DESULPHURISATION OF UNSYMMETRICAL DISULPHIDES

BY TERVALENT PHOSPHORUS NUCLEOPHILES

BY

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I must also thank SK&F Research Ltd and my parents and parents-in-law for their financial support.

DEDICATION

This thesis is dedicated to my wife Joanne,and my children Laith and Tala.

ABSTRACT

This thesis reports the study of the preparation of symmetrical and unsymmetrical disulphides and their desulphurisation with tervalent phosphorus compounds.The reaction products,kinetics,mechanism have been investigated.

The introduction (Chapter one) contains the background to this project with brief reviews on nucleophilic attack by P(III) compounds on a variety of nucleophilic centres and functional groups.These include saturated carbon,unsaturated carbon,carbonyl carbon,saturated oxygen,nitrogen,halogen,and sulphur (II).

Chapter two is divided into six sections.The first gives a brief review on the purpose and objective of the this thesis.Section two investigates the best analytical technique employed to monitor reaction mechanism,kinetics,and reaction products.Section three illustrates the problems associated with the preparation of unsymmetrical disulphides while section four details the products obtained from the desulphurisation reaction in various media.Section five and six report a comparison in desulphurisation kinetics between cyclic and acyclic aminophosphine reagents.

Chapter three discusses in details three physical methodes monitoring reaction pathway(CIDNP),reaction mechanism and kinetics(HPLC),and reaction products in various solvent systems(MC-LC).

Chapter four has full experimental procedures.

Chapter five lists the refrences.

CONTENTS

CHAPTER 1

NUCLEOPHILIC ATTACK BY P(III) NUCLEOPHILES

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1.1 General Introduction

The triply-connected phosphorus atom is a highly reactive centre in which reactivity is controlled by the availability of the non-bonding 3S electrons for co-ordination with electrophilic centres.

Thus the reactions of phosphorus compounds bearing three singly-bond atoms at carbon, nitrogen, oxygen or sulphur generally involve the phosphorus centre as a nucleophile.

1.2 Attack on Saturated Carbon
(The Michaelis-Arbuzov Reaction)

The Arbusov reaction is the best known example of a nucleophilic attack of phosphorus on saturated carbon. In the reaction, phosphites attack alkyl halides to produce phosphonate esters[1,2] (scheme 1).

$$(RO)_3P + R'X \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}R' + RX$$

Scheme 1

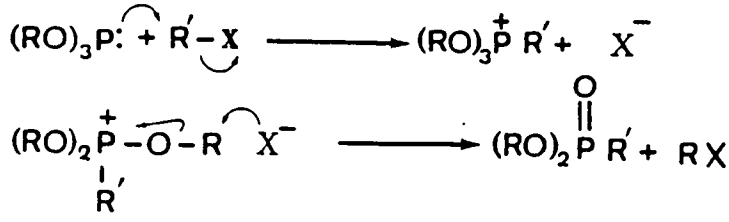
Phosphites react less readily than the corresponding phosphines at saturated carbon, usually requiring many hours at reflux temperature, whereas phosphines are often alkylated in the cold.

Razumov[3,4] has established the reactivity series

$Et_2POEt > EtP(OEt)_2 > (EtO)_3P$ and
$Ph_2POEt > PhP(OEt)_2 > (PhO)_3P$

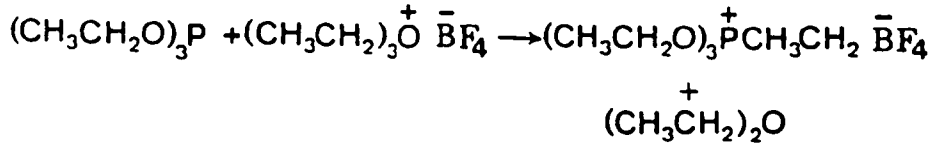
It is generally accepted that the reaction proceeds in two stages, an initial quaternisation of the phosphite by nucleophilic attack on the halide.

followed by attack on the alkoxyphosphonium cation by the anion displaced (scheme 2).



