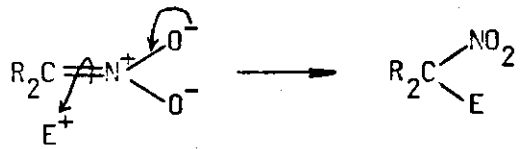
d) To study the reaction of 2-substituted-2-nitropropanes with thiolate anions as an *in vitro* guide to their mode of action and potential antimicrobial activity.

e) To investigate the use of e.s.r. spectroscopy to predict the behaviour of radical-anions of $Me_2C(X)NO_2$ in solution reactions at room temperature as a guide to their antimicrobial activity.

2.2 Synthesis of 2-substituted-2-nitropropanes

2.2.1 Preparation of 2-substituted-2-nitropropanes by electrophilic attack on nitro-anions

Nitro-anions are ambident anions and can react with electrophiles *via* carbon or oxygen. Oxygen alkylation is favoured in reactions with alkyl and acyl halides and is therefore of little value in the preparation of 2-substituted-2-nitropropanes[43,61,85]. C-alkylation, however, is favoured with many electrophiles and can be successfully used in the preparation of a number of these compounds (eqn. 2-98).



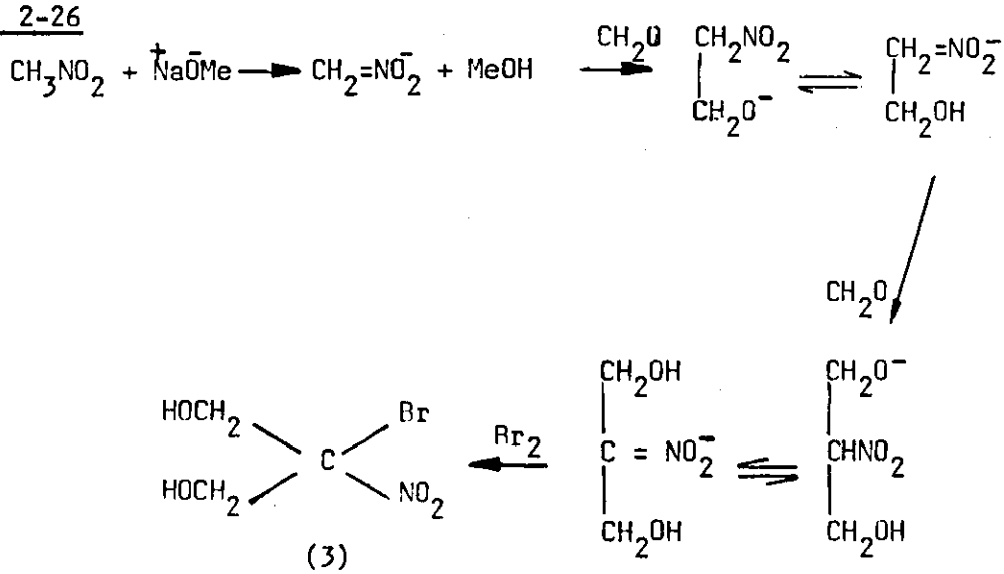
2-98

One particularly useful synthetic method is the Henry reaction[85,86]. Henry discovered the aldol-type, alkali-catalyzed, addition of nitromethane and homologous primary nitroalkanes to aliphatic aldehydes. The reaction was later extended to include secondary nitroalkanes and many substituted nitroalkane derivatives. In its most general form, the Henry reaction is illustrated by eqn. 2-99 .

$$R^1CHO + R^2CH_2NO_2 \xrightarrow{\text{base}} R^1CHOHCH(R^2)NO_2 \qquad (2\text{-}99)$$

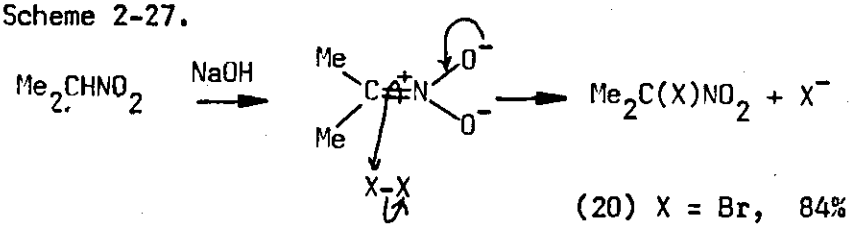
It requires the presence of a hydrogen atom on the carbon that carries the nitro group, i.e. the primary and secondary nitroalkanes, while tertiary nitroalkanes do not react[85]. A good example of the Henry reaction is the synthesis of bronopol(3) (2-bromo-2-nitropropane-1,3-diol).[87] See Scheme (2-26).

Scheme 2-26



a) Preparation of 2-bromo, 2-chloro, and 2-iodo-2-nitropropane (20), (21), and (22)

The 2-halo-2-nitropropanes were prepared by the method of Seigle and Hass[65]. The method is straightforward and worked well. The mechanism is outlined in Scheme 2-27.



Scheme 2-27

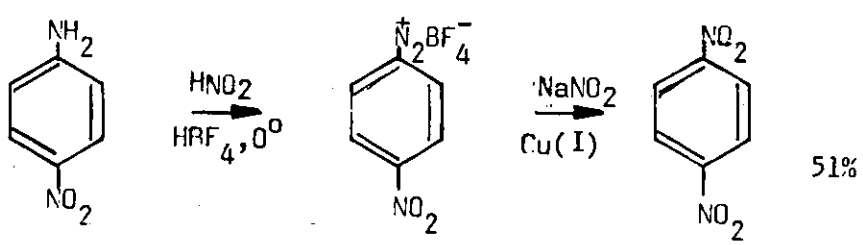
(20) X = Br, 84%

(21) = Cl, 52%

(22) = I, 71%

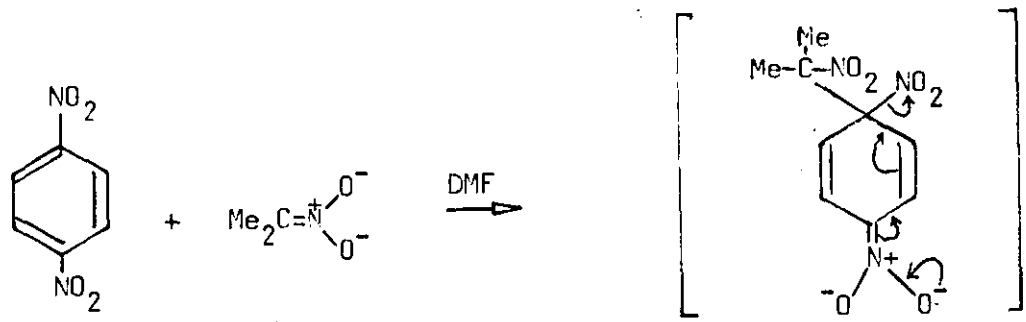
b) Synthesis of α, *p*-dinitrocumene (24)

The synthesis of α, *p*-dinitrocumene has been reported by Kornblum and co-workers[88] (eqns. 2-100 and 2-101).

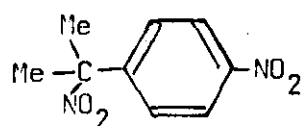


2-100

p-DNB (23)



2-101



75%

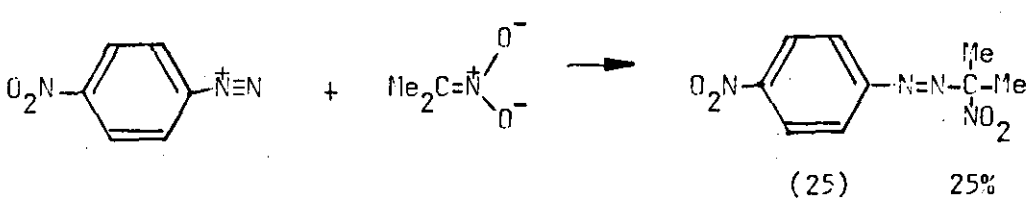
α, *p*-dinitrocumene (24)

The first step was the preparation of *p*-dinitrobenzene[89] (23) *via* diazotization and replacement of the nitrogen of the diazonium salt by nitrite in 51% yield. The dinitrobenzene readily underwent aromatic nucleophilic substitution (S_NAr) of the nitro group at room temperature in DMSO to afford α, *p*-dinitrocumene (24) in 75% yield. The displacement of the nitro group occurred readily due to the use of the dipolar aprotic solvent (DMSO).

c) Preparation of 2-(p-nitrophenylazo)-2-nitropropane[90](25)

Electrophilic attack can also be demonstrated with aromatic compounds such as in the reaction of *p*-nitrophenyldiazonium chloride with the anion of 2-nitropropane to give 2-(*p*-nitrophenylazo)-2-nitropropane (25) in 25% yield. The mechanism in Scheme 2-28 is proposed.

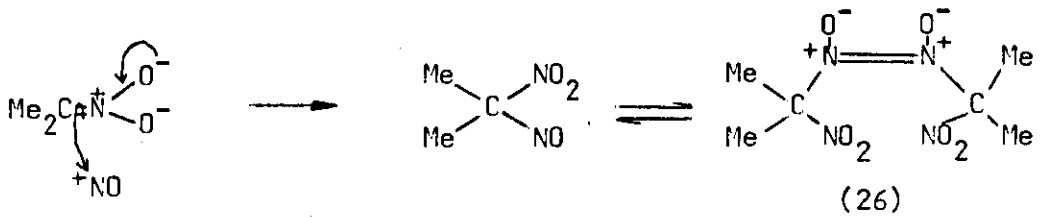
Scheme 2-28



(25) 25%

d) Preparation of 2-nitro-2-nitrosopropane (26)

Another example of electrophilic attack was the preparation of 2-nitro-2-nitrosopropane[91] (eqn. 2-102).

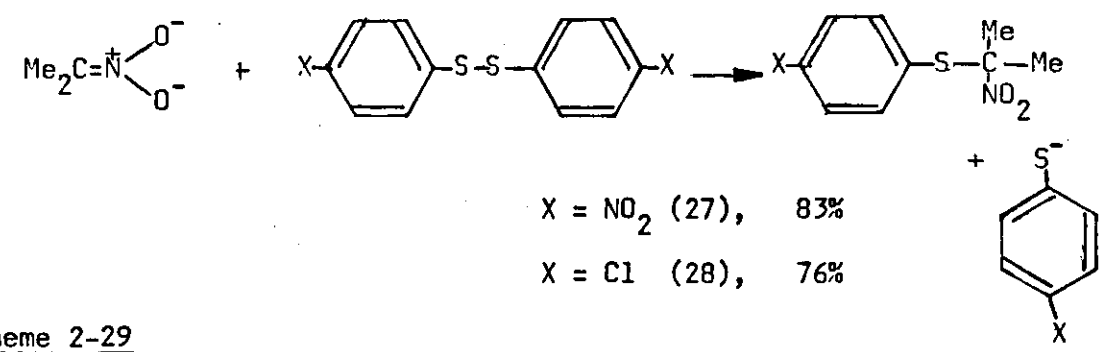


(26) 2-102

2-nitro-2-nitrosopropane was not considered for testing due to its instability and the strong potential carcinogenicity of nitroso groups. The compound, however, was prepared as an intermediate for the attempted preparation of 2-azido-2-nitropropane (40).

e) Preparation of α-nitrosulphides

The preparation of the α-nitrosulphides has been reported[34]. The anion of 2-nitropropane reacts with symmetrical disulphides in DMF to yield α-nitrosulphides. The S_N2 mechanism proposed is shown in Scheme 2-29.



X = NO_2 (27), 83%

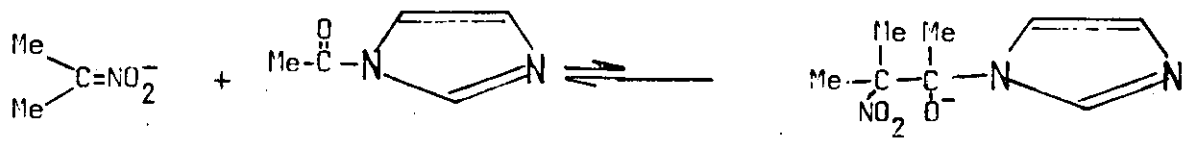
X = Cl (28), 76%

Scheme 2-29

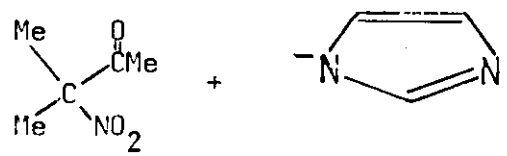
We have repeated the reaction shown in Scheme 2-29 and obtained (27) in 83% and (28) in 76% yield. The reaction proceeds only if the disulphide has strong electron withdrawing substituents.

f) Attempted preparation of 3-methyl-3-nitro-butan-2-one(30)

The C-acylation of nitromethane with acylimidazoles to obtain α-nitro-ketones in good yield has been reported[92]. An attempt to prepare the target α-nitro-ketone *via* C-acylation of the anion of 2-nitropropane was unsuccessful (Scheme 2-20).



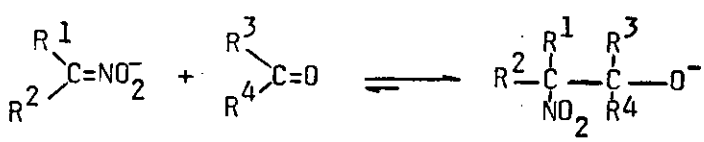
(29)



(30)

Scheme 2-30

The first stage will take place to form the intermediate (29) which is most likely to be sterically hindered and therefore thermodynamically unstable forcing the equilibrium over to the left (i.e. starting material). This suggestion is supported by the steric limitations of the well-known Henry[85] reaction (eqn. 2-103). In order for the reaction to proceed it must have at least two of the R^1, R^2, R^3, or R^4 groups as hydrogen.



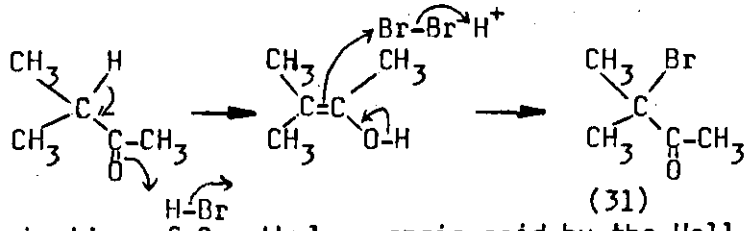
1-103

This evidence is in agreement with our observation and therefore we conclude that C-acylation can occur using acetyl imidazoles and nitromethane, or possibly primary nitroalkanes, but that secondary nitroalkanes do not react.

2.2.2 Synthesis of 2-substituted-2-nitropropanes by nucleophilic substitution of halide by nitrite

3-Methyl-3-nitrobutan-2-one[93] (33) and ethyl 2-methyl-2-nitropropionate[93] (34) were prepared from the corresponding α-bromo compounds. The bromination of the ketone is a simple process with a well understood mechanism and was carried out in good yield (51%). The bromination proceeds *via* an acid catalysed reaction, in this case hydrogen bromide formed in the reaction

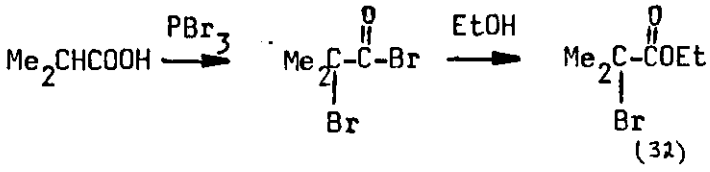
itself was the catalyst (eqn. 2-104). The α-bromoester was prepared by



2-104

(31)

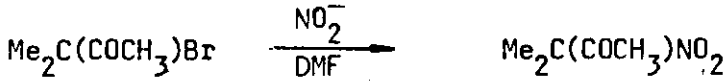
bromination of 2-methylpropanoic acid by the Hell-Volhard-Zelinskii reaction (Scheme 2-31). The second stage in the synthesis of



(32)

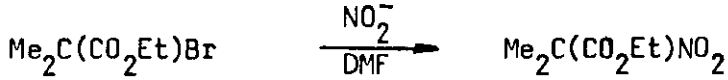
Scheme 2-31

α-nitroketones and α-nitroesters, i.e. the substitution of bromide by nitrite, has been reported[93] to proceed by an S_N2 type mechanism (eqns. 2-105 and 2-106). However, S_N2 substitution on a tertiary carbon center



(33) 85%

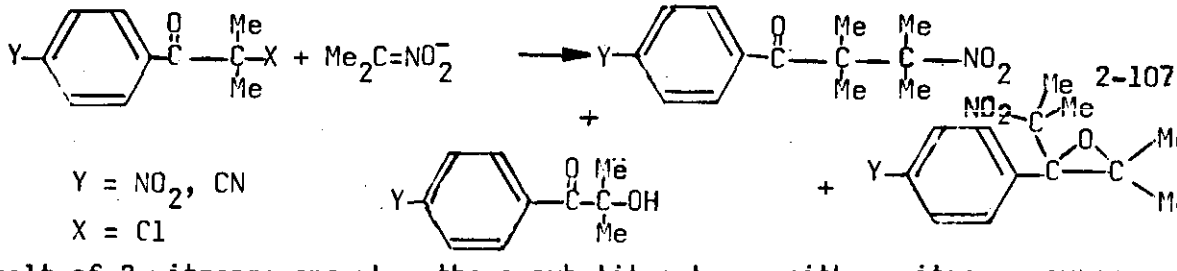
2-105



(34) 53%

2-106

is unlikely because of steric hindrance. Russell and Ros[94] have reported the reactions of nucleophiles with α-haloketones (eqn. 2-107). They found that sterically hindered α-haloisobutyrophenones only reacted with the



2-107

Y = NO_2, CN
X = Cl

salt of 2-nitropropane when the p-substituent was either nitro or cyano. Competition between ionic and free-radical ($S_{RN}1$) substitution lead to different products (eqn. 2-107). However, since the free-radical process was not observed in the reaction of nucleophiles with the unsubstituted α-chloroisobutyrophenone, they concluded that substitution on α-haloketones by an electron transfer mechanism ($S_{RN}1$) is limited even when S_N2

substitution is sterically hindered. However, no inhibition studies have been reported for these reactions (eqns. 2-105 and 2-106) and therefore they could possibly proceed by an $S_{RN}1$ mechanism shown in (Scheme 2-32).

Scheme 2-32

$$Me_2C(COCH_3)Br + NO_2^- \xrightarrow{S.E.T.} [Me_2C(COCH_3)Br]^{\cdot -} + NO_2$$

$$[Me_2C(COCH_3)Br]^{\cdot -} \longrightarrow Me_2\dot{C}(COCH_3) + Br^-$$

$$Me_2\dot{C}COCH_3 + NO_2^- \longrightarrow [Me_2C(NO_2)COCH_3]^{\cdot -}$$

$$[Me_2C(NO_2)COCH_3]^{\cdot -} + Me_2C(Br)COCH_3 \longrightarrow Me_2C(NO_2)COCH_3 + [Me_2C(Br)COCH_3]^{\cdot -}$$

Further research is required to determine the mechanism involved in these substitutions. Inhibition studies and light catalysis would easily indicate the absence or presence of the $S_{RN}1$ mechanism.

2.2.3 Synthesis of 2-substituted-2-nitropropanes by oxidative addition of anions to the salts of nitroalkanes

The first oxidative addition was reported[95] in 1961. This was the preparation of geminal dinitroalkanes (eqn. 2-108).

$$R_2\text{—}\underset{NO_2}{\overset{R_1}{C}}\text{—H} \xrightarrow[AgNO_3/NaNO_2]{NaOH} R_2\text{—}\underset{NO_2}{\overset{R_1}{C}}\text{—}NO_2 + Ag^{(0)} \qquad 2\text{-}108$$

The mechanism[96], however, was not elucidated until several years later in 1964. The mechanism proposed invoked the initial oxidation of the nitroanion with Ag(I) to give a nitro-radical which reacted with the nitrite to yield a dinitro radical-anion. The radical-anion then yielded the dinitroalkane product after further oxidation by Ag(I) as shown in (Scheme 2-33).

Scheme 2-33

$$R_2C{=}NO_2^- + Ag^+ \xrightarrow{S.E.T.} R_2\dot{C}{-}NO_2 + Ag^{(o)}$$

$$R_2\dot{C}{-}NO_2 + NO_2^- \longrightarrow [R_2C(NO_2)_2]^{\pm}$$

$$[R_2C(NO_2)_2]^{\pm} + Ag^+ \longrightarrow R_2C(NO_2)_2 + Ag^{(o)}$$

Matcz *et al*[97] reported in 1979 that aqueous potassium ferricyanide was a useful reagent for the oxidative addition of anions to the salts of secondary nitrocompounds (eqn. 2-109).

$$Me_2C{=}NO_2^- + A^- \xrightarrow{-2e} Me_2C(A)NO_2 \qquad 2\text{-}109$$

where A = NO_2, CN, *p*-ClC_6H_4S, $PhSO_2$.

The simplicity and short reaction time of the method, in addition to the cheapness of the reagents, was further exploited by Bowman and Rakshit[98] for the preparation of a series of heterocyclic sulphides e.g. 1-methyl-1-nitroethyl pyrimidin-2-yl sulphide (75%) and 1-methyl-1-nitroethyl 1-methylimidazol-2-yl sulphide (42%) with none of the corresponding disulphide being formed. Likewise, we have prepared 2-cyano-2-nitropropane (35, 42%) and 2,2-dinitropropane (36, 31%) by the same method (eqns. 2-110 and 2-111. respectively).

$$Me_2CHNO_2 \xrightarrow{NaOH} Me_2C{=}NO_2^- \xrightarrow[K_3Fe(CN)_6]{NaCN} Me_2C(CN)NO_2 \qquad 2\text{-}110$$

$$Me_2CHNO_2 \longrightarrow Me_2C{=}NO_2^- \xrightarrow[K_3Fe(CN)_6]{NaNO_2} Me_2C(NO_2)_2 \qquad 2\text{-}111$$

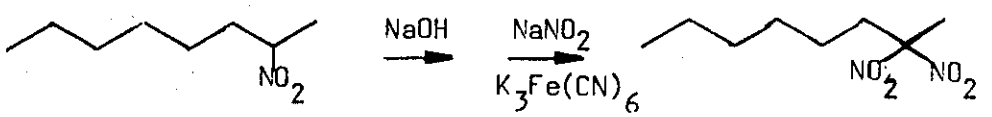
The products were purified by fractional distillation and identified by ^{1}H.n.m.r., i.r and b.p. Attempts to use the diethylphosphonate anion for preparation of diethyl 1-methyl-1-nitroethylphosphonate (37) failed;

only unreacted diethylphosphite was recovered (eqn. 2-112).

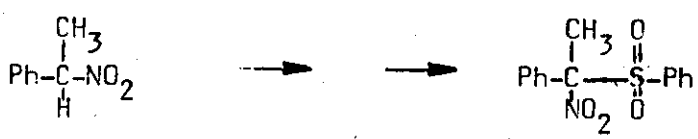
$$Me_2CHNO_2 \xrightarrow{NaOH} Me_2C{=}NO_2^- \xrightarrow[K_3Fe(CN)_6]{(EtO)_2PO^-} Me_2C(NO_2)PO_3Et_2 \quad (37) \qquad 2\text{-}112$$

We suggest that the lack of reaction could be due to the phosphonate anion being protonated by water and thus preventing any electron transfer. We have, however, prepared diethyl 1-methyl-1-nitroethylphosphonate (37) by the $S_{RN}1$ route (see section 2.2.4).

The versatility of the ferricyanide reaction (eqns. 2-109, 2-110 and 2-111) and the availability of the requisite secondary nitrocompounds has made it a useful synthetic route. Kornbulm *et al*[99] have reviewed the reaction and prepared a wide range of α-nitronitriles, α-nitrosulphones, and α-dinitroparaffins (eqns. 2-113-114) in excellent yields.



2-113



2-114

We, likewise, found the ferricyanide reaction to be very useful for the preparation of other target compounds e.g. 2-nitro-2-thiocyanatopropane (67) and 2-azido-2-nitropropane (40). These and others are discussed in (sections 2.4, and 2.5). The oxidative addition reaction proceeds *via* the mechanism shown in scheme 2-33.

Scheme 2-33

$$R_2C{=}NO_2^- \xrightarrow[Fe(III)\ Fe(II)]{-e^-} R_2\dot{C}{-}NO_2$$

$$R_2\dot{C}{-}NO_2 \xrightarrow{A^-} [R_2C(A)NO_2]^{\cdot-}$$

$$[R_2C(A)NO_2]^{\cdot-} \xrightarrow[Fe(III)\ Fe(II)]{-e^-} R_2C(A)NO_2$$

overall:

$$R_2C{=}NO_2^- + A^- \longrightarrow R_2C(A)NO_2 \qquad 2\text{-}115$$

2,3-Dimethyl-2,3-dinitrobutane (38), an impurity in some of the oxidative additions is formed by the mechanism shown.

$$Me_2C{=}NO_2^- + Fe(III) \longrightarrow Me_2\dot{C}{-}NO_2 + Fe(II)$$

$$Me_2\dot{C}{-}NO_2 + Me_2C{=}NO_2^- \longrightarrow [Me_2C(NO_2)C(NO_2)Me_2]^{\dot{-}}$$

$$[Me_2C(NO_2)C(NO_2)Me_2]^{\dot{-}} + Fe(III) \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + Fe(II)$$

(28)

Fortunately, the addition of the anion of 2-nitropropane to the 2-nitropropyl radical is slower than most other anions.

2.2.4 Synthesis of 2-substituted-2-nitropropanes by the $S_{RN}1$ substitution

The $S_{RN}1$ substitution can also be used for the preparation of 2-substituted-2-nitropropanes. The 2-halo-2-nitropropanes, which are readily prepared, can be substituted to yield new substituted nitropropanes which cannot be obtained by other routes. The mechanism and scope is fully discussed in the introduction and is shown (Scheme 2-34).

Scheme 2-34

$$Me_2C(X)NO_2 + e^-(A\cdot) \xrightarrow{h\upsilon} [Me_2C(X)NO_2]^{\dot{-}} + (A\cdot) \qquad 2\text{-}116$$

$$[Me_2C(X)NO_2]^{\dot{-}} \longrightarrow Me_2\dot{C}NO_2 + X^- \qquad 2\text{-}117$$

$$Me_2\dot{C}NO_2 + A^- \longrightarrow [Me_2C(A)NO_2]^{\dot{-}} \qquad 2\text{-}118$$

$$[Me_2C(A)NO_2]^{\dot{-}} + Me_2C(X)NO_2 \xrightarrow{S.E.T.} Me_2C(A)NO_2 + [Me_2C(X)NO_2]^{\dot{-}} \qquad 2\text{-}119$$

$$\text{or } [Me_2C(X)NO_2]^{\dot{-}} \longrightarrow Me_2\dot{C}{-}X + NO_2 \qquad 2\text{-}120$$

$$Me_2\dot{C}{-}X + A^- \longrightarrow [Me_2C(A)X]^{\dot{-}} \qquad 2\text{-}121$$

$$[Me_2C(A)X]^{\dot{-}} + Me_2C(X)NO_2 \xrightarrow{S.E.T.} Me_2C(A)X + [Me_2C(X)NO_2]^{\dot{-}} \qquad 2\text{-}122$$

Equations 2-117-119 demonstrate loss of the α-substituent[71](X) e.g. X = I, Br, Cl, SO_2R, SR, NO_2, and S(O)R, while equations 2-120-122 demonstrate loss of nitrite[65,67,76] e.g. X = COR, CO_2R, CN, NO_2, p-$NO_2C_6H_4N_2$ and Me. The latter route is not of any use for the preparation of 2-substituted-2-nitropropanes.

Russell and Hershberger[70] reported the preparation of diethyl 1-methyl 1-nitroethylphosphonate (37) (eqn. 2-123).

$$Me_2C(Br)NO_2 + (EtO)_2\overset{O}{\overset{\|}{P}}H \xrightarrow[THF/1h]{t\text{-}BuOK} \underset{(37)}{Me_2C(PO_3Et_2)NO_2}\ {}_{76\%} \qquad 2\text{-}123$$

We prepared the compound (37) in good yield (76%), ^{1}H.n.m.r., i.r, and b.p were in agreement with the literature[70] data for the proposed structure. However, we were not able to observe the parent peak. A fragment in the electron impact mass spectrum (M^+-46) was obtained which corresponds to loss of the nitro group.

We observed that this type of reaction is very sensitive to oxygen, and the course of the reaction can be inhibited by the presence of a trace quantity of oxygen in the reaction atmosphere.

The reaction has been reported to proceed *via* an $S_{RN}1$ mechanism (Scheme 2-34 , with A = PO_3Et_2[70]).

Likewise, we prepared 1-methyl-1-nitroethyl phenyl sulphone (39) in good yield (77%) by reaction of 2-bromo-2-nitropropane with the sodium salt of benzene sulphinic acid (eqn. 2-124).

$$Me_2C(Br)NO_2 + PhSO_2^- \xrightarrow{h\upsilon,DMF} \underset{(39)}{Me_2C(SO_2Ph)NO_2}\ {}_{77\%} \qquad 2\text{-}124$$

The ^{1}H.n.m.r., i.r, and m.p. were in agreement with the literature[68] data for the proposed structure. Kornblum and co-workers[68] reported that the reaction (eqn. 2-124) proceed *via* an $S_{RN}1$ mechanism (Scheme 2-34, with A = $PhSO_2$).

2.2.5 Preparation of α-nitroazides

2.2.5.1 Preparation of α-nitroazides by oxidative addition of azide to nitronate anions

Oxidative addition has been used to synthesize a number of 2-substituted-2-nitropropane compounds by Matcz *et al*[97]. The preparation of 2-azido-2-nitropropane (40) was attempted using the oxidative addition method as shown in Scheme 2-40.

Scheme 2-40

$$Me_2CNO_2^- + Fe^{(III)} \longrightarrow Me_2\dot{C}\text{-}NO_2 + Fe^{(II)}$$

$$Me_2\dot{C}\text{-}NO_2 + N_3^- \longrightarrow [Me_2C(N_3)NO_2]^{\cdot-}$$

$$[Me_2C(N_3)NO_2]^{\cdot-} + Fe^{(III)} \longrightarrow Me_2C(N_3)NO_2 + Fe^{(II)}$$

(40)

Potassium ferricyanide was used as the oxidising agent for the oxidative addition with an excess of azide for the preparation of 2-azido-2-nitropropane (40). The t.l.c. (silica, $CHCl_3$) showed a single spot, and g.l.c. (SE30, 10%) showed one pure compound as product. The spectroscopic data suggested that the product was 2,2-diazidopropane (41). The ^{1}H.n.m.r. spectrum, δ1.5p.p.m. (s); the i.r. spectrum which showed very a strong absorption bond at υ_{max} 2100cm^{-1}, the mass spectrum with m/e 69 (M^+-57) identified as the base peak; and the ^{13}C.n.m.r. spectrum δC25.96 (q, Me) and δC79.10 (s, quaternary carbon), were within the expected values for the proposed structure. The elemental analysis was unsatisfactory due to the explosive properties of the product. The product was obtained in a fair yield (41%). However, from the spectroscopic data, it is clear that the product was not our target. The i.r spectrum, for instance, showed the absence of a nitro peak at υ_{max} 1555cm^{-1}. The chemical shift of the singlet in the ^{1}H.n.m.r. spectrum appears at a lower δ-value (1.5p.p.m.) than would be expected due to the deshielding effect of a nitro group; the singlet should appear at lower field, around

δ1.8-2.2p.p.m. This evidence led us to suggest that the compound was not our target (40) but possibly 2,2-diazidopropane (41). In order to prove the structure of the product a derivative was prepared by reacting the azide product with norbornene to form an adduct (Section 2.3.1).

Initially, we were surprised that the oxidation of the anion of 2-nitropropane in the presence of azide gave 2,2-diazidopropane. A possible explanation is that the breakdown of the intermediate radical anion, (40), is faster than its oxidation by ferricyanide i.e. ($k_2 > k_1$) in Scheme 2-41.

Scheme 2-41

$$Me_2C{=}NO_2^- + Fe^{(III)} \xrightarrow{N_3^-} [Me_2C(N_3)NO_2]^{\cdot -} + Fe^{(II)} \qquad 2\text{-}125$$

(40)

$$[Me_2C(N_3)NO_2]^{\cdot -} + Fe^{(III)} \xrightarrow{k_1} Me_2C(N_3)NO_2 + Fe^{(II)} \qquad 2\text{-}126$$

(40) (40)

or

$$[Me_2C(N_3)NO_2]^{\cdot -} \xrightarrow{k_2} (Me_2CN_3)^{\cdot} + NO_2^- \qquad 2\text{-}127$$

(40)

$$(Me_2CN_3)^{\cdot} + N_3^- \longrightarrow [Me_2C(N_3)_2]^{\cdot -} \qquad 2\text{-}128$$

$$[Me_2C(N_3)_2]^{\cdot -} + Fe^{(III)} \longrightarrow Me_2C(N_3)_2 + Fe^{(II)} \qquad 2\text{-}129$$

In order to obtain some information regarding the mechanism, the reaction was repeated for different times (Table 2-1). The results suggested that the2,2-diazidopropane (41) was formed from 2-azido-2-nitropropane (40) and not directly by decomposition of the intermediate radical-anion. (eqn. 2-127).

Table 2-1. Preparation of 2-azido-2-nitropropane

$$Me_2C{=}NO_2^- + 2N_3^- \longrightarrow Me_2C(N_3)NO_2 + Me_2C(N_3)_2$$
(40) (41)

Time (min.)	1	15	20	40	60
% yield of $Me_2C(N_3)NO_2$ (40)	28	24	19	7	0
% yield of $Me_2C(N_3)_2$ (41)	19	22	22	38	41

We have shown (Section 2.4.1) that the 2-azido-2-nitropropane (40) does in fact react with azide *via* an $S_{RN}1$ mechanism under these reaction conditions to give 2,2-diazidopropane (41) (eqn. 2-130). We suggest therefore, that the 2,2-diazidopropane (41) is formed by an $S_{RN}1$ reaction of excess azide with the 2-azido-2-nitropropane.

$$Me_2C(N_3)NO_2 + N_3^- \xrightarrow{CH_2Cl_2/H_2O} Me_2C(N_3)_2 \qquad 2\text{-}130$$
(41)

Likewise, we have shown that 2-azido-2-nitropropane (40) can be prepared by an $S_{RN}1$ mechanism from 2-bromo-2-nitropropane (section 2.2.5.2). Our results suggest that a single electron is removed from the intermediate radical-anion (40) (eqn. 2-126) in the ferricyanide oxidation or in the $S_{RN}1$ chain reaction, faster than its breakdown, i.e. $k_1 > k_2$ in Scheme 2-41.

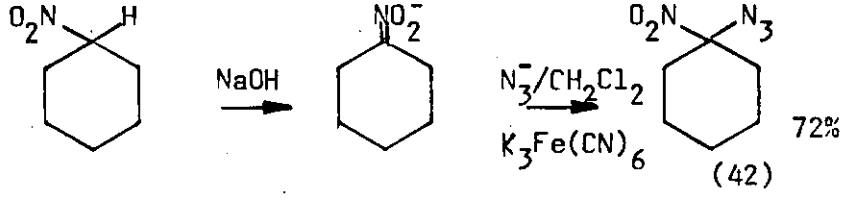
Wright and Ward[100] have reported the preparation of 2-azido-2-nitropropane (40) by an electrochemical reaction as shown in eqn. 2-131.

$$Me_2C{=}NO_2^- + N_3^- \xrightarrow[(0.9V)]{\text{Pt anode}} Me_2C(N_3)NO_2 \qquad 2\text{-}131$$
(40)

The electrochemical method supports our argument that loss of an electron from the radical-anion must be faster than breakdown of the radical-anion. The oxidation potential used (Pt = 0.9V) is higher than the oxidation potential of ferricyanide (0.46V). The potential difference between the two reactions allowed the electrochemical reaction to have the electron more rapidly removed than in the ferricyanide oxidation reaction.

When the nitronate salt was added to a solution of two equivalents of ferricyanide and one equivalent azide in methylene chloride and water, rather than ferricyanide being added to the nitronate anion and azide, followed by immediate work-up, a mixture of 2,2-diazidopropane (41) and 2-azido-2-nitropropane (40) was obtained, which was fractionally distilled to give(40)(28%) and 41 (19%). The spectroscopic data were in agreement with the proposed structure for (40). ^{1}H.n.m.r., δ1.8 (s); i.r. υ_{max} 2120cm^{-1} (N_3) and 1555cm^{-1} (NO_2) .

1-Azido-1-nitrocyclohexane (42) was also prepared by the addition of the anion of nitrocyclohexane to a solution of ferricyanide and azide in methylene chloride in 72% yield (eqn. 2-132).



2-132

The spectroscopic data were in agreement with the proposed structure. G.l.c. (SE30, 10%) showed a major peak due to the product and a minor peak which corresponded to cyclohexanone. The lower yield observed for the equivalent reactions with the anion of 2-nitropropane could be explained by a more rapid decomposition of the intermediate radical to acetone which was not observed because it would be lost by evaporation in the work-up. The nitrocyclohexane reaction was also carried out in diethyl ether to afford the product in 48% yield.

2.2.5.2 Preparation of 2-azido-2-nitropropane by radical nucleophilic substitution ($S_{RN}1$)

The preparation of 2-azido-2-nitropropane (40) was also carried out using radical nucleophilic substitution ($S_{RN}1$). The reaction of equimolar quantities of 2-bromo-2-nitropropane with azide was carried out in HMPA under an atmosphere of nitrogen and using fluorescent laboratory lights (eqn. 2-133). 2-Azido-2-nitropropane (40) was obtained in 38% yield.

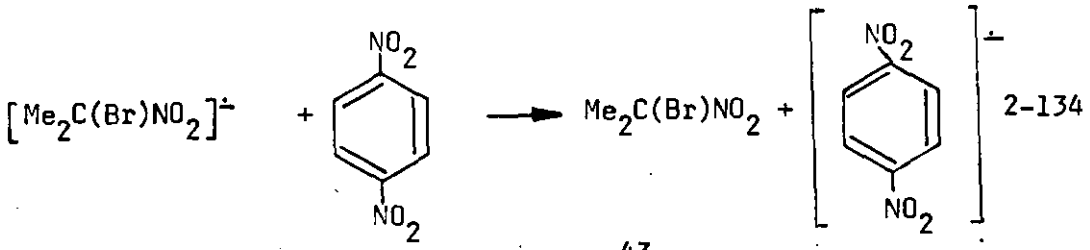
$$Me_2C(Br)NO_2 + N_3^- \xrightarrow[h\upsilon]{HMPA} Me_2C(N_3)NO_2 \qquad 2\text{-}133$$

The possibility of the reaction proceeding by an $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism[44]. The results of these studies are shown in Table 2-2.