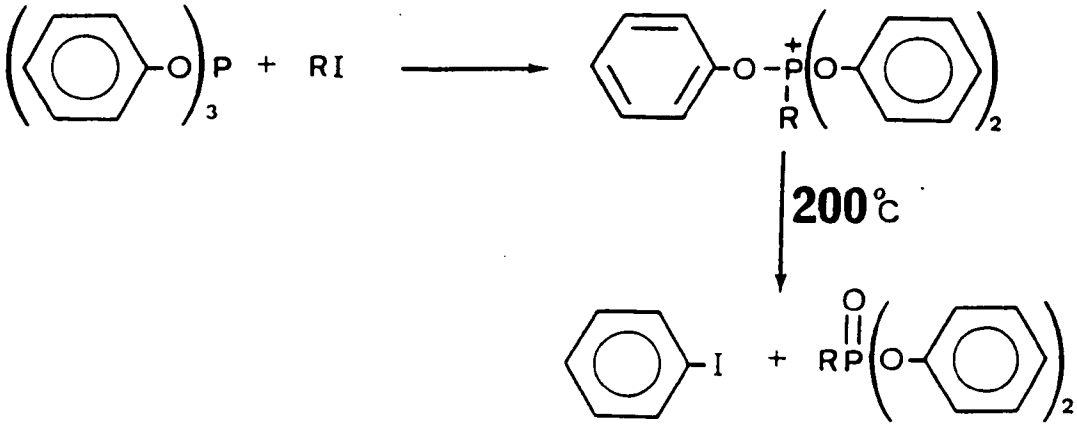
Scheme 2

Gerrard and Green[5] have established by reacting an optically active phosphite with ethyl iodide and observing inversion at the chiral carbon of the phosphite that the second dealkylation step was a simple bimolecular displacement on carbon. Isolation of the intermediate alkoxyphosphonium salts can only be achieved using weakly nucleophilic anions such as tetrafluoroborate (scheme 3).



Scheme 3

However, the reaction of triphenyl phosphite with alkyl iodides results in the formation of a very stable phosphonium salt which only decomposes on heating to 200°C (scheme 4).



Scheme 4

Convincing quantitative evidence for a rate-determining first step is available from a careful study by Aksnes and Aksnes[6] of the Arbusov rearrangement of triethyl phosphite to diethyl ethyl phosphinate in the presence of ethyl iodide. They showed by measurement of the rate of product formation, using infrared analysis, that the ethyl iodide is not consumed to a measurable extent at any stage, the rate is proportional to the concentration of ethyl idode, the rate is not affected by added iodide ion and the reaction is much faster in acetonitrile than in benzene or in the absence of solvent. These results are all consistent with a rate-determining first step, the formation of the phosphonium intermediate.

1.3 Attack at Unsaturated Carbon Atom

There is an enormous volume of literature concerning nucleophilic attack by tervalent phosphorus on olefins and acetylenes. Therefore, this section will be divided into two main parts.

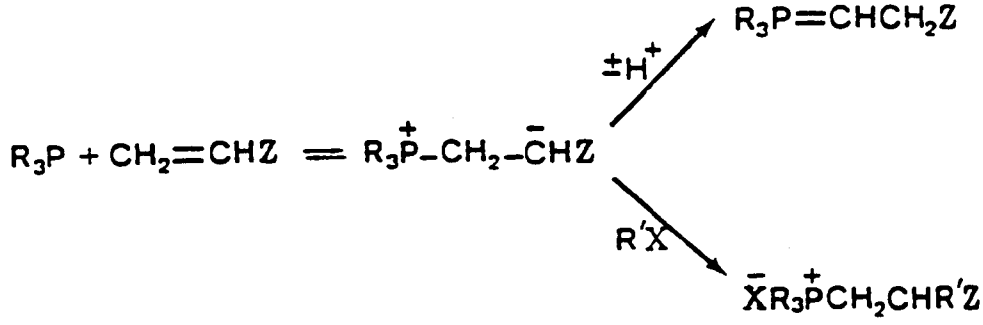
(A) Attack on Unsaturated Carbon Carbon Bonds Leading to Addition Products

(I) Additions to olefins

With neutral phosphines and phosphites the olefin bond must be activated by electron withdrawing groups before any significant reaction can occur.[7,8]

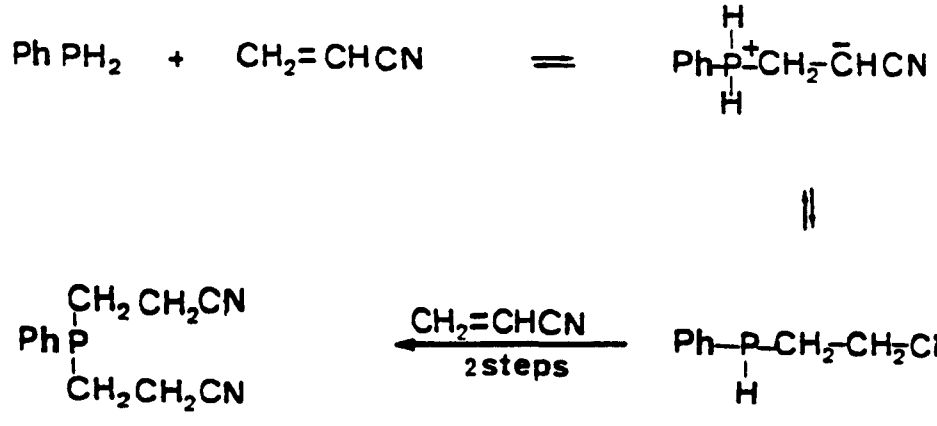
The initial products of the nucleophilic addition, betaines, may be trapped in a number of ways which are generalised in the following reactions.