Table 2-2: Reaction of azide with 2-bromo-2-nitropropane

Conditions	Time (min.)	% recovery $Me_2C(Br)NO_2$	% yield $Me_2C(N_3)NO_2$
Standard	15,60,(24h)	17, 11, 0	25, 22, 38
Dark	15, 60	20, 17	21, 21
5 molar % p-DNB	15	22	17
10 molar % DTBN	15, 60	28, 13	23, 20

Addition of 5 molar % of *p*-DNB to the reaction of azide with 2-bromo-2-nitropropane reduced the yield of 2-azido-2-nitropropane from 25% to 17% which was small but significant. *p*-Dinitrobenzene forms a relatively stable radical-anion and will readily accept an electron from most other radical-anions and electron donors (eqn. 2-134). p-DNB has been used as a diagnostic method[43] for the $S_{RN}1$ mechanism because it is able to intercept intermediate radical-anions in the free radical-anion radical chain sequence and thus inhibit the reaction. A reduction in the yield of 2-azido-2-nitropropane to 21% resulted when the reaction flask was wrapped in aluminium foil to exclude light. Di-*tert*-butyl-



2-134

nitroxide (DTBN) is an efficient scavenger[43] and addition of 10 molar % of DTBN to the reaction reduced the yield of 2-azido-2-nitropropane to 22% and increased the recovery of starting material from 17 to 28%. Although these results are not clear-cut, we however, suggest that these small, but significant, inhibitions (especially at shorter times) indicate that the $S_{RN}1$ mechanism is probably operative as shown in Scheme 2-42.

Scheme 2-42

$$Me_2C(Br)NO_2 + N_3^- \xrightarrow[h\upsilon]{S.E.T.} [Me_2C(Br)NO_2]^{\cdot-} + N_3^{\cdot} \qquad 2\text{-}135$$

(43)

$$[Me_2C(Br)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}\text{-}NO_2 + Br^- \qquad 2\text{-}136$$

$$Me_2\dot{C}\text{-}NO_2 + N_3^- \longrightarrow [Me_2C(N_3)NO_2]^{\cdot-} \qquad 2\text{-}137$$

$$[Me_2C(N_3)NO_2]^{\cdot-} + Me_2C(Br)NO_2 \xrightarrow{S.E.T.} Me_2C(N_3)NO_2 + [Me_2C(Br)NO_2]^{\cdot-} \qquad 2\text{-}138$$

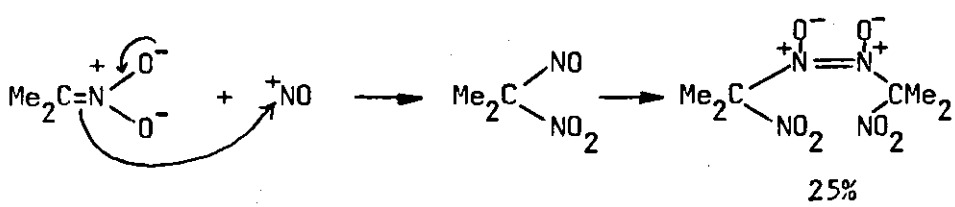
The mechanism shown in Scheme 2-42 is a chain process with initiation, propagation, and termination steps. The initiation (eqn. 2-135) occurs by an electron transfer from the azide anion to 2-bromo-2-nitropropane to give the radical-anion (43). In the absence of *p*-DNB the radical-anion breaks down to form the 2-nitropropyl radical and bromide anion (eqn. 2-136) initiating the propagation. The azide anion couples with the 2-nitropropyl radical (eqn. 2-137), followed by an electron transfer between the resulting radical-anion and the starting material (eqn. 2-138), to complete the propagation cycle. Radical-anions are known to be able to easily transfer electrons to neutral species. The termination steps of the sequence are not

well understood.

The use of stronger photolysis lights for catalysis led to rapid decomposition of 2-azido-2-nitropropane, which is not surprising because the photolytic decomposition of azides is well known.[101] 2-Azido-2-nitropropane will probably react further with azide by an $S_{RN}1$ mechanism to yield 2,2-diazidopropane which is even more susceptible to photolytic or thermal decomposition. The use of other solvents (DMF) did show some 2,2-diazidopropane but did not give improved yields. These problems will certainly complicate the observed results and may explain the poor inhibitions.

2.2.5.3 Attempted preparation of 2-azido-2-nitropropane (40) by the method of Maffei and Co-workers[102]

Maffei and co-workers have reported[102] the preparation of 2-azido-2-nitropropane. We have attempted to repeat Maffei's method, the first stage of which was the preparation of 2-nitro-2-nitrosopropane (26) (eqn. 2-139).

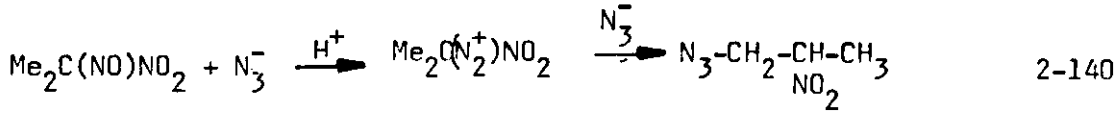


2-139

25%

(26)

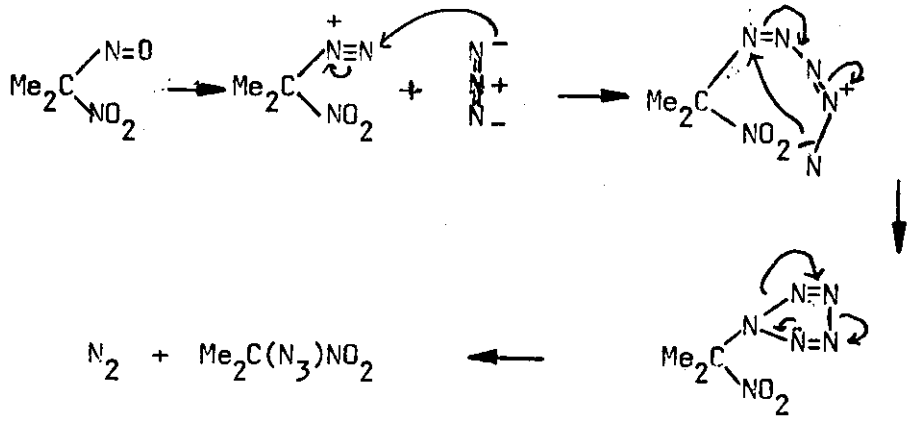
We prepared the nitroso dimer (26) in 25% yield; ^{1}H.n.m.r., i.r. and m.p. were in agreement with the literature[91] data for the proposed structure. The dimer (26) was then reacted in chloroform with sodium azide and acetic acid. The reaction was worked up after 22h yielding a crude product which was purified by preparative t.l.c. (silica/toluene). The pure product was identified by ^{1}H.n.m.r. $\delta(CDCl_3)$ 4.55 (1H, ABX, m) 3.73 (2H, ABq), δ1.55p.p.m. (3H, d). The i.r. spectra showed strong absorption peaks at 2120 and 1555 cm^{-1} corresponding to azido and nitro groups respectively. The spectroscopic data suggest that the product is 1-azido-2-nitropropane (44) (eqn. 2-140).



(44) 89%

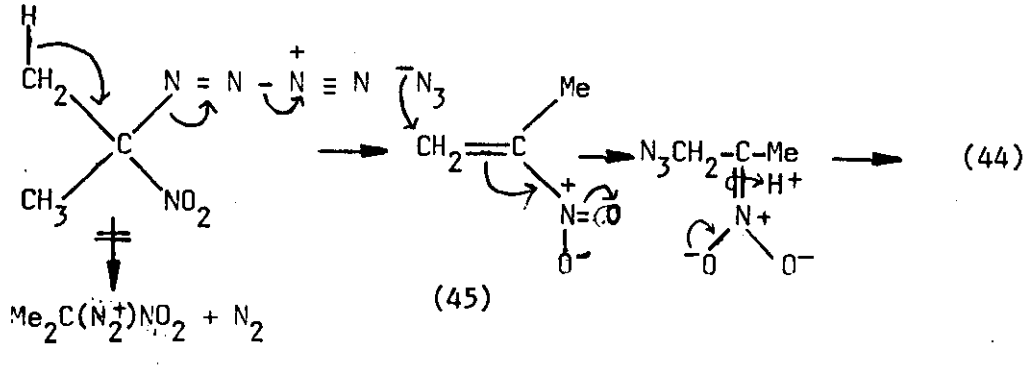
In support of our suggestion Svetlakov *et al*[103] reported the preparation of 1-azido-2-nitropropane. The reported refractive index was in agreement with that for the product. The mechanism reported (Scheme 2-43)[104] is based on the reaction of nitrosobenzene and hydrazoic acid to form phenyl azide.

Scheme 2-43



We suggest that elimination takes place during the reaction of hydrazoic acid with 2-nitro-2-nitrosopropane to give the nitro olefin intermediate (45), followed by an ionic attack by azide anion to afford the product (44). A possible mechanism is shown in Scheme 2-44. The addition of azide to 2-nitropropene is reported[103] to proceed in high yield.

Scheme 2-44



Maffei and co-workers[102] assigned their structure on the basis of the nitrosobenzene reaction with hydrazoic acid to form azidobenzene and on combustion analysis. The empirical formula of their proposed product is the same as ours. We, therefore suggest that their assignment is wrong and that they also prepared 1-azido-2-nitropropane.

2.3 Preparation of norbornene adducts of azides

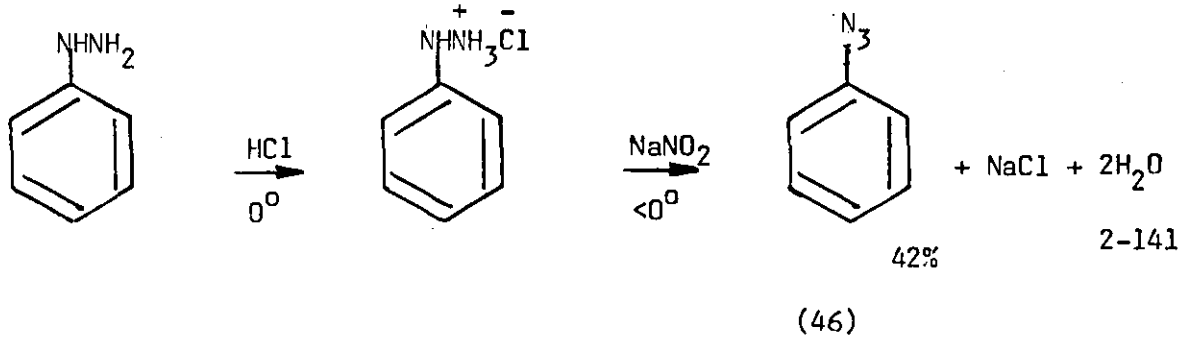
The explosive nature of the azido group prevented us from obtaining conclusive evidence in the form of combustion analysis for the prepared azido-compounds. Although their synthesis have been reported[100] no data for comparison purposes was reported. This directed our attention to the preparation of derivatives of the azido compounds which we hoped would be safe and easy to analyse.

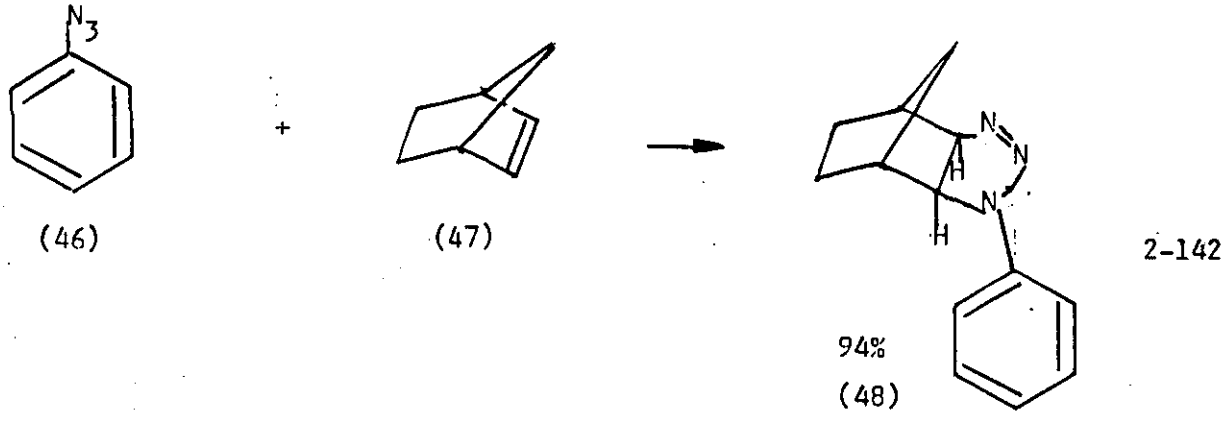
The reaction of organic azides with alkenes by a 1,3-dipolar cycloaddition mechanism encouraged us to react the azido compounds with norbornene. Norbornene was chosed because it is a strained molecule and the addition reaction therefore takes place rapidly forming the 1,2,3-triazoline system[105,106].

2.3.1 Reaction of phenylazide with norbornene

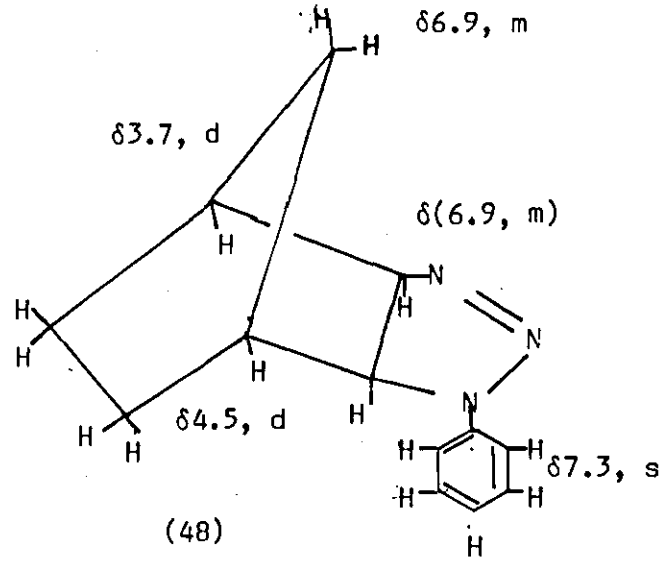
The reaction of phenyl azide (46) with norbornene (47) has been reported in the literature[107] and appeared a suitable standard reaction. We prepared the phenylazide adduct (48) and used it as a standard (with known m.p., ^{13}C and ^{1}H.n.m.r., and i.r.) for comparison purposes with other azide adducts. The adduct (48) was prepared (Scheme 2-45) in (94%) yield.

Scheme 2-45





The first step was the preparation of phenylazide by diazotisation of phenylhydrazine with sodium nitrite (eqn. 2-141) in 42% yield. The spectroscopic data were in agreement with the proposed structure of the product. Phenylazide was then reacted with norbornene to obtain a crude phenylazide adduct (48) (eqn. 2-142). The adduct was recrystallised from aqueous methanol to afford a pure product in 94% yield. The m.p. of the adduct was in agreement with that reported in the literature[107]. The ^{1}H.n.m.r. and ^{13}C.n.m.r. data are shown in figs. 2-1 and 2-2 .



(48)

Fig. 2-1

^{1}H.n.m.r. data for the norbornene adduct of phenylazide

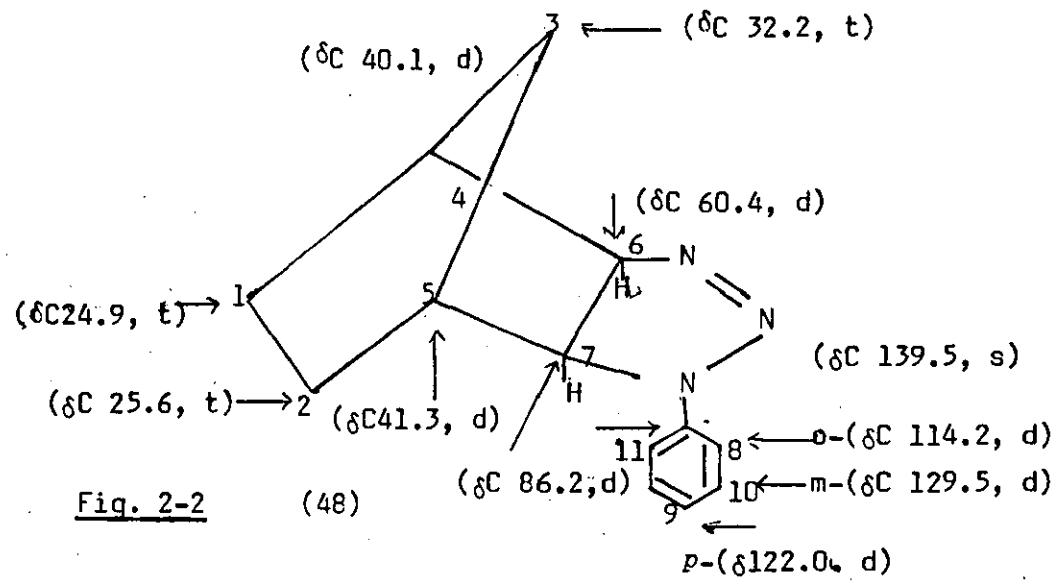
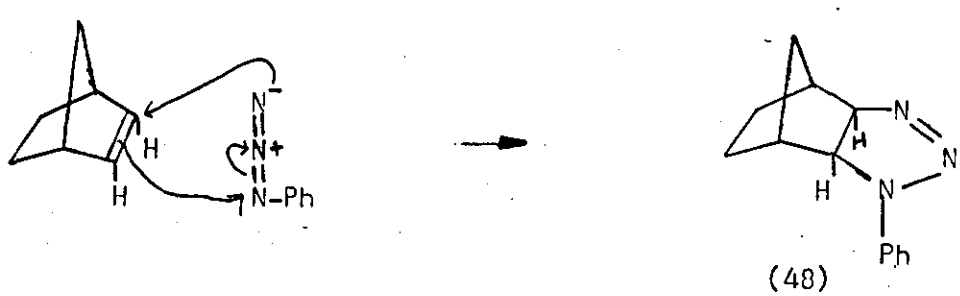


Fig. 2-2 (48)

^{13}C n.m.r. data for the (δC) norbornene adduct of phenylazide

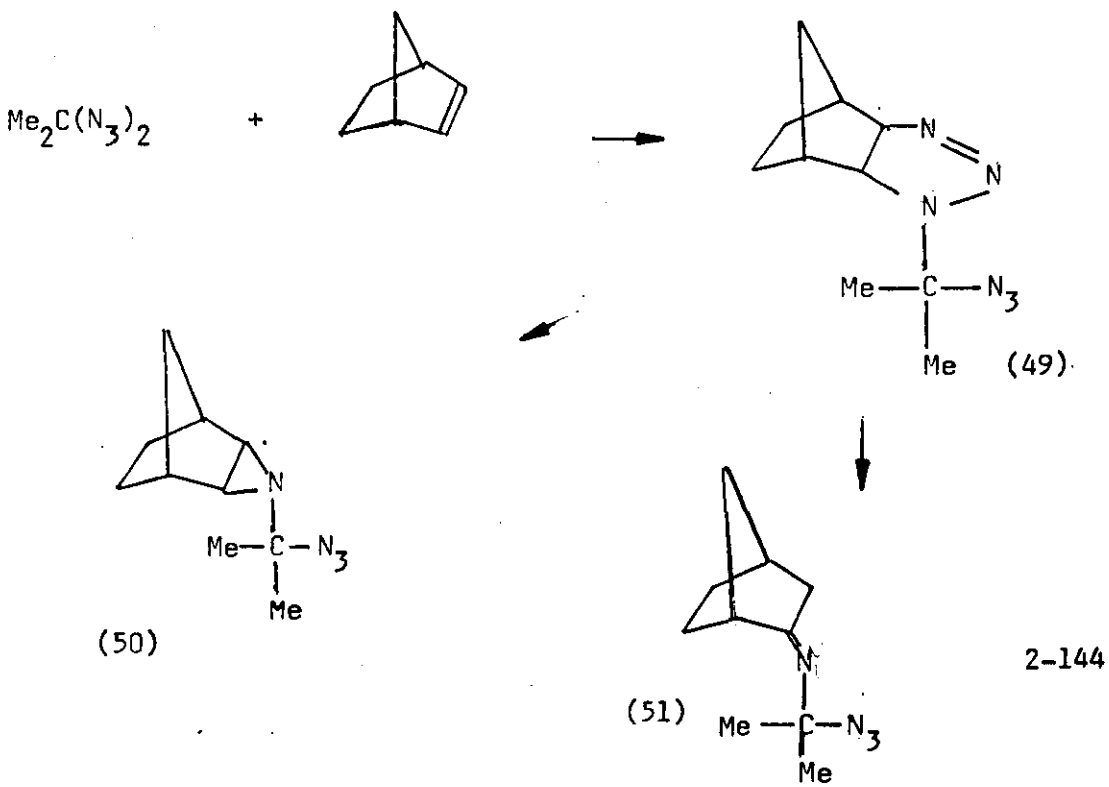
The addition occurs from the less hindered *exo* side as shown in eqn. 2-143.



(48) 2-143

2.3.2 Reaction of 2,2-diazidopropane with norbornene

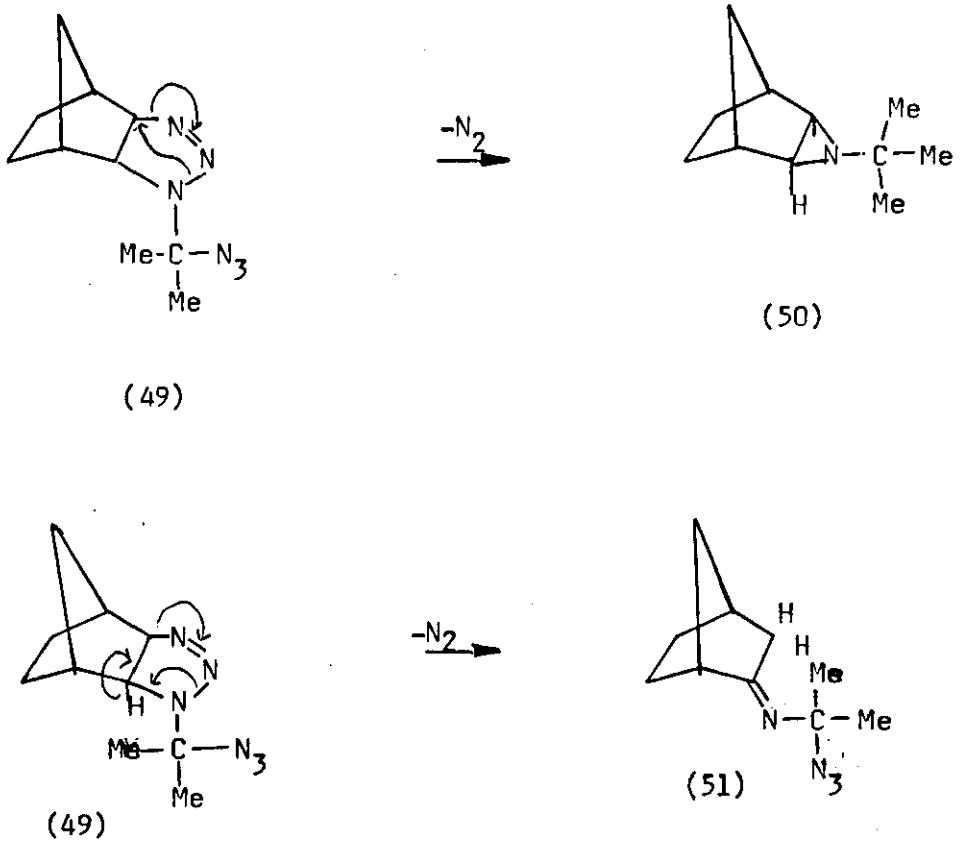
The reaction of 2,2-diazidopropane (41) with norbornene (47) was conducted in a similar manner to that of phenylazide (eqn. 2-144) to yield a crystalline product (49).



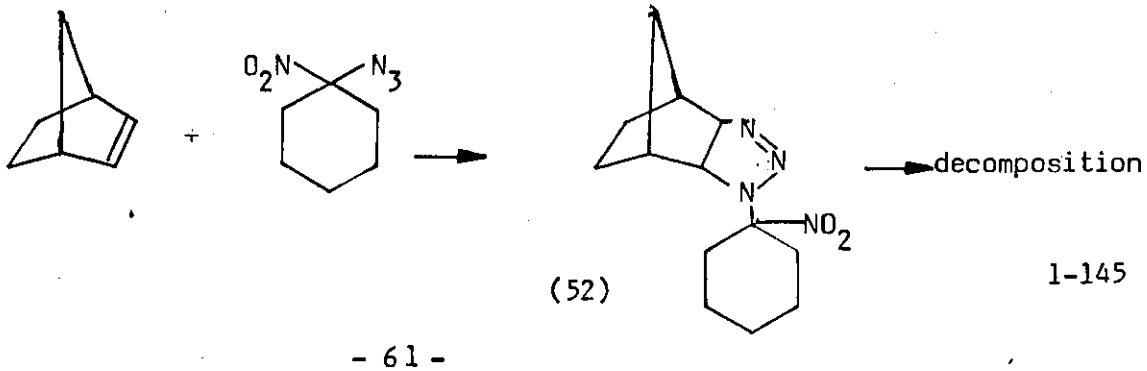
2-144

The spectroscopic data (υ_{max} 2040cm^{-1}) indicated that a mono-adduct had been formed. The product was recrystallised and a m.p. taken. Combustion analysis unfortunately, even after several attempts, showed small amounts of nitrogen loss. The azide peak in the i.r. spectrum is lower than expected, but this shift could be due to the triazole system. The ^{1}H.n.m.r. spectrum revealed the presence of all the protons expected. The ^{13}C.n.m.r. was not run due to the instability of the adduct. It appears that the product (49) is not stable enough for analysis and slowly eliminates nitrogen. The triazole system is reported in the literature[108,109] to slowly decompose to give the corresponding aziridine (50) and/or imine (51) products at room temperature. The mechanism of these rearrangements is shown in Scheme 2-46.

Scheme 2-46



We also reacted 2-azido-2-nitropropane (40) with norbornene (49) at short and long reaction times. In both cases the products obtained were unidentifiable, the products were oily with messy t.l.c's and ^{1}H.n.m.r. spectra. We suggest that, if the desired product had been formed it decomposed to give a complicated mixture of products. However, unlike 2-azido-2-nitropropane, 1-azido-1-nitrocyclohexane reacted with norbornene to yield a crystalline product (52) (eqn. 2-145).



1-145

The spectroscopic data indicated that a mono-adduct (52) had been formed. Combustion analysis unfortunately, even after several attempts was unsatisfactory.

2.4 Reactions of α-nitroazides

2.4.1 Reactions of 2-azido-2-nitropropane with azide

The formation of the unexpected 2,2-diazidopropane (41) as the major product in the oxidative addition reaction (section 2.3.1) led us to study the reaction further, and to investigate the mechanism.

Reaction of 2-azido-2-nitropropane with azide in DMF or DMSO gave steady decomposition of the starting material and no products, but when reacted under similar conditions to the oxidative addition reaction i.e. CH_2Cl_2/H_2O, 2,2-diazidopropane (41) was obtained in 91% yield (eqn. 2-146).

$$Me_2C(N_3)NO_2 + N_3^- \xrightarrow{CH_2Cl_2/H_2O} Me_2C(N_3)_2 + NO_2^- \qquad 2\text{-}146$$

(41) 91%

The substitution of nitrite under such mild conditions has not been previously observed. However, (as mentioned in the introduction) nitrite substitution has been reported[65,67,76] to proceed in dipolar aprotic solvents eqn. 2-147.

$$Me_2C(X)NO_2 + Me_2C{=}NO_2^- \longrightarrow Me_2C(X)C(NO_2)Me_2 + NO_2^- \qquad 2\text{-}147$$

X = CN, CO_2Et, $COCH_3$

This means that substitution of the nitro group as shown in eqn. 2-146 is feasible.

Complete inhibition using *p*-DNB, DTBN, and absence of light, as shown in table 2-3, suggests that the production of 2,2-diazidopropane (41) proceeded entirely *via* a pathway involving a chain reaction with radical and radical-anion intermediates; i.e. the $S_{RN}1$ mechanism as shown in Scheme 2-47 is proposed.

Table 2-3 Reaction of 2-azido-2-nitropropane with azide

Anion	Conditions	% $Me_2C(N_3)_2$	% recovery $Me_2C(N_3)NO_2$
N_3^-	CH_2Cl_2, 40 min.	91%	-
	CH_2Cl_2, 40 min. dark	-	90%
	5 molar % *p*-DNB	-	91%
	10 molar % DTBN	-	95%

Scheme 2-47

$$Me_2C(N_3)NO_2 + N_3^- \xrightarrow[h\upsilon]{S.E.T.} [Me_2C(N_3)NO_2]^{\cdot -} + N_3^{\cdot} \qquad 2\text{-}148$$

$$[Me_2C(N_3)NO_2]^{\cdot -} \longrightarrow [Me_2CN_3]^{\cdot} + NO_2^- \qquad 2\text{-}149$$

(53)

$$[Me_2CN_3]^{\cdot} + N_3^- \longrightarrow [Me_2C(N_3)_2]^{\cdot -} \qquad 2\text{-}150$$

$$Me_2C(N_3)NO_2 + [Me_2C(N_3)_2]^{\cdot -} \rightarrow Me_2C(N_3)_2 + [Me_2C(N_3)NO_2]^{\cdot -} \qquad 2\text{-}151$$

The inhibition results, which showed 90-95% recovery of starting material were in support of the proposed mechanism. However, if the proposed $S_{RN}1$ mechanism is operative, the intermediate 2-azidopropyl radical (53) (eqn. 2-149) must have a sufficiently long life-time to react with azide to form the new radical-anion. To our knowledge, at the time, there was no proof in the literature that this intermediate (53) is able to exist.

Roberts and co-workers[101] had suggested that the intermediate (53) did exist but was very unstable and decomposed rapidly to give the iminyl radical (54) (eqn. 2-152), which they were able to observe by e.s.r. spectroscopy. They were not able to observe the 2-azidopropyl radical by e.s.r. spectroscopy.

$$[Me_2CN_3]^{\cdot} \xrightarrow{k_1} Me_2C{=}N^{\cdot} + N_2 \qquad 2\text{-}152$$
(53) (54)

$$[Me_2CN_3]^{\cdot} + N_3^- \xrightarrow{k_2} [Me_2C(N_3)_2]^{\cdot -} \qquad 2\text{-}153$$

Subsequent to our publication[110] showing that the 2-azidopropyl radical undergoes bimolecular reaction faster than decomposition i.e.($k_2 > k_1$) Roberts *et al*[111] repeated their experiments with a spin-trap for the 2-azidopropyl radical (53) (eqns. 2-154-159).

$$Bu^tON{=}NOBu^t \xrightarrow{\Delta} 2Bu^tO^{\cdot} + N_2 \qquad 2\text{-}154$$

$$Bu^tO^{\cdot} + Me_2CHN_3 \longrightarrow Bu^tOH + [Me_2CN_3]^{\cdot} \qquad 2\text{-}155$$

$$[Me_2CN_3]^{\cdot} + Bu^tN{=}O \longrightarrow Me_2C(N_3)N(O^{\cdot})Bu^t \qquad 2\text{-}156$$
(53) (55) (56)

$$Bu^tO^{\cdot} + Bu^tN{=}O \longrightarrow Bu^tON(O^{\cdot})Bu^t \qquad 2\text{-}157$$

$$Bu^tON(O^{\cdot})Bu^t \longrightarrow Bu^tON{=}O + Bu^{t\cdot} \qquad 2\text{-}158$$

$$Bu^{t\cdot} + Bu^tN{=}O \longrightarrow (Bu^t)_2NO^{\cdot} \qquad 2\text{-}159$$

Initially, when a benzene solution containing isopropyl azide and di-t-butylhyponitrite (TBHN) was heated in the cavity of an E-109 spectrometer, the e.s.r. spectrum of the iminyl radical (54) was observed[101]. However, when 2-methyl-2-nitrosopropane was included as a spin-trap, overlapping spectra of three nitroxide radicals were observed, and (53) was not detectable, even at low concentration of 2-methyl-2-nitrosopropane (55) (eqns. 2-155, 157 and 159). Also, with a fixed concentration of (55), the initial relative concentration of the trapped 2-azidopropyl radical (56) increased as the concentration of isopropyl azide increased. They found no conclusive evidence for trapping the iminyl radical (54) to give the hydrazon-N-oxyl radical[112] (57) (eqn. 2-160)

$$Me_2C{=}N^{\cdot} + Bu^tN{=}O \longrightarrow Me_2C{=}N{-}N(O^{\cdot})Bu^t \qquad 2\text{-}160$$
(57)

Roberts *et al*[111] confirmed these results by repeating the experiment with benzylazide. The e.s.r. spectrum obtained was assigned to the nitroxide (58) (eqns. 2-161-162).

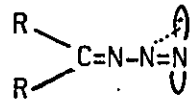
$$Bu^tO^{\cdot} + PhCH_2N_3 \longrightarrow [PhCHN_3]^{\cdot} + Bu^tOH \qquad 2\text{-}161$$

$$[PhCHN_3]^{\cdot} + Bu^tN{=}O \longrightarrow PhCH(N_3)N(O^{\cdot})Bu^t \qquad 2\text{-}162$$

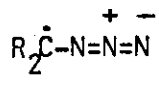
(58)

Roberts and co-workers[111] therefore concluded that the 2-azidopropyl radical reacts faster with the spin trap (i.e. bimolecular reaction) than decomposition to the iminyl radical (i.e. a unimolecular reaction). These results provide excellent evidence for the proposed $S_{RN}1$ mechanism for the reaction of azide with 2-azido-2-nitropropane. Hence the preliminary conclusion that the reaction of the 2-azidopropyl radical with azide anion is faster than its breakdown to iminyl radical and nitrogen appears to be correct (i.e. the bimolecular reactions of α-azidoalkyl radicals are faster than their breakdown).

Furthermore, preliminary e.s.r. studies[113] in solid matrices at 77K have shown that the 2-azidopropyl radical has a detectable lifetime. Initial analysis of the e.s.r. spectrum suggests that the odd electron resides largely on the terminal nitrogen and is partly delocalised onto the central nitrogen of the azide as shown in (59a) and definitely not on the carbon as shown in (59b).



(59a)



(59b)

2.4.2 Reactions of α-azidonitro-compounds with the sodium salt of benzenesulphinic acid

Kornblum and co-workers[68] have reported the reaction of α-substituted nitro-compounds with the salts of sulphinic acids by an ($S_{RN}1$) mechanism (eqn. 2-163). We reacted 2-azido-2-nitropropane (40) with the sodium salt

$$Me_2C(X)NO_2 \xrightarrow{PhSO_2^-} Me_2C(SO_2Ph)NO_2 + X^- \qquad 2\text{-}163$$

where X = I, Br, Cl, NO_2

of benzenesulphinic acid to obtain 1-azido-1-methyl phenyl sulphone (60) in 70% yield (eqn. 2-164). The product was initially identified by i.r.

$$Me_2C(N_3)NO_2 + PhSO_2^- \longrightarrow Me_2C(SO_2Ph)N_3 + NO_2^- \qquad 2\text{-}164$$

70%

(60)

spectroscopy which clearly showed absorption for the azido group at υ_{max} 2103 cm^{-1} and for a sulphono group at υ_{max} 1300 cm^{-1} and 1150 cm^{-1}, and the absence of nitro absorption (at υ_{max} *ca* 1550 cm^{-1}). The combustion analysis and ^{1}H.n.m.r. spectrum were in agreement with the proposed structure.

When the reaction was repeated in DMF the product (60) was obtained in 59% yield as well as a trace of starting material (40). This indicates that the reaction was not complete in DMF and hence the rate of reaction of 2-azido-2-nitropropane is greater in DMSO than in DMF. The reaction was also repeated in HMPA with photolysis, but only decomposed material was isolated.

The possibility of the reaction proceeding by the $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism[44]. Addition of 10 molar % of *p*-DNB to the reaction reduced the yield to 47%. Likewise, addition of 20 molar % DTBN also reduced the yield to 47%. These results indicate that a radical radical-anion chain mechanism ($S_{RN}1$) is operative as shown in Scheme 2-48.

Scheme 2-48

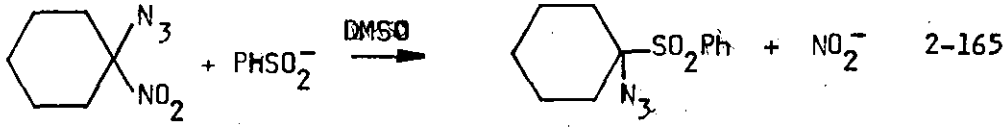
$$Me_2C(N_3)NO_2 + PhSO_2^- \xrightarrow{S.E.T.} [Me_2C(N_3)NO_2]^{\cdot -} + (PhSO_2)^{\cdot}$$

$$[Me_2C(N_3)NO_2]^{\cdot -} \longrightarrow (Me_2CN_3)^{\cdot} + NO_2^-$$

$$(Me_2CN_3)^{\cdot} + PhSO_2^- \longrightarrow [Me_2C(SO_2Ph)N_3]^{\cdot -}$$

$$Me_2C(N_3)NO_2 + [Me_2C(SO_2Ph)NO_2]^{\cdot -} \longrightarrow Me_2C(SO_2Ph)NO_2 + [Me_2C(N_3)NO_2]^{\cdot -}$$

Loss of nitrite was also observed when 1-azido-1-nitrocyclohexane (42) was reacted with the sodium salt of benzenesulphinic acid in which case 1-(1-azidocyclohexyl) phenyl sulphone (61) was obtained in 53% yield (eqn. 2-165).



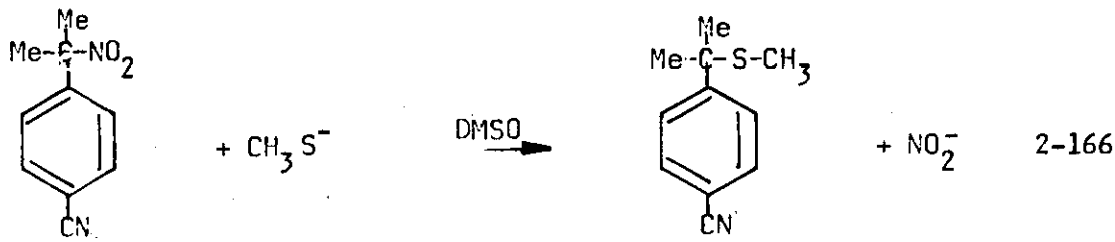
2-165

(61) 53%

The identity of the product was confirmed by i.r. spectroscopy which clearly showed absorption for an azido group at υ_{max} 2120 cm^{-1} and a sulphono group at υ_{max} 1300 cm^{-1} and 1150 cm^{-1} and the absence of nitro absorption (at υ_{max} *Ca* 1550 cm^{-1}). The combustion analysis and ^{1}H.n.m.r. were in agreement with the assigned structure. We suggest that this reaction (eqn. 2-165) also proceeded *via* the $S_{RN}1$ mechanism shown in Scheme 2-48.

2.4.3 Reaction of 2-azido-2-nitropropane with *p*-chlorophenylthiolate

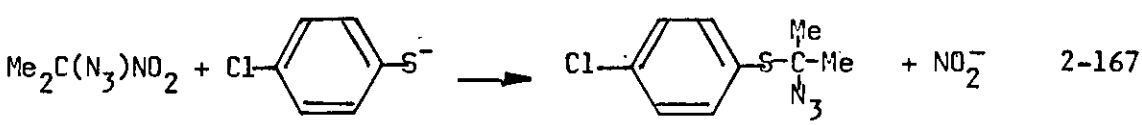
The participation of thiolate anion in $S_{RN}1$ substitution was initially reported[72b] for reactions of *p*-cyano-α-nitrocumene. An example is the replacement of nitrite by methane thiolate as shown in eqn. 2-166.



2-166

Later, the reaction of thiolates with 2-substituted-2-nitropropanes by the $S_{RN}1$ mechanism was reported by Bowman and Richardson[34,35].

We reacted 2-azido-2-nitropropane (40) with *p*-chlorophenylthiolate in DMF to obtain 1-azido-1-methylethyl *p*-chlorophenyl sulphide (62) in 70% yield (eqn. 2-167). The product (62) was identified by i.r.

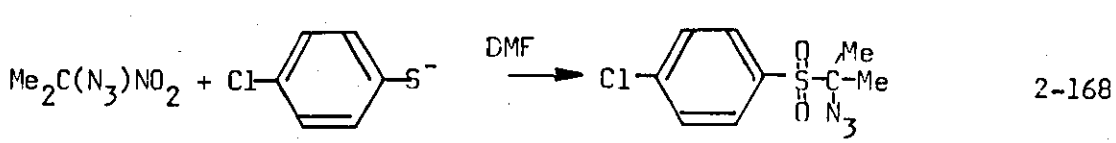


2-167

(62) 70%

spectroscopy (υ_{max} 2110 cm^{-1} (azide), and no nitro absorption) and ^{1}H.n.m.r., δ($CDCl_3$) a singlet at 1.51 p.p.m. which indicates loss of nitrite. The combustion analysis was also correct.

When the reaction was repeated using an old batch of *p*-chlorophenylthiolate which had largely oxidised to the corresponding sulphinate compound the product obtained was 1-azido-1-methylethyl *p*-chlorophenyl sulphone (63) in 20% yield (eqn. 2-168). The product was identified as before by combustion analysis and i.r. and ^{1}H.n.m.r. spectroscopy.

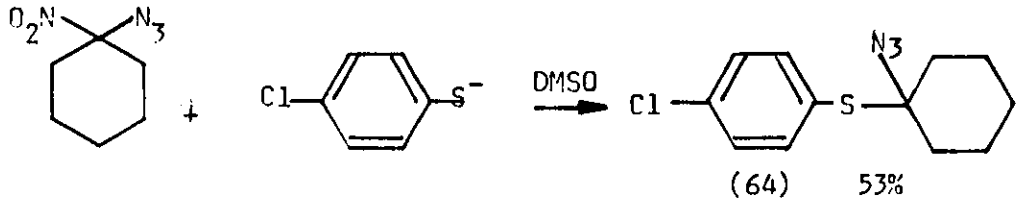


2-168

20%

(63)

Similarly, the reaction of 1-azido-1-nitrocyclohexane (42) with sodium *p*-chlorophenylthiolate was carried out in DMSO to give 1-(1-azidocyclohexyl) *p*-chlorophenyl sulphide (64) in 53% yield (eqn. 2-169).

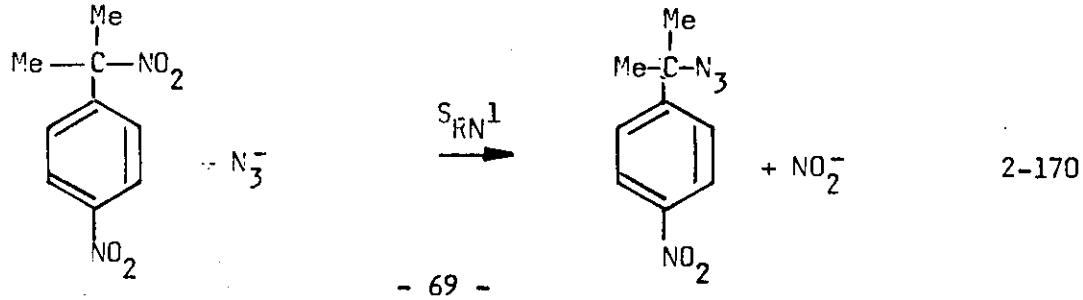


(64) 53% 2-169

I.r. and ^{1}H.n.m.r. spectroscopy indicated that the expected product had been formed. The product was purified by t.l.c. (alumina, EtOAc/diethyl ether) and showed only one spot, but the combustion analysis was not as accurate as required. Further purification failed. The compound was not distilled due to the high temperature required and the danger thereof due to the explosive properties characteristic of azido and nitro groups.

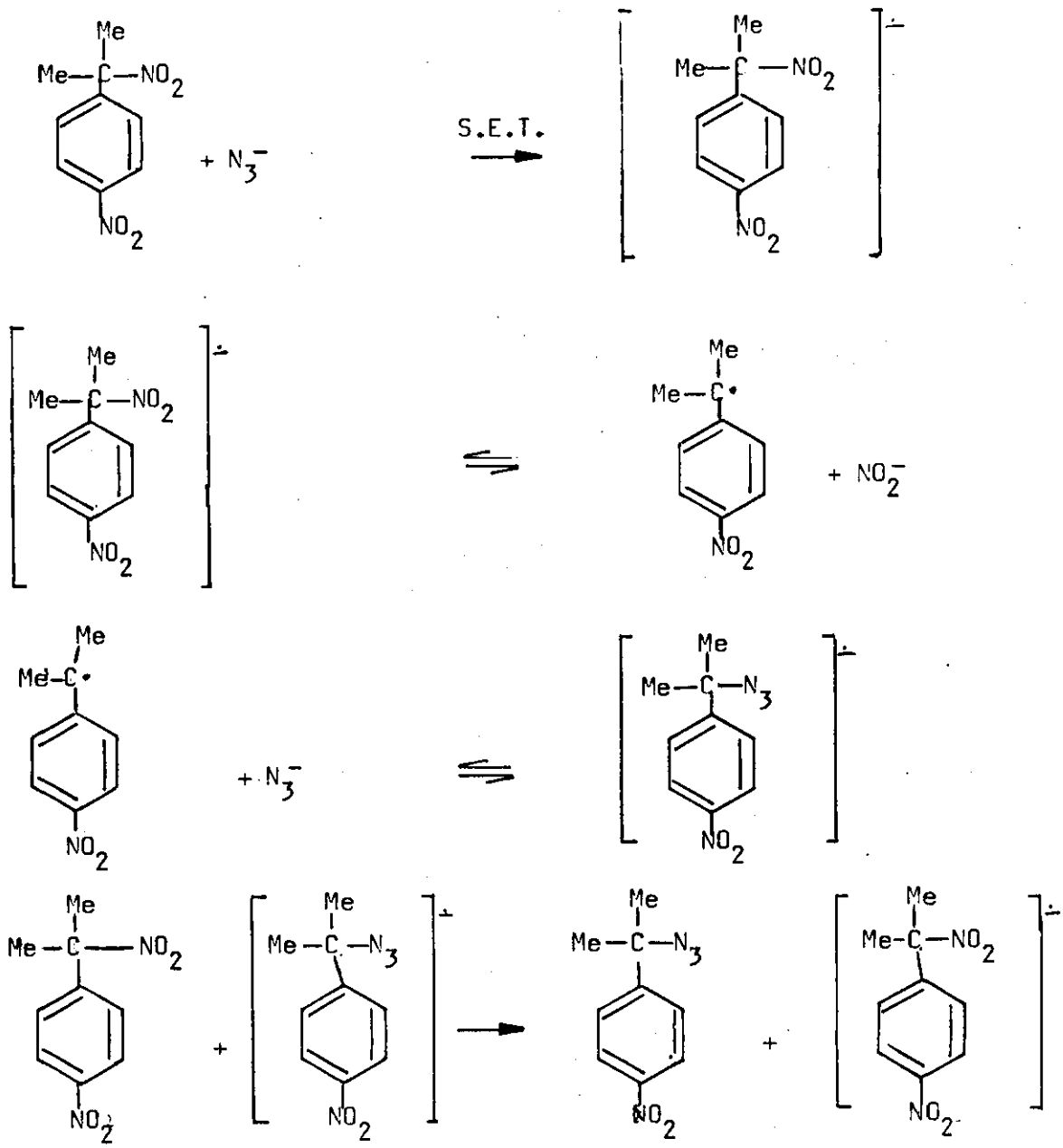
The results of the reactions of 2-azido-2-nitropropane (40) with azide, phenylsulphinate, and *p*-chlorophenylthiolate showed high yields of the α-substituted azides. The inhibition studies suggest that a radical radical-anion light catalysed chain reaction mechanism ($S_{RN}1$) is operative. A number of conclusions can therefore be made. 1-Nitrite is superior to azide as a nucleofugal group in radical-anions. Whilst not strictly comparable, Kornblum[69] has reported a reaction in the α, *p*-dinitrocumene series (eqn. 2-170) which indicates that loss of nitrite is favoured over loss of azide. The reaction proceeds *via* an $S_{RN}1$ mechanism and is shown in Scheme 2-49.

The reverse of the reaction in eqn. 2-170 is possible but was not observed.



2-170

Scheme 2-49



2. It has been reported[101] that the intermediate radical (53) breaksdown with loss of nitrogen to give the long-lived iminyl σ-radical (54). We found no signs of the iminyl radical in the form of the usually observed dimer[101] (D). However, the iminyl radical could abstract

$Me_2C{=}N{-}N{=}CMe_2$

(D)

a hydrogen radical to form a primary imine which would hydrolize rapidly on work-up to yield acetone, which would be lost in the work-up.

3. The 2-azidopropyl radical is able to add to anions *via* carbon to form a new species of radical-anion.

$[Me_2C(A)N_3]^{\cdot-}$

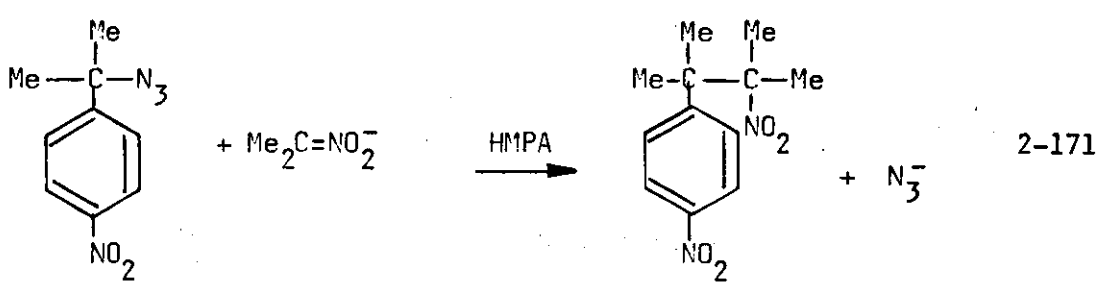
4. The intermediate α-substituted azide radical-anions are sufficiently long lived to allow loss of an electron to yield the neutral α-substituted azides.

5. This $S_{RN}1$ reaction route can be used for the synthesis of α-substituted azides.

6. Loss of the nitro group rather than the α-substituted nitro-compounds has been reported[69]. This group now includes α-nitroazides, -cyanides, -ketones and -esters.

2.4.4 Reaction of 2-azido-2-nitropropane with sodium salt of 2-nitropropane

To our knowledge, there have been no reports of azide acting as a leaving group in $S_{RN}1$ reactions except Kornblum and co-workers[69] report of the reaction of *p*-nitrocumylazide with the sodium salt of 2-nitropropane (eqn. 2-171). The reaction of 2-azido-2-nitropropane with the sodium salt



2-171

of 2-nitropropane in HMPA at room temperature gave 2,3-dimethyl-2,3-dinitrobutane in 24% yield, i.e. loss of azide rather than nitrite (eqn. 2-172).

$$Me_2C(N_3)NO_2 + Me_2C{=}NO_2^- \xrightarrow[h\upsilon]{HMPA} \underset{24\%}{Me_2C(NO_2)C(NO_2)Me_2} \qquad 2\text{-}172$$

The reaction was much slower and lower yielding than the previous reactions.

The possibility of the reaction proceeding by an $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism[44]. The results of these studies are shown in Table 2-4.

Table 2-4 : Reaction of 2-azido-2-nitropropane with sodium salt of 2-nitropropane

Conditions	% recovery $Me_2C(N_3)NO_2$	% yield of $Me_2C(NO_2)C(NO_2)Me_2$
HMPA, N_2, Tungstenlamps	0	24
+ 10 molar % *p*-DNB	0	24
+ 10 molar % DTBN	0	24
+ 40 molar % DTBN	trace	trace
Dark	0	19

The inhibition studies indicated that little, if any, of product was formed by an $S_{RN}1$ substitution. The proposed mechanism is shown in Scheme 2-50.

Scheme 2-50

$$Me_2C(N_3)NO_2 + Me_2C{=}NO_2^- \xrightarrow{S.E.T.} [Me_2C(N_3)NO_2]^{\cdot -} + Me_2\dot{C}{-}NO_2$$

$$Me_2\dot{C}{-}NO_2 + Me_2C{=}NO_2^- \longrightarrow [Me_2C(NO_2)C(NO_2)Me_2]^{\cdot -}$$

$$[Me_2C(NO_2)C(NO_2)Me_2]^{\cdot -} + Me_2C(N_3)NO_2 \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + [Me_2C(N_3)NO_2]^{\cdot -}$$

Also $$[Me_2C(N_3)NO_2]^{\cdot -} \longrightarrow [Me_2CN_3]^{\cdot} + NO_2^-$$

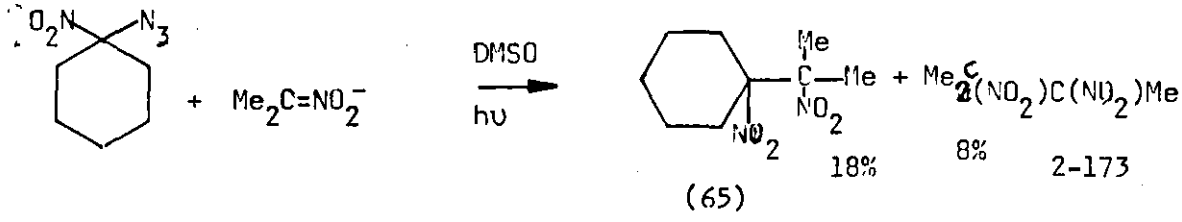
$$Me_2\dot{C}N_3 \longrightarrow \text{Decomposition}$$

$$[Me_2CN_3]^{\cdot} + Me_2C{=}NO_2^- \not\longrightarrow [Me_2C(N_3)C(NO_2)Me_2]^{\cdot -}$$

Thus we suggest that 2,3-dimethyl-2,3-dinitrobutane was formed by a radical radical-anion non-chain mechanism. This means that small amounts of inhibitor will only inhibit chain reactions but large amounts will inhibit

a non-chain radical reaction. This non-chain mechanism has been previously observed and reported in the literature[34,114].

The reaction of 1-azido-1-nitrocyclohexane (42) with the sodium salt of 2-nitropropane was also carried out and gave 1-(1-methyl-1-nitroethyl)-1-nitrocyclohexane (65) in 18% yield and 2,3-dimethyl-2,3-dinitrobutane in 8% yield (eqn. 2-173). This reaction was also low yielding and slow.



The inhibition studies were performed and the results are shown in Table 2-5. These results suggest that the product (65) was formed by an $S_{RN}1$ mechanism and that 2,3-dimethyl-2,3-dinitrobutane was formed by a radical radical-anion non-chain mechanism as shown in Scheme 2-50. These reactions, in contrast to the reactions of azide, sulphinate, and thiolate, gave lower yields of product and also gave slow loss of azide instead of nitrite.

Table 2-5 Reaction of 1-azido-1-nitrocyclohexane with the sodium salt of 2-nitropropane

$$R_2C(N_3)NO_2 + Me_2C{=}NO_2^- \longrightarrow \underset{(65)}{R_2C(NO_2)C(NO_2)Me_2} + \underset{(d)}{Me_2C(NO_2)C(NO_2)Me_2}$$

R_2C	Conditions	$\%R_2C(N_3)NO_2$ recovery	% yield (65)	% yield (d)
Cyclohexyl	DMSO, 2h, N_2	0	18	8
	Tungsten lamps	0	18	8
	Dark	50	0	0
	lab light + 10 molar % *p*-DNB	50	0	10
	lab light + 40 molar % *p*-DNB	100	0	0
	lab light + 10 molar % DTBN	64	0	0

We therefore suggest that the best explanation for the dual nucleofugal behaviour in the α-nitroazide radical-anion is that loss of azide is more rapid than nitrite, and that the resulting intermediate 2-azidopropyl radical adds rapidly to anions in the absence of steric control, e.g. N_3^- and thiolates. However, when steric control becomes important e.g. ($Me_2C{=}NO_2^-$) the addition is blocked and the nitrocyclohexyl radical, resulting from the less favoured loss of azide, is able instead to add to the anion of 2-nitropropane as shown in Scheme 2-51a. This alternative breakdown does not appear to take place for the 2-azido-2-nitropropane radical anion $[Me_2C(N_3)NO_2]^{\cdot-}$.

Scheme 2-51a.

$$R_2C(N_3)NO_2 + A^- \xrightarrow{S.E.I.} [R_2C(N_3)NO_2]^{\cdot-} + A^{\cdot}$$

$$[R_2C(N_3)NO_2]^{\cdot-} \overset{Fast}{\rightleftharpoons} (R_2CN_3)^{\cdot} + NO_2^-$$

$$(R_2CN_3)^{\cdot} + A^- \rightleftharpoons [R_2C(A)N_3]^{\cdot-}$$

$$[R_2C(N_3)NO_2]^{\cdot-} \overset{Slow}{\rightleftharpoons} R_2\dot{C}NO_2 + N_3^-$$

$$R_2\dot{C}NO_2 + A^- \rightleftharpoons [R_2C(A)NO_2]^{\cdot-}$$

2.4.5 Reaction of 2-azido-2-nitropropane with sodium salt of diethyl ethyl malonate

In order to test another sterically hindered anion, 2-azido-2-nitropropane was reacted with the anion of diethyl ethylmalonate in DMSO with photolysis for 3h to give tetraethyl hexane-3,3,4,4-tetracarboxylate (66) in 22% yield, i.e. the reaction again proceeded without addition of the anion to the 2-azidopropyl radical (eqn. 2-174).

$$Me_2C(N_3)NO_2 + Et\bar{C}(CO_2Et)_2 \longrightarrow EtC(CO_2Et)_2C(Et)(CO_2Et)_2$$

(66) 22% 2-174

The product (66) was identified by i.r., ^{1}H.n.m.r. spectroscopy and b.p. Again the reaction was slow and low yielding. A radical radical-anion mechanism has been reported by Kornblum[69] for redox reaction of this type and is shown in Scheme 2-51b.

Scheme 2-51b

$$Me_2C(N_3)NO_2 + Et\bar{C}(CO_2Et)_2 \xrightarrow{S.E.T.} [Me_2C(N_3)NO_2]^{\cdot} + Et\dot{C}(CO_2Et)_2$$

$$[Me_2C(N_3)NO_2]^{\cdot} \longrightarrow [Me_2CN_3]^{\cdot} + NO_2^-$$

$$2\ Et\dot{C}(CO_2Et)_2 \longrightarrow EtC(CO_2Et)_2C(Et)(CO_2Et)_2$$

$$[Me_2CN_3]^{\cdot} \longrightarrow \text{Decomposition}$$

$$[Me_2CN_3]^{\cdot} + Et\bar{C}(CO_2Et)_2 \not\longrightarrow [Me_2C(N_3)C(Et)(CO_2Et)_2]^{\cdot -}$$

This reaction gives some support to the Kornblum[69] theory that $S_{RN}1$ reactions only take place when a nitro group is present to hold the extra electron to give a stable radical-anion (eqns. 2-175-176)

$$R^{\cdot} + A^- \longrightarrow R{-}A^{\cdot -} \qquad 2\text{-}175$$

$$R^{\cdot} + A^- \longrightarrow R^{\cdot +}{-}A \qquad 2\text{-}176$$

where (A^-) or ($R^{\cdot}$) must contain a nitro group to stabilize the intermediate radical-anion.

Kornblum suggested that in these cases (i.e. where nitrite is lost) reaction takes place. It is possible that this is correct, i.e. in malonate for example, the ester groups do not easily hold an extra electron, and that our examples of $S_{RN}1$ reactions with loss of azide proceed because the extra electron is stabilised in the aromatic π-orbital of the arylthio or arylsulphono groups. This argument does not however explain the formation of 2,2-diazidopropane which would require the extra electron in the intermediate radical-anion to reside in the azido group.

2.4.6 Summary

1) α-Nitroazides have been prepared by two routes involving intermediate radical-anions; the $S_{RN}1$ route (Scheme 2-42) and oxidative addition route (Scheme 2-40).

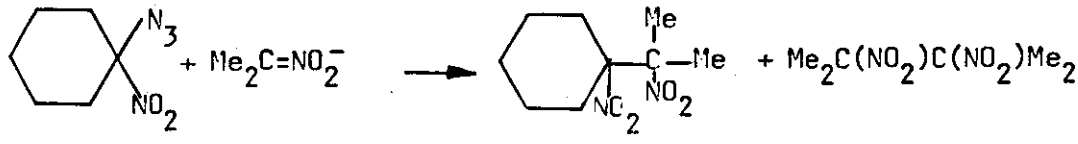
2) α-Nitroazides undergo substitution by an $S_{RN}1$ mechanism with a series of anions (e.g. azide, sulphinate, and thiolates) to give loss of nitrite.

$$Me_2C(N_3)NO_2 + A^- \longrightarrow Me_2C(N_3)A + NO_2^-$$

with $A^- = N_3^-$, $PhSO_2^-$, $p\text{-}Cl\text{-}C_6H_4S^-$, $p\text{-}Cl\text{-}C_6H_4SO_2^-$

3) α-Nitroazides undergo reaction with nitronate anions by a radical radical-anion non-chain mechanism and/or a $S_{RN}1$ mechanism with loss of azide.

(a) $Me_2C(N_3)NO_2 + Me_2C{=}NO_2^- \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + N_3^-$

(b) 

4) Our results provide important evidence for a new species of radical-anions $[Me_2C(N_3)X]^{\cdot}$, with X = NO_2, N_3, SO_2Ph, and $p\text{-}Cl\text{-}C_6H_4S$, and dual nucleofugal behaviour for α-nitroazide radical-anion of nitro-cyclohexane.

5) Loss of nitrite is preferred over loss of azide from the intermediate radical-anion.

2.5 Preparation of α-nitrothiocyanates

2.5.1 Preparation of α-nitrothiocyanates by oxidative addition of thiocyanate to nitro-anions

We next turned our attention to the synthesis of a number of α-nitrothiocyanates using oxidative addition. We hoped further to demonstrate the versatility of this synthetic method. 2-Nitro-2-thiocyanatopropane (67) was prepared by this method as shown in Scheme 2-52.

Scheme 2-52

$$Me_2C{=}NO_2^- + Fe^{(III)} \longrightarrow Me_2\dot{C}{-}NO_2 + Fe^{(II)}$$

$$Me_2\dot{C}{-}NO_2 + {}^-SCN \longrightarrow [Me_2C(SCN)NO_2]^{\cdot-}$$

$$[Me_2C(SCN)NO_2]^{\cdot-} + Fe^{(III)} \longrightarrow Me_2C(SCN)NO_2 + Fe^{(II)}$$

overall

$$Me_2\bar{C}NO_2 + {}^-SCN + 2Fe^{(III)} \longrightarrow Me_2C(SCN)NO_2 + 2Fe^{(II)} \qquad 2\text{-}177$$

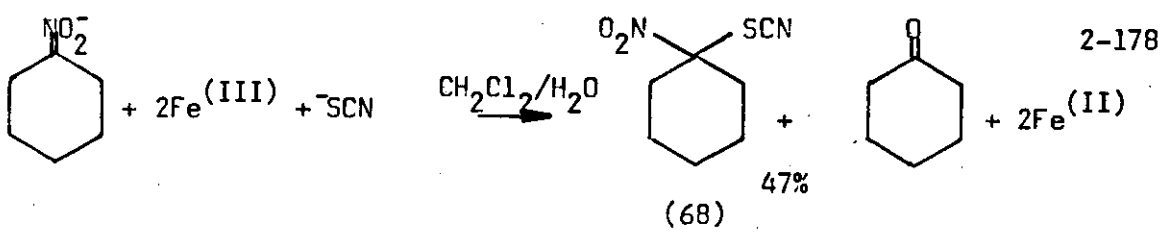
(67)

Initially, the reaction was attempted with the addition of a saturated solution of potassium ferricyanide to a stirred mixture of sodium thiocyanate in diethyl ether and water. The ^{1}H.m.n.r. spectrum showed a mixture of products; the peak at δ1.75 p.p.m. was identified as 2,3-dimethyl-2,3-dinitrobutane, and the peak at δ2.10 p.p.m. was later shown to be the chemical shift for the proposed product (67). The two separate singlets at δ1.90 and 1.98 p.p.m. respectively were not identified. Attempts to isolate the unidentified compounds were unsuccessful. However, when the nitronate solution was added to a mixture of potassium ferricyanide and sodium thiocyanatein diethyl ether and water only two products were obtained. The ^{1}H.n.m.r. spectrum showed a peak at δ1.75 p.p.m. corresponding to 2,3-dimethyl-2,3-dinitrobutane, and a peak at δ2.10 p.p.m. corresponding to the proposed product (67). The i.r, spectrum showed absorption at υ_{max} 2160 cm^{-1} (SCN), and υ_{max} 1550 cm^{-1} (NO_2). Fractional distillation of the mixture gave pure 2-nitro-2-thiocyanatopropane (67) in 35% yield.

The identity of the product was confirmed by combustion analysis and spectroscopic data. The ^{1}H.n.m.r. spectrum showed a singlet at δ2.10 p.p.m. (Me_2C). The i.r. spectrum showed an absorption at υ_{max} 2160 cm^{-1} (SCN), and υ_{max} 1550 cm^{-1} (NO_2).

Replacement of diethyl ether by methylene chloride as a solvent in the previous reaction gave product (67) (98% pure by ^{1}H.n.m.r.analysis, containing a trace of dimer). Fractional distillation again gave pure 2-nitro-2-thiocyanatopropane (67) in 40% yield.

Similarly, 1-nitro-1-thiocyanatocyclohexane (68) was prepared by addition of the corresponding nitronate to the solution of ferricyanide and thiocyanate in CH_2Cl_2/H_2O (eqn. 2-178). The i.r. spectrum of the crude



2-178

product showed absorption at υ_{max} 2160 cm^{-1} (SCN), 1550 cm^{-1} (NO_2), and 1720 cm^{-1} (c=o). The latter peak was due to a minor by-product (5%) which was identified as cyclohexanone by comparison with authentic material using g.l.c. (SE30, 10%). Pure 1-nitro-1-thiocyanatocyclohexane was obtained by preparative thin layer chromatography (silica, CCl_4/Hexane; 60 : 40). When the reaction was repeated in diethyl ether and water as the solvent mixture a lower yield (34%) of product was obtained.

2.5.2 Attempted preparation of 2-nitro-2-thiocyanatopropane by $S_{RN}1$ substitution

Attempts to prepare 2-nitro-2-thiocyanatopropane (67) by the $S_{RN}1$ route (Scheme 2-53) failed, yielding only unreacted starting material.

Scheme 2-53

$$Me_2C(X)NO_2 + {}^-SCN \xrightarrow{S.E.T.} [Me_2C(X)NO_2]^{\cdot-} + {}^{\cdot}SCN$$

$$[Me_2C(X)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}NO_2 + X^-$$

$$Me_2\dot{C}NO_2 + {}^-SCN \longrightarrow [Me_2C(SCN)NO_2]^{\cdot-}$$

$$[Me_2C(SCN)NO_2]^{\cdot-} + Me_2C(X)NO_2 \longrightarrow Me_2C(SCN)NO_2 + [Me_2C(X)NO_2]^{\cdot-}$$

where X = I, Br

Some $S_{RN}1$ chain reactions can be initiated by using anions. The anion of 2-nitropropane is known[44] to easily undergo S.E.T. to generate radical-anions, which then enter the chain reaction to form the desired product as shown in Scheme 2-54. This process is known as entrainment and the anion is termed an entrainment agent[44].

Scheme 2-54

$$Me_2C(Br)NO_2 + {}^-SCN \xrightarrow{S.E.T.} [Me_2C(Br)NO_2]^{\cdot-} + {}^{\cdot}SCN$$

$$Me_2C(Br)NO_2 + Me_2CNO_2^- \xrightarrow{S.E.T.} [Me_2C(Br)NO_2]^{\cdot-} + Me_2\dot{C}NO_2$$

$$[Me_2C(Br)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}NO_2 + Br^-$$

$$Me_2\dot{C}NO_2 + {}^-SCN \longrightarrow [Me_2C(SCN)NO_2]^{\cdot-}$$

$$[Me_2C(SCN)NO_2]^{\cdot-} + Me_2C(Br)NO_2 \xrightarrow{S.E.T.} Me_2C(SCN)NO_2 + [Me_2C(Br)NO_2]^{\cdot-}$$

The use of catalytic chain initiation[44] (entrainment) with catalytic amounts of the anion of 2-nitropropane did not yield any α-nitrothiocyante, but did yield traces of 2,3-dimethyl-2,3-dinitrobutane. The latter compound was also a significant impurity in the ferricyanide method. This observation suggests that the anion of 2-nitropropane successfully competes with thiocyanate for addition to the 2-nitropropyl radical. Similar lack of reactivity of thiocyanate in $S_{RN}1$ reactions with haloquinolines has been reported[114b]. The lack of reactivity in our system is surprising because of the synthesis of 2-nitro-2-thiocyanatopropane (67) with ferricyanide shows that thiocyanate is able to add to the 2-nitropropyl radical as shown in eqn. 2-179.

$$Me_2\dot{C}NO_2 + {}^-SCN \longrightarrow [Me_2C(SCN)NO_2]^{\dot{-}} \qquad 2\text{-}179$$

(70)

Likewise, results from e.s.r. spectroscopy suggest[115] that the dissociation of the intermediate radical-anion (70) is reversible as shown in eqn. 2-180. The dissociation takes place readily. The intermediate radical-anions of

$$[Me_2C(SCN)NO_2]^{\dot{-}} \rightleftharpoons Me_2\dot{C}NO_2 + {}^-SCN \qquad 2\text{-}180$$

2-bromo-(71) and 2-chloro-2-nitropropane (72) have also been shown to dissociate readily explaining why 2-bromo-and 2-chloro-2-nitropropane cannot be made by $S_{RN}1$ substitution.

$[Me_2C(Br)NO_2]^{\dot{-}}$ (71) $[Me_2C(Cl)NO_2]^{\dot{-}}$ (72)

We suggest that the equilibrium lies well over on the side of dissociation, thus inhibiting the chain reaction. The lack of reactivity could also be due to poor electron transfer between the thiocyanate anion and 2-bromo-2-nitropropane. This electron transfer is required for initiation of the $S_{RN}1$ chain reaction. In addition, attempts to prepare α-nitrothiocyanates by oxidative addition of cupric thiocyanate, which has been reported in the literature[116], failed, and the only product isolated was 2,3-dimethyl-2,3-dinitrobutane.

Thiocyanate is an ambident anion[117] but only adds to the 2-nitropropyl-radical *via* the sulphur atom as shown in eqns. 2-181 and 182. This

$$Me_2\dot{C}NO_2 + {}^-SCN \longrightarrow [Me_2C(SCN)NO_2]^{\dot{-}} \longrightarrow Me_2C(SCN)NO_2 \qquad 2\text{-}181$$

(70) (67)

$$[Me_2C(NCS)NO_2]^{\dot{-}} \longrightarrow Me_2C(NCS)NO_2 \qquad 2\text{-}182$$

(73)

observation was confirmed by i.r. spectroscopy which only showed absorption for thiocyanate at υ_{max} 2160 cm^{-1}. No absorption was observed at υ_{max} 2140-2080 cm^{-1} corresponding to isothiocyanate. The course of the reaction represented in equation 2-182 appears unlikely. Also, no isomerisation of (67) to (73) was observed. We suggest that this phenomena is possibly explained by kinetic control of the addition of thiocyanate to the 2-nitropropyl radical because the "sulphur-anion" is more nucleophilic towards carbon than the nitrogen. Tolbert and Siddiqui[118] have suggested that the addition of anion to the radical in the $S_{RN}1$ mechanism is kinetic rather than thermodynamic control.

2.6 Reactions of α-nitrothiocyanates

2.6.1 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of 2-nitropropane

2-Nitro-2-thiocyanatopropane (67) was reacted with the sodium salt of 2-nitropropane in DMSO at room temperature under nitrogen with photolysis to give 2,3-dimethyl-2,3-dinitrobutane in 72% yield (eqn. 2-183).

$$Me_2C(SCN)NO_2 + Me_2C{=}NO_2^- \xrightarrow[h\upsilon]{DMSO} Me_2C(NO_2)C(NO_2)Me_2 + {}^-SCN \qquad 2\text{-}183$$

72%

The reaction proceeded with loss of thiocyanate and not nitrite from 2-nitro-2-thiocyanatopropane. The identity of the product was confirmed by m.p. and i.r. comparison with authentic material. The i.r. spectrum showed the absence of absorption for thiocyanate at υ_{max} 2160 cm^{-1}. When the reaction was repeated using DMF as the solvent a lower yield (51%) was obtained.

The possibility of the reaction proceeding by an $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism[44]. The results of these studies are shown in Table 2-6. The inhibition results are similar to those observed for other reactions known to proceed by an $S_{RN}1$ mechanism, suggesting that the reaction proceeds by an $S_{RN}1$ mechanism as shown in Scheme 2-55.

Table 2-6 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of 2-nitropropane

Conditions	% yield $Me_2C(NO_2)C(NO_2)Me_2$
Standard, DMSO, N_2, hυ, 2h	72%
Dark N_2, 2h	42%
O_2, 2h	38%
5% molar of *p*-DNB	34%
10% molar of DTBN	34%

Scheme 2-59

$$Me_2C(SCN)NO_2 \ (67) + Me_2C{=}NO_2^- \xrightarrow{S.E.T.} [Me_2C(SCN)NO_2]^{\cdot-} \ (70) + Me_2\dot{C}\text{-}NO_2 \qquad 2\text{-}184$$

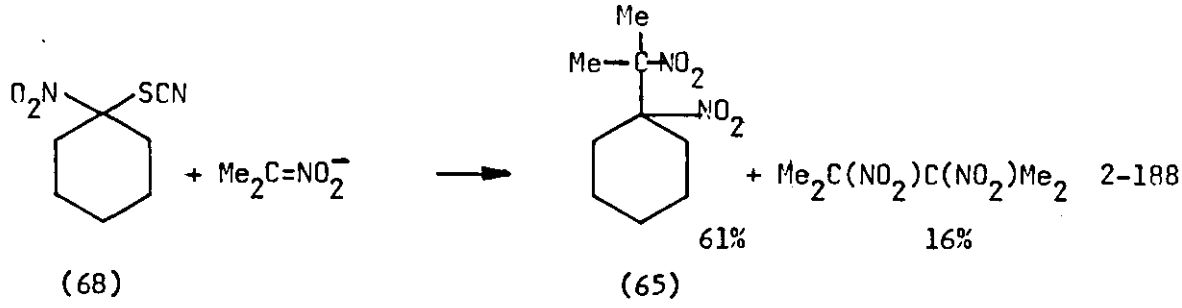
$$[Me_2C(SCN)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}\text{-}NO_2 + {}^-SCN \qquad 2\text{-}185$$

$$Me_2\dot{C}\text{-}NO_2 + Me_2C{=}NO_2^- \longrightarrow [Me_2C(NO_2)C(NO_2)Me_2]^{\cdot-} \qquad 2\text{-}186$$

$$[Me_2C(NO_2)C(NO_2)Me_2]^{\cdot-} + Me_2C(SCN)NO_2 \xrightarrow{S.E.T.} Me_2C(NO_2)C(NO_2)Me_2 + [Me_2C(SCN)NO_2]^{\cdot-} \qquad 2\text{-}187$$

Recently, Bowman and Symons have reported[115] the detection of the intermediate radical-anion (70) by e.s.r. spectroscopy in solid matrices at 77°k (eqns. 2-184 and 185). They observed the electron capture by (67) to form the radical-anion (70) (eqn. 2-184), and its dissociation to the 2-nitropropyl radical and thiocyanate anion (eqn. 2-185). Their results are therefore in agreement with our results in solution.

1-Nitro-1-thiocyanatocyclohexane (68) also reacted with the sodium salt of 2-nitropropane in DMSO with photolysis to give the corresponding α-substituted product 1-(1-methyl-1-nitroethyl)-1-nitrocyclohexane (65) in 61% yield and 2,3-dimethyl-2,3-dinitrobutane in 16% yield (eqn. 2-188). The reaction again proceeded with loss of thiocyanate. The products were

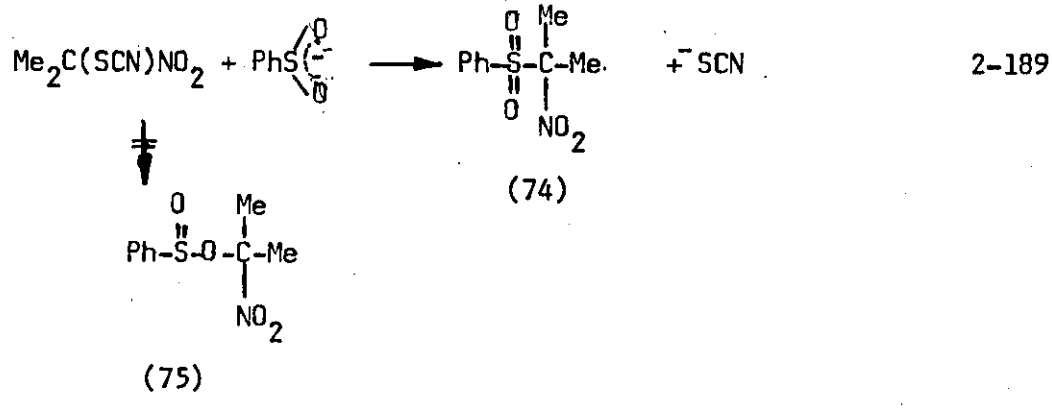


(68) (65)

separated by recrystallisation and identified by m.p. and i.r. comparison with authentic materials. We suggest that the formation of (65) also proceeded by an $S_{RN}1$ mechanism (Scheme 2-55) and the formation of 2,3-dimethyl-2,3-dinitrobutane proceeded by a radical radical-anion non-chain mechanism as shown in Scheme 2-49.