The simple addition of primary and secondary phosphines, often base catalysed. (Scheme 5).



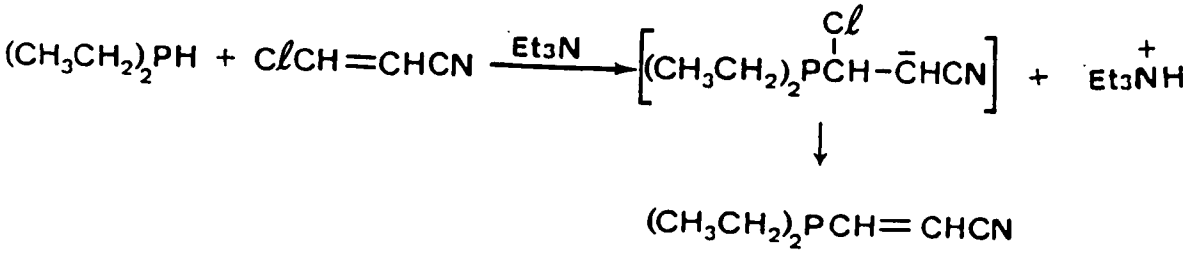
Scheme 5

Betaine protonation, alkylation or intramolecular proton transfer (scheme 6).



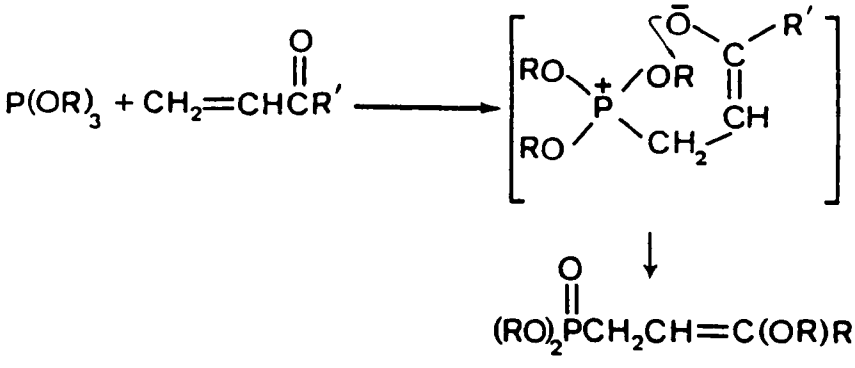
Scheme 6

If the olefin molecule contains a good leaving group (e.g. halogen) the initial addition followed by elimination can occur (scheme 7).



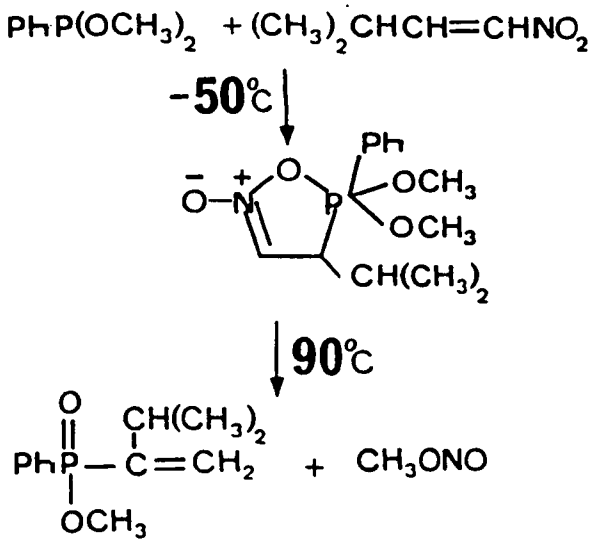
Scheme 7

When the tervalent phosphorus compound contains a P-OR bond dealkylation is possible (scheme 8).

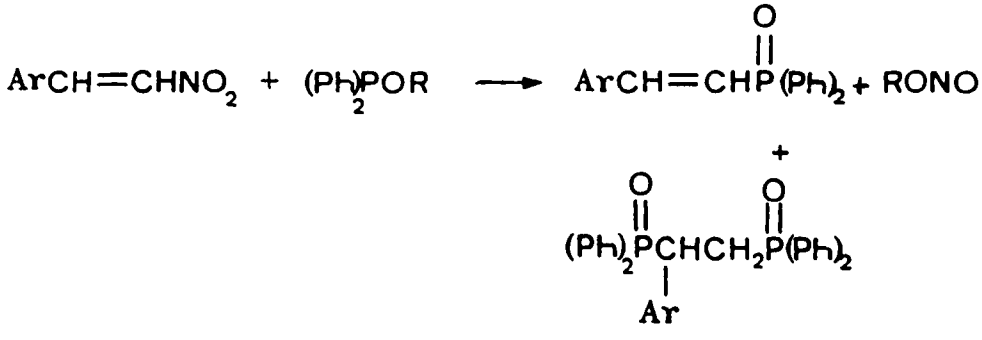


Scheme 8

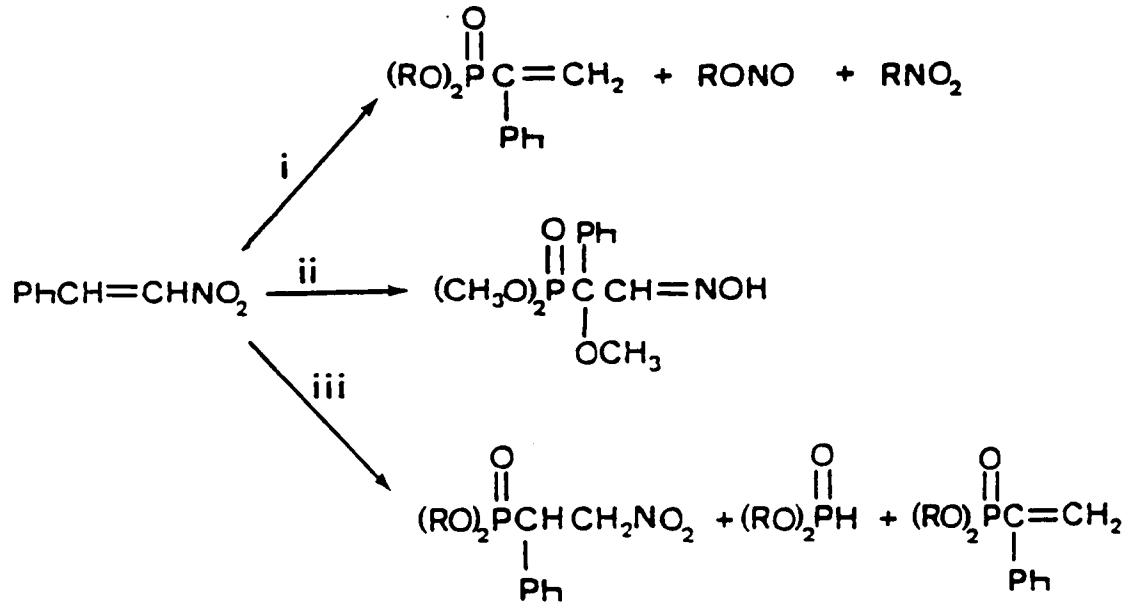
In more recent years, the chemical literature has cited many examples where variation of the initial reaction conditions can have a profound effect on the reaction products, most commonly phosphorane formation instead of the expected addition products. Examples of this appear from work with nitroalkenes.[9,10,11] (scheme 9, 10, 11).



Scheme 9



Scheme 10



(i) $(RO)_3P$ in 1,2-dimethoxyethane

(ii) $(MeO)_3P$ in tertiary butanol

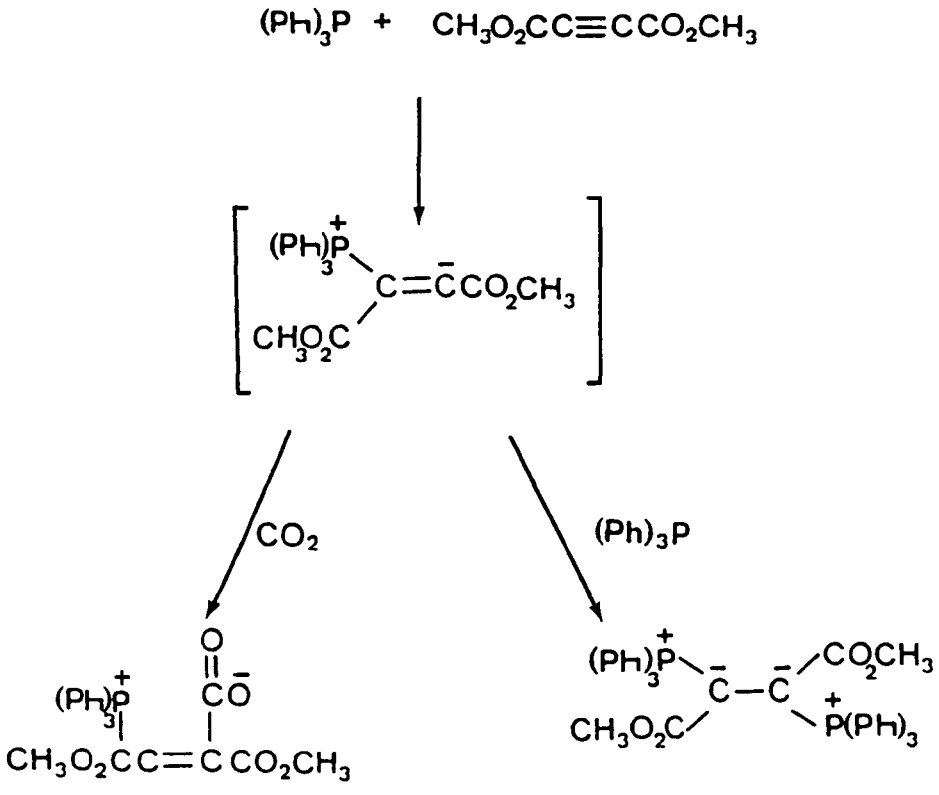
(iii) $(RO)_3P$ in 1,2-dimethoxymethane, H_2O