2.6.2 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of benzenesulphinic acid

The reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of benzenesulphinic acid in DMSO with photolysis was carried out and yielded 1-methyl-1-nitroethyl phenyl sulphone (74) in 49% yield (eqn. 2-189). Again the reaction as shown in eqn. 2-189, proceeded with loss of thiocyanate to give the product (74). The identity of the product was confirmed by



(74) (75)

m.p. and ^{1}H.n.m.r. spectroscopy and i.r. comparison with the literature material. The i.r. spectrum for example, showed no absorption at υ_{max} 2160 cm^{-1} corresponding to thiocyanate.

The possibility of the reaction proceeding by an $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism[44]. The results of these studies are shown in Table 2-7.

Table 2-7 Reaction of 2-nitro-2-thiocyanatopropane with benzenesulphinate

Conditions	% recovery $Me_2C(SCN)NO_2$	% yield $PhSO_2C(NO_2)Me_2$ (74)
Standard, DMSO, N_2, hυ,	0	49
Dark, DMSO, N_2	40	0
O_2, DMSO	37	0
5 molar % p-DNB	40	0
10 molar % DTBN	35	0

The results of the inhibition studies suggest that the formation of product (74) was inhibited by radical inhibitors and demonstrates that a radical radical-anion chain reaction is involved. We suggest that the reaction proceeds by an $S_{RN}1$ mechanism shown in Scheme 2-56. In addition

Scheme 2-56

$$Me_2C(SCN)NO_2 + PhSO_2^- \xrightarrow{S.E.T.} [Me_2C(SCN)NO_2]^{\cdot-} + (PhSO_2)^{\cdot}$$

$$[Me_2C(SCN)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}NO_2 + {}^-SCN$$

$$Me_2\dot{C}NO_2 + PhSO_2^- \longrightarrow [PhS(=O)_2-C(NO_2)Me_2]^{\cdot-}$$

$$Me_2C(SCN)NO_2 + [PhS(=O)_2-C(NO_2)Me_2]^{\cdot-} \longrightarrow PhS(=O)_2-C(NO_2)Me_2 + [Me_2C(SCN)NO_2]^{\cdot-}$$

it is worth noting that the reaction, as shown in equation 2-189 could proceed by an alternative route to give the sulphinate ester (75). Benzenesulphinate is an ambident anion and can react either *via* the oxygen or sulphur atoms. No product from attack by the "oxygen anion" was observed, i.e. the sulphinate ester.

2.6.3 Reaction of 2-nitro-2-thiocyanatopropane with azide

2-Nitro-2-thiocyanatopropane (67) was reacted with sodium azide in HMPA. 2-Azido-2-nitropropane (40) was obtained in 8% yield and 27% of starting material was recovered (eqn. 2-190).

$$Me_2C(SCN)NO_2 + NaN_3 \xrightarrow[h\upsilon]{HMPA} \underset{8\%}{Me_2C(N_3)NO_2} + \underset{27\%}{Me_2C(SCN)NO_2} \qquad 2\text{-}190$$

The identity of the products was confirmed by i.r. and ^{1}H.n.m.r. spectral comparison with authentic material. This reaction gives further support for the loss of thiocyanate as observed with previous reactions. Therefore, we suggest that the 2-azido-2-nitropropane was also formed by an $S_{RN}1$ mechanism. The reason for lower yields obtained in this reaction could be due to steady decomposition[110] of 2-azido-2-nitropropane (40). A repeat experiment at longer time gave the same yield of product (8%), while the recovery of starting material dropped from 39% at 90 min to 27% at 5h.

2.7 Reactions of 2-nitro-2-thiocyanatopropane with thiolates

Thiolate anions are recognised as being some of the most nucleophilic species known[119], and can be expected to participate readily in bimolecular nucleophilic displacement reactions. On the other hand thiolate anions are easily oxidised by a variety of reagents e.g. peroxides, halogens and ferricyanide to the corresponding thiyl radicals. The latter combine rapidly to form disulphide[120]. (eqns. 2-191-194)

$$2RS^- + 2Fe^{(III)} \longrightarrow 2RS^{\cdot} + 2Fe^{II} \qquad 2\text{-}191$$

$$2RS^{\cdot} \longrightarrow RSSR \qquad 2\text{-}192$$

also

$$RS^- + X_2 \longrightarrow RSX + X^- \qquad 2\text{-}193$$

$$RSX + RS^- \longrightarrow RSSR + X^- \qquad 2\text{-}194$$

where X = I, Br, Cl

The presence of the nitro group profoundly influences the properties of the α-substituted nitropropanes. In general the latter are easily reduced by S.E.T. The electron density on the α-substituent is also markedly lowered due to the inductive electron withdrawing effect of the nitro group, and this permits the abstraction of the α-substituent by a suitable nucleophile.

Bowman and Richardson[34,35] reported the reactions of a variety of thiolates with 2-substituted-2-nitropropanes and suggested 2-substituted-2-nitropropanes undergo substitution reactions with thiolates and proceed by an $S_{RN}1$ mechanism (Scheme 2-57).

Scheme 2-57

$$Me_2C(X)NO_2 + RS^- \xrightarrow[h\upsilon]{S.E.T.} [Me_2C(X)NO_2]^{\cdot -} + RS^{\cdot}$$

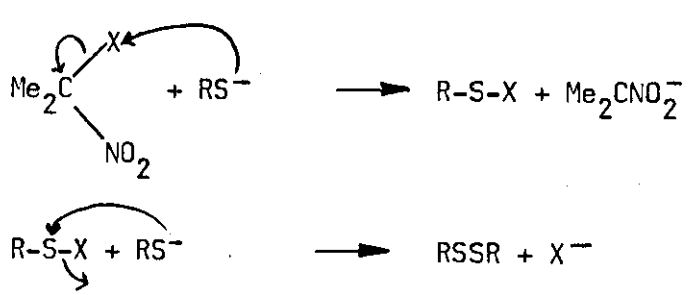
$$[Me_2C(X)NO_2]^{\cdot -} \longrightarrow Me_2\dot{C}-NO_2 + X^-$$

$$Me_2\dot{C}NO_2 + RS^- \longrightarrow [Me_2C(SR)NO_2]^{\cdot -}$$

$$[Me_2C(SR)NO_2]^{\cdot -} + Me_2C(X)NO_2 \xrightarrow{S.E.T.} Me_2C(SR)NO_2 + [Me_2C(X)NO_2]^{\cdot -}$$

This mechanism (as discussed in the introduction) has been shown to operate with a variety of substrates[77,34,35]. Alternatively, Bowman and Richardson[34,35] suggested an ionic mechanism involving nucleophilic attack by the thiolate anion on the α-substituent and subsequent reaction of a second molecule of thiolate with the sulphenyl intermediate as shown in Scheme 2-58 to explain the formation of disulphide.

Scheme 2-58



A competition between an S_N2 mechanism and the $S_{RN}1$ mechanism takes place, which accounts for their observed results.

Russell and Co-workers[36a] have proposed a non-chain radical mechanism to account for oxidative dimerisation for various anions not including thiolates. The mechanism applied to thiolates is shown in Scheme 2-59.

Scheme 2-59

$$Me_2C(X)NO_2 + RS^- \xrightarrow{S.E.T.} [Me_2C(X)NO_2]^{\cdot-} + RS^{\cdot}$$

$$[Me_2C(X)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}NO_2 + X^-$$

$$Me_2\dot{C}NO_2 + RS^- \longrightarrow Me_2CNO_2^- + RS^{\cdot}$$

$$2RS^{\cdot} \longrightarrow RSSR$$

Recently, Russell and co-workers[121,122] have reported for oxidative dimerisation a chain mechanism for the reaction of enolates with an α-substituted nitro compound. The mechanism applied to thiolates is shown in Scheme 2-60.

Scheme 2-60

$$Me_2C(X)NO_2 + RS^- \xrightarrow{S.E.T.} [Me_2C(X)NO_2]^{\cdot-} + RS \qquad \text{Initiation}$$

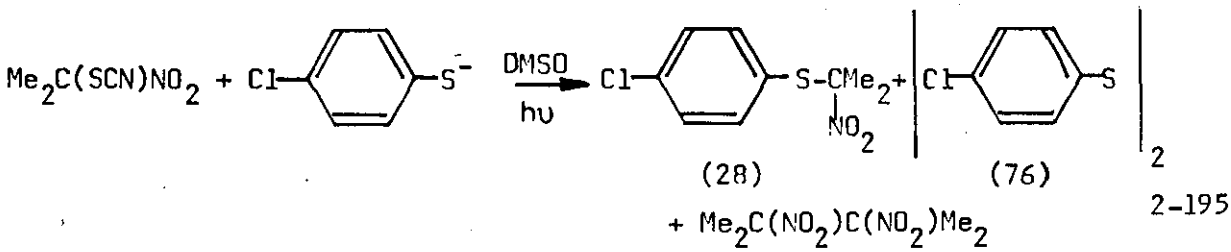
$$\left.\begin{array}{l} [Me_2C(X)NO_2]^{\cdot-} + RS^- \longrightarrow RS^{\cdot} + Me_2CNO_2^- + X^- \\ RS^{\cdot} + RS^- \longrightarrow [RSSR]^{\cdot-} \\ [RSSR]^{\cdot-} + Me_2C(X)NO_2 \longrightarrow RSSR + [Me_2C(X)NO_2]^{\cdot-} \end{array}\right\} \text{Propagation}$$

A variety of thiolate anions were reacted with 2-nitro-2-thiocyanatopropane. The thiolate anions were chosen because of their availability and diversity of structure. The thiolate anions also act as a good model to indicate the possible biological activity of α-nitrothiocyanates.

2.7.1 Reaction of 2-nitro-2-thiocyanatopropane with *p*-chlorophenylthiolate

2-Nitro-2-thiocyanatopropane was reacted with *p*-chlorophenylthiolate to give 1-methyl-1-nitroethyl *p*-chlorophenyl sulphide (28) (37%), di-(*p*-chlorophenyl) disulphide[(76)] (19%), and 2,3-dimethyl-2,3-dinitrobutane

(16%) (eqn. 2-195). The products were separated by preparative thin layer



2-195

chromatography and identified by comparison with authentic materials.

The possibility of the reaction proceeding by an $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism[44]. The results of these studies are shown in Table 2-8. These inhibition results

Table 2-8 Reaction of 2-nitro-2-thiocyanatopropane with *p*-chlorophenylthiolate

	% yield			
Conditions	$Me_2C(SR)NO_2$	RSSR	dimer	$Me_2C(SCN)NO_2$
Standard; DMSO, N_2, 2h	37	14	16	0
Dark	20	16	20	10
O_2	12	4	10	41
40 molar % *p*-DNB	17	26	8	34
40 molar % DTBN	26	0	0	11

clearly showed that the production of the α-nitrosulphide (28) proceeded by a pathway involving radical intermediates. We therefore suggest that the α-nitrosulphide (28) was formed by an $S_{RN}1$ mechanism as shown in Scheme 2-61.

Scheme 2-61

$$Me_2C(SCN)NO_2 + RS^- \longrightarrow Me_2C(SR)NO_2 + {}^-SCN \quad (SRN^1) \qquad 2\text{-}196$$

$$\longrightarrow RSSCN + Me_2C{=}NO_2^- \quad (S_N2) \qquad 2\text{-}197$$

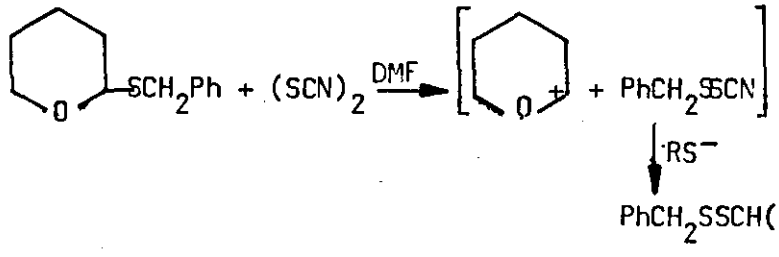
$$RSSCN + RS^- \longrightarrow RSSR + {}^-SCN \qquad (S_N2) \qquad 2\text{-}198$$

(77) (76)

$$Me_2C{=}NO_2^- + Me_2C(SCN)NO_2 \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + {}^-SCN \quad (S_{RN}1) \quad 2\text{-}199$$

$$Me_2(SR)NO_2 + RS^- \longrightarrow RSSR + Me_2C{=}NO_2^- \ (S_N2) \qquad 2\text{-}200$$

2,3-Dimethyl-2,3-dinitrobutane (eqn. 2-199) was formed by the known reaction of 2-nitro-2-thiocyanatopropane with the anion of 2-nitropropane (Section 2.6.1) *via* an $S_{RN}1$ mechanism. Di-(*p*-chlorophenyl) disulphide (76) formation could be due to the abstraction of the α-substituent by thiolate (eqn. 2-197). The presence of the nitro group makes the α-substituent relatively positively charged by reducing its electron density, i.e. the thiocyanate atom is activated to attack by nucleophiles. Thiolates are strong nucleophiles and are able to participate in such an abstraction to form a sulphenyl thiocyanate intermediate (eqn. 2-197) which reacts further with thiolate to form the disulphide. We have not been able to isolate the sulphenyl thiocyanate intermediate (77) because it reacts rapidly with further thiolate with loss of thiocyanate to yield disulphide. The reactions of sulphenyl thiocyanates with thiolates are well known and had been reported in the literature[123-125] e.g. (eqn. 2-201).



2-201

The formation of disulphide (eqn. 2-198) was not greatly inhibited which suggests that a non-chain mechanism such as the S_N2 mechanism was operating.

Russell *et al*[36] have proposed the $S_{RN}2$ mechanism shown in Scheme 2-62 as well as a closely related chain oxidative dimerisation (Scheme 2-60).

Scheme 2-62

$$Me_2C(SCN)NO_2 + RS^- \xrightarrow{S.E.T.} [Me_2C(SCN)NO_2]^{\cdot-} + RS^{\cdot}$$

$$[Me_2C(SCN)NO_2]^{\cdot-} + RS^- \longrightarrow [Me_2C(SR)NO_2]^{\cdot-} + {}^-SCN$$

(70)

$$[Me_2C(SR)NO_2]^{\cdot-} + Me_2C(SCN)NO_2 \longrightarrow Me_2C(SR)NO_2 + [Me_2C(SCN)NO_2]^{\cdot-}$$

(78)

with R = Cl-C$_6$H$_4$-

This could also explain the formation of the α-nitrosulphide and disulphide respectively. The formation of disulphide cannot be explained by this mechanism owing to the observed lack of inhibition. The α-nitrosulphide however, could be formed by the $S_{RN}2$ mechanism.

Russell's argument is based on the observation that the competition between the $S_{RN}2$ and the related chain oxidative dimerisation mechanisms for the same substituent with different anions depends on the stability of the radical-anion intermediate (70). More nucleophilic anions favour $S_{RN}2$ rather than the chain oxidative dimerisation i.e. *p*-chlorophenylthiolate would be more likely to yield disulphide, and phenylthiolate more likely to yield α-nitrosulphide. As phenylthiolate only yields disulphide it would suggest that the formation of α-nitrosulphide with *p*-chlorophenylthiolate is by an $S_{RN}1$ mechanism but the $S_{RN}2$ mechanism cannot be excluded.

2.7.2 Reaction of 2-nitro-2-thiocyanatopropane with phenylthiolate

2-Nitro-2-thiocyanatopropane was reacted with phenylthiolate to give only diphenyl disulphide (79) (52%) and 2,3-dimethyl-2,3-dinitrobutane (50%) (eqn. 2-202).

$$Me_2C(SCN)NO_2 + PhS^- \xrightarrow[h\upsilon]{DMSO} PhSSPh + Me_2C(NO_2)C(NO_2)Me_2 \qquad 2\text{-}202$$

(79)

The possibility of the reaction proceeding by an $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism.[44] The results of these studies are shown in Table 2-9. These inhibition results clearly demonstrate that the production of diphenyl disulphide (79)

Table 2-9 Reaction of 2-nitro-2-thiocyanatopropane with phenylthiolate

Conditions	% yield			
	$Me_2C(SR)NO_2$	Ph-S-S-Ph	$Me_2C(NO_2)C(NO_2)Me_2$	$Me_2C(SCN)NO_2$
DMSO, 10 min (2h)	0 (0)	36 (52)	34 (50)	10 (0)
Dark	0	38	41	0
O_2	0	26	11	24
20 molar % *p*-DNB	0	38	12	9
20 molar % DTBN	0	37	13	6

proceeded by a non chain mechanism i.e. S_N2 mechanism, and that the 2,3-dimethyl-2,3-dinitrobutane was formed by an $S_{RN}1$ mechanism as shown in Scheme 2-61. Phenylthiolate is a stronger nucleophile than *p*-chlorophenylthiolate and therefore S_N2 attack by the thiolate on the thiocyanato-substituent to give the sulphenylthiocyanate intermediate is favoured over the slower electron-transfer required for the $S_{RN}1$ mechanism.

2.7.3 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of benzylthiol

2-Nitro-2-thiocyanatopropane was reacted with the salt of benzylthiolate in DMSO to give dibenzyl disulphide (80) (30%) and 2,3-dimethyl-2,3-dinitrobutane (22%) along with a high yield of polymeric aromatic material (16%) as shown in eqn. 2-203. The possibility of the reaction proceeding

$$Me_2C(SCN)NO_2 + PhCH_2S^- \longrightarrow \underset{(80)}{PhCH_2S\text{-}SCH_2Ph} + (PhCHS)_n + Me_2C(NO_2)C(NO_2)Me_2 \qquad 2\text{-}203$$

by an $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism.[44] The results of these studies are shown in Table 2-10.

Table 2-10 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of benzylthiol

	% Yields			
Conditions	$Me_2C(SCN)NO_2$	$(PhCHS)_n$	dimer	$PhCH_2S\text{-}SCH_2Ph$
DMSO, N_2, 2h	15	16	22	30
O_2 + dark	31	-*	3	3
20 molar % *p*-DNB + dark	18	22	4	3
20 molar % DTBN + dark	39	19	3	trace

*benzoic acid 15% was also isolated.

The inhibition results show that the yield of dibenzyl disulphide was reduced to *ca* 3%. This indicates that the formation of disulphide was inhibited and that it must be formed by a chain radical radical-anion mechanism. Russell *et al*[121] have reported a chain radical radical-anion redox mechanism for the reaction of α-substituted compounds with enolate anions as shown in Scheme 2-63. A similar reaction can be proposed, with

Scheme 2-63

$$Me_2C(X)NO_2 + RCOCH_2^- \xrightarrow{S.E.T} [Me_2C(X)NO_2]^{\cdot-} + RCOCH_2^{\cdot}$$

$$[Me_2C(X)NO_2]^{\cdot-} + RCOCH_2^- \longrightarrow Me_2C{=}NO_2^- + RCOCH_2^{\cdot} + X^-$$

$$RCOCH_2^{\cdot} + RCOCH_2^- \longrightarrow [RCOCH_2CH_2COR]^{\cdot-}$$

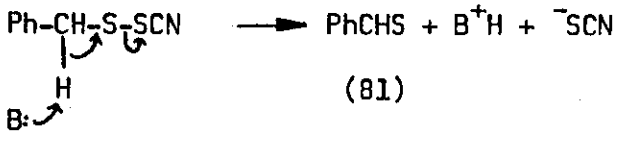
$$[RCOCH_2CH_2COR]^{\cdot-} + Me_2C(X)NO_2 \xrightarrow{S.E.T} RCOCH_2CH_2COR + [Me_2C(X)NO_2]^{\cdot-}$$

benzylthiolate replacing the enolate anion. Disulphide radical-anions have been observed by e.s.r. spectroscopy[126] and are known to be in an equilibrium with thiyl radical and thiolate as shown in eqn. 2-204.

$$RS^{\cdot} + RS^{-} \longrightarrow [RSSR]^{\cdot -} \qquad 2\text{-}204$$

This result is unusual as all the other redox reactions of α-substituted nitro compounds and thiolates, which yield disulphide, proceed by an "ionic" S_N2 mechanism as fully discussed for *p*-chlorophenyl and phenylthiolate (sections 2.7.1 and 2.7.2).

The other problem to be explained is the formation of aromatic polymer. The ^{1}H.n.m.r. for the separated polymer showed only aromatic protons at δ7.1-7.5 p.p.m. and no benzyl protons ($-CH_2$) were observed. We suggest that the polymer arises from thiobenzaldehyde produced by an elimination process (eqn. 2-105).

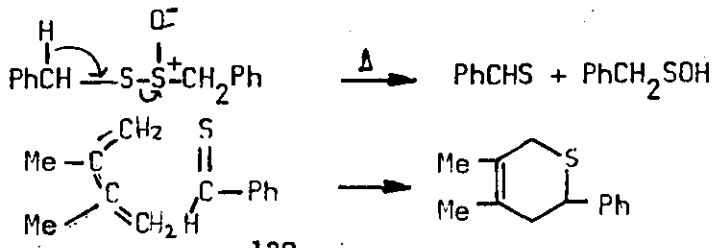


2-205

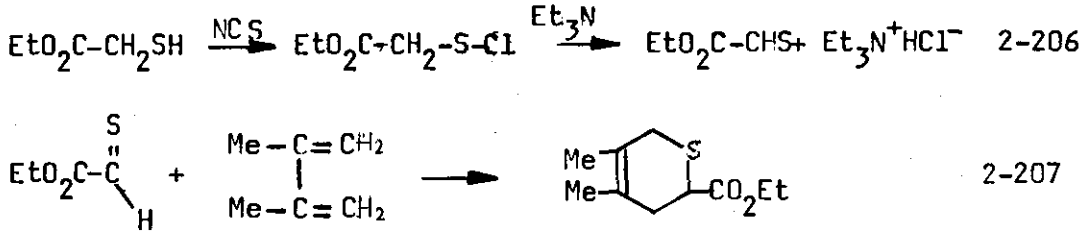
Thiobenzaldehyde [127](81) is not a stable species and undergoes rapid polymerisation. The formation of benzoic acid in place of the polymer in the oxygen inhibition reaction strongly suggests that thiobenzaldehyde is an intermediate and that it is oxidised to benzoic acid faster than it polymerises.

Baldwin and Lopez[128] have reported their failure to isolate thiobenzaldehyde, but do report trapping it as a Diels-Alder adduct (Scheme 2-64). The elimination mechanism they report, although concerted, could explain the possibility of thiobenzaldehyde being formed in our reaction.

Scheme 2-64



Kirby and co-workers[129] have reported an E_2 elimination to form a thioaldehyde which likewise cannot be isolated but can be trapped as an adduct with anthracene, thebaine, or 3,3-dimethylbutadiene (eqns. 2-206-207).



We, therefore consider that an E_2 elimination from benzylsulphenylthiocyanate to form thiobenzaldehyde and subsequent polymerisation is a reasonable explanation of the result. Reactions of benzylthiolate with other α-substituted nitro compounds proceeding *via* benzylsulphenyl intermediates do not appear to yield large amounts of polymer and give only the corresponding disulphide[33-35]. It is however quite possible that small amounts of polymer were formed and not noticed during purification of dibenzyl disulphide. In conclusion the overall reaction sequence is shown in Scheme 2-65.

Scheme 2-65

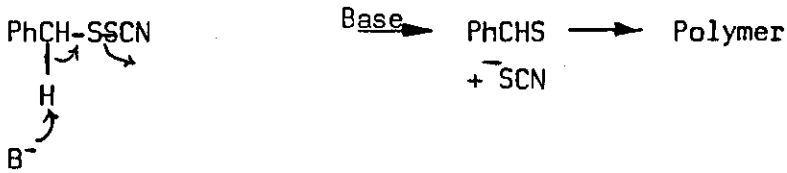
$$Me_2C(SCN)NO_2 + 2PhCH_2S^- \longrightarrow PhCH_2S\text{-}SCH_2Ph + Me_2C{=}NO_2^- + {}^-SCN$$

$$Me_2C{=}NO_2^- + Me_2C(SCN)NO_2 \xrightarrow{S_{RN}1} Me_2C(NO_2)C(NO_2)Me_2 + {}^-SCN$$

And

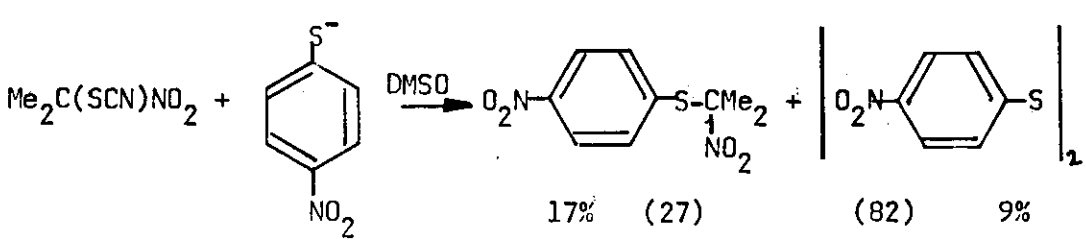
$$Me_2C(SCN)NO_2 + PhCH_2S^- \xrightarrow{S_N2} PhCH_2SSCN + Me_2C{=}NO_2^-$$

or



2.7.4 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of *p*-nitrophenylthiol

2-Nitro-2-thiocyanatopropane was reacted with *p*-nitrophenylthiolate in DMSO to give largely the corresponding α-nitrosulphide,1-methyl-1-nitroethyl *p*-nitrophenyl sulphide (27), as well as di-(*p*-nitrophenyl) disulphide (82) in 17% and 9% yield respectively (eqn. 2-208). The spectroscopic data for the products were in agreement with the assigned



2-208

structures.

The possibility of the reaction proceeding by an $S_{RN}1$ mechanism was investigated using the accepted diagnostic tests for the mechanism.[44] The results of these studies are shown in Table 2-11. The inhibition results clearly demonstrate that the formation of α-nitrosulphide (27) was inhibited, which suggest that its formation proceeded by a radical

Table 2-11 Reaction of 2-nitro-2-thiocyanatopropane with *p*-nitrophenyl-thiolate

	% yield			
Conditions	$\%Me_2C(SR)NO_2$	RSSR	dimer	$Me_2C(SCN)NO_2$
DMSO, 15 mins, N_2	17	9	3	18
+ 20 molar % *p*-DNB	5	20	4	36
+ 20 molar % DTBN	trace	15	3	36
+ O_2	trace	22	4	62

radical-anion chain reaction ($S_{RN}1$) mechanism. The disulphide is most likely to be formed by an "ionic" S_N2 mechanism. The two mechanisms are discussed fully in Section 2.7.1.

2.8 Reaction of 2-nitro-2-thiocyanatopropane with the anion of diethyl ethylmalonate

2-Nitro-2-thiocyanatopropane was reacted with the sodium salt of diethyl ethylmalonate in DMSO to give the respective dimers, 2,3-dimethyl-2,3-dinitrobutane (47%) and tetraethyl hexane-3,3,4,4-tetracarboxylate (66) (20%) as shown in eqn. 2-209. The products were identified by i.r. and ^{1}H.n.m.r. spectroscopy, and b.p. The reaction was slow and low yielding. The reaction proceeded without addition of the anion to the 2-nitropropyl-radical to yield the expected substituted product.

$$Me_2C(SCN)NO_2 + Et\bar{C}(CO_2Et)_2 \longrightarrow \underset{(66)}{EtC(CO_2Et)_2C(Et)(CO_2Et)_2} + Me_2C(NO_2)C(NO_2)Me_2 \qquad 2\text{-}209$$

The $S_{RN}1$ mechanism as shown in Scheme 2-66 would be expected to yield the $S_{RN}1$ product (83) which was not obtained. It is well known that the anion of diethyl ethylmalonate will add to the 2-nitropropyl radical yielding the substituted product (83). The reaction of $Me_2C(X)NO_2$ (with X = Br) with

Scheme 2-66

$$Me_2C(SCN)NO_2 + Et\bar{C}(CO_2Et)_2 \xrightarrow{S.E.T.} \cdot[Me_2C(SCN)NO_2]^{\pm} + Et\dot{C}(CO_2Et)_2$$

$$[Me_2C(SCN)NO_2]^{\pm} \longrightarrow Me_2\dot{C}\text{-}NO_2 + {}^{-}SCN$$

$$Me_2\dot{C}\text{-}NO_2 + Et\bar{C}(CO_2Et)_2 \longrightarrow \left[Me_2C(NO_2)\text{—}C(Et)(CO_2Et)_2\right]^{\pm}$$

$$\left[Me_2C(NO_2)\text{-}C(Et)(CO_2Et)_2\right]^{\pm} \longrightarrow Me_2C(NO_2)\text{—}C(Et)(CO_2Et)_2 \quad (83)$$

the anion of diethyl ethylmalonate has been reported[66,114] to proceed by abstraction but when X = Cl[114], NO_2[114], or SR[33-35] an $S_{RN}1$ reaction takes place.

We therefore suggest that an abstraction mechanism followed by a non-chain redox mechanism to form (66) as shown in Scheme 2-67 takes place.

Scheme 2-67

$$Me_2C(SCN)NO_2 + Et\bar{C}(CO_2Et)_2 \longrightarrow Me_2C{=}NO_2^{-} + NCS\text{-}C(Et)(CO_2Et)_2 \quad (84)$$

$$Me_2C{=}NO_2^{-} + Me_2C(SCN)NO_2 \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + {}^{-}SCN$$

$$NCS\text{-}C(Et)(CO_2Et)_2\ (84) + Et\bar{C}(CO_2Et)_2 \longrightarrow [NCS\text{-}C(Et)(CO_2Et)_2]^{\pm} + Et\dot{C}(CO_2Et)_2$$

$$[NCS\text{-}C(Et)(CO_2Et)_2]^{\pm} \longrightarrow Et\text{-}\dot{C}(CO_2Et)_2 + {}^{-}SCN$$

$$2Et\dot{C}(CO_2Et)_2 \longrightarrow EtC(CO_2Et)_2C(Et)(CO_2Et)_2 \quad (66)$$

It has been suggested[130] that the well known (iodine) oxidative dimerisation of 1,3-diketoneanions (eqn. 2-210) takes place *via* the mechanism shown in Scheme 2-68.

$$R\text{-}\bar{C}(CO_2Et)_2 + I_2 \longrightarrow RC(CO_2Et)_2C(R)(CO_2Et)_2 \qquad 2\text{-}210$$

Scheme 2-68

$$R\text{-}\bar{C}(CO_2Et)_2 + I_2 \longrightarrow R\text{—}\underset{\underset{I}{|}}{C}(CO_2Et)_2 + I^-$$

$$R\text{-}\underset{\underset{I}{|}}{C}(CO_2Et)_2 + R\bar{C}(CO_2Et)_2 \longrightarrow \left[R\text{-}\underset{\underset{I}{|}}{C}(CO_2Et)_2\right]^{\cdot-} + R\dot{C}(CO_2Et)_2$$

$$\left[R\text{-}\underset{\underset{I}{|}}{C}(CO_2Et)_2\right]^{\cdot-} \longrightarrow R\text{-}\dot{C}(CO_2Et)_2 + I^-$$

$$2R\text{-}\dot{C}(CO_2Et)_2 \longrightarrow RC(CO_2Et)_2C(R)(CO_2Et)_2$$

Evidence for the suggested mechanism (Scheme 2-67) came from experimental observations which indicated that the malonate anion was abstracting the thiocyanate group to form the corresponding diethyl ethyl thiocyanatomalonate (84). This suspected product could not be isolated but the i.r. and ^{1}H.n.m.r. spectrum indicated its possible presence.

We attempted the preparation of (84) by reacting the sodium salt of diethyl ethylmalonate with copper (II) thiocyanate, but only tetraethyl hexane-3,3,4,4-tetracarboxylate (66), (Scheme 2-69) was formed.

Scheme 2-69

$$Et\bar{C}(CO_2Et)_2 + Cu^{(II)}(SCN)_2 \longrightarrow Et\dot{C}(CO_2Et)_2 + Cu^{(I)}SCN + {}^{\cdot}SCN$$

$$2Et\dot{C}(CO_2Et)_2 \longrightarrow EtC(CO_2Et)_2C(Et)(CO_2Et)_2$$

(66)

overall

$$Et\bar{C}(CO_2Et)_2 + Cu^{II}(SCN)_2 \longrightarrow EtC(CO_2Et)_2C(Et)(CO_2Et)_2$$

(66)

The use of copper (II) thiocyanate for thiocyanation is well documented[131] but the mechanism is unknown.

We also attempted the preparation of diethyl ethyl thiocyanatomalonate using thiocyanogen[132](85)(eqns. 2-212-213).

$$Br_2 + Pb(SCN)_2 \longrightarrow (SCN)_2 + PbBr_2 \qquad 2\text{-}212$$

(85)

$$EtC^{-}(CO_2Et)_2 + (SCN)_2 \not\longrightarrow EtC(SCN)(CO_2Et)_2 + {}^{-}SCN \qquad 2\text{-}213$$

Thiocyanogen[132](85) is a relatively unstable liquid and was therefore used immediately to avoid hydrolysis to thiocyanic acid and hypothiocyanous acid (eqn. 2-214). Unfortunately, we obtained a polymeric form of

$$(SCN)_2 + H_2O \longrightarrow HSCN + HOSCN \qquad 2\text{-}214$$

thiocyanogen in every attempt.

2.9 Reaction of 2-nitro-2-thiocyanatopropane with the anion of diethylphosphite

The preparation of diethyl 1-methyl-1-nitroethyl-phosphite was attempted, using the same conditions reported[70] for its preparation from 2-chloro-2-nitropropane and diethylphosphite. However, when 2-nitro-2-thiocyanatopropane was reacted with the anion of diethyl phosphite in THF, 2,3-dimethyl-2,3-dinitrobutane (10%) was isolated with a large amount of starting material being recovered (eqn. 2-215).

$$Me_2C(SCN)NO_2 + {}^{-}P(OEt)_2 \xrightarrow{THF} Me_2C(NO_2)C(NO_2)Me_2 + SCN\text{-}PO_3Et_2 \qquad 2\text{-}215$$

(86)

We suggest that the diethylphosphite participates in an "ionic" S_N2 abstraction. The resulting nitro anion then undergoes $S_{RN}1$ reaction with 2-nitro-2-thiocyanatopropane to give the dimer. However, the isothiocyanate derivative (86) rather than the thiocyanate derivative would be predicted (HSAB Principle) due to the "hard" basicity of phosphite. The phosphorous anion would be predicted to react with the "hard" nitrogen atom rather than the "soft" sulfur atom.

The isothiocyanate derivative (86) was not isolated and presumably underwent hydrolysis to diethylphosphate which would have been lost on work-up due to its water solubility. This has been reported in the literature[133] (eqn. 2-216).

$$S{=}C{=}N{-}\overset{\overset{O}{\|}}{P}(OEt)_2 \xrightarrow{H_2O} (EtO)_2\overset{\overset{O}{\|}}{P}OH + HSCN \qquad 2\text{-}216$$

<u>Summary</u>

To our knowledge there are no reports in the literature of thiocyanate acting as a leaving group in $S_{RN}1$ reactions.

1) α-Nitrothiocyanates have been prepared by oxidative addition in good yields. The ease of the reaction and the availability, as well as, the low cost of the reagents used makes this a valuable synthetic method.

2) α-Nitrothiocyantes underwent the $S_{RN}1$ substitution with various anions e.g. nitronate, $PhSO_2^-$ and N_3^-. In each case thiocyanate was the leaving group.

3) The reaction of 2-nitro-2-thiocyanatopropane with thiolates e.g. (p-$NO_2C_6H_4S^-$) yields the corresponding α-nitrosulphide by an $S_{RN}1$ mechanism or the corresponding disulphide by an S_N2 abstraction mechanism. The reaction with benzylthiolate gave a polymer of thiobenzyaldehyde, and dibenzyl disulphide by a chain oxidative dimerisation mechanism.

4) 2-Nitro-2-thiocyanatopropane reacted with the anion of diethyl ethylmalonate to yield the corresponding dimers in low yields.

5) Our synthetic studies of the $S_{RN}1$ reactions of 2-nitro-2-thiocyanatopropane confirmed the e.s.r. observations (see section 2.6) which showed the breakdown of the 2-nitro-2-thiocyanatopropane radical-anion to nitropropyl radical and thiocyanate. We, therefore suggest that e.s.r. spectroscopy provides a good probe for predicting the reactivity of radical-anions in $S_{RN}1$ reactions.

Some of these results have been published in preliminary form.[134]

2.10 Miscellaneous reaction of 2-substituted-2-nitropropanes

2.10.1 Reactions of diethyl 1-methyl-1-nitroethylphosphonate

Diethyl methyl-1-nitroethylphosphonate (37) was reacted with the anion of 2-nitropropane in DMSO to give unreacted starting material and an unidentified product (eqn. 2-217). The ^{1}H.n.m.r. spectrum was complex

$$Me_2C(PO_3Et_2)NO_2 + Me_2C{=}NO_2^- \xrightarrow{DMSO} (37) + \underset{(86)}{Me_2C(PO_3Et)CMe_2(NO_2)} \qquad 2\text{-}217$$

due to the mixture of product and starting material and the splitting of all peaks due to ^{31}P coupling. A tentative assignment from the ^{1}H.n.m.r. spectrum suggested that the unidentified material was (86). The products could not be separated due to their similar properties. Repeat reactions using an excess of the anion of 2-nitropropane and longer reaction times did not force the reaction to completion but did eventually cause decomposition. The reaction was very slow, *ca* 42h, indicating that the α-nitrophosphonate was very unreactive. Similar lack of reactivity has been observed by Russell *et al.*[130]

The reaction was carried out in DMF for 42h and gave 2,3-dimethyl-2,3-dinitrobutane in 60% yield (eqn. 2-218).

$$Me_2C(PO_3Et_2)NO_2 + Me_2C{=}NO_2^- \xrightarrow{DMF} \underset{60\%}{Me_2C(NO_2)C(NO_2)Me_2} \qquad 2\text{-}218$$

This suggests that oxidation of the anion to the dimer takes place rather than substitution but no proof was obtained. The mechanism could possibly be an $S_{RN}1$ mechanism but this is very unlikely. The proposed mechanism is shown in Scheme 2-70.