Scheme 11

(ii) Addition to acetylenes

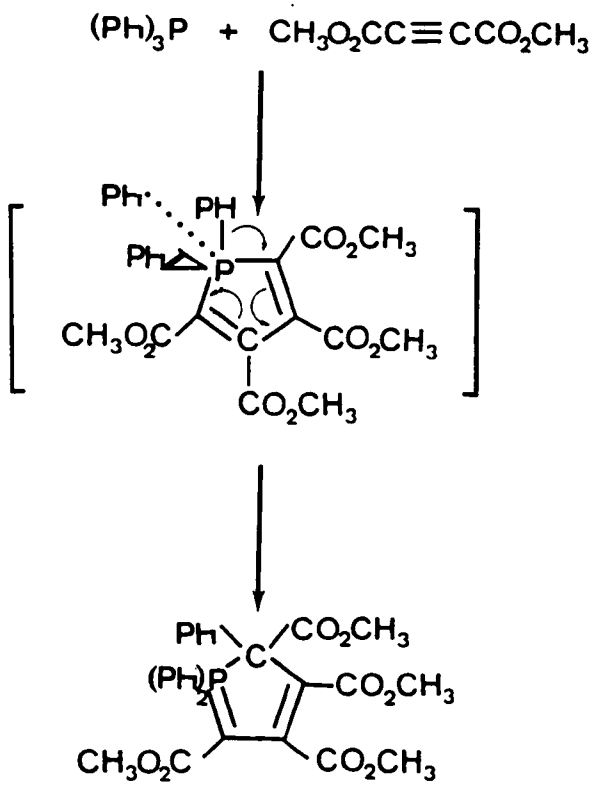
As with the carbon-carbon double bond, carbon-carbon triple bonds need to be polarised by electron withdrawal before any significant reaction with trico-ordinate phosphorus compounds will take place.

Tebby et al.[12] were able to trap an adduct of triphenylphosphine and dimethylacetylidicarboxylate as a betaine with carbon dioxide and using an excess of phosphine a stable adduct was obtained (scheme 12).



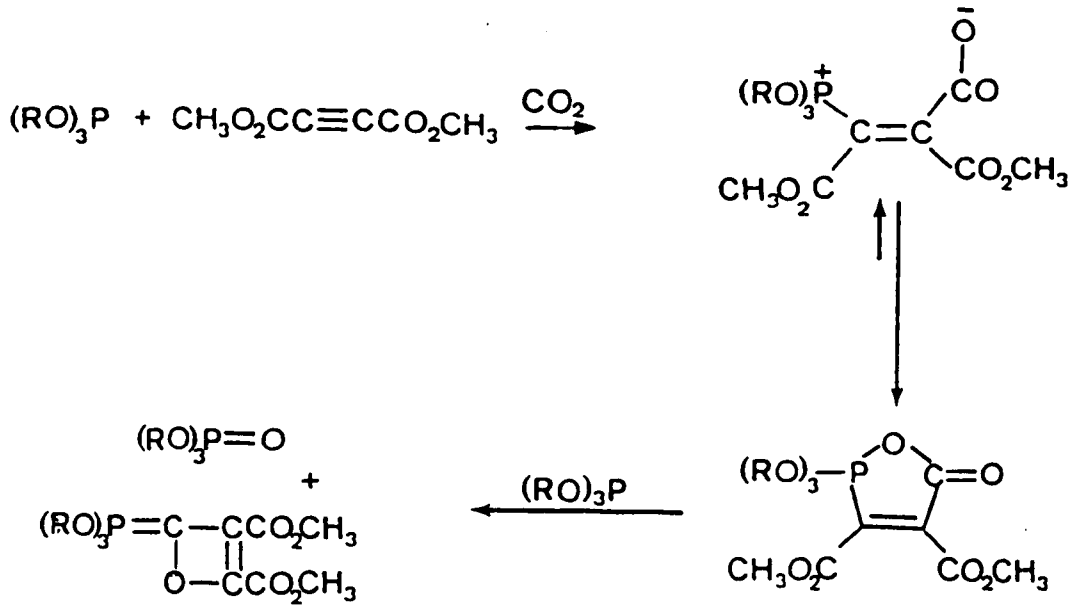
Scheme 12

A 1:2 ratio of phosphine to acetylene in ether reacted to form a cyclic product[13,14] resulting from phenyl migration within an intermediate phosphorane (scheme 13).