Scheme 2-70

$$Me_2C(PO_3Et_2)NO_2 + Me_2C{=}NO_2^- \longrightarrow [Me_2C(PO_3Et_2)NO_2]^{\cdot-} + Me_2\dot{C}{-}NO_2$$

$$Me_2\dot{C}{-}NO_2 + Me_2C{=}NO_2^- \longrightarrow [Me_2C(NO_2)C(NO_2)Me_2]^{\cdot-}$$

$$[Me_2C(NO_2)C(NO_2)Me_2]^{\cdot-} + Me_2C(PO_3Et_2)NO_2 \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + [Me_2C(PO_3Et)NO_2]^{\cdot-}$$

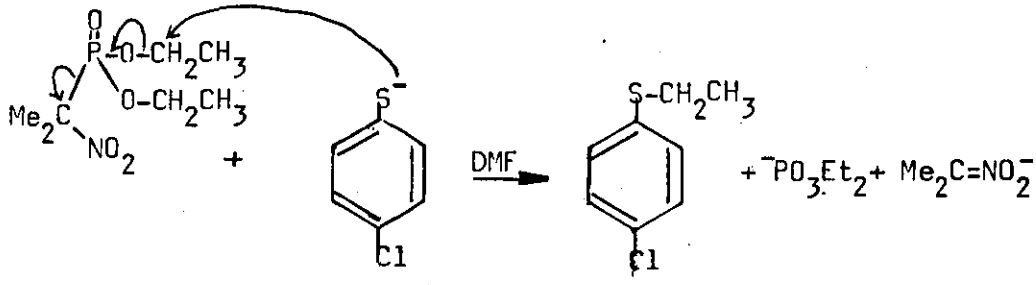
In their e.s.r. studies, Symons and Bowman[115] reported that the corresponding radical-anion clearly breaks down to nitrite anion and phosphite radical (eqn. 2-219) and not to the nitropropyl radical and

$$[Me_2C(PO_3Et_2)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}{-}PO_3Et_2 + NO_2^- \qquad 2\text{-}219$$

$$[Me_2C(PO_3Et_2)NO_2]^{\cdot-} \not\longrightarrow Me_2\dot{C}{-}NO_2 + {}^-PO_3Et_2 \qquad 2\text{-}220$$

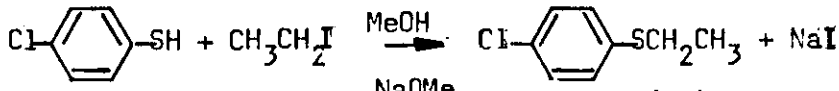
diethylphosphite (eqn. 2-220). The e.s.r. studies also indicated that the radical-anion is very stable and does not dissociate readily to the phosphonate radical and nitrite, supporting the lack of reactivity of the system in solution as well as the prediction of the identity of the product (86).

Diethyl 1-methyl-1-nitroethylphosphonate (37) was also reacted with *p*-chlorophenylthiolate in DMF to give *p*-chlorophenyl ethyl sulphide (87) in 45% yield (eqn. 2-221).



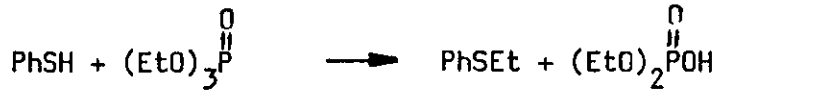
2-221

The reaction was repeated at different times, all of which yielded *p*-chlorophenyl ethyl sulphide (87), (41-46%). The identity of the product was confirmed by comparison with authentic material which was prepared according to the literature[135] method (eqn. 2-222).



(87) 2-222

Triethylphosphite and thiophenol have been reported[136] to undergo simultaneous ionic and radical reactions to give ethyl phenyl sulphide and diethyl phosphate (eqn. 2-223).



2-223

This reaction could be used to explain our results. Taking into consideration the inductive effect of the nitro group in the α-nitrophosphonate (37) ionic attack at the ethyl group of the phosphonate ester is more likely.

2.10.2 Reaction of 2-cyano-2-nitropropane with thiolates

2-Cyano-2-nitropropane (35) was reacted with phenyl thiolate in HMPA to give 1-cyano-1-methylethyl phenyl sulphide (88) in 53% yield (eqn. 2-224). The identity of the product was confirmed by the ^{1}H.n.m.r. and i.r. spectrum.

(88) 2-224

Our results confirmed those of Kornblum and Kester[69] who suggested that the reaction proceeded by an electron transfer ($S_{RN}1$) mechanism.

The reaction of *p*-chlorophenylthiolate with 2-cyano-2-nitropropane gave only recovered starting material. Further investigation of these reactions is required.

The e.s.r. studies of the radical-anion of 2-cyano-2-nitropropane have shown that it breaks down to nitrite and the 2-cyanopropyl radical (eqn. 2-225). The e.s.r. studies also show that the radical-anion is relatively

$$[Me_2C(CN)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}CN + NO_2^- \qquad 2\text{-}225$$

stable and breaks down less easily than other α-substituted-nitro radical anions. These observations are in agreement with the solution reactions reported above.

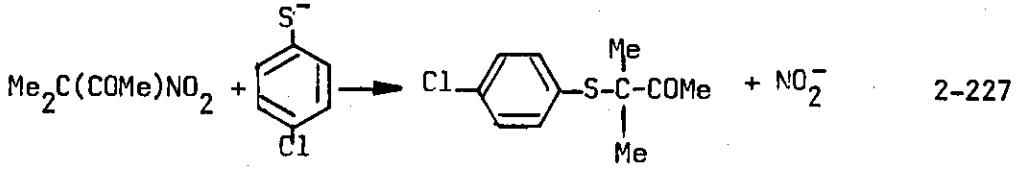
The reactions of 2-cyano-2-nitropropane with phenyl thiolates (and the associated e.s.r. studies support the observed loss of nitrite[114] from 2-cyano-2-nitropropane when reacted with the anion of 2-nitropropane (eqn. 2-226), i.e. the slow reaction rate and low reactivity cause

$$Me_2C(CN)NO_2 + Me_2C{=}NO_2^- \xrightarrow{h\upsilon} Me_2C(CN)C(NO_2)Me_2 + NO_2^- \qquad 2\text{-}226$$

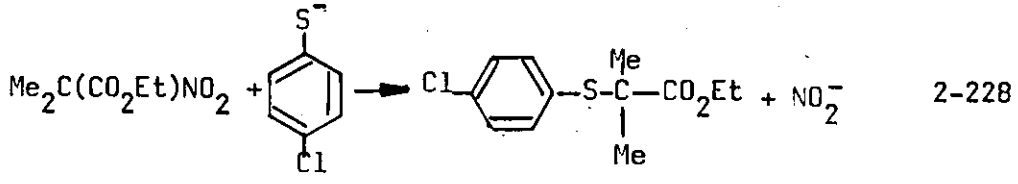
substitution of nitrite rather than cyanide.

2.10.3 Reactions of 3-methyl-3-nitrobutan-2-one (33) and ethyl 2-methyl-2-nitropropionate (34) with *p*-chlorophenylthiolate

3-Methyl-3-nitrobutan-2-one (33) and ethyl 2-methyl-2-nitropropionate (34) were reacted with *p*-chlorophenylthiolate in DMF and MeOH respectively to give low recovery of starting materials in both cases and no other products. Longer reaction times gave lower recovery of starting materials, i.e. more decomposition.



2-227



2-228

We were surprised by these results because the e.s.r. spectroscopy studies of both compounds showed that the corresponding radical-anions breakdown to nitrite and the 3-methyl-3-butan-2-one radical or the ethyl 2-methyl-2-propionate radical respectively (eqns. 2-229 and 230).

We suggest that either the radical anions are very stable in solution

$$[Me_2C(COMe)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}\text{-}COMe + NO_2^- \qquad 2\text{-}229$$

$$[Me_2C(CO_2Et)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}CO_2Et + NO_2^- \qquad 2\text{-}230$$

reactions or that an unknown alternative reaction takes place leading to decomposition. Both of these compounds have been shown[71] to react *via* a slow $S_{RN}1$ mechanism with the anion of 2-nitropropane with loss of nitrite (eqn. 2-231).

$$Me_2C(COMe)NO_2 + Me_2C{=}NO_2^- \longrightarrow Me_2C(COMe)C(NO_2)Me_2 + NO_2^- \qquad 2\text{-}231$$

2.11 The use of e.s.r. spectroscopy to predict the direction of $S_{RN}1$ reactions.

In studies of α-substituted nitro-compounds proceeding by the $S_{RN}1$ mechanism (eqns. 2-233-235), loss of the α-substituent (X) from the

$$Me_2C(X)NO_2 + A^- \xrightarrow{S.E.T.} [Me_2C(X)NO_2]^{\cdot-} + A^{\cdot} \qquad 2\text{-}232$$

$$[Me_2C(X)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}\text{-}NO_2 + X^- \qquad 2\text{-}233$$

$$Me_2\dot{C}\text{-}NO_2 + A^- \longrightarrow [Me_2C(A)NO_2]^{\cdot-} \qquad 2\text{-}234$$

$$[Me_2C(A)NO_2]^{\cdot-} + Me_2C(X)NO_2 \longrightarrow Me_2C(A)NO_2 + [Me_2C(X)NO_2]^{\cdot-} \qquad 2\text{-}235$$

$$[Me_2C(X)NO_2]^{\cdot-} \longrightarrow Me_2\dot{C}\text{-}X + NO_2^- \qquad 2\text{-}236$$

$$Me_2\dot{C}\text{-}X + A^- \longrightarrow [Me_2C(A)X]^{\cdot-} \qquad 2\text{-}237$$

$$[Me_2C(A)X]^{\cdot-} + Me_2C(X)NO_2 \longrightarrow Me_2C(A)X + [Me_2C(X)NO_2]^{\cdot-} \qquad 2\text{-}238$$

intermediate radical-anion has been observed[36,38,39,40] for X = I, Br, Cl, SO_2R, SR,[34] S(O)R,[34] and SCN[135]. Loss of nitrite has been observed[36,38,4] for X = COR, CO_2R, CN, NO_2, *p*-$NO_2C_6H_4N_2$, and Me[72](eqns. 2-236 to 2-238). A growing number of anions have been shown to participate in $S_{RN}1$ reactions with α-nitro-compounds e.g. A^- = $R_2CNO_2^-$, RSO_2^-, RS^-, N_3^-, $SO_2^{\cdot-}$, $(RO)_2PO^-$, and carbanions $R\bar{C}XY$ (with X,Y = COR, CO_2R, CN, SO_2R and combinations thereof.

E.s.r. studies[115] of the radical-anions from various α-substituted nitro compounds of the type $Me_2C(X)NO_2$, which we have prepared, are being carried out at Leicester University by Professor M.C.R. Symons and co-workers. This section has been included because of the relevance to the understanding of the reactivity of the compounds under study.

Degassed samples were irradiated as dilute solutions (*ca* 1% v/v) in methanol (CD_3OD was used to avoid overlap with solvent radical features) or methyltetrahydrofuran. They were frozen as small beads in liquid nitrogen and irradiated at 77K in a Vickrad ^{60}Co x-ray source to doses of up to 1 Mrad. E.s.r. spectra were measured on a Varian E109 spectrometer calibrated with proton resonance. Samples were annealed to the selected temperature or until significant changes occurred (*ca* 140K) in the e.s.r. spectrum, and re-cooled to 77K for study.

The purpose of the study is to show that:

a) α-Substituted nitro-compounds are able to capture an electron to form "stable" radical-anions (eqn. 2-232).

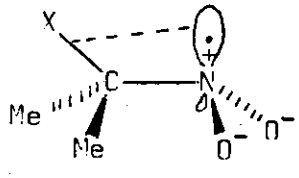
b) These radical-anions are able to dissociate to radicals and anions (eqns. 2-333 and 2-236).

c) These radicals and anions can combine to form radical-anions (reverse of eqns. 233, 236 and 234, 237).

d) The direction of breakdown can be observed (eqn. 2-233 versus 2-236).

e) The structure and stability of the radical-anion and radicals.

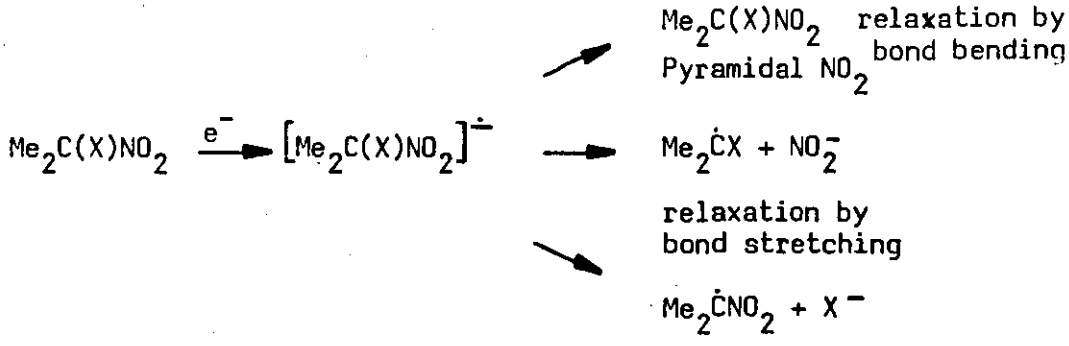
The e.s.r. spectroscopy results show that the structure of $Me_2C(X)NO_2$ radical-anions is pyrimidal at nitrogen (89). This structure has been



(89)

suggested to explain the isotropic coupling which corresponds to *Ca* 5% 2 s-character, and the anisotropic coupling which corresponds to *Ca* 57% 2*p*-character. This gives a ratio of P /'s of *Ca* 11 as opposed to *Ca* 30 for a planar π-radical such as $NH_3^{+\bullet}$. Despite this pyramidality, results indicate that there is a tendency to adopt the conformation shown (89) i.e. delocalisation into the C-X σ-bond for X = SCN, Br, Cl, PO_3Et_2, and SO_2R. The proposed mechanism is shown in Scheme 2-71. The breakdown of the parent radical-anions was difficult to detect which indicates that

Scheme 2-71



initial formation of $Me_2\dot{C}X$ and $Me_2\dot{C}NO_2$ is a "hot" process. This suggests that the initial electron addition occurs on the planar nitro-group and that relaxation proceeds subsequently, involving either bond-stretching, giving $Me_2\dot{C}X$ or $Me_2\dot{C}NO_2$, or bond-bending, giving the stable radical-anion $[Me_2C(X)NO_2]^{\pm}$ with a pyramidal nitro-group. This relaxation stabilises the radical-anion, thereby retarding dissociation.

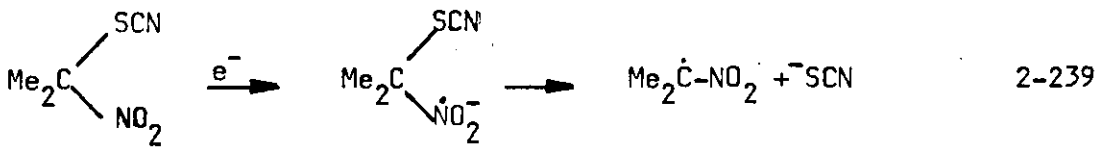
All the compounds studied showed stable radical-anions i.e. $Me_2C(X)NO_2$ with X = Br, Cl, NO_2, N_3, SCN, PO_3Et_2, COMe, CO_2Et, SO_2Ph, SO_2Me, Me, and CN. Compounds with X = Br, Cl, NO_2, SCN, SO_2R underwent dissociative electron capture to yield $Me_2\dot{C}NO_2$ and anion X^-. These results are in accord with those observed in liquid-phase (solution) studies.

Some of the other compounds with X = PO_3Et_2, CO_2Et, and CN, underwent dissociative electron capture to yield nitrite and the corresponding free radical ($Me_2\dot{C}PO_3Et_2$, $Me_2\dot{C}CO_2Et$, and $Me_2\dot{C}CN$). Again, these results were

in accord with solution studies for the latter two compounds.

The results of the e.s.r. studies which are particularly relevant to our work are summarised:

a) 2-Nitro-2-thiocyanatopropane (eqn. 2-239). This dissociation of radical



2-239

anions is in agreement with our results from solution studies of $S_{RN}1$ reactions, which clearly indicated loss of thiocyanate rather than nitrite (see section 2.5).

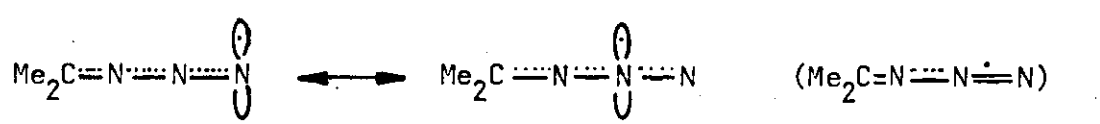
b) 2-Azido-2-nitropropane (eqn. 2-240). Interpretation of the e.s.r.

2-240

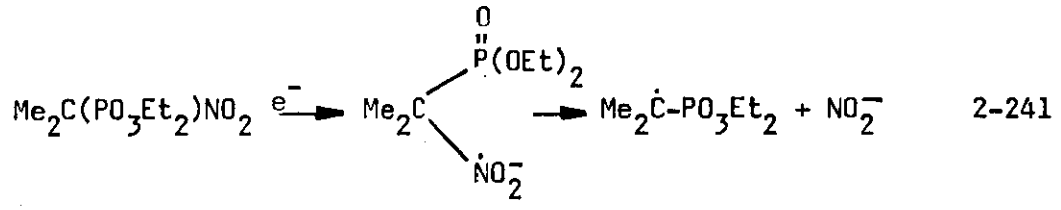
spectra of $[Me_2CN_3]^{\cdot}$ is still in progress. Localisation of the odd electron on the carbon atom $[Me_2\dot{C}—N_3]$ has been definitely shown not to exist.

The spectra indicate, so far as interpretation allows, that most of the odd-electron density lies on the terminal nitrogen, some on the central nitrogen, and very little on the $[\,C—N]$. The electron is thought to be in a *p*-orbital and not a σ-orbital. This is shown in fig. 2-3. These

Fig. 2-3



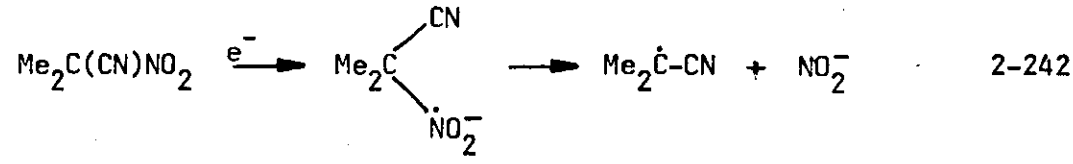
initial observations are in agreement with our results from solution studies which clearly indicated the loss of nitrite in $S_{RN}1$ reactions (see section 2-4).



2-241

c) Diethyl 1-methyl-1-nitroethylphosphonate (eqn. 2-241). The e.s.r. spectrum showed loss of nitrite. Our results in solution reactions gave an unidentified product, but appeared to indicate loss of nitrite (see section 2.10.1)

d) 2-Cyano-2-nitropropane (eqn. 2-242). The e.s.r. studies showed loss



2-242

of nitrite which is in agreement with our results in solution reactions (see section 2.10.2).

e) The reactivity of 2-substituted-2-nitropropanes observed in our reactions correlates closely with the stability observed by e.s.r. spectroscopy for the radical-anions $[Me_2C(X)NO_2]^{\cdot-}$ with:

i) X = Br >SCN >Cl >NO_2 relatively unstable radical-anions.

ii) X = $COCH_3$, SO_2Ph, the radical-anions do not dissociate in solid state i.e. they are very unreactive.

iii) X = PO_3Et_2, CO_2Et, CN, very slow dissociation.

f) The overall relative stability for the radical-anions $[Me_2C(X)NO_2]^{\cdot-}$ as observed by e.s.r. spectroscopy (i.e. the relative amounts of radical-anion and its dissociation) is as follows:

Br >SCN >Cl >NO_2 >PO_3Et_2, CO_2Et, CN, N_3 >COMe, SO_2Ph >Me.

2.12 Reactions of aliphatic α-substituted nitro-compounds with thiolates in protic solvents

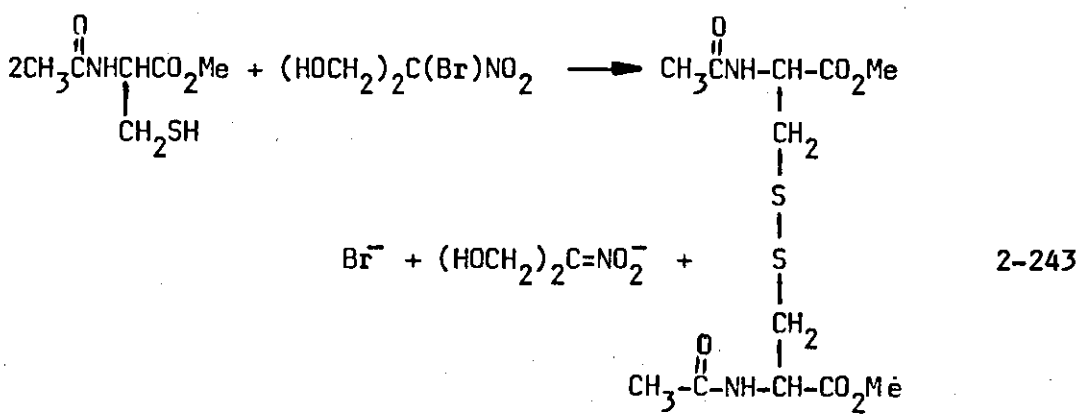
An important characteristic of the action of drugs is their solubility in water or organic solvent. Water solubility plays a key role as to whether a drug can be useful medicinally or not. The solubility of a drug can be tested in model *in vitro* experiments using systems which mimic the biological ones. Therefore, in order to test the reactivity of our prepared compounds as a guide to *in vitro* activity, we carried out a series of reactions of α-substituted nitropropanes with thiolates in protic solvents (water and/or methanol). Most of the 2-substituted-2-nitropropanes are insoluble in water, therefore MeOH/H_2O mixtures had to be used to solubilise reactants.

Thiolates have been reacted with 2-substituted-2-nitropropanes in dipolar aprotic solvents to yield α-nitrosulphides by an $S_{RN}1$ mechanism[34,35] and/or disulphide by an X-philic mechanism involving attack by thiolate on the α-substituent to yield a sulphenyl intermediate (RSX) which subsequently gives disulphide on reaction with thiolate (section 2.7).

In our studies on the mode of action of the antimicrobial agent, 2-bromo-2-nitropropan-1,3-diol (3) (bronopol), which owes its activity to the oxidation of protein thiol groups to disulphides, we studied the reaction in water and in methanol and found that bronopol gave only disulphides when reacted with thiolates. These results encouraged us to set out an investigation on the effect of protic solvents on the course of the reaction of 2-substituted-2-nitropropane with different thiolates i.e. why do some 2-substituted-2-nitropropanes undergo $S_{RN}1$ reactions in dipolar aprotic solvents while bronopol in water only yields disulphides when reacted with thiolates?

Stretton and Manson[16] have suggested that the primary mode of action of bronopol is due to its ability to oxidise sensitive thiol groups to disulphides (see introduction). They have shown that bronopol oxidises (L)-cysteine, glutathione, and coenzyme A to the corresponding disulphides. They also demonstrated loss of enzyme activity (e.g. papain) due to oxidation with bronopol.

Bowman and Burton[136] carried out series of reactions with bronopol. They showed that bronopol oxidises (L)-cysteine and N-acetyl-(L)-cysteine-methylester to their corresponding disulphides in 70-90% yield (eqn. 2-243). They also showed that the stoichiometry was 2:1 (RSH: Bronopol).



2-243

Considerable effort was made to isolate the nitronate resulting from the redox reaction but without success. The resulting nitronate is known to be unstable, decomposing to formaldehyde, and hence to polymeric material, and to nitromethane, which also decomposes further. The reaction was also shown not to proceed at low pH(1-2) showing that ionization of thiol to thiolate is essential for reaction.

2.12.1 Reactions of 2-substituted-2-nitropropan-1,3-diol with thiolates

2-Bromo-2-nitropropan-1,3-diol and 2-chloro-2-nitropropan-1,3-diol were reacted with different thiolates in water or in water/methanol to give the corresponding disulphides in excellent yield (eqn. 2-244). The results of these reactions are shown in Table 2-12.

Table 2-12 Reactions of 2-substituted-2-nitropropane-1,3-diol with thiolates

$$(HOCH_2)_2C(X)NO_2 + 2RS^- \longrightarrow RSSR + (HOCH_2)_2C{=}NO_2^- + X^- \qquad 2\text{-}244$$

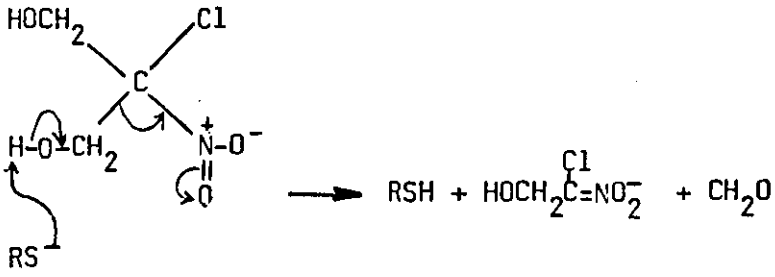
X = Br, Cl

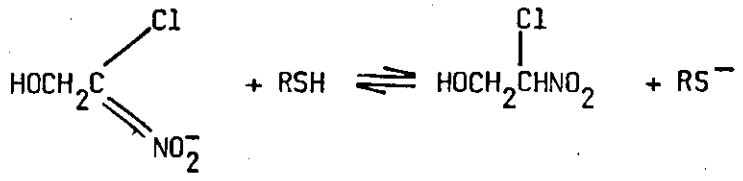
R	Conditions, X	% yield RSSR
4-Chlorophenyl	H_2O, N_2, 4h, Br	92
	H_2O, N_2, 4h, Cl	64
4-Nitrophenyl	H_2O, N_2, 48h, Br	98
	H_2O/MeOH, 20h, Br	96
Benzyl	H_2O, 4h, N_2, Br	94
	H_2O, 4h, N_2, Cl	52 (24 benzyl thiol)

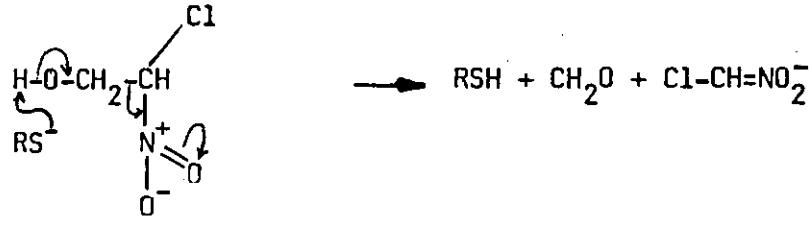
These results show that bronopol only oxidizes thiolates to their corresponding disulphides in protic solvents and that no $S_{RN}1$ products are formed. Even reaction with the non-nucleophilic *p*-nitrophenylthiolate only gave disulphide, whereas 2-bromo-2-nitropropane on reaction with *p*-nitrophenylthiolate in DMF yields 89% of the $S_{RN}1$ product (α-nitrosulphide).[34,35] 2-Chloro-2-nitropropan-1,3-diol oxidizes the relatively non-nucleophilic thiolate, i.e. *p*-chlorophenylthiolate (pka7.06) to disulphide in good yield. However, when the more nucleophilic benzyl thiolate was used, proton abstraction was more important, i.e. chlorine is much less easily abstracted than bromine and therefore proton

abstraction becomes important as shown in Scheme 2-72.

Scheme 2-72

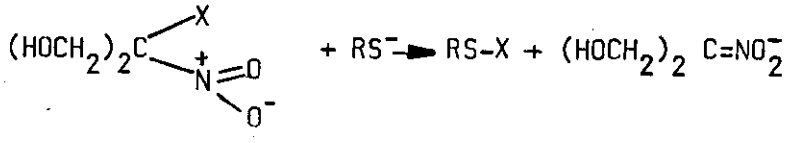


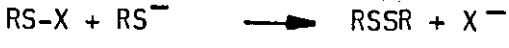




Our results confirmed those of Bowman and Burton[136], and Stretton and Manson[16]. These *invitro* oxidations of thiolates to disulphide are therefore a good indication of the primary mode of action of bronopol *in vivo* . The reaction mechanism is shown in Scheme 2-73. The α-substituent is abstracted by the nucleophilic thiolate to yield a reactive sulphenyl

Scheme 2-73





overall

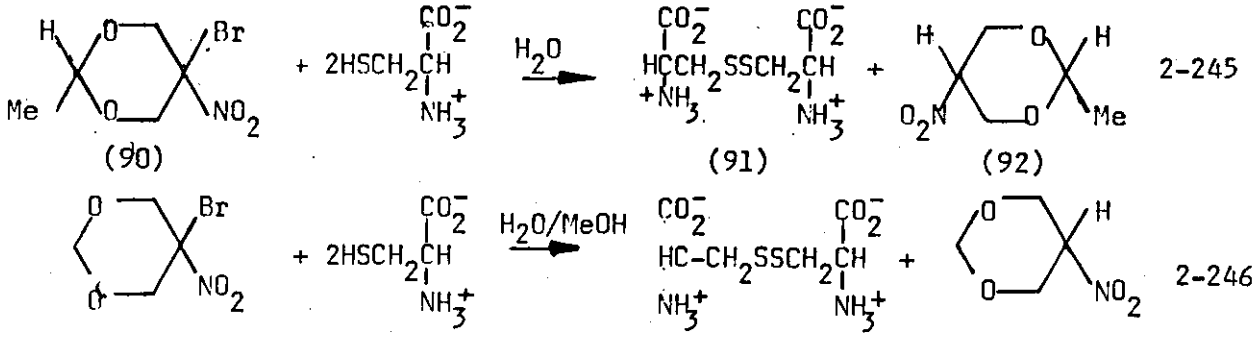
intermediate (RS-X) which rapidly reacts with further thiolate to give the corresponding disulphide. The alternative single electron transfer (S.E.T.) mechanism suggested by Russell *et al*[36] (Scheme 1-3) has been shown not to be operative.[33-35]

2.12.2 Reaction of 5-bromo-5-nitro-1,3-dioxane with thiolates

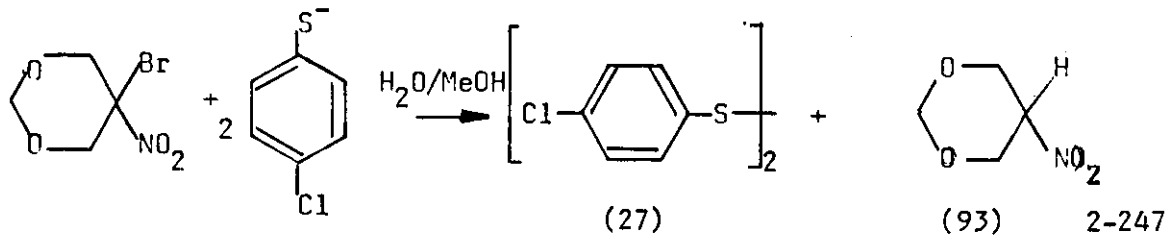
Bronidox, 5-bromo-5-nitro-1,3-dioxane (7), an analogue of bronopol, is also marketed for medicinal use as a preservative. The similarity of structure would suggest that its reactivity and mode of action is the same as that of bronopol.

In their investigation to demonstrate the importance of an α-bromine as a substituent in the 5-nitro-1,3-dioxane series, Lappas and co-workers[21] reacted 5-bromo-2-methyl-5-nitro-1,3-dioxane (90) with (L)-cysteine in water to give (L)-cystine (91) and 2-methyl-5-nitro-1,3-dioxane (92) (eqn. 2-245).

We have reacted 5-bromo-5-nitro-1,3-dioxane with (L)-cysteine in water and methanol (50 : 50) to give (L)-cystine (91) in 70% yield, and traces of 5-nitro-1,3-dioxane (93) (eqn. 2-246). The identity of the product was confirmed by m.p. and ^{1}H.n.m.r.



We reacted 5-bromo-5-nitro-1,3-dioxane with *p*-chlorophenylthiolate in MeOH/H_2O (pH5.5) to give the corresponding di-(*p*-chlorophenyl) disulphide (27) in 70% yield and traces of 5-nitro-1,3-dioxane (93) (eqn. 2-247). The stoichiometry of the reaction was 2 : 1 (RSH : Bronidox).



(27) (93) 2-247

The reaction was also shown not to proceed at low pH (1-2) showing that ionization of thiol to thiolate is essential for reaction. These results are similar to those for bronopol which suggests that bronidox may have a similar mode of action i.e. oxidation of sensitive protein thiols to the corresponding disulphides.

A microbiological *in vivo* study of the mode of action of bronidox is in progress. Preliminary results suggest that the mode of action is similar to that of bronopol.[137]

2.12.3 Reactions of 2-substituted-2-nitropropanes with thiolates

Thiolates have been shown to react with 2-substituted-2-nitropropanes in dipolar aprotic solvents to yield α-nitrosulphides by an $S_{RN}1$ mechanism[34,35] (eqn. 2-248) and/or disulphide by an X-philic[78] mechanism (eqn. 2-249) involving attack by thiolate on the α-substituent to yield a sulphenyl intermediate which subsequently gives disulphide (Scheme 2-74). The X-philic reaction is favoured over the $S_{RN}1$ by more strongly nucleophilic

Scheme 2-74

$$Me_2C(X)NO_2 + RS^- \longrightarrow Me_2C(SR)NO_2 + X^- \quad S_{RN}1 \quad 2\text{-}248$$

$$Me_2C(X)NO_2 + RS^- \longrightarrow Me_2C{=}NO_2^- + RS\text{-}X \quad \text{X-philic} \quad 2\text{-}249a$$

$$RS\text{-}X + RS^- \longrightarrow RSSR + X^- \quad \text{X-philic} \quad 2\text{-}249b$$

thiolates and by more easily abstracted α-substituents i.e. I> Br> Cl[34,35].

Although most of the earlier work on the $S_{RN}1$ mechanism of $Me_2C(X)NO_2$ reactions was carried out in ethanol, dipolar aprotic solvents have since been used, and no comments so far we are aware, have been made on the effect of protic solvents.

We have carried out series of reactions of various $Me_2C(X)NO_2$ and various thiolates in dipolar aprotic solvents and in MeOH or $MeOH/H_2O$ as solvent. All the reactions of $Me_2C(X)NO_2$ with thiolates which give $S_{RN}1$ or mixed $S_{RN}1$/redox products in dipolar aprotic solvents yielded exclusively redox products, i.e. disulphide and nitronate, in methanol solution (eqn. 2-250). The results of these reactions and some reactions

$$Me_2C(X)NO_2 + RS^- \xrightarrow{MeOH} Me_2C{=}NO_2^- + RS\text{-}X \qquad 2\text{-}250a$$

$$RS\text{-}X + RS^- \longrightarrow RSSR + X^- \qquad 2\text{-}250b$$

$$X = Br,\ Cl,\ SCN$$

carried out by Bowman and Valmas[138], and Bowman and Richardson[34,35] are tabulated in Table 2-13. The identity of products was confirmed by i.r., ^1H.n.m.r., and m.p. comparison with authentic materials. Looking at the results in the table it can be seen that the most pronounced change was the reaction of $Me_2C(Br)NO_2$ with *p*-nitrophenylthiolate which gave 89% of the $S_{RN}1$ product in DMF and 51% of disulphide in a faster reaction in methanol.

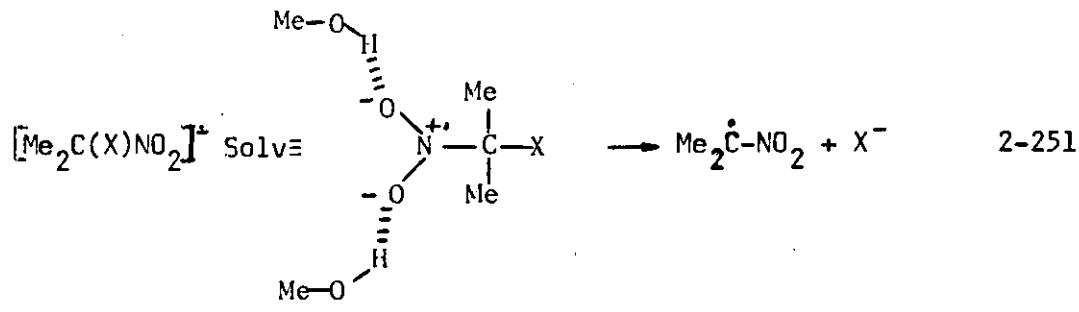
$S_{RN}1$ reactions of $Me_2C(X)NO_2$ with nitronates proceed faster[36] in DMF or DMSO than in EtOH, but the differences in rate are relatively small. Russell[139] has reported striking differences in reactivity in the $S_{RN}1$ reactions of $Me_2C(X)NO_2$ due to solvation of the nucleophiles (protic solvents were not used).

We propose that our results can be explained by strong methanol solvation of the intermediate radical-anion in the $S_{RN}1$ mechanism, which retards the dissociation of $[Me_2C(X)NO_2]^{\cdot-}$ to $Me_2\dot{C}NO_2$ and anion (eqn. 2-251) and hence retards the $S_{RN}1$ chain reaction. The dissociation of the radical-anion to radical and anion is the rate determining step in the $S_{RN}1$ mechanism, therefore a retarding of this step would slow the

Table 2-13: $Me_2C(X)NO_2 + RS^- \longrightarrow RSSR + Me_2C(SR)NO_2$

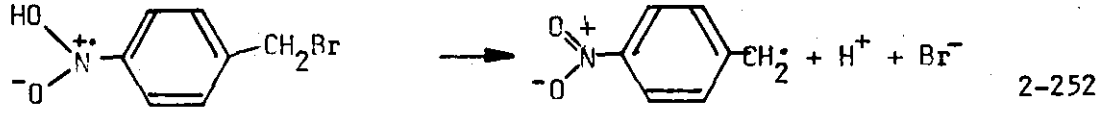
X	R	Conditions[a]	% Yield[b]	
			RSSR	$Me_2C(SR)NO_2$
Br	*p*-nitrophenyl	DMF[c], 4h; MeOH:H_2O (85:15), 1h[d]	0;51	89;0
	2-pyridyl	DMF[c], 2h; HMPA[c], 1h; MeOH[c], 21h	5;28;66	10(25)[f];12;0
	p-chlorophenyl	DMF, 2h; MeOH:H_2O (85:15), 5min	70;94	0;0
	p-chlorophenyl	MeOH, 20min	71	0
		+20mol % *p*DNB[e]; +20mol % DTBN[e]	70;68	0:0
Cl	*p*-chlorophenyl	DMF, 4h	32	35
	p-chlorophenyl	MeOH, 4h	55	0
		+dark, +O_2	32;33	0;0
		+5mol % *p*DNB[e]; +5mol % DTBN[e]	26,28	0;0
	p-chlorophenyl	MeOH, 20min	36(6)[b]	0
		+O_2; +20mol % *p*DNB[e]	21(12)[f];18(22)[f]	0;0
		+20mol % DTBN[e]	30	0
SCN	*p*-nitrophenyl	DMSO, 15min	18(18)[f]	17
		+dark; +O_2	28(38)[f];44(62)[f]	21; trace
		+15mol % *p*DNB[e]; 15mol % DTBN[e]	40(36)[f];30(36)[f]	5; trace
	p-nitrophenyl	MeOH:H_2O (80:20), 20min[d]	39	0
	p-chlorophenyl	DMSO, 20min	35(7)[f]	54
	p-chlorophenyl	MeOH, 20min	60	0
		+dark; +O_2	55;53	0;0
		+20mol % *p*DNB[e]; +20mol % DTBN[e]	55;56	0;0
2-thiopyrimidine	*p*-chlorophenyl	DMF[c], 5h; MeOH[c], 5h	20;47	32;0
2-thio-(N-methyl)-imidazole	*p*-chlorophenyl	DMF[c], 5h; MeOH[c], 5h	23;55	46;0

(a) Reactions were carried out under an atmosphere of nitrogen, with light catalysis (2 x 150W Tungsten 'white light' lamps) with a molar ratio of RS^-: $Me_2C(X)NO_2$ of 2:1. (b) % yields are based on RS^-, calculated by ^1H n.m.r. spectroscopy with an internal standard or by isolation. (c) Equi-molar ratio of RS^-: $Me_2C(X)NO_2$. (d) The red colour of *p*-nitrophenylthiolate disappeared within 2min indicating complete reaction. (e) mol % of $Me_2C(X)NO_2$, *p*DNB = *p*-dinitrobenzene, DTBN = di-*t*-butyl nitroxide. (f) Unreacted $Me_2C(X)NO_2$.



rate of reaction. The solvation will withdraw electron density from the nitro group in the radical-anion making the reorganisation of π^* to σ^* orbitals required for dissociation more difficult. The alternative X-philic reaction (eqn. 2-249), however, is not greatly retarded because of the small difference in solvation of thiolates in protic and dipolar aprotic solvents[140-142] and therefore predominates, and only disulphide is obtained. Solvation of anions in S_N2 reactions normally considerably retards the rate of reaction, hence most S_N2 reactions are much faster in dipolar aprotic solvent than in protic solvents.

The nucleophilicity of *p*-nitrophenylthiolate is nearly the same in methanol as in DMF. Neta[143] has reported that the protonated radical-anion of *p*-nitrobenzyl bromide dissociates 60 times slower than the non-protonated radical-anion (eqn. 2-252). Strong H-bonding (protic solvation),



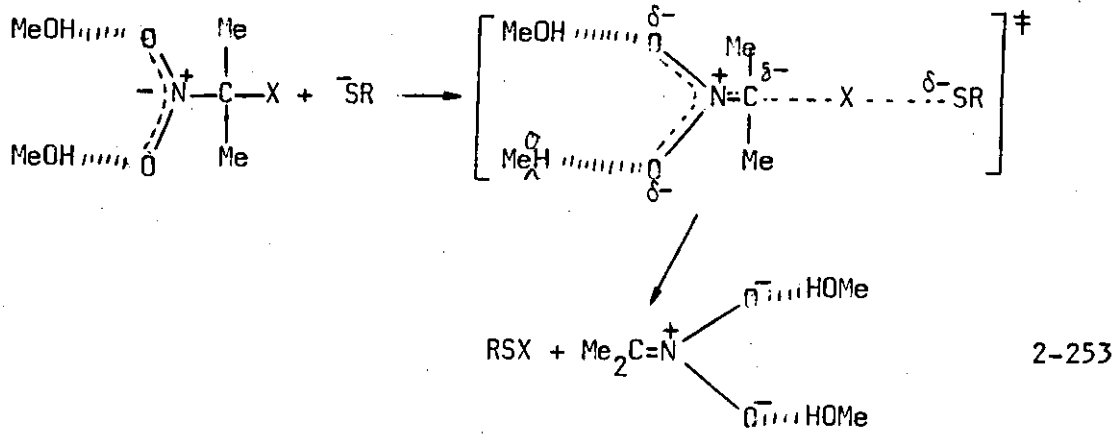
of the radical-anion would be expected to exert a similar, albeit smaller, effect on the dissociation of the halo-nitro radical-anion.

The X-philic mechanism (eqn. 2-249) for the formation of the sulphenyl intermediate (RS-X) i.e. (S_N2 attack by thiolate on the α-substituent), and hence the disulphide, is supported by the lack of inhibition by a radical trap (O_2 and DTBN), strong electron acceptors (O_2 and *p*-DNB), and the absence of light (these are the well-known diagnostic inhibitors[44]

for reactions proceeding by an $S_{RN}1$ mechanism). This lack of inhibition of disulphide formation in DMF and DMSO also has been reported[35], and the lack of significant inhibition in MeOH for the reactions of $Me_2C(Br)NO_2$ and $Me_2C(SCN)NO_2$ with *p*-chlorophenyl thiolate (Table 2-13) excludes a radical radical-anion chain mechanism.

Surprisingly, the methanol reactions appeared to proceed faster than those in dipolar aprotic solvent. A more definitive difference in rate could be observed for the reactions of $Me_2C(SCN)NO_2$ with *p*-chloro and *p*-nitrophenylthiolate in MeOH which were complete in 20 minutes, but in DMSO, still had unreacted starting material after 20 minutes. Even when the $S_{RN}1$ reaction of $Me_2C(SCN)NO_2$ and *p*-nitrophenyl thiolate in DMSO was inhibited, the X-philic reaction was not fast enough to consume all the starting material i.e. the $S_{RN}1$ reaction uses only part, and not all, of the starting material and cannot therefore be used as an explanation for a slow S_N2 reaction. These results suggest that the redox reaction to disulphide is faster in MeOH than in DMF or DMSO.

We suggest that the most likely explanation is that the nitro-group of $Me_2C(X)NO_2$ is solvated by MeOH but not by DMF and DMSO, and that this solvation becomes very strong in the S_N2 transition state thereby lowering the energy of the transition state and increasing the rate of reaction (eqn. 2-253). Normally solvation of the neutral species (electrophile)



2-253

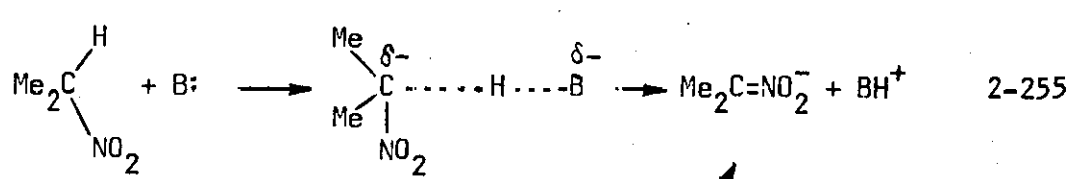
solvation may become dominant.

If our explanation is correct, this reaction shows a novel increase in rate for S_N2 substitution in MeOH over DMF and DMSO. Several factors, however, militate against this explanation. Firstly, although thiolates are reported[140] to be similarly solvated in protic and dipolar aprotic solvents, the solvation must be taken into account. Using pka values as a guide[140] [e.g. ρ-nitrophenylthiol, pka 8.4 (MeOH), 6.3 (DMF), 5.6 (DMSO)], higher solvation and therefore lower nucleophilicity would be expected in methanol relative to DMF and DMSO.

Secondly, several reports[141, 144] clearly show that in the deprotonation of 2-nitropropane the nitro-group is not strongly solvated by protic solvent (H_2O) in the transition state. The rate of deprotonation is therefore faster in DMSO than in water which is in sharp contrast to the large difference in pka of 2-nitropropane between water (7.6) and DMSO (16.9).[141] The pka is determined by the thermodynamic equilibrium (eqn. 2-254) in

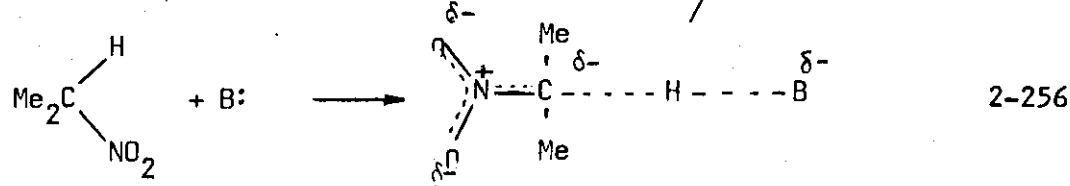
$$Me_2CHNO_2 \rightleftharpoons Me_2C{=}NO_2^- + H^+ \qquad 2\text{-}254$$

which the nitro-anion is strongly solvated making nitro-compounds uniquely acidic. The rate of deprotonation is, however, very slow due to the reorganisation of sp^3 to sp^2 orbitals that is required. Several authors[145] have suggested that in the transition state for deprotonation the negative charge is largely on carbon in a sp^3 type intermediate as shown in eqns. 2-255 and 256. The transition state (A) (eqn. 2-255) would not be



2-255

(A)



2-256

(B)

strongly solvated but a transition state such as (B) (eqn. 2-256) would be strongly solvated. This difference is called the 'nitro anomaly."[141,144] Even when the solvation of the base is taken into account[146] the rate of deprotonation is faster in DMSO than in water, suggesting by comparison, that abstraction of the α-substituent should be slower in protic solvents than in dipolar aprotic solvents. The differences in reactivity between water and methanol, and between abstraction of (H^+) and α-substituents may, however, be counter to the above observations, allowing solvation of the transition state to be used as an argument.

Thirdly, $Me_2CNO_2^-$ is reported[147] to be a poor leaving group. Finally, the more strongly basic the anion the greater the likelihood that it will react by a single electron transfer mechanism[145] rather than by a S_N2 pathway. Our explanation suggests the opposite, i.e. $S_{RN}1$ (initial S.E.T.) by weakly nucleophilic thiolates, and S_N2 by strongly nucleophilic thiolates which may indicate that our explanation is wrong.

We therefore suggest that a non-chain mechanism proceeding by initial S.E.T. (eqn. 2-257), closely similar to the $S_{ET}2$ (substitution,electron transfer, second order) (eqn. 2-258) proposed by Russell[36a] and reported by Ashby[148] must be considered.

$$Me_2C(X)NO_2 + RS^- \xrightarrow{\text{S.E.T.}} [Me_2C(X)\dot{N}O_2^-RS^{\cdot}] \qquad 2\text{-}257a$$

$$[Me_2C(X)\dot{N}O_2^-RS^{\cdot}] \longrightarrow Me_2CNO_2^- + RS\text{-}X \qquad 2\text{-}257b$$

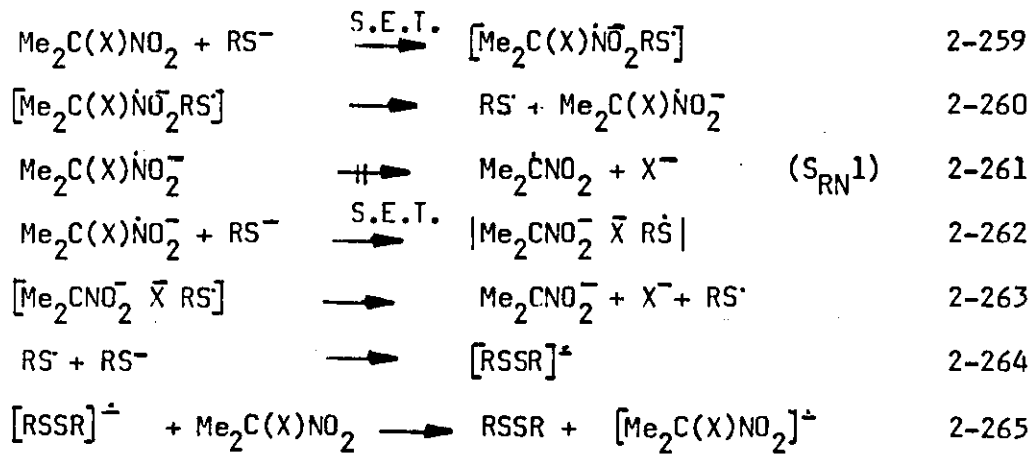
$$Me_2C(X)NO_2 + R^- \xrightarrow{\text{S.E.T.}} [Me_2C(X)\dot{N}O_2^-R^{\cdot}] \qquad 2\text{-}258a$$

$$[Me_2C(X)\dot{N}O_2^-R^{\cdot}] \longrightarrow Me_2C(R)NO_2 + X^- \qquad 2\text{-}258b$$

Protic solvation of the intermediate radical-anion would by strong, retarding dissociation to $Me_2\dot{C}NO_2$ and X^- in the $S_{RN}1$ mechanism, but possibly favouring reaction with the thiyl radical to give the sulphenyl intermediate. The observed lack of inhibition or trapping of thiyl radical[34,35] can be explained by the radical-anion and thiyl radical being tightly held

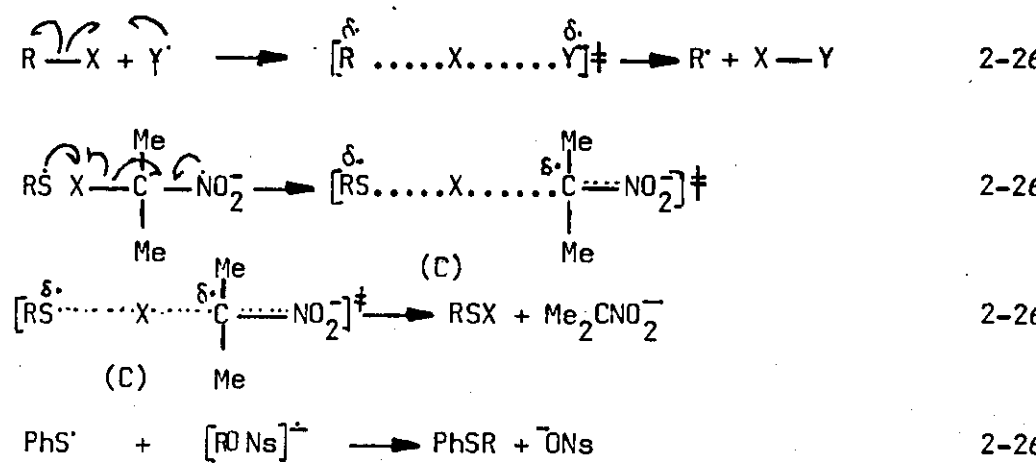
in a solvent cage. Similarly, the initial S.E.T. would be rapid and light catalysis would not be expected (Scheme 2-75).

Scheme 2-75



There is no evidence to suggest that protic solvated halo-nitro radical-anions undergo dissociation to nitronate and $\cdot X$ [115,143]. We therefore suggest the reaction in the cage is an S_H2[149] type reaction (Scheme 2-76) with a transition state (C). This alternative breakdown

Scheme 2-76



only takes place in the presence of a reactive free radical (RS·) in the solvent cage. S_H2 is more likely with a terminal or isolated halogroup as in our molecule. This mechanism can apply to reactions in DMF/DMSO and in MeOH, but would be more favoured in MeOH because of solvation would improve the nucleofugicity of $Me_2CNO_2^-$ in the substitution. This reaction

of a thiyl radical with a radical-anion (eqn. 2-269) has been reported.[150]

The reaction of $Me_2C(Cl)NO_2$ with *p*-chlorophenyl thiolate is slow in MeOH and in DMF. The DMF reaction yields $S_{RN}1$ and redox products but the MeOH reaction yields only disulphide and is slightly inhibited by O_2, *p*-DNB, and DTBN. We suggest[151] that this inhibition is explained either by slight inhibition of the non-chain $S_{ET}2$ mechanism expounded above or by a chain oxidative dimerisation mechanism[121] (Scheme 2-75) as proposed for the reaction of enolates with $Me_2C(X)NO_2$. Lower reactivity (weaker and less reactive halide i.e. Cl) would allow diffusion from the solvent cage before dissociation or a S_H2 reaction with (RS·) radical (eqn. 2-260). Methanol solvation would favour a second S.E.T. (eqns. 2-262 and 263) rather than dissociation of the radical-anion ($S_{RN}1$ in DMF). The sulphenyl chloride would not be an intermediate in this sequence which is possible as it has not been trapped or observed.

Summary

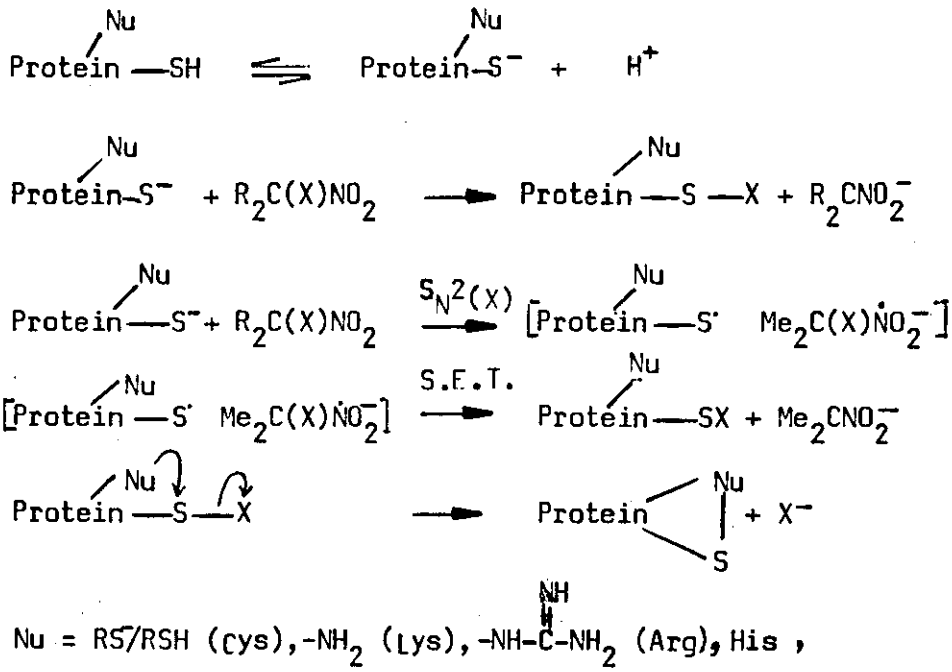
We have shown that all the α-substituted nitro-compounds studied react in protic solvent with thiolates to yield only disulphides, and no $S_{RN}1$ products (α-nitrosulphides) were formed, as was observed in many reactions in DMF and DMSO. Although there is a choice of mechanisms (S_N2 (X) or $S_{ET}2$) for this redox reaction the products are the same, i.e. nitronate and sulphenyl intermediate (RSX). The apparent faster rate in protic solvents over dipolar aprotic solvents is also of significance.

These observations are of particular importance as they make our observations of the *in vitro* reaction much closer to the *in vivo* reaction of α-substituted nitro-compounds with thiolates.

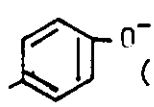
Our results therefore provide extra evidence that the *in vivo* observation of the mode of action of bronopol and bronidox (i.e. oxidation of protein thiolate) can be explained by *in vitro* reactions. By analogy

the biological mode of action can be by either of the mechanisms shown in Scheme 2-77.

Scheme 2-77



Nu = RS^-/RSH (Cys), $-NH_2$ (Lys), $-NH-\overset{\overset{NH}{\|}}{C}-NH_2$ (Arg), His ,



(Tyr), $-CO_2^-$ (Glu, Asp), $CONH_2$ (Gln, Asn), CH_2OH (Ser), Thr , SMe (Met), or -CONH-(peptide bonds in proteins).

2.1.3 Biological activity

The main aim of the work has been to determine the structure activity relationship (S.A.R.) for compounds with the structure $R_2C(X)NO_2$ and to correlate their antimicrobial activity with their chemical reactivity (by reaction, and observation of their radical-anions by e.s.r. spectroscopy respectively). It was also hoped that these observations could provide extra evidence for their antimicrobial mode of action.

2.1.3.1 Antimicrobial activity of 2-substituted-2-nitropropanes

To this initial aim the antimicrobial activity of the prepared 2-substituted-2-nitropropanes [$Me_2C(X)NO_2$ with X = I, Br, Cl, NO_2, PO_3Et_2, COMe, CO_2Et, SR (with R = *p*-chlorophenyl), SO_2R (with R = phenyl), *p*-$NO_2C_6H_4$, *p*-$NO_2C_6H_4N_2$, CN, SCN, and N_3] were tested *in vivo*. The minimum inhibitory concentration (M.I.C.) was recorded against a representative range of micro-organisms (Table 2-14). All the compounds tested, except bronopol, have low solubility in water which is a problem for accurate testing. The problem of poor aqueous solubility was overcome by using minimum volumes of organic solvents (acetone, or dimethyl sulphoxide) to effect solubility. The volume of solvent used was, in all cases, without detectable effect on bacterial or fungal growth[152]. The solutions were sterilized by membrane filtration (Sartorius membrane filter, 0.2μm porosity).

A cross-section of different types of micro-organisms were used for the testing. The organisms used for the estimation of antimicrobial activity were a Gram-positive bacterium: *Staphylococcus aureus* NCIB 8625, a Gram-negative bacterium: *Pseudomonas aeruginosa* NCIB 6749, a fungus: *Aspergillus niger* CMI 31821, and a yeast: *Candida albican* A3a (Boots strain).

Table 2-14 Minimum inhibitory concentration values for 2-substituted-2-nitropropanes

Compound	M.I.C. ($\mu g ml^{-1}$)			
	S. Aureus	*P. Aeruginosa*	*A. Niger*	*C. Albican*
2-Bromo-2-nitropropan-1,3-diol (3)	31	15	500	>500
2-Iodo-2-nitropropane (22)	25	20	250	250
2-Bromo-2-nitropropane (20)	30	60	250	300
2-Nitro-2-thiocyanatopropane (67)	62	250	125	62
1-Nitro-1-thiocyanatocyclohexane (68)	62	250	125	62
α,*p*-Dinitrocumene (24)	62[a]	62[a]	62[a]	62[a]
1-Methyl-1-nitroethyl *p*-chlorophenyl sulphide (28)	62[a]	62[a]	62[a]	62[a]
2-Cyano-2-nitropropane (35)	>2000[b]	>2000[b]	>2000[b]	>2000[b]
3-Methyl-3-nitrobutan-2-one (33)	>2000[b]	>2000[b]	>2000[b]	>2000[b]
Ethyl 2-methyl-2-nitropropionate (34)	>2000[b]	>2000[b]	>2000[b]	>2000[b]
Diethyl 1-methyl-1-nitroethyl-phosphonate (37)	>2000[b]	>2000[b]	>2000[b]	>2000[b]
2-Azido-2-nitropropane (40)	>1000	>1000	>1000	>1000
1-Azido-1-nitrocyclohexane (42)	>1000	>1000	>1000	>1000
1-Methyl-1-nitroethyl phenyl-sulphone (39)	>2000[b]	>2000[b]	>2000[b]	>2000[b]
2-(*p*-Nitrophenylazo)-2-nitropropane (25)	>2000[b]	>2000[b]	>2000[b]	>2000[b]

a - M.I.C. values at saturated solution.

b - Disc method

Minimum inhibitory concentration (M.I.C.) values were determined in nutrient broth against bacteria by using a tube dilution method (end point) or disc method (agar cup test), and for fungi, by a dilution method in Czapek Dox medium. The inoculum was 0.01 ml of an 18h broth culture of the test bacterium and yeast or 0.01 ml of a spore suspension prepared from 1 7 day culture of fungus. The M.I.C. values were noted after 24h at 37° for the bacteria, 48h at 25° for the yeast, and 120h at 25° for the fungus.

An approximate bactericidal end-point was obtained by subculturing a loopful of medium from tubes showing no growth into an additional 10 ml of medium.

Minimum inhibition concentration (M.I.C.) values were also determined by an alternative method to the agar cup test which is the disc method. In this method bronopol was used as a marker to compare the size of zones of activity produced by compound when allowed to diffuse from an impregnated paper disc placed on an agar plate seeded with micro-organism.

Minimum inhibitory concentration values of the compounds are shown in Table 2-14. Bronopol was used as a marker for comparisons of activity. The results for I, Br, Cl, and NO_2 are the same as previously determined by Stretton and Bowman.[15] The compounds tested fall into three catagories of activity; 1-Similar to or more active than bronopol. 2-Poorly active relative to bronopol. 3- Inactive.

The first group contained those compounds with α-nitro-substituents of I, Br, SCN, *p*-ClC_6H_4S, and *p*-$NO_2C_6H_4$.

2-nitro-2-thiocyanatopropane (67) and 1-nitro-1-thiocyanatocyclohexane (68) were active against bacteria and both the fungus and the yeast. Remarkably, their activity against Gram-positive bacteria was in the range of that for bronopol, and less active than bronopol against Gram-negative bacteria. However, their activity against the fungus and the yeast was more pronounced and they were more active than bronopol. The α-nitrothiocyanates (67 and 68) were shown to have a bacterial acid activity at

ca 500µg/ml. The nature of the alkyl group (dimethyl or cyclohexyl) does not appear to affect the activity.

2-Iodo-2-nitropropane (22) was the most active compound tested. It was more active against the Gram-positive bacterium, and shown a similar range of activity against the Gram-negative bacterium to that of bronopol. It was more active than bronopol against both the fungus and the yeast.

2-Bromo-2-nitropropane (20) was as active as bronopol against the Gram-positive bacterium, less active against the Gram-negative bacterium, and more active than bronopol against both the fungus and the yeast. The nature of dimethyl group has no effect on activity.

α, *p*-Dinitrocumene (24) and 1-methyl-1-nitroethyl *p*-chlorophenyl sulphide (28) were less active than bronopol (at the same concentration in diethyl ether using the disc method). However, attempts were made to dissolve them in water solution and an activity of 62µg/ml was measured in saturated solution i.e. less active than bronopol. Higher activity than measured is possible but may not be observed due to poor water solubility. The α, *p*-dinitrocumene (24) is not particularly reactive in $S_{RN}1$ reactions and initial results indicate that the radical-anion is stable and does not easily dissociate. The antimicrobial activity, therefore does not appear to be closely correlated as with the other compounds. The relatively high activity may be due to the nitro-aryl moiety rather than an α-substituent to the nitro group.

The reactivity of the α-nitro sulphide (28) does however correlate with chemical reactivity, i.e. thiolates are rapidly oxidized by the α-nitro sulphide (28), to disulphide.[34] Improved activity could be possibly obtained by using a more reactive α-nitro sulphide such as 1-methyl-1-nitroethyl *p*-nitrophenyl sulphide (27) which oxidizes thiolate to disulphide more rapidly than (28).

The second group contains the poorly active compounds relative to bronopol which includes $Me_2C(Cl)NO_2$ (21) and 2,2-dinitropropane (36). Both were less active than bronopol against the bacteria, the fungus and the yeast. Their antimicrobial activity correlates well with their ability to oxidize thiolate to the corresponding disulphide, i.e. not as rapid as those compounds of the first group (I, Br or SCN).

The third group [$Me_2C(X)NO_2$ with X = CN (35), COMe (33), CO_2Et (34), PO_3Et_2 (37), N_3 (40), $PhSO_2$ (39), and *p*-NO_2PhN_2 (25)], were all inactive. This lack of activity again correlates well with their chemical reactions. The ketone (33) and the ester (34), for example, gave no reaction with thiolate (section 2.9.3). The α-nitroazides (40 and 42) gave substitution rather than oxidation with thiolate (section 2.4.3). 2-(*p*-Nitrophenylazo)-2-nitropropane (25) has been reported[33] to react with benzyl thiolate to give disulphide, with *p*-chlorophenylthiolate to give the $S_{RN}1$ product (α-substituted sulphide), and with phenylthiolate to give the $S_{RN}1$ product and oxidation (disulphide); all these reactions of (25) with thiolate were very slow and only with very nucleophilic thiolates was the oxidation product dominant. The α-nitrophosphonate (37) did not give the oxidation product disulphide (section 2.9.1). The 1-methyl-1-nitroethyl phenyl sulphone (39) is generally unreactive with thiolate; reaction with *p*-chlorophenylthiolate has been reported to give some $S_{RN}1$ product and some oxidation product (disulphide), but again a very slow reaction. The reaction is probably slow enough to preclude observation of any activity. Likewise the e.s.r. spectrum of the radical-anion shows no dissociation at 77-140 K, i.e. it is a very stable intermediate.

From chemical reactions, e.s.r. and antimicrobial studies we can assign the following:

1. An order of antimicrobial activity for $Me_2C(X)NO_2$ with X = I >SCN, Br >*p*-ClC_6H_4S, *p*-$NO_2C_6H_4$ >Cl, NO_2 >N_3, CN, COMe, CO_2Et, PO_3Et_2, *p*-$NO_2C_6H_4N_2$ and $PhSO_2$.

2. From e.s.r. observations[115] of the radical-anions at 77-140 K, an order of stability of the radical-anions can be approximately assigned as follows:

a. Immediate dissociation Br >SCN >Cl >NO_2

b. No dissociation, i.e. very stable SO_2Ph, *p*-$NO_2C_6H_4$, $COCH_3$

c. Dissociation with loss of nitrite; N_3,CN, CO_2Et, PO_3Et_2

3. An approximate order of the ability of α-substituted-2-nitropropanes to oxidise thiolate to disulphide. A comparison made from reactions carried out in protic and dipolar aprotic solvents is as follows;

I >SCN >Br >*p*-ClC_6H_4S >Cl >NO_2 >SO_2Ph, *p*-$NO_2C_6H_4N_2$.

The COMe, CO_2Et, PO_3Et_2, N_3 and CN compounds either gave substituted product or did not react.

With the exception of α, *p*-dinitrocumene, these three facets of the behaviour of $R_2C(X)NO_2$ compare very closely, suggesting that the rate of oxidation of thiolate to disulphide and the stability of their radical-anions are implicated in their antimicrobial mode of action.

The comparison between antimicrobial activity and the rate of oxidation of thiolate to disulphide strongly confirms the studies of Stretton and Manson[16] who have shown that the mode of action of bronopol is due to oxidation of protein thiol to disulphide.

Our studies therefore suggest that active α-substituted nitro compounds ($Me_2C(X)NO_2$) have the same mode of action as bronopol. Our studies also suggest that the reaction of $Me_2C(X)NO_2$ *in vitro* with thiolate is an accurate guide to the potential antimicrobial activity. The mechanisms ($S_N2(X)$ or S.E.T.) are proposed[151] in section 2.11.

It is not clear exactly why the antimicrobial activity correlates with the stability of their radical-anions. Symons and Bowman[115] have suggested that the stability of the radical-anions is related to the bond-strength of the (C-X) bond, and therefore radical-anion stability will correlate with either the $S_N2(X)$ or S.E.T. mechanisms. This correlation may implicate the radical-anions of $Me_2C(X)NO_2$ as intermediates in the biological mode of action which points towards the single electron transfer mechanism.

EXPERIMENTAL

Experiment number

a - Preparation of 2-azido-2-nitropropane by nucleophilic substitution.

b - Inhibition studies.

3.24 Attempted preparation of 2-azido-2-nitropropane *via* the method of Maffei *et al.*

3.25 Preparation of 1-azido-1-nitrocyclohexane.

3.26 Preparation of phenyl azide.

3.27 Reaction of phenyl azide with norbornene.

3.28 Reaction of 2,2-diazidopropane with norbornene.

3.29 Reaction of 1-azido-1-nitrocyclohexane with norbornene.

3.30 Reaction of 2-azido-2-nitropropane

a - with sodium azide

b - Inhibition studies

3.31a Reaction of 2-azido-2-nitropropane with the sodium salt of benzenesulphinic acid.

b Inhibition studies.

3.32 Reaction of 1-azido-1-nitrocyclohexane with the sodium salt of benzene sulphinic acid.

3.33 Reaction of 2-azido-2-nitropropane with sodium salt *p*-chlorophenyl-thiolate.

3.34 Reaction of 1-azido-1-nitrocyclohexane with sodium salt of *p*-chlorophenylthiolate.

3.35a Reaction of 2-azido-2-nitropropane with the sodium salt of 2-nitropropane.

b Inhibition studies

3.36a Reaction of 1-azido-1-nitrocyclohexane with the sodium salt of 2-nitropropane.

b Inhibition studies.

3.37 Reaction of 2-azido-2-nitropropane with the sodium salt of diethyl ethylmalonate.

3.38 Preparations of 2-nitro-2-thiocyanatopropane.

a - By oxidative addition "Normal".

b - By oxidative addition "reverse order".

c - Attempted preparation of 2-nitro-2-thiocyanatopropane by nucleophilic substitution.

d - Attempted preparation of 2-nitro-2-thiocyanatopropane using entraining agent.

3.39 Preparation of 1-nitro-1-thiocyanatocyclohexane.

3.40 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of 2-nitropropane and inhibition studies.

3.41 Reaction of 1-nitro-1-thiocyanatocyclohexane with the sodium salt of 2-nitropropane.

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i. With the sodium salt of *p*-chlorothiophenol and inhibition studies.

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a - With the sodium salt of 2-nitropropane.

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3.49 Reactions of 2-cyano-2-nitropropane with thiolates

a - With the sodium salt of phenylthiol.

b - With the sodium salt of *p*-chlorophenylthiol.

3.50 Reactions of 3-methyl-3-nitrobutane-2-one and ethyl-2-methyl-2-nitropropionate with *p*-chlorophenylthiolate.

3.51 Reactions of α-substituted nitrocompounds with thiolate anions in protic solvents.

a - Reactions of 2-bromo-2-nitropropan-1,3-diol.

i - With the sodium salt of *p*-chlorophenylthiol

ii - With the sodium salt of benzylthiol.

iii - With the sodium salt of *p*-nitrophenylthiol

3.52a Preparation of 2-chloro-2-nitropropan-1,3-diol

b Reactions of 2-chloro-2-nitropropan-1,3-diol with thiolate anions in protic solvents.

3.53 Reactions of 5-bromo-5-nitro-1,3-dioxane with thiolate anions in protic solvents.

a - With (L) cysteine.

b - With the sodium salt of *p*-chlorophenylthiol

c - With *p*-chlorophenylthiol

3.54 Reactions of 2-substituted-2-nitropropanes with thiolate anions in protic solvents.

a - Reactions of 2-chloro-2-nitropropane with the sodium salt of *p*-chlorophenylthiol and inhibition studies.

b - Reactions of 2-bromo-2-nitropropane with the sodium salt of *p*-chloro phenylthiolate and inhibition studies

c - Reactions of 2-nitro-2-thiocyanatopropane with thiolate anions.

i - With the *p*-nitrophenylthiolate.

ii - With the sodium salt of *p*-chloro phenylthiolate,inhibition studies.

iii - With the sodium salt of phenylthiol.

3.55 Microbiology.

Experimental

The following conditions apply unless otherwise stated. All solvents were distilled and dried by conventional methods. Analytical thin layer chromatography was performed using silica gel (GF_{254} according to Stahl), supplied by Merck, on 0.25 mm thick plates. Preparative thin layer chromatography was performed using silica gel as above for 0.75 mm thick plates.

Analytical gas chromatography was carried out using a Pye 114 series gas chromatograph with a flame ionisation detector on a 5 ft. column of 10% SE30 on Gas Chrom Q.

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Proton magnetic resonance spectra were recorded by a Varian EM360A spectrometer (60MHZ) and Perkin-Elmer R32 spectrometer (90MHZ) in solutions of deuteriochloroform and/or DMSO-d6 with tetramethylsilane (TMS) as internal standard. The following abbreviations are used in the presentation of the spectra, s = singlet, d = douplet, q = quartet, t = triplet, m = multiplet, br = broad.

Quantitative analyses by ^{1}H.n.m.r. of reaction product mixtures were carried out using an added internal standard (p-dimethoxybenzene) of known amount. The relative integration of peaks was used for the calculation of molar quantities.

Infrared spectra were recorded as KBr discs, Nujol mulls, liquid films or chloroforms solutions by means of Perkin-Elmer 177 grating spectrometer and the quoted absorbances are strong except where indicated (m = medium, w = weak). Mass spectra were recorded on a DS-55 Mass spectrometer

Refractive indices were determined at 25^{o}C on an Abbe refractometer.

Analysis were performed by the microanalytical departments of Manchester University and Nottingham University.

Nitrogen was dried and deoxygenated by passing it through a series of wash bottles containing Fieser's solution, conc. sulphuric acid, and

potassium hydroxide.

Common abbreviations used are: DMF - N,N-dimethylformamide, DMSO - dimethylsulphoxide, HMPA - Hexamethylphosphoramide, MeOH-Methanol, $MgSO_4$ - anhydrous magnesium sulphate, THF - Tetrahydrofuran, t.l.c. - thin layer chromatography, O_2 - oxygen gas, N_2 - nitrogen gas, *p*-DNB - *p*-dinitrobenzene, DTBN - Di-*tert*-butyl-nitroxide.

3.1 Preparation of 2-bromo-2-nitropropane[65]

Aqueous sodium hydroxide (40 g in 200 ml H_2O) and 2-nitropropane (89 g, 1 mol) were mixed in a round-bottomed flask until a single layer was formed. Bromine (216 g, 1.35 mol) was added slowly until the reaction mixture retained a slight brownish colour. The resultant two phases were separated, the aqueous layer discarded, and the organic layer washed successively with 10% thiosulphate solution, 5% aqueous sodium hydroxide, and distilled water. The crude liquid was dried ($MgSO_4$) and distilled *in vacuo* to yield a colourless lachrymatory liquid of 2-bromo-2-nitropropane (141 g, 84%), b.p. 30°C (1 mm) (lit[65], 61-62°C at 29 mm), ν_{max} (neat) 1554 cm^{-1}; $\delta(CDCl_3)$ 2.27 (s).

3.2 Preparation of 2-chloro-2-nitropropane[65]

Freshly distilled 2-nitropropane (25 g, 0.28 mol) and sodium hydroxide (12 g, 0.3 mol) in water (120 ml) were mixed in a 250 ml 3-necked round bottom flask until a single layer was obtained. Chlorine gas was then passed through the solution until it was no longer absorbed. The excess of halogen was removed at the water pump. The organic layer was separated, washed with 10% aqueous sodium thiosulphate (2 x 25 ml), 5% aqueous sodium hydroxide (2 x 25 ml), and water (2 x 25 ml) and dried ($MgSO_4$). The product was distilled *in vacuo* to yield a colourless liquid of 2-chloro-2-nitropropane (17 g, 52%), b.p. 48-51° (30 mm), (lit[65] b.p. 48-50° at 26-30 mm) ν_{max} 1550 cm^{-1} $\delta(CDCl_3)$ 2.15 (s).

3.3 Preparation of 2-iodo-2-nitropropane[65]

2-Nitropropane (22.5 g 0.28 mol) was added to a solution of sodium methoxide (0.28 mol) in methanol. The mixture was stirred for an hour and the solvent removed *in vacuo*. The resulting white solid was dissolved in ice-water (780 ml) to which iodine (50.8 g, 0.4 mol) in diethyl ether (250 ml) was added rapidly. The resultant two layers were separated and the aqueous portion extracted twice with diethyl ether (2 x 80 ml). The organic fractions were combined, washed with 10% thiosulphate solution, and dried ($MgSO_4$). The solvent was removed *in vacuo*, with the exclusion of light, to yield a colourless, lachrymatory liquid of 2-iodo-2-nitropropane, which darkened on standing (30 g, 71%); ν_{max} 1540 cm^{-1}; $\delta(CCl_4)$ 2.46 (s).