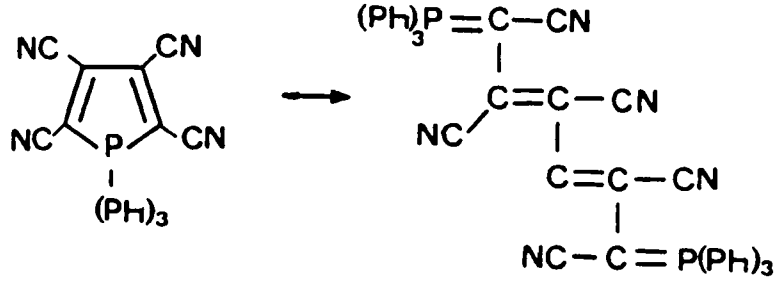
Scheme 13

More recent work by Tebby[15] on the analogous trialkylphosphite acetylendicarboxylate system has resulted in the detection of a pentacoordinate intermediate on route to the formation of an ylid (scheme 14).



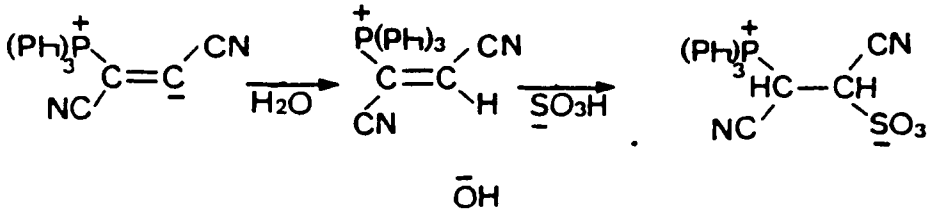
Scheme 14

A red crystalline product results from the reaction of triphenylphosphine and dicyanoacetylene. The pentacovalent phosphate structure was originally proposed but later work by Tebby[16] using mass spectrometry and more recently X-ray studies have confirmed the existence of a 3:2 adduct (scheme 15).



Scheme 15

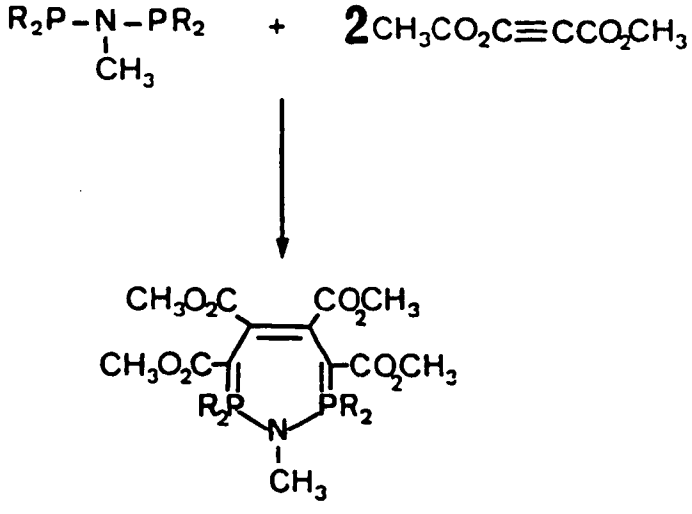
Further study of this system has led to the successful trapping at an adduct between phosphine and dicanoacetylene using sulphur dioxide and water to yield the phosphoniumethanesulphonate betaines[17] (scheme 16).



Scheme 16

However, carbon dioxide failed to trap the adduct.

Other work on this subject has come from Zeiss and Henjes[18] who reported the formation of a cyclic product from the reaction of aminodiphosphine and dimethylacetylenedicarboxylate (scheme 17).