3.4 Preparation of *p*-dinitrobenzene[89]

a) Preparation of *p*-nitrophenyl diazonium fluoborate:

p-Nitroaniline (34 g, 0.25 mol) was dissolved in fluoboric acid solution (110 ml) in an Erlenmeyer flask which was cooled in an ice-bath. The solution was stirred with an efficient stirrer. A cold solution of sodium nitrite (17 g, 0.25 mol) in water (34 ml) was added dropwise. When the addition was completed, the mixture was stirred for a few minutes and the crystals filtered off. The solid diazonium fluoborate was washed with cold fluoboric acid (1 x 30 ml), 95% alcohol (2 x 50 ml), and finally several times with diethyl ether (3 x 50 ml). The solid had to be well stirred in each washing and this was achieved by using a sintered glass filter. The diazonium fluoborate was dried in a desiccator over phosphorus pentoxide (56 g, 95%).

b) Preparation of *p*-Dinitrobenzene

Sodium nitrite (200 g, 2.9 mol) was dissolved in water (400 ml) in a 2 l Erlenmeyer flask. Copper powder (40 g, 0.63 mol)was added. The mixture was stirred efficiently. A suspension of the *p*-nitrophenyldiazonium fluoborate

(56 g, 0.26 mol) in water (200 ml) was added slowly. Diethyl ether (4-5 ml) was added at this stage in order to break the foam that had formed. The reaction was complete by the time all the diazonium compound had been added and a precipitate was formed. The product was filtered and washed with water dilute aqueous sodium hydroxide, and water. The solid was dried in an oven at 110°C, powdered, and extracted overnight with toluene (300 ml) using a soxhlet system. The solvent was removed *in vacuo* to obtain a reddish residue which was recrystallised from chloroform to yield reddish brown crystals of *p*-dinitrobenzene (22.1 g, 51%); m.p. 175-177° (lit.[89] m.p. 177°); υ_{max} 3140, 2980, 2860, 1560, 1460, 1380, 1350, 1120, 860, 840, 720 cm^{-1}; $\delta(CDCl_3)$ 8.3 (s).

3.5 Preparation of α, *p*-dinitrocumene.[88]

p-Dinitrobenzene (10.1 g, 60 mmol) was dissolved with stirring in DMSO (100 ml) in a 250 ml round-bottomed flask under an atmosphere of nitrogen and anhydrous conditions. After 30 min the sodium salt of 2-nitropropane (6.3 g, 56 mmol) was added and the stirring continued for 3h at 25°. The resulting deep reddish-brown reaction mixture was poured into ice-water (400 ml) and extracted with benzene (4 x 100 ml). The benzene extracts were combined, washed with water (4 x 50 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a crude brown residue which was recrystallised from hexane - benzene to yield unreacted starting material (2.3 g, 23%). The mother-liquor was left to stand in a deep-freezer; the resulting crystals were filtered and re-crystallised from hexane - benzene (50 : 50) to yield pure crystals of α,*p*-dinitrocumene (9.5 g, 75%); m.p. 67-69° (lit.[88] m.p. 69-70°); ν_{max} 1605, 1550, 1455, 860, 720 cm^{-1}; $\delta(CDCl_3)$ 7.6 (4H, ^{A}Bq) 2.12 (6H, s).

3.6 Preparation of 2-(*p*-nitrophenylazo)-2-nitropropane[76]

p-Nitrobenzenediazonium tetrafluoroborate (2.3 g, 10 mmol) was dissolved in dry DMF (50 ml) in a three-necked round bottomed flask and the solution deoxygenated for 15 min with dry N_2. The sodium salt of 2-nitropropane (1.1 g, 10 mmol) was added and the reaction mixture stirred for a further 15 min under N_2. The reaction mixture was poured into ice-water (100 ml), and extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water (4 x 30 ml), and dried ($MgSO_4$). Removal of the solvent *in vacuo* yielded a yellow solid which was recrystallised from methanol to give yellow crystals of 2-(*p*-nitrophenylazo)-2-nitropropane (0.5 g, 25%); m.p. 102-104° (lit.[76] 104°); υ_{max} 1550, 1530 cm^{-1}, $\delta(CDCl_3)$ 1.95 (6H,S, $2CH_3$), 7.87 (2H, d, arom.), 8.35 (2H, d, arom).

3.7 Preparation of 2-nitro-2-nitrosopropane[91]

2-Nitropropane (45 g, 0.5 mol) was dissolved in sodium hydroxide solution (22 g, 0.55 mol) in water (100 ml) in a 1 l round-bottomed flask. The flask and contents were cooled to 0° (salt/ice). Sodium nitrite (37 g, 0.53 mol) was added, followed by dropwise addition of 6N hydrochloric acid (20 ml), keeping the temperature below 5°C. The addition of hydrochloric acid was continued until the solution became just acidic. A deep blue colour appeared followed by precipitation of crystals of the nitroso dimer. The crystals were filtered, washed with distilled water (4 x 50 ml) and diethyl ether (2 x 30 ml) to obtain a colourless crude product which was dried overnight in the desiccator. Double recrystallisation from diethyl ether yielded crystalline propyl pseudonitrole dimer (21 g, 25%); m.p. 75-76°C (lit.[91] m.p. 76°C); υ_{max}, 1560 cm^{-1}; $\delta(CDCl_3)$ 1.5 (s).

3.8 Preparation of 1-methyl-1-nitroethyl *p*-nitrophenyl sulphide[33]

Sodium *p*-nitro-phenylthiolate (0.54 g, 3.0 mmol) was added to DMF (25 ml) under an atmosphere of nitrogen. When the salt had completely dissolved 2-bromo-2-nitropropane (0.5 g, 3.0 mmol) was added. The reaction mixture was stirred and illuminated with two 15-W fluorescent lamps. The initial deep red colour of the thiolate anion faded after *ca*.20 min After 1h the reaction mixture was poured into ice-water (50 ml) and extracted with diethyl ether (4 x 30 ml). The combined ether extracts were washed with distilled water (4 x 20 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a crude product which on recrystallisation from diethyl ether yielded yellow crystals of the α-nitrosulphide (0.6 g, 83%); m.p. 102-104° (lit.[33] 102-104°); υ_{max} 1535; 1345 and 1600 cm^{-1}; $\delta(CDCl_3)$ 1.90 (6H, s, 2Me) and 7.88 (4H, ABq, arom.).

3.9 Preparation of 1-methyl-1-nitroethyl *p*-chlorophenyl sulphide[33]

A stream of oxygen was passed through a solution of di-(*p*-chlorophenyl) disulphide (1.11 g, 3.86 mmol) in DMF (150 ml). The sodium salt of 2-nitropropane (1.15 g, 13.5 mmol) was added and the mixture stirred for 2h. The reaction mixture was poured into ice-water (500 ml), extracted with diethyl ether (4 x 60 ml), and the combined ether extracts washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a yellow-white solid which was recrystallised from hexane to give the α-nitrosulphide as colourless crystals (0.67 g, 76%); m.p. 81-82° (lit.[33] 82-83°); υ_{max} 1550 cm^{-1}; $\delta(CDCl_3)$ 1.83 (6H, s), 7.37 (4H, s).

3.10 Attempted preparation of 3-methyl-3-nitrobutan-2-one by C-acylation of 2-nitropropane sodium salt[92]

Dry THF (40 ml) was pipetted into a three necked round bottomed flask fitted with a nitrogen bleed a magnetic stirrer bar and a reflux condenser. The sodium salt of 2-nitropropane (3 g, 27mmol) was added followed by 1-acetyl-imidazole (3 g, 27 mmol). The suspension formed was heated under reflux

with stirring for 20h.

The reaction mixture was poured into ice-water (50 ml) extracted with diethylether (4 x 20 ml), the combined ether layers washed with distilled water (2 x 20 ml), and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave back the starting material.

3.11 Preparation of 3-bromo-3-methylbutan-2-one

3-Methylbutan-2-one (43 g, 0.5 mol) was dissolved in ethanol (50 ml) in a 500 ml three necked round bottomed flask fitted with pressure equalizing funnel, a drying tube and a magnetic bar. Bromine (112 g, 1.4 mol) was added dropwise until the reaction mixture retained a dark bromine colouration. The mixture was cooled and poured into ice-water overlayered with diethyl ether (50 ml). The organic layer was separated, and the aqueous layer was further extracted with diethyl ether (2 x 30 ml). The combined ether extracts were washed with distilled water (2 x 30 ml), sodium bicarbonate solution (5% $^{w}/v$) (2 x 30 ml) and sodium thiosulphate solution (5% $^{w}/v$) (2 x 20 ml), and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a red oil. The crude product was fractionally distilled to give 3-bromo-3-methylbutan-2-one (40.8 g, 51%); b.p.$_{15}$ 46-48°C; υ_{max} (neat), 2995, 2900, 2930, 1710, 1450, 1360, 1350, 1280, 1180, 1100, 960, 899 cm^{-1}; $\delta(CDCl_3)$, 1.85 (6H,s) 2.4 (3H,s); g.l.c. (SE30, 10%) only one peak.

3.12 Preparation of 3-methyl-3-nitrobutan-2-one[93]

Dry DMSO (200 ml) was poured into a 500 ml round bottomed flask fitted with a drying tube and a magnetic bar. 3-Bromo-3-methylbutan-2-one (6.75 g, 40 mmol) was added to a stirred mixture of sodium nitrite (15 g, 0.16 mol) and resorcinol (13 g, 0.11 mol). The reaction mixture was stirred for 20h. The reaction mixture was poured into a beaker containing ice-water overlayered with diethyl ether (400/100 ml). The organic layer was separated and the aqueous layer further extracted with diethyl ether (4 x 25 ml). The ether extracts were combined and washed with distilled water (4 x 30 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give

a crude reddish liquid which was fractionally distilled (42-44° at 16 mmHg) gave white crystals of 3-methyl-3-nitrobutan-2-one. Recrystallisation from (Pet ether 60-80/hexane) gave colourless crystals of 3-methyl-3-nitrobutan-2-one (4.6 g, 85%) m.p. 30-31° (lit.[153] m.p. 29-30°); υ_{max} 2980, 2850, 1730, 1550, 1470, 1380, 1240, 1180, 1120, 860 cm^{-1}; $\delta(CDCl_3)$ 1.72 (6H,s) 2.21 (3H,s); g.l.c. (SE30, 10%) only one peak.

3.13 Preparation of ethyl 2-methyl-2-nitropropionate[93]

The procedure in experiment 3.12 was followed, using the following quantities; ethyl 2-bromo-2-methylpropionate (19.5 g, 0.1 mol), sodium nitrite (12 g, 0.13 mol) and resorcinol (13 g) in DMSO (200 ml) were reacted for 2.5h. The crude reddish oil was fractionally distilled to give ethyl 2-methyl-2-nitroprpionate (1.95 g, 53%) b.p. 69-71°C (lit[93] 70-71°C); $\upsilon_{max(neat)}$ 1553 cm^{-1}, $\delta(CDCl_3)$ 1.29 (3H, t) 1.8 (6H,s) 4.22 (2H, q); g.l.c. (SE30 10%) one peak only.

3.14 General procedure for oxidative addition of anions to nitro-anions ("Normal" addition)[97]

a - Preparation of 2-cyano-2-nitropropane

Freshly distilled 2-nitropropane (4.45 g, 50 mmol) was dissolved in a solution of sodium hydroxide (2.8 g, 70 mmol) in water (30 ml) in a three necked round bottom flask. Sodium cyanide (4.9 g, 0.1 mol) and diethyl ether (30 ml) were added. A saturated aqueous solution of potassium ferricyanide (32.9 g, 0.1 mol) in water (75 ml) was added dropwise to the stirred solution at 20-25°. When the addition was completed the reaction mixture was stirred for 30 min at room temperature. The ether layer was separated and the aqueous layer extracted with diethyl ether (2 x 20 ml) The ethereal layers were combined, washed with water (2 x 20 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to obtain a crude product.

Vacuum distillation of crude product afforded 2-cyano-2-nitropropane (98%) pure with an impurity of 2,3-dimethyl-2,3-dinitrobutane (2%) by ^{1}H.n.m.r. The 2-Cyano-2-nitropropane was purified by distillation to give (2.1 g, 42%); b.p.$_{13}$ 76-78^o; υ_{max} 2260, 1555 cm^{-1}; $\delta(CDCl_3)$ 2.04 (s).

3.15 Preparation of 2,2-dinitropropane[97]

2,2-Dinitropropane was prepared using the general procedure for oxidative addition (expt. 3.14). 2-Nitropropane (17.8 g, 0.2 mol), sodium nitrite (27.6 g, 0.4 mol) and a saturated solution of potassium ferricyanide (131.7 g, 0.4 mol) were reacted to afford a crude product, which was distilled to yield a colourless solid of 2,2-dinitropropane (8.3 g, 31%); b.p.$_9$ 68-70^o , [lit.[97] 56-60^o (3 mm)]; υ_{max} 1555 cm^{-1}; $\delta(CDCl_3)$ 2.15 (s, 2 Me).

3.16 Preparation of diethyl 1-methyl-1-nitroethylphosphonate[70]

Dry THF* (30 ml) was pipetted into a three necked, round bottomed flask fitted with a nitrogen bleed and a magnetic bar. Diethylphosphite (1.4 g, 10 mmol) was added, followed by potassium *t*-butoxide (1.0 g, 9 mmol). The reaction was cooled down to -45^{o}C (Dry ice/Acetone). 2-Chloro-2-nitropropane (1.1 g, 9 mmol) was added dropwise and the reaction was stirred for 30 min. Potassium chloride was precipitated out during the reaction. The reaction mixture was warmed to 25^{o}C. The precipitate was filtered-off, the THF removed *in vacuo*, and the residue extracted from brine with diethyl ether (2 x 50 ml). The ether extracts were washed with distilled water (3 x 20 ml), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude product. ^{1}H.n.m.r. analysis of the crude product indicated diethyl 1-methyl-1-nitroethylphosphonate (75%) pure and 2-chloro-2-nitropropane (8%). Fractional distillation afforded pure diethyl 1-methyl-1-nitroethylphosphonate (1.5 g, 76%), b.p.$_{2.5}$ 94-96^o (lit.[70] b.p.$_2$ 94-95^o); $\upsilon_{max(neat)}$ 2980, 2950, 1550, 1470, 1400, 1370, 1340, 1260, 1160, 1045, 1015, 970, 855, 770 cm^{-1}, $\delta(CDCl_3)$ 4.25 (4H,m) 1.75 (6H, d) 1.35 (6H, t). The above reaction was repeated several times

and yielded 74-78% of diethyl 1-methyl-1-nitromethylphosphonate.

N.B. The chain reaction failed to proceed in reactions where the THF was not vigorously purified and dried.

3.17 Preparation of 1-methyl-1-nitroethyl phenyl sulphone[68]

2-Bromo-2-nitropropane (3.36 g, 10 mmol) and the sodium salt of benzene sulphinic acid (4.92 g, 30 mmol) were stirred together in dry DMF (190 ml) at -20°C under an atmosphere of N_2 for 2h. The reaction mixture was illuminated with two 15 W fluorescent tubes. The reaction mixture was poured into a beaker containing distilled water (200 ml) overlayered with benzene (200 ml). The aqueous fraction was extracted with benzene (2 x 50 ml) and the combined benzene fractions washed thoroughly with distilled water (3 x 50 ml). Removal of the benzene *in vacuo* gave a white solid which was recrystallised from absolute ethanol to give 1-methyl-1-nitroethyl phenyl sulphone as colourless crystals (3.45 g, 77%); m.p. 115-7° (lit.[68] 116-7°); υ_{max} 1550, 1343, 1334, 1160, 1140 cm^{-1}; $\delta(CDCl_3)$ 1.95 (6H, s) 7.71 (5H,m).

3.18 Preparation of the sodium salt of 2-nitropropane

Sodium (5.8 g, 0.25 g.atom) was slowly added to dry methanol (100 ml) with stirring under nitrogen. When all the sodium had dissolved 2-nitropropane (22 g, 0.25 mol) was added and stirring continued for 30 min. The excess solvent was removed *in vacuo* and evacuated at 60° and 1 mmHg to yield a free-flowing white powder (27.7 g, 100%), $\delta(D_2O)$ 2.0 (s).

3.19 Preparation of the sodium salt of diethyl ethylmalonate

Dry ethanol (100 ml) was placed in a three necked round bottomed flask flushed with nitrogen and stirring was commenced. Sodium metal (1.25 g, 54 mmol) was added in small lumps and the mixture stirred until the metal dissolved. Diethyl ethylmalonate (10 g, 53 mmol) was added and the reaction mixture stirred for 1h.

The solvent was removed *in vacuo* to yield a white powder which was dried *in vacuo* at 1 mm overnight (11.1 g, 100%); $\delta(CDCl_3)$ 1.10 (3H,t);

1.24 (6H,t), 3.64 (2H,q), 4.16 (4H,q).

3.20 Preparation of the sodium salt of *p*-chlorophenylthiol

Clean fresh sodium (4.8 g, 0.21 g.atom) was added as small lumps, with stirring to dry methanol (150 ml). A steady stream of nitrogen was passed through the flask throughout the preparation. When all the metal had dissolved *p*-chlorophenylthiol (30 g, 0.21 mol) was introduced over 15 min and the reaction mixture stirred for 2h.

The solvent was removed *in vacuo* at 40^{o} to yield a white powder which was washed with copious amounts of dry diethyl ether under an atmosphere of nitrogen and redried *in vacuo* (33g, 94%), m.p. 232-234^{o} (lit[33] m.p. 232-235^{o}); $\delta(CDCl_3)$ 7.5 (s).

All phenylthiol salts were stored *in vacuo*. All the salts are susceptible to oxidation to the corresponding sulphinate salts, and it should be stressed that oxygen must be vigorously excluded.

It was found preferable to prepare fresh thiolate salts shortly before use. The following thiolates were prepared in the same way as the sodium salt of *p*-chlorophenylthiolate:
p-nitrophenylthiolate m.p. >275^{o}; $\delta(CDCl_3)$ 6.67 (AB q); Benzylthiolate m.p. >275^{o}; $\delta(CDCl_3)$ 3.45 (2H,s), 7.15 (5H,s); phenylthiolate m.p. >260^{o} $\delta(CDCl_3)$ 7.1 (5H,s).

3.21 Preparation of 2,2-diazidopropane

Using the general procedure for oxidative addition (expt. 3.14), 2-nitropropane (4.45 g, 0.05 mol), sodium hydroxide (2.3 g, 0.06 mol), sodium azide (6.5 g, 0.1 mol), and potassium ferricyanide (32.9 g, 0.1 mol) were reacted for 60 min. The ^{1}H.n.m.r. analysis of crude product showed only one singlet at δ1.5 and the i.r. spectrum showed no nitro absorption. The liquid was fractionally distilled* to afford a colourless liquid of 2,2-diazidopropane (1.21 g, 19%); b.p.$_{0.1}$ 35-37^{o}; υ_{max} 2100cm^{-1} (vs, N_3) λ_{max}(Ethanol) 284 nm; $\delta(CDCl_3)$ 1.5 (s); ^{13}C.n.m.r. ($CDCl_3$)p.p.m. 25.969 (q, 2Me), 79.11 (s, quaternary carbon).

The reaction was repeated several times on 2x scale to yield 2,2-diazidopropane in an average yield of 39%.

* The fractional distillation and all procedures were carried out in a fume cupboard behind a safety screen in case of possible explosion. The 2,2-diazidopropane was cooled to *Ca* -50° and allowed to slowly warm up, distilling at 35-37° at 0.1 mm Hg. Attempted combustion analysis of 2,2-diazidopropane ended up with a shattered combustion tube.

3.22 General procedure for oxidative addition

a) Preparation of 2-azido-2-nitropropane

Freshly distilled 2-nitropropane (4.45 g, 0.05 mol) was dissolved in a solution of sodium hydroxide (2.3 g, 0.06 mol) in water (30 ml). The nitronate solution was added dropwise to a mixture of sodium azide (3.25 g, 0.05 mol) in a saturated aqueous solution of potassium ferricyanide (32.9 g, 0.1 mol) in H_2O (100 ml) and diethyl ether (70 ml) with stirring at such a rate that the temperature remained at 20-25°. After completion of the addition the mixture was stirred for a further 20 min. The ether layer was separated, and the aqueous phase extracted with diethyl ether (2 x 40 ml). The ether extracts were combined, washed with water (4 x 30 ml) dried ($MgSO_4$), and the solvent removed *in vacuo* at low temperature to yield a yellowish liquid. ^{1}H.n.m.r. analysis showed a peak at δ1.5 which corresponds to 2,2-diazidopropane (9%), a peak at δ1.8 corresponds to 2-azido-2-nitropropane (22%), and a trace of 2,2-dinitropropane at δ2.20. The above procedure was repeated with various molar quantities of materials ^{1}H.n.m.r. analysis of the crude reaction products showed a similar mixture.

The crude product was fractionally distilled using the method described in procedure (3.21) in each run to yield pure 2-azido-2-nitropropane.

b-

Optimum reaction conditions for preparation of 2-azido-2-nitropropane *via* oxidative addition

Freshly distilled 2-nitropropane (4.45 g, 0.05 mol) was dissolved in a solution of sodium hydroxide (2.8 g, 0.06 mol) in water (30 ml). Sodium azide (6.5 g, 0.1 mol) and methylene chloride (70 ml) were added, and the solution stirred. A saturated aqueous solution of potassium ferricyanide (32.9 g, 0.1 mol) in water (100 ml) was added.

Immediate work-up afforded a yellowish crude product. ^{1}H.n.m.r. analysis of the crude product showed a peak at δ1.5 which corresponds to 2,2-diazidopropane (19%) and at δ1.8 which corresponds to 2-azido-2-nitropropane (28%).

The reaction was repeated for different times. The yields 2,2-diazidopropane and 2-azido-2-nitropropane in the crude products were analysed by ^{1}H.n.m.r. using an internal standard. The results are shown in Table 2.1 on page 51.

The crude product was fractionally distilled as in expt. 3.21 to yield a yellowish oil of pure 2-azido-2-nitropropane b.p.$_{15}$ 20-25°; υ_{max} 3000, 2460, 2120, 1555, 1455, 1390, 380, 1295, 1250, 1180, 1140, 830 cm^{-1}, δ($CDCl_3$) 1.8 (6H,s); ^{13}Cppm ($CDCl_3$/TMS) 25.09 (q, 2Me) 100.48 (s, quaternary carbon).

3.23 General procedure for nucleophilic substitution reactions

a - Preparation of 2-azido-2-nitropropane by nucleophilic substitution

Sodium azide (0.65 g, 0.01 mol) was added with stirring to HMPA (30 ml) in a 100 ml three necked round bottomed flask under an atmosphere of nitrogen (the flask was fitted with a rubber septum in one of the necks). 2-Bromo-2-nitropropane (1.68 g, 0.01 mol) was added after 10 min by injection through the septum using a syringe. The reaction went red in colour during the addition. The progress of the reaction was monitored periodically by the removal of aliquots (1 ml) from the reaction mixture. Each aliquot was pipetted into a sample tube containing diethyl ether (5 ml)

and ice-cold water (5 ml), and shaken. The ether layer was separated, dried ($MgSO_4$), and the solvent removed by evaporation under a stream of nitrogen. The residue was analysed by t.l.c. (chloroform /silica gel) and ^{1}H.n.m.r. to check the extent of the reaction. The course of the reaction was terminated after 24h. The reaction mixture was poured into ice-cold distilled water (100 ml) and extracted with diethyl ether (3 x 25 ml). The ether extracts were combined and washed with distilled water (2 x 40 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a yellowish liquid of crude 2-azido-2-nitropropane (0.5 g, 38%); υ_{max} 2120, 1555 cm^{-1}; $\delta(CDCl_3)$ 1.8 (6H,^{s}).

The above procedure was repeated, except that the duration of reaction was varied, to yield mixtures of products which were analysed by ^{1}H.n.m.r. spectroscopy. The results are shown in Table 2-2 on page 53. The crude product was fractionally distilled as in (3.21) to yield a pure product of 2-azido-2-nitropropane.

b - Inhibition studies for the preparation of 2-azido-2-nitropropane *via* nucleophilic substitution

1) Control: The reaction was carried out as in expt. 3.23a for 15 min and 60 min.The yields of2-bromo-2-nitropropane (17%) and 2-azido-2-nitropropane (25%)wereestimated by ^{1}H.n.m.r. analysis. A duplicate run of control reaction gave similar results.

2) Exclusion of light: The reaction was repeated as in (b1) for 15 and 60 min except that the flask was completely wrapped in aluminium foil to exclude light.

3) *p*-Dinitrobenzene inhibition: The reaction was repeated as in (b1) for 15 min except that 5 molar % of *p*-DNB was added to the reaction mixture prior to the addition of 2-bromo-2-nitropropane and photolysis. A duplicate run of the experiment (15 min) gave similar results.

4) Di-t-butyl-nitroxide inhibition: The reaction was repeated as in (b1) for 15 and 60 min except that 10 molar % of DTBN was added to the

reaction mixture prior to the addition of the 2-bromo-2-nitropropane and photolysis. A duplicate run of the experiment (15 and 60 min) gave similar results.

The yields of all these reactions were calculated from ^{1}H.n.m.r., using an internal standard, of the crude product. The results are reported in Table 2-2 on page 53.

3.24 Attempted preparation of 2-azido-2-nitropropane *via* the method of Maffei *et al*[102]

Dry propylpseudonitrole (5.9 g, 0.05 mol) was dissolved in chloroform (90 ml) in a round bottomed flask equipped with an efficient magnetic stirrer. Distilled glacial acetic acid (6.5 ml) was added and the reaction vessel and contents cooled to 0° (salt/ice). Sodium azide (7.1 g, 0.11 mol) was added portionwise over 2h keeping the temperature at 5°. The course of the reaction was terminated when the reaction mixture became colourless from bright blue (20-22h). The reaction mixture was cooled, washed with cold water (4 x 100 ml), neutralized by washing with 5% sodium carbonate solution (4 x 50 ml), and washed again with ice-cold water (4 x 50 ml). The organic layer was separated, dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a yellowish liquid (3.14 g, 96%). The product was not distilled due to the explosive nature of the functional groups. The product was chromatographed (silica/Toluene) to afford pure 1-azido-2-nitropropane (2.7 g, 89%); υ_{max} 2930, 2120, 1555, 1455, 1400, 1355, 1285, 770 cm^{-1}; $\delta(CDCl_3)$ 4.55 (1H, m), 3.75 (2H, m) 1.55 (3H, d); n_d^{20} 1.46 (lit.[103] n_D^{20} 1.46).

3.25 Preparation of 1-azido-1-nitrocyclohexane

Using the procedure reported in expt. 3.22, 1-nitrocyclohexane (3.25 g, 0.025 mol), sodium hydroxide (3.2 g, 0.08 mol), sodium azide (6.5 g, 0.1 mol), potassium ferricyanide (32.9 g, 0.1 mol) and methylene chloride (80 ml) in place of diethyl ether afforded a light green liquid as the crude product. The crude product was not distilled due to explosive properties of the functional groups and the higher temperature required.

the yield was (2.95 g, 70%); υ_{max} 2950, 2870, 1215, 1550, 1450, 1358, 1290, 1230, 1155, 1110, 956, 907, 807, 740 cm^{-1}; $\delta(CDCl_3)$ 1.5 (6H, m) 2.12 (4H, m) T.l.c. and g.l.c. analysis showed a pure product except for traces of cyclohexanone.

A similar reaction, carried out by the "normal" oxidative addition procedure (expt. 3.14) in CH_2Cl_2, gave the same results as above (2.9 g, 69%) reaction, and in dry diethyl ether, gave a lower yield (2.02 g, 48%).

3.26 Preparation of phenyl azide[154]

Distilled water (100 ml) and concentrated hydrochloric acid (13.8 ml) were placed in a 500 ml three necked round-bottomed flask, fitted with a stirrer, thermometer, and a dropping funnel. The flask was cooled in an ice/salt bath, stirring started, and phenylhydrazine (8.3 g, 0.077 mol) added dropwise. The phenylhydrazine hydrochloride separated as fine white plates. Stirring was continued, and after the temperature had fallen to 0^{o}, diethyl ether (100 ml) was added, after which a previously prepared solution of sodium nitrite (6.25 g) in water (100 ml) was added from a dropping funnel at a rate such that the temperature NEVER rose above $3^{o}C$. The mixture was then subjected to steam distillation and about 200 ml of distillate were collected. The organic layer was separated and the aqueous layer further extracted with diethyl ether (2 x 20 ml). The ether extracts were combined, washed with distilled water (2 x 10 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* at low temperature to yield a crude oil of phenylazide (3.8 g, 42%); υ_{max}(neat) 2120, 1595, 1490, 810, 750, 690, 670 cm^{-1}.

The crude product was used for next stage without distillation due to the explosive nature of the functional group.

3.27 Reaction of phenyl azide with norbornene[107]

Norbornene (0.5 g, 5 mmol) and phenyl azide (0.9 g, 7.5 mmol) were placed in a small Erlenmeyer flask which was allowed to stand overnight in a fume cupboard.The flask was rubbed with a glass rod to give the product as a crystalline mass which was recrystallised from aqueous methanol to afford the pure dihydrotriazole (1.07 g, 94%); m.p. 101-102° (lit.[107] 101-102°); υ_{max}(Nujol) 2920, 1600, 1500, 1470, 1380, 1260, 1140, 1120, 1105, 1030, 990, 960, 850, 760, 700 cm^{-1}. $\delta(CDCl_3)$ 1.15 (4H, m) 2.65 (2H, d) 3.7 (1H d)$_{4.5(1H,d)}$ 6.9 (2H, m) 7.3 (5H, s); ^{13}Cppm ($CDCl_3$ /TMS) 1,(24.98, t); 2,(25.64, t); 3,(32.20, t); 4,(40.13, d); 5,(41.33, d); 6,(60.46, d); 7,(86.27, d); 8,(114.21, d); 9,(122.0, d); 10,(129.5, d); 11,(139.55, s). (See page 59)

3.28 Reaction of 2,2-diazidopropane with norbornene

Norbornene (0.5 g, 5 mmol) and 2,2-diazidopropane (0.9 g, 71 mmol) were allowed to stand overnight in diethyl ether (10 ml) in a stoppered Erlenmeyer flask. Needle-like crystals were formed. The ether was decanted and the crystals recrystallised from ethyl acetate to afford pure adduct (1.02 g, 87%); m.p. 108-110° ; (Found: C, 54.7; H, 7.4; N, 34.1, $C_{10}H_{16}N_6$ require: C, 54.52; H, 7.3; N, 38.15; υ_{max} 2040 cm^{-1}; $\delta(CDCl_3)$ 1.4 (10H, bm) 1.7 (2H, s) 2.19 (2H, s) 3.19 (1H, s).

The above reaction was also attempted with 2-azido-2-nitropropane but yielded only decomposed and unidentified material.

3.29 Reaction of 1-azido-1-nitrocyclohexane with norbornene

Norbornene (0.5 g, 5 mmol) and 1-azido-1-nitrocyclohexane (1.2 g, 7.05 mmol) were allowed to stand overnight in diethyl ether (10 ml in a stoppered Erlenmeyer flask. A crystalline solid was formed. The diethyl ether was decanted and the solid recrystallised from ethyl acetate to afford product (0.55 g, 39%); m.p. 104-106° ; υ_{max} 1550 cm^{-1} (NO_2), the combustion analysis was unsatisfactory.

3.29 a Reaction of 2-azido-2-nitropropane with sodium azide

Sodium azide (0.5 g, 7 mmol) was dissolved in distilled water (20 ml) and methylene chloride (20 ml) in a 250 ml round bottomed flask equipped with a stirrer. 2-Azido-2-nitropropane (250 mg, 1.9 mmol) was added and the reaction stirred for 1h. The organic layer was separated, washed with distilled water (2 x 20 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to yield pure 2,2-diazidopropane (220 mg, 91%) υ_{max} 2100 cm^{-1} (vs); $\delta(CDCl_3)$ 1.5 (s). The i.r. spectrum was identical with that of authentic material.

b) Inhibition studies

The control reaction was carried out as detailed in expt. 3.30a, with methylene chloride and water as solvent for 40 min to give 2,2-diazidopropane (91%).

Inhibition studies with *p*-DNB, DTBN and exclusion of light were carried out as detailed in expt. 3.23b. The results are shown in Table 2-3 on page 63.

3.31 a - Reaction of 2-azido-2-nitropropane with the sodium salt of benzene sulphinic acid

Using the standard procedure (expt. 3.23) the sodium salt of benzenesulphinic acid (1 g, 6 mmol) and 2-azido-2-nitropropane in DMSO (40 ml) were reacted for 5 min.

The crude product was recrystallised from hexane to give *1-azido-1-methylethyl phenyl sulphone* (600 mg, 70%); m.p. 72-73°; (Found: C, 47.6; H, 4.6; N, 18.6 $C_9H_{11}N_3O_2S$ requires C, 48.0; H, 4.8; N, 18.6%); υ_{max} (nujol) 2103, 1595, 1300, 1150, 760, 700 cm^{-1}; $\delta(CDCl_3)$ 1.52 (6H, brs) 7.5 (5H, m).

The above reaction was repeated in DMF for 10 and 40 min. Both reactions gave 59% of the product and a trace of 2-azido-2-nitropropane. When the reaction was repeated for 24h, 46% of product was obtained.

Photolysis with tungsten "white light" lamps (2 x 150 w) of the reaction in HMPA for 2h gave decomposed and unidentified material.

b - Inhibition studies

Expt. 3.31a (DMSO, 5 min) was taken as the control reaction. Inhibition studies with p-DNB and DTBN were carried out as detailed in expt. 3.23b. The results are shown on page 67.

3.32 Reaction of 1-azido-1-nitrocyclohexane with the sodium salt of benzenesulphinic acid

Using the standard procedure (expt. 3.23), 1-azido-1-nitrocyclohexane (500 mg, 3 mmol)& the sodium salt of benzenesulphinic acid (1.09, 6 mmol) in DMSO (40 ml)were stirred overnight (14h). The crude colourless solid product was recrystallised from hexane to give *1-(1-azidocyclohexyl) phenyl sulphone* (410 mg, 53%), m.p. 88-89^{o} (Found: C, 54.5; H, 5.6; N, 16.1%, $C_{12}H_{15}N_3O_2S$ requires C, 54.3; H, 5.6; N, 15.8%); υ_{max}(Nujol) 2120, 1595, 1300, 1150, 760, 700 cm^{-1}; $\delta(CDCl_3)$ 1.65 (10H, m) 7.3 (5H, m). The reaction was repeated for 2h. The spectroscopic data showed presence of unreacted starting material.

3.33 Reaction of 2-azido-2-nitropropane with the sodium salt of *p*-chlorophenyl thiolate

Using the standard procedure (expt. 3.23), the sodium salt of *p*-chlorophenylthiolate (1.4 g, 8 mmol) and 2-azido-2-nitropropane (0.5 g, 3.8 mmol) in DMF (40 ml) were reacted for 40 min. The product was purified by column chromatography (Alumina EtOAC/diethyl ether) to yield a pure liquid of *1-azido-1-methylethyl p-chlorophenyl sulphide (640 mg, 70%)*; (Found: C, 48.0; H, 4.3; N, 18.00; $C_9H_{10}N_3SCl$ requires: C, 47.5; H, 4.3; N, 18.45) υ_{max}(neat), 2110, 1590, 840, 760 cm^{-1}; ($CDCl_3$) 7.3 (4H, ABq) 1.51 (6H,)

The reaction had previously been carried out using one month old

p-chlorophenylthiolate (which had largely oxidised to the corresponding sulphinate compound). The work-up gave a yellowish solid which was recrystallised from hexane to yield pure *1-azido-1-methylethyl p-chlorophenyl sulphone* (0.2 g, 20%); m.p. 67-68° ;(Found: C, 41.9; H, 4.0; N, 16.55, $C_9H_{10}N_3S\ ClO_2$ requires C, 41.62; H, 3.88; N, 16.18%); υ_{max} 2110, 1600, 1320, 1150, 840, 760 cm^{-1}, $\delta(CDCl_3)$ 7.5 (4H, ABq) 1.6 (6H, s).

Similar results were obtained when the reaction was repeated with pure *p*-chlorophenylthiolate in DMSO for 18h.

3.34 Reaction of 1-azido-1-nitrocyclohexane with sodium salt of *p*-chlorophenylthiolate

Using the procedure reported in (3.23) 1-azido-1-nitrocyclohexane (0.5 g, 3 mmol) and sodium *p*-chlorophenylthiolate (1.9 g, 7.9 mmol) in DMSO (40 ml) were reacted for 1h. The work up gave a yellow oily liquid which was purified by column chromatography on alumina (EtOAC/ether) (90/10) to yield pure *1-(1-azidocyclohexyl)p-chlorophenyl sulphide* (0.42 g, 53%); (Found: C, 53.5; H, 5.4; N, 15.6, $C_{12}H_{14}N_3ClS$ requires C, 53.8; H, 5.2; N, 15.7%); υ_{max} 2110, 1580, 1250, 830, 760 cm^{-1}; $\delta(CDCl_3)$ 1.55 (10H, m. broad), 7.3 (4H, ABq).

The above reaction was repeated twice and gave the same results.

3.35 a - Reaction of 2-azido-2-nitropropane with the sodium salt of 2-nitropropane

Using the standard procedure (expt. 3.23), the sodium salt of 2-nitropropane (2 g, 18 mmol) and 2-azido-2-nitropropane in HMPA were reacted with illumination with 2 x 150 w tungsten "white light"lamps for 60 min. The crude solid product obtained was recrystallised from ethanol to yield pure 2,3-dimethyl-2,3-dinitrobutane (160 mg, 24%) m.p. 206-208° (lit.[65] 208-209°); υ_{max} 1550 cm^{-1}; $\delta(CDCl_3)$ 1.75 (s). The reaction was repeated for 16h without photolysis and yielded (54%) of 2,3-dimethyl-2,3-dinitrobutane.

b- Inhibition studies

Expt. 3.35a was used as the control reaction. Inhibition studies with *p*-DNB, DTBN, and absence of light were carried out as detailed in expt. 3.23b. The results are shown in Table 2-4 on page 72.

3.36 a - Reaction of 1-azido-1-nitrocyclohexane with the sodium salt of 2-nitropropane

Using the standard procedure (expt. 3.23), the sodium salt of 2-nitropropane (1 g, 9 mmol) and 1-azido-1-nitrocyclohexane (500 mg, 3 mmol) in DMSO were illuminated for 2h with 2 x 150 w Tungsten "white light" lamps. The ^{1}H.n.m.r. spectroscopy and g.l.c. (Se30 10%) analysis of the crude product showed 1-(1-methyl-1-nitroethyl)-1-nitrocyclohexane (116 mg, 18%) was the main product; with a trace of 2,3-dimethyl1-2-2,3-dinitrobutane. Recrystallisation from ethanol gave pure 1-(1-methyl-1-nitroethyl)-1-nitrocyclohexane m.p. 148-150°C (lit.[90] m.p. 149-150°C); υ_{max} 1553 cm^{-1}; $\delta(CDCl_3)$ 1.63 (6H,s) 1.5 (6H, m) 2.4 (4H, m).

b - Inhibition studies

Expt. 3.36a was used as the control reaction. Inhibition studies with *p*-DNB, DTBN, and absence of light were carried out as detailed in expt. 3.23b. The results are shown in Table 2-5 on page 73.