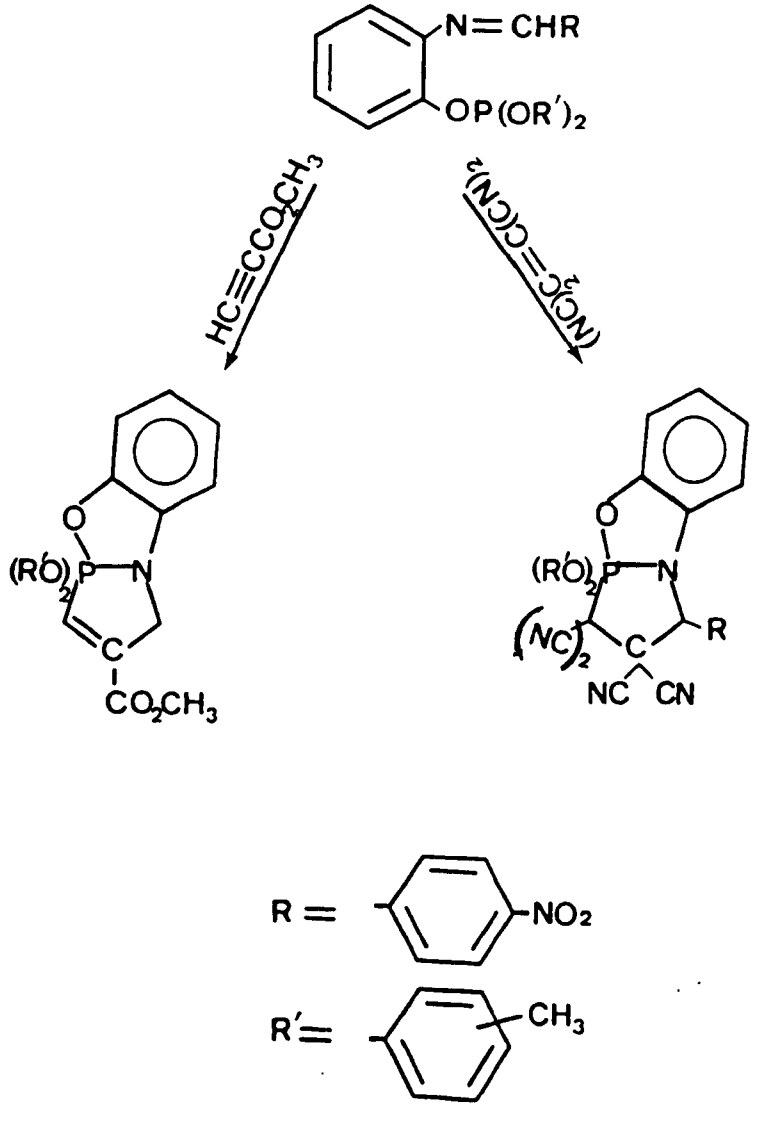


Scheme 17

B) Nucleophilic attack on activated multiple bonds leading to phosphorane formation

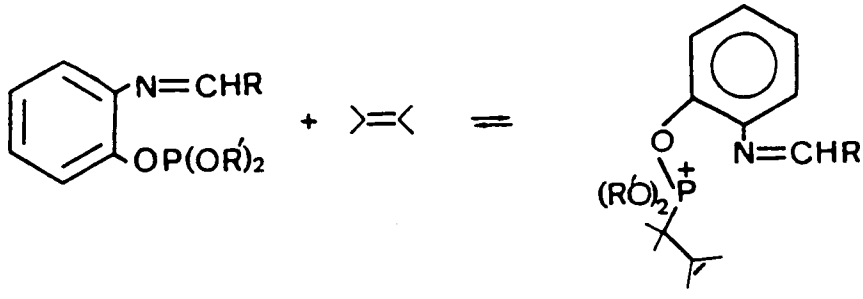
The synthesis of phosphoranes via carbon multiple bonds has been reported by several groups of workers.

Schmidpeter[19] studied the reaction of N-methylene aminophenyl phosphites with a variety of unsaturated substrates (scheme 18).



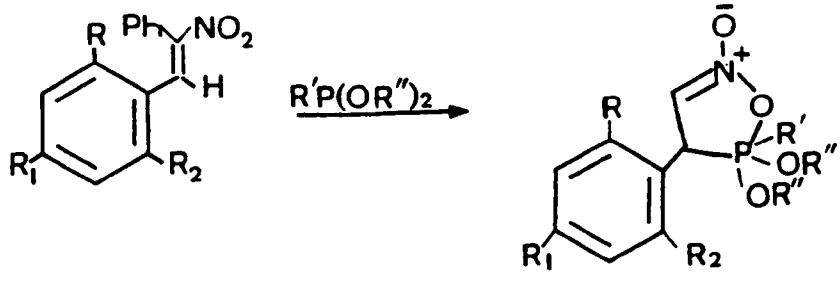
Scheme 18

The suggested mechanism was nucleophilic attack by phosphorus on the multiple bond to form a 1,3 dipolar intermediate and subsequent ring closure (scheme 19).