3.37 Reaction of 2-azido-2-nitropropane with the sodium salt of diethyl ethylmalonate

The sodium salt of of diethyl ethylmalonate (500 mg, 1.8 mmol) and 2-azido-2-nitropropane in DMSO (40 ml), using the standard procedure (expt. 3.23), were illuminated with 2 x 150 w "white light" lamps for 3h. The crude yellow oily liquid showed one spot on t.l.c. (silica/$CHCl_3$) of tetraethyl hexane 3,3,4,4-tetracarboxylate (100 mg, 22%); b.p.$_{40}$ 173-175°C (using Kugelrohr distillation) (lit.[155] b.p.$_{0.5}$ 128-129°C); $\upsilon_{max(neat)}$ 1740 cm^{-1}; $\delta(CDCl_3)$ 0.92 (6H, t) 1.1 (12H, t) 1.95 (4H, q) 4.15 (8H, q). The reaction was repeated several times under the same conditions and yielded 20-22% of product.

3.38 Preparation of 2-nitro-2-thiocyanatopropane

a - By oxidative addition ("Normal")

2-Nitropropane (4.45 g, 0.05 mol), sodium hydroxide (2.8 g, 0.07 mol), sodium thiocyanate (8.18 g, 0.1 mol), and potassium ferricyanide (32.9 g, 0.1 mol) were reacted as in expt. 3.14 for 60 min. The ^{1}H.n.m.r. analysis showed a mixture of products. The product mixture was fractionally distilled and afforded a bright yellow oil (2.4 g). Again the ^{1}H.n.m.r. analysis and g.l.c. (SE 30 10%) showed the product to be a mixture; $\nu_{max(neat)}$ 2170 (SCN), 1550 cm^{-1} (NO_2); $\delta(CDCl_3)$ 1.75 (s, 2,3-dimethyl-2,3-dinitrobutane), 1.9 (s, unidentified), 2.12 (s, 2-nitro-2-thiocyanatopropane).

b - By oxidative addition ("reverse order")

2-Nitropropane (4.45 g, 0.05 mol), sodium hydroxide (2.8 g, 0.07 mol), sodium thiocyanate (8.18 g, 0.1 mol) and potassium ferricyanide (32.9 g, 0.1 mol) were reacted as in expt. 3.22 for 20 min. The ^{1}H.n.m.r. analysis of the product showed 2-nitro-2-thiocyanatopropane and a trace of "dimer" 2,3-dimethyl-2,3-dinitrobutane. The crude product was fractionally distilled to afford a bright yellow oil of 2-nitro-2-thiocyanatopropane (2.45 g, 40%) b.p.$_{1.5}$ 66-68°C; (Found: C, 32.7; H, 4.3, N, 18.4; S, 22.1, $C_4H_6N_2SO_2$ requires: C, 32.86: H, 4.14; N, 19.2; S, 21.94%); $\upsilon_{max(neat)}$ 2880, 2170 (SCN), 1550 cm^{-1} (NO_2); $\delta(CDCl_3)$ 2.1 (s); m/e 100 (M-46), 41 (M-59); n^{20}_d 1.48.

The above method was repeated several times giving 38-40% yields. A similar yield was also obtained in a scaled up run.

c - Attempted preparation of 2-nitro-2-thiocyanatopropane by nucleophilic substitution

2-Bromo-2-nitropropane (500 mg, 2.9 mmol) and sodium thiocyanate (500 mg, 6.1 mmol) in DMSO (40 ml) were reacted as in expt. 3.23 and illuminated with tungsten "white light" lamps (2 x 150 w) for 2h. The ^{1}H.n.m.r. analysis showed only the presence of starting material (0.48 g, 96%). The reaction was repeated in THF and again, only starting material was recovered. (0.5 g, 100%)

d - Attempted preparation of 2-nitro-2-thiocyanatopropane using the sodium salt of 2-nitropropane as an entraining agent

2-Iodo-2-nitropropane (640 mg, 2.9 mmol), sodium thiocyanate (500 mg, 6.1 mmol), and a catalytic amount of the sodium salt of 2-nitropropan (10 molar %) were reacted as in expt. 3.23 with illumination by tungsten "white light" lamps (2 x 150 w) in DMSO for 2h. The crude white solid product was recrystallised from ethanol to give 2,3-dimethyl-2,3-dinitrobutane in trace amounts, enough to do the m.p. 207-208°C (lit.[65] m.p. 208-209°C); $\upsilon_{max(nujol)}$ 1552 cm^{-1}; ($CDCl_3$) 1.75 (s). The reaction was repeated without using entrainment; only starting material was recovered. The reaction was also repeated with 2-bromo-2-nitropropane (0.5 g, 3 mmol) in THF for 20h. The ^{1}H.n.m.r. analysis showed 90% recovery of starting material and 10% of 2,3-dimethyl-2,3-dinitrobutane.

3.39 Preparation of 1-nitro-1-thiocyanatocyclohexane

1-Nitrocyclohexane (6.45 g, 0.05 mol), sodium hydroxide (3.2 g, 0.08 mol), sodium thiocyanate (8.1 g, 0.1 mol), and potassium ferricyanide (32.9 g, 0.1 mol) were reacted as in expt. 3.22 in methylene chloride and afforded a light-yellowish oil. G.l.c. (SE30 10%), i.r., and t.l.c. (silica/$CHCl_3$) analysis indicated that the crude product was contaminated with cyclohexanone. The crude oil was purified by preparative t.l.c. (silica, CCl_4/hexane: 60/40) to afford 1-nitro-1-thiocyanatocyclohexane (4.02 g, 43%); (Found: C, 45.6; 5.6; N, 15.0 S, 16.8, $C_7H_{10}N_2O_2S$ requires C, 45.16; H, 5.37; N, 15.05; S, 17.20%); $\upsilon_{max(neat)}$ 2160 (SCN), 1550 cm^{-1} (NO_2); $\delta(CDCl_3)$ 1.6 (6H, m), 2.3 (4H, m).

The above reaction was repeated in diethyl ether and gave 1-nitro-1-thiocyanatocyclohexane (3.2 g, 34%). The product could not be distilled, even under reduced pressure, because of decomposition.

3.40 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of 2-nitropropane

The sodium salt of 2-nitropropane (1 g, 9 mmol) and 2-nitro-2-thiocyanatopropane (550 mg, 3.7 mmol) in DMSO (50 ml),using the standard procedure (expt 3.23), were illuminated with tungsten "white light" lamps (2 x 150 w) for 2h. The crude product was recrystallised from ethanol to afford colourless crystals of 2,3-dimethyl-2,3-dinitrobutane (0.48 g, 72%); m.p. 207-208^{0} (lit.[65] 208-209^{0}); $\upsilon_{max(nujol)}$ 1552 cm^{-1}; $\delta(CDCl_3)$ 1.75 (s). The reaction was repeated several times giving 70-72% yields. When the reaction was repeated in DMF instead of DMSO a 51% yield of product was obtained.

Inhibition studies

The above reaction in DMSO was used as the control reaction. Inhibition studies with *p*-DNB, DTBN, O_2, and absence of light were carried out as detailed in expt. 3.23b. The results are shown in Table 2-6 on page 82.

3.41 Reaction of 1-nitro-1-thiocyanatocyclohexane with the sodium salt of 2-nitropropane

The sodium salt of 2-nitropropane (1 g, 9 mmol) and 1-nitro-1-thiocyanatocyclohexane (0.55 g, 3 mmol) in DMSO (40 ml) were reacted using the standard procedure (expt. 3.23) with photolysis for 4h to give 1-(1-methyl-1-nitroethyl)-1-nitro-cyclohexane (0.39 g, 61%) and 2,3-dimethyl-2,3-dinitrobutane (80 mg, 16%). The products were separated by crystallisation and the identity of the products was confirmed by their m.p., i.r. and ^{1}H.n.m.r. A repeat reaction gave similar results.

3.42 Reaction of 2-nitro-2-thiocyanatopropane with the sodium salt of benzene sulphinic acid.

The sodium salt of benzene sulphinic acid (1 g, 6 mmol), and 2-nitro-2-thiocyanatopropane (0.55 g, 3.7 mmol) were reacted in DMSO (40 ml), using the standard procedure (expt. 3.23)under photolysis with tungsten

"white light" (2 x 150 w) for 2h. The crude product was recrystallised from ethanol to afford colourless crystals of 1-methyl-1-nitroethyl phenyl sulphone (420 mg, 49%); m.p. 116-118°C (lit.[68] m.p. 116-117°C); $\upsilon_{max(nujol)}$ 1590, 1550, 760, 690 cm^{-1}; $\delta(CDCl_3)$ 1.95 (6H, S), 7.69 (5H, m). The reaction was repeated several times under the same conditions and gave yields of 46-49%. When the reaction was carried out for 30 min under the same conditions 22% of starting material was recovered as well as product.

Inhibitions studies

The above reaction was used as the control reaction. Inhibition studies with O_2, DTBN, *p*-DNB, and absence of light were carried out as detailed in expt. 3.23b. The results are shown in Table 2-7 in page 84.

3.43 Reaction of 2-nitro-2-thiocyanatopropane with sodium azide

Sodium azide (500 mg, 7.6mmol) and 2-nitro-2-thiocyanatopropane (0.55 g, 3.7 mmol) were reacted in HMPA (40 ml) for 90 min using the standard procedure (expt. 3.23). ^{1}H.n.m.r. and i.r. spectroscopy, and t.l.c. (silica/$CHCl_3$) indicated a mixture of products. The ^{1}H.n.m.r. analysis indicated that 8% of 2-azido-2-nitropropane and 31% of the starting material (2-nitro-2-thiocyanopropane) were present. The reaction was repeated under the same conditions for 5h. The spectroscopic data and t.l.c. showed a 27% recovery of starting material and 8 % of 2-azido-2-nitropropane (analysis by ^{1}H.n.m.r.) The reaction was repeated in DMSO instead of HMPA for 6h. Spectroscopic analysis showed a trace of 2-azido-2-nitropropane and a large recovery (98% by ^{1}H.n.m.r.) of starting material.

3.44 a - General procedure for the reaction of 2-substituted-2-nitropropanes with thiolate anions

Dry solvent* (30 ml) was pipetted into a three necked round bottomed flask fitted with a magnetic stirrer bar and nitrogen inlet. Nitrogen was bubbled through the solvent for 30 min before, and throughout, the reaction. The salt of the thiol, or the thiol and an equivalent of sodium methoxide, was introduced into the flask and stirring was commenced. After a few

minutes an equimolar amount of the 2-substituted-2-nitropropane was added and the reaction mixture illuminated with tungsten "white light" lamps (2 x 150 w). After a suitable time the reaction mixture was poured into ice-water (50 ml) and extracted into diethyl ether (4 x 20 ml). Sodium chloride was sometimes added to aid separation. The combined ether layers were washed with distilled water (4 x 20 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* yield the crude product. The unreacted thiolate remained in the aqueous extract.

*Solvent = Dipolar aprotic solvents (DMF, DMSO and HMPA) or protic solvents (H_2O and MeOH or H_2O/MeOH).

b - Reactions of 2-nitro-2-thiocyanatopropane with thiolates

i - With the sodium salt of *p*-chlorophenylthiol

The sodium salt of *p*-chlorophenylthiol (500 mg, 3 mmol) and 2-nitro-2-thiocyanatopropane (500 mg, 3.4 mmol) were reacted in DMSO (40 ml) for 2h using the standard procedure detailed in expt. 3.44a. The crude product was leached with hexane leaving a residue of 2,3-dimethyl-2,3-dinitrobutane (16%). Evaporation of hexane gave a residue which was recrystallised from hexane to give 1-methyl-1-nitroethyl*p*-chlorophenyl sulphide (37%); m.p. 81-82° (lit.[33] 82-83°); $\upsilon_{max(nujol)}$ 1590, 1552 cm^{-1}; $\delta(CDCl_3)$ 1.83 (6H, s), 7.37 (4H; s). Evaporation of the mother liquor gave di-(*p*-chlorophenyl) disulphide (14%). The spectroscopic data for the disulphide and the dimer were in agreement with assigned structures as well as their m.p.'s. The reaction was repeated under similar conditions and gave similar yields of products. The % yields were calculated by ^{1}H.n.m.r. analysis of the crude product.

Inhibition studies

The reaction detailed in expt. 3.44b was used as the control reaction. Inhibition studies with *p*-DNB, DTBN, O_2, and the absence of light were carried out as detailed in expt. 3.23b. The results are shown in Table 2-8 on page 88.

ii - With the sodium salt of phenylthiol

The sodium salt of phenylthiol (500 mg, 3.7 mmol) and 2-nitro-2-thiocyanatopropane (500 mg, 3.7 mmol) were reacted in DMSO for 2h using the standard method (expt. 3.44a). The crude product was leached with hexane. Removal of the solvent *in vacuo* and recrystallisation of the residue from ethanol gave diphenyldisulphide (400 mg, 52%); m.p. 59-61° (lit.[56] m.p. 58-60°); δ($CDCl_3$) 7.2 (10H,m). Recrystallisation of the residue after leaching gave 2,3-dimethyl-2,3-dinitrobutane (330 mg, 50%). The reaction was repeated for 10 min and ^{1}H.n.m.r. analysis indicated diphenyldisulphide (36%), 2.3-dimethyl-2,3-dinitrobutane (34%) and recovery of starting material (10%).

Inhibition studies

The above reaction (10 min) was used as the control reaction. Inhibition studies with *p*-DNB, DTBN, O_2 and absence of light were carried out as detailed in expt. 3.23b for 10 min. The results are shown in Table 2-9 on page 91.

iii - With the sodium salt of benzylthiol

The sodium salt of benzylthiol (500 mg, 3.4 mmol) and 2-nitro-2-thiocyanatopropane (550 mg, 3.7 mmol) were reacted in DMSO (40 ml) using the standard procedure (expt. 3.44a) for 2h under irradiation with fluorescent laboratory lights. ^{1}H.n.m.r. analysis of the crude product indicated dibenzyl disulphide (30%), 2,3-dimethyl-2,3-dinitrobutane (22%), starting material (15%) and thiobenzaldehyde polymer? (16%). The reaction was repeated using two equivalents of the salt under the same conditions. ^{1}H.n.m.r. analysis of this reaction indicated dibenzyl disulphide (24%), 2,3-dimethyl-2,3-dinitrobutane (28%), starting material (22%), and a trace of thiobenzaldehyde polymer?

The reaction was repeated with illumination with tungsten "white light" lamps (2 x 150 w) for 2h. ^{1}H.n.m.r. analyses of the product indicated dibenzyl disulphide (8%), 2,3-dimethyl-2,3-dinitrobutane (10%)

starting material (33%) and thiobenzaldehyde polymer? (25%). The reaction was also repeated for 10 min in DMF under the same conditions. G.l.c. (SE30, 160°C) analysis of the crude product showed three significant peaks: dibenzyl disulphide, 2,3-dimethyl-2,3-dinitrobutane and an unidentified peak. ^{1}H.n.m.r. analysis indicated dibenzyl disulphide (12%), 2,3-dimethyl-2,3-dinitrobutane (10%), starting material (16%), and an unidentified product (thiobenzaldehyde polymer?) (12%). T.l.c. (silica/Pet.ether 60 : 80) showed three spots. Preparative t.l.c. (silica/Pet. ether 60 : 80) gave three bands which were separated. ^{1}H.n.m.r. and g.l.c. (SE30, 160°C) of the least polar band indicated that it consisted of dibenzyl disulphide and the thiobenzaldehyde polymer. Mass spectrometry indicated dibenzyl disulphide (m/e, M^+ 246, 123, 91, 65) and thiobenzaldehyde were present (m/e, M^+ 122, 121 ($PhC{\equiv}S^+$) 77).

Inhibition studies

The above reaction (2h) was used as the control reaction. Inhibition studies with *p*-DNB, DTBN, O_2, and absence of light were carried out as detailed in expt. 3.23b. The results are shown in Table 2-10 on page 92.

iv - With the sodium salt of *p*-nitrophenylthiol

Using the standard procedure (expt. 3.44a), *p*-nitrophenylthiol (170 mg, 1.1 mmol) and potassium-t-butoxide (80 mg, 0.7 mmol) in DMSO (50 ml) were initially reacted for 15 min to form the anion of *p*-nitrophenylthiol (a deep red colour resulted). 2-Nitro-2-thiocyanatopropane (170 mg, 1.2 mmol) was added to the solution and the reaction mixture stirred for 15 min by which time the red colour had disappeared. ^{1}H.n.m.r. analysis of the crude product indicated 1-methyl-1-nitroethyl *p*-nitrophenyl sulphide (17%), 2,3-dimethyl-2,3-dinitrobutane (3%), di-(*p*-nitrophenyl) disulphide (19%), and starting material (18%). The mixture of products was analysed by ^{1}H.n.m.r. spectroscopy. The reaction was repeated under the same conditions for 1h, 2h and 4h resp; similar results were obtained.

Inhibition studies

The above reaction was used as the control reaction. Inhibition studies with *p*-DNB, DTBN, and O_2 were carried out as detailed in expt. 3.23b. The results are shown in Table 2-11 on page 96.

3.45 Reaction of 2-nitro-2-thiocyanatopropane

With the sodium salt of diethyl ethylmalonate

Dry DMSO (60 ml) was pipetted into a three necked, round bottomed flask fitted with a nitrogen bleed and a magnetic stirrer bar. The sodium salt of diethyl ethylmalonate (100 mg, 0.47 mmol) was added and the reaction was stirred for 30 min until most of the salt dissolved. 2-Nitro-2-thiocyanatopropane (70 mg, 0.47 mmol) was added and the reaction was illuminated with tungsten "white light" lamps (2 x 150 w) for 5h. After 5h the reaction was worked up as in expt. 3.37. ^{1}H.n.m.r. analysis of the crude product indicated a mixture of tetraethyl hexane-3,3,4,4-tetracarboxylate and 2,3-dimethyl-2,3-dinitrobutane. The mixture was leached with hexane. Removal of the solvent *in vacuo* gave tetraethyl hexane-3,3,4,4-tetracarboxylate (47 mg, 20%), the identity of which was confirmed by i.r. and ^{1}H.n.m.r. comparison with previously prepared authentic material (section 3.37). The residue after leaching was recrystallised from ethanol and gave 2,3-dimethyl-2,3-dinitrobutane (40 mg, 47%), again the identity of the product was confirmed by m.p., i.r. and ^{1}H.n.m.r. spectroscopy.

The above reaction was repeated under the same conditions for 6h with the same results.

3.46 Attempted preparation of diethyl ethylthiocyanatomalonate

Dry methanol (40 ml) was pipetted into a three necked, round bottomed flask fitted with a nitrogen bleed and a magnatic bar. The sodium salt of diethyl ethylmalonate (0.6 g, 2.2 mmol) was added and the reaction was stirred for 30 min until most of the salt dissolved. Copper (II) thiocyanate (2.8 g, 15 mmol) was added and the reaction mixture was refluxed

for 48h. The reaction mixture was poured in water and diethyl ether. The layers were separated and the aqueous layer washed with ether (3 x 30 ml). The combined ether extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a yellowish liquid of tetraethyl hexane-3,3,4,4-tetracarboxylate (50 mg 10%). The identity of the product was confirmed by comparison of the t.l.c., and i.r. and ^{1}H.n.m.r. spectra with the previously prepared compound (expt. 3.37).

Attempts to prepare the thiocyanatomalonate using thiocyanaogen[132] (prepared by the standard route from lead thiocyanate and bromine)and the sodium salt of diethyl ethylmalonate gave only a polymer of thiocyanogen (orange crystals of the trimer).

Other attempts using thiocyanogen (prepared from bromine and sodium thiocyanogen)[132] in methanol and ethanol also yielded the trimeric thiocyanogen and none of the desired product.

3.47 Reaction of 2-nitro-2-thiocyanatopropane with diethylphosphite

Dry THF (30 ml) was pipetted into a three necked, round bottomed flask fitted with a nitrogen bleed and a magnetic bar. Diethyl phosphite (1.4 g, 10 mmol) was added, followed by potassium t-butoxide (1.0 g, 9 mmol). The reaction was cooled down to -45°C (Dry ice/Acetone) and 2-nitro-2-thiocyanatopropane (1.3 g, 9 mmol) added dropwise, and the reaction stirred for 30 min. The reaction mixture was warmed to 25°. The reaction mixture was poured into water and extracted with diethyl ether (3 x 30 ml). The ether extracts were combined (2 x 50 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give largely starting material and some 2,3-dimethyl-2,3-dinitrobutane (10% by ^{1}H.n.m.r.) Repeat reactions in DMF and ethanol gave low yields of unidentified material.

3.48 Reactions of diethyl 1-methyl-1-nitroethylphosphonate

a - With the sodium salt of 2-nitropropane

Dry DMF (40 ml) was pipetted into a three necked, round bottomed flask fitted with a nitrogen bleed, and a magnetic bar. The sodium salt of 2-nitropropane (660 mg, 5.9 mmol) was added and the reaction mixture stirred until most of the salt had dissolved. Diethyl 1-methyl-1-nitrophosphonate (400 mg, 1.8 mmol) was added and the reaction flask illuminated with tungsten "white light" lamps (2 x 150 w) for 42h. The reaction was worked up as in expt. 3.36a and yielded 2,3-dimethyl-2,3-dinitrobutane (190 mg, 60%). The identity of the product was determined by m.p. and i.r., ^{1}H.n.m.r. spectroscopy.

When the above reaction was repeated in THF for 18h and 9h under the same conditions, ^{1}H.n.m.r. analysis indicated a quantitative recovery of starting material.

The above reaction was also repeated in HMPA (the course of the reaction was followed periodically by taking aliquots) for 28h. ^{1}H.n.m.r. analysis indicated that decomposition took place steadily throughout the reaction with no formation of products. However, when the reaction was repeated in DMSO for 6h under the same conditions, ^{1}H.n.m.r. analysis of the crude product indicated unreacted nitrophosphonate (^{1}H.n.m.r. values are given in expt. 3.16) and an unidentified product $\delta(CDCl_3)$ 4.2 (m) 1.7 (d) 1.4 (s) 1.36 (t) (tentative assignment). T.l.c. (silica/ $CHCl_3$) showed two spots very close together of which one was starting material. Longer reaction times did not improve conversion and both compounds decomposed steadily with time.

b - With the sodium salt of *p*-chlorophenylthiol

The sodium salt of *p*-chlorophenylthiol (540 mg, 3 mmol) and diethyl 1-methyl-1-nitroethylphosphonate (400 mg, 1.8 mmol) were reacted under the same conditions using the standard procedure (expt. 3.44a) for 1h. The reaction mixture was poured into ice-water (50 ml) and extracted

with diethyl ether (4 x 30 ml). The ether extracts were combined, washed with distilled water (2 x 30 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to give an oil of *p*-chlorophenyl ethyl sulphide (250 mg, 45%) $\upsilon_{max(neat)}$ 1590, 1100, 820, 750, 690 cm^{-1}; $\delta(CDCl_3)$ 7.25 (4H, s) 7.85 (2H, q) 1.25 (3H, t). The aqueous phase was acidified with hydroxy ammonium hydrochloride (500 mg) extracted with diethyl ether (2 x 30 ml), and dried ($MgSO_4$). Removal of the solvent *in vacuo* yielded nothing.

The above reaction was repeated under the same conditions for 2h, 18h, and 48h, all of which yielded *p*-chlorophenyl ethyl sulphide (41-46%). The identity of the sulphide was proven by comparison (i.r. and ^{1}H.n.m.r.) with an authentic sample which was prepared as follows: Dry methanol (50 ml) was placed in a three necked round bottomed flask flushed with nitrogen. Sodium metal (0.7 g, 33 mol) was added in small lumps and the mixture stirred until the metal dissolved. *p*-Chlorophenylthiol (5 g, 34 mmol) was added and the reaction mixture stirred for 1h. Ethyl iodide (5 g, 32 mmol) was added and the course of the reaction was terminated after 90 min. The precipitated sodium iodide was filtered off and the solvent was removed *in vacuo* to yield an oil of *p*-chlorophenyl ethyl sulphide (3.02 g, 47%). Spectroscopic analysis (i.r. and ^{1}H.n.m.r.) was in agreement with the proposed structure.

3.4a Reactions of 2-cyano-2-nitropropane with thiolates

a - With the sodium salt of phenylthiol

The sodium salt of phenylthiol (230 mg, 1.74 mmol) and 2-cyano-2-nitropropane (200 mg, 1.75 mmol) in HMPA (40 ml) were reacted for 3h with lab. light photolysis using the standard procedure (expt. 3.44a). The crude product was separated by preparative t.l.c. (silica, $CHCl_3$/diethyl ether) to yield 1-cyano-1-methylethyl phenyl sulphide (180 mg, 53%); $\upsilon_{max(neat)}$ 1595, 1150, 1070, 750, 695 cm^{-1}; $\delta(CDCl_3)$ 1.95 (6H, s) 7.3 (5H, m) and a trace of diphenyl disulphide. The reaction was repeated with illumination by tungsten "white light" lamps (2 x 150 w) under the same conditions and gave similar results.

b - With the sodium salt of *p*-chlorophenylthiol

The above expt. was repeated with the sodium salt of *p*-chlorophenylthiol under the same conditions but only gave unreacted starting material as shown by t.l.c, i.r., and n.m.r. spectroscopy.

3.50 Reactions of 3-methyl-3-nitrobutane-2-one and ethyl 2-methyl-2-nitropropionate with *p*-chlorophenylthiolate

3-Methyl-3-nitrobutane-2-one and ethyl 2-methyl-2-nitropropionate were each reacted with the sodium salt of *p*-chlorophenylthiol for 10h, 14h, 24h, resp. using the standard procedure (expt. 3.44a) and gave only small amounts of starting material (20%, 15%, nitroketone and nitroester resp.,10h).

Similar results were obtained when the reactions were repeated using DMSO or HMPA.

3.51 Reactions of α-substituted nitro compounds with thiolate anions in protic solvents

a - Reactions of 2-bromo-2-nitropropan-1,3-diol

i. With the sodium salt of *p*-chlorophenylthiolate

The sodium salt of *p*-chlorophenylthiol (2 g, 12 mmol) and 2-bromo-2-nitropropan-1,3-diol (1 g, 5 mmol) in distilled water (60 ml) were reacted for 4h without photolysis under an atmosphere of nitrogen. The resulting precipitated crude solid was filtered and recrystallised from ethanol to afford di-(*p*-chlorophenyl) disulphide (1.6 g, 92%); m.p. 73-75° (lit.[156] 75°); $\upsilon_{max(nujol)}$ 1590, 820 cm^{-1}, $\delta(CDCl_3)$ 7.2 (ABq).

ii. With the sodium salt of benzythiol

The sodium salt of benzylthiol (2 g, 13.6 mmol) and 2-bromo-2-nitropropan-1,3-diol (1 g, 5 mmol) in distilled water (60 ml) were reacted for 4h without photolysis under an atmosphere of nitrogen. The precipitated crude solid was filtered and recrystallised from ethanol to afford dibenzyl disulphide (1.5 g, 94%), m.p. 71-72° (lit.[156] m.p. 72°); $\delta(CDCl_3)$ 3.63 (4H, s), 7.3 (10H, s).

iii. With the sodium salt of *p*-nitrophenylthiol

p-Nitrophenylthiol (100 mg, 6.4 mmol), sodium hydroxide (100 mg, 12.5 mmol), sodium methoxide (100 mg, 18.5 mmol and 2-bromo-2-nitropropan-1,3-diol (1 g, 5 mmol) were reacted in distilled water (60 ml) for 48h. The red colour of the anion of *p*-nitrophenylthiol disappeared within minutes. The precipitated crude solid was filtered and recrystallised from ethanol to afford di-(*p*-nitrophenyl) disulphide (850 mg, 98%); m.p. 182-183° (lit.[156] m.p. 182-183°); $\delta(CDCl_3)$ 7.62 (ABq). The reaction was repeated in $MeOH/H_2O$ (85/15 v/v) (60 ml) for 20h and gave the product in 96% yield.

3.52a. Preparation of 2-chloro-2-nitropropan-1,3-diol[157]

i. Preparation of the sodium salt of 2-nitropropan-1,3-diol

Dry methanol (450 ml) was placed into a three necked round bottomed flask fitted with an inlet for nitrogen gas, reflux and magnatic stirrer. Nitrogen gas was bubbled through the solvent for 30 min. Sodium metal (11.5 g, 0.5 g-atom) was added slowly, with stirring, followed by paraformaldehyde (trioxane) (30 g, 0.24 mol) at room temperature. The solution was cooled to 0° and nitromethane (30.5 g, 0.5 mol) added dropwise over a 3h period, keeping the temperature below 0°. When the addition was completed a white solid had formed which was filtered off and washed with dry methanol (2 x 25 ml). The product was heated in an oven at 40-50° to remove the methanol of co-crystallisation to give a quantitative yield of 2-nitropropan-1,3-diol.

ii. Chlorination of the sodium salt of 2-nitropropan-1,3-diol

Dry ether (125 ml) was poured into a three necked round bottomed flask fitted with an inlet for nitrogen gas; andnitrogen gas bubbled through for 30 min. The sodium salt of 2-nitropropan-1,3-diol (5.1 g, 0.025 mol) was suspended in the solvent and chlorine gas slowly bubbled through the reaction vessel for 15 min. The outflow was led through a flask of sodium hydroxide solution to trap unreacted chlorine. A rapid reaction took place followed by precipitation of sodium chloride. The excess chlorine was driven out by continuing the passage of nitrogen gas for 1h. The sodium chloride was

filtered and the solvent was removed *in vacuo* to afford a crude product which was recrystallised from chloroform to afford colourless crystals of 2-chloro-2-nitropropan-1,3-diol (3.42 g, 61%); m.p. 134-136° (lit.[157] m.p. 135); $\delta(D_2O)$ 4.2 (ABq).

b - Reaction of 2-chloro-2-nitropropan-1,3-diol with thiolate anions in protic solvents

Similar reactions (expt. 3-51) were carried in MeOH and MeOH/H_2O. The results are shown in Table 2-12 on page 112.

3.53 Reaction of 5-bromo-5-nitro-1,3-dioxane with thiolate anions in protic solvents

a. With (L)-cysteine

(L)-Cysteine (760 mg, 4.7 mmol) and 5-bromo-5-nitro-1,3-dioxane (500 mg, 2.4 mmol) in MeOH and phosphate buffer pH5.5 (10: 90 $^{v}/_{v}$) (50 ml) were reacted for 1h without photolysis under an atmosphere of nitrogen. The precipitated crude solid was filtered and dried to give (L)-cystine (400 mg, 70%); m.p. 260-262° (lit.[156] m.p. 260-261°). The aqueous layer was extracted with diethyl ether (2 x 30 ml) and the solvent was evaporated *in vacuo* to afford small amount of impure material which possibly contained some of the expected 5-nitro-1,3-dioxane.

b. With the sodium salt of *p*-chlorophenylthiol

The sodium salt of *p*-chlorophenylthiol (500 mg, 3 mmol) and 5-bromo-5-nitro-1,3-dioxane (650 mg, 3 mmol) in MeOH and phosphate buffer pH5.5 (50 : 50 $^{v}/_{v}$) (60 ml) for 15 min without photolysis under an atmosphere of nitrogen. The resulting precipitate was filtered and recrystallised from ethanol to give di-(*p*-chlorophenyl) dispulphide (300 mg, 70%). The product was identified by m.p. and ^{1}H.n.m.r. The aqueous layer was extracted with diethyl ether (2 x 30 ml) and the solvent evaporated *in vacuo* to give a mixture in low yield. The ^{1}H.n.m.r. spectrum showed a mixture of starting material (the dioxane) and the reduced product, 5-nitro-1,3-dioxane. A repeat reaction with equivalents of thiolate gave the same yield of

disulphide (600 mg, 70%) and no starting material (dioxane).

c. With *p*-chlorophenylthiol

The same reaction conditions as above (3.53b) used for reaction of p-chlorophenylthiol (880 mg, 6 mmol) and 5-bromo-5-nitro-1,3-dioxane (650 mg, 3 mmol) in MeOH and 1M hydrochloric acid (50 : 50 $^{v}/_{v}$) (60 ml) for 15 min. No reaction took place.

3.54 Reactions of 2-substituted-2-nitropropanes with thiolate anions in methanol or methanol/water

a. Reactions of 2-chloro-2-nitropropane with the sodium salt of *p*-chlorophenylthiol

The sodium salt of *p*-chlorophenylthiol (2 g, 12 mmol) and 2-chloro-2-nitropropane (0.75 g, 6 mmol) in methanol (60 ml) were reacted for 4h under an atmosphere of nitrogen. The precipitated solid was filtered and recrystallised from ethanol to give di-(*p*-chlorophenyl) disulphide (950 mg, 55%). The identity of the product was confirmed by m.p. and ^{1}H.n.m.r. and i.r. spectroscopy.

Inhibition studies

The reaction in part (a) was used as the control reaction. Inhibition studies with *p*-DNB, DTBN, O_2, and absence of light were carried out as detailed in expt. 3.23b and in part (a). The results are shown in Table 2-13 on page 117.

The reaction was also carried out as in part (a) but instead of a 4h period, the reaction time was cut down to 20 min to give di-(*p*-chlorophenyl) disulphide (660 mg, 38%). Inhibition studies for the 20 min reaction with *p*-DNB, DTBN, O_2, and absence of light were also carried out. The results are shown in Table 2-13 on page 117.

b. Reaction of 2-bromo-2-nitropropane with the sodium salt of *p*-chlorophenylthiol

The sodium salt of *p*-chlorophenylthiol (1.2 g, 7.2 mmol) and 2-bromo-

nitropropane (600 mg, 3.6 mmol) were reacted in MeOH : H_2O (85/15 $^{v}/_{v}$ (60 ml) for 5 min under an atmosphere of nitrogen. The precipitated solid was filtered and recrystallised from ethanol to give di-(*p*-chlorophenyl) disulphide (970 mg, 94%). The identity of the product was confirmed by m.p. ^{1}H.n.m.r. and i.r. spectroscopy.

The reaction was repeated in MeOH for 20 min to give di-(*p*-chlorophenyl) disulphide (730 mg, 71%).

Inhibition studies

The above reaction (20 min) was used as the control reaction. Inhibition studies with *p*-DNB, and DTBN were carried out as detailed in expt. 3.23b. The results are shown in Table 2-13 on page 117.

c. Reactions of 2-nitro-2-thiocyanatopropane with thiolate anions in methanol/water

i. With the sodium salt of *p*-nitrophenylthiol

The sodium salt of *p*-nitrophenylthiol (1 g, 6.8 mmol) and 2-nitro-2-thiocyanatopropane (0.55 g, 3.7 mmol) were reacted in MeOH : H_2O (80/20 $^{v}/_{v}$) (60 ml) for 20 min under an atmosphere of nitrogen. The precipitated solid was filtered to give di-(*p*-nitrophenyl) disulphide (390 mg, 39%). The identity of the product was confirmed by m.p., and ^{1}H.n.m.r. and i.r. spectroscopy.

ii. With the sodium salt of *p*-chlorophenylthiol

The sodium salt of *p*-chlorophenylthiol (1.2 g, 7.2 mmol) and 2-nitro-2-thiocyanatopropane (0.55 g, 3.7 mmol) in MeOH/H_2O (80/20) (60 ml) were reacted for 20 min under an atmosphere of nitrogen. The precipitated crude solid was filtered and recrystallised from ethanol to give di-(*p*-chlorophenyl) disulphide (640 mg, 60%). The identity of the product was confirmed by m.p. and ^{1}H.n.m.r. and i.r. spectroscopy.

Inhibition studies

The above reaction was used as the control. Inhibition studies were carried out as detailed in expt. 3.23b. The results are shown in Table 2-13

on page 117.

ii. With the sodium salt of phenylthiol

The sodium salt of phenylthiol (1 g, 7.5 mmol) and 2-nitro-2-thiocyanatopropane (0.55 g, 3.7 mmol) in MeOH : H_2O (80/20 $^{v}/_{v}$)(50 ml), were reacted under an atmosphere of nitrogen under the same conditions as in expt. c.i and c.ii for 20 min. The precipitated product was filtered and recrystallised from ethanol to afford diphenyl disulphide (150 mg, 18%). The identity of the product was confirmed by m.p., and ^{1}H.n.m.r. and i.r. spectroscopy.

Similar reactions were carried out in DMF or DMSO solvents instead of MeOH : H_2O system. These reactions are reported in expt. 3.44a. The results of these reactions are also shown in Table 2-13 on page 117.

3.55 Biological activity

Microbiology

Minimum inhibitory concentration determination (MIC)

a. Organisms

A cross-section of different types of micro-organisms were used for the testing and these were:

Staphylococcus	*Aureus*	NCIB	8625
Pseudomonas	*Aeruginosa*	NCIB	6749
Candida	*Albican*	A39	(Boots strain)
Aspergillus	*Niger*	CMI	31821

b. Composition of Media The following media were used:

(i) Nutrient agar

Lab Lemco or Beef extract	1.0 g
Yeast extract	2.0 g
Bacteriological peptone	5.0 g
Sodium chloride	5.0 g
Agar powder	15.0 g
Distilled water	1000 ml

(2) Czapek-Dox agar

Sodium nitrate	2.0 g
Potassium chloride	0.50 g
Magnesium glycerophosphate	0.05 g
Sucrose	30.0 g
Ferrous sulphate	0.01 g
Potassium sulphate	0.35 g
Agar powder	15.0 g
Distilled water	1000 ml

c. Sterilization of solutions and equipment: Sterilization of all solutions was carried out either in the autoclave at a temperature of 121°C, at a pressure of 15 psi, for 15 min, or by membrane filtration using 0.2 µm filters.

All glassware was sterilized at 160°C for 3h.

d. Cultivation of Organisms: All cultures were available as freeze dried specimens from standard collections.

e. The inoculum: The inoculum was 0.01 ml of an 18h broth culture of test bacteria and yeast or 0.01 ml of a spore suspension prepared from a 7 day culture of fungus.

f. Preparation of antimicrobial solutions: The diol derivatives were all water soluble, and solutions were sterilized by membrane filtration (sartorious membrane filter, 0.2 µm porosity). The other derivatives were soluble in acetone and DMSO and in acetone water mixtures. The volumes of acetone or DMSO used were in all cases without detectable effect on bacterial, yeast, or fungal growth.

g. Methods of determining MIC values:

1-End point method (tube dilution techniques): In this method a series of broth tubes containing known concentrations of the substance were inoculated with the organism and incubated. The MIC values were noted after 24h at 37°C for the bacteria, 48h at 25°C for the yeast, and 120h at

25°C for the fungus. The results of the MIC values are shown in Table 2-14 on page 126.

2-Disc method (Agar cup test): In this method the antimicrobial activity of the new compound was measured in terms of another (control), by comparing the size of zones of activity produced when the compounds were allowed to diffuse from an impregnated paper disc placed on an agar plate seeded with micro-organisms. This method is as follows:

Inoculum (10.1 ml) was added to melted nutrient agar (14 ml) and then poured into a sterile Petri dish and solidified. A series of discs (filter paper 6 mm diameter) were dipped in antibacterial solutions in ether (1µg/ml) and quickly removed and the ether allowed to evaporate in very short time. The discs were then placed firmly on the seeded plate and incubated at 37°C for 18h in case of bacteria, for 48h at 25°C for yeast, and 120h for the fungus. The results are shown in Table 2-14 on page 126.

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