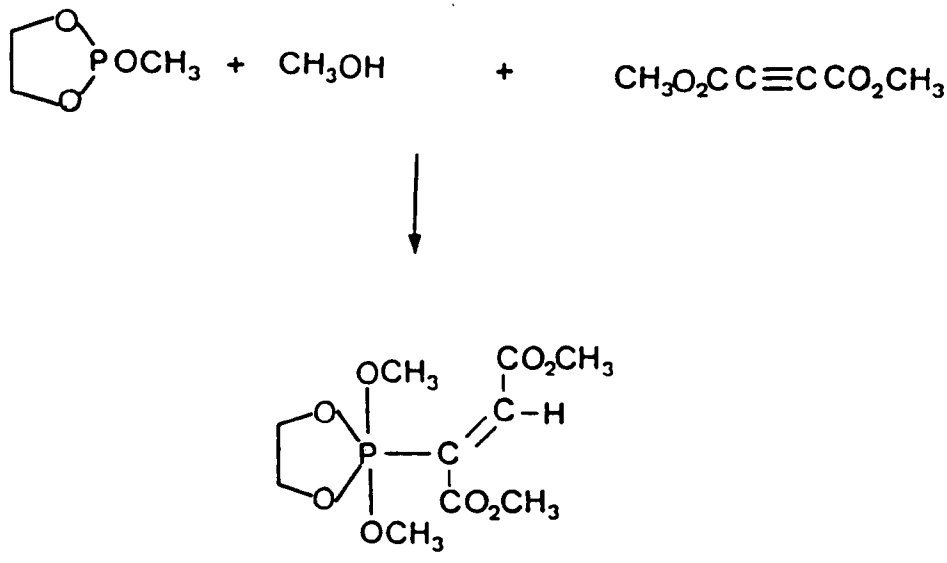
Scheme 19

In a related reaction substituted nitroethylenes were found to form adducts with phosphinites.[20] (Scheme 20).



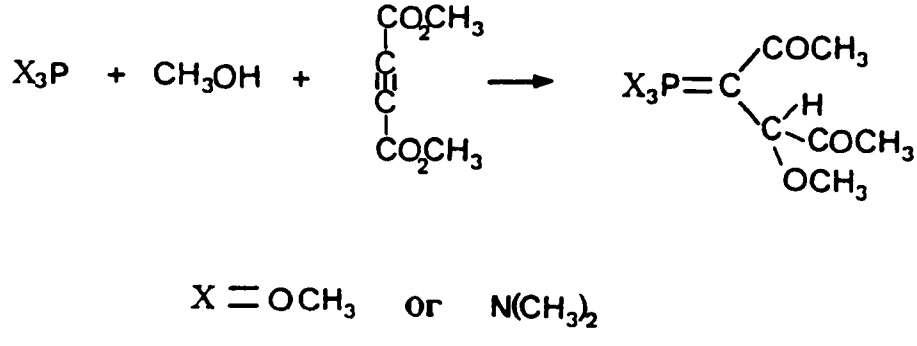
Scheme 20

Burgadan[21] et al. reported a noval synthesis of monocyclic phosphoranes from cyclic phosphites and acetylene (Scheme 21).



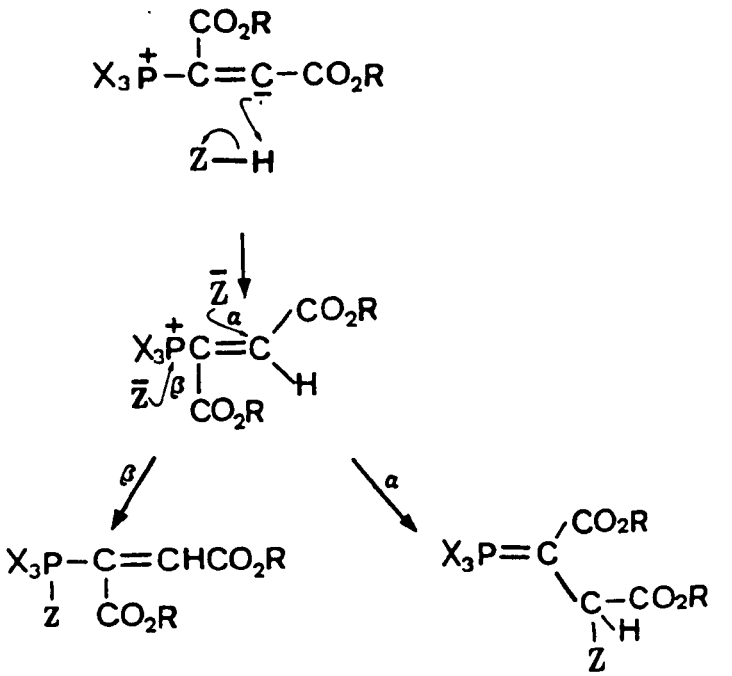
Scheme 21

They discovered that varying the structure of the trico-ordinate phosphorus compound determines whether the final product was a phosphorane or a ylid (scheme 22).



Scheme 22

The proposed mechanism of nucleophilic attack by phosphorus on the triple bond predicts formation of the carbanionic species which can be trapped using alcohols or carbon dioxide (scheme 23).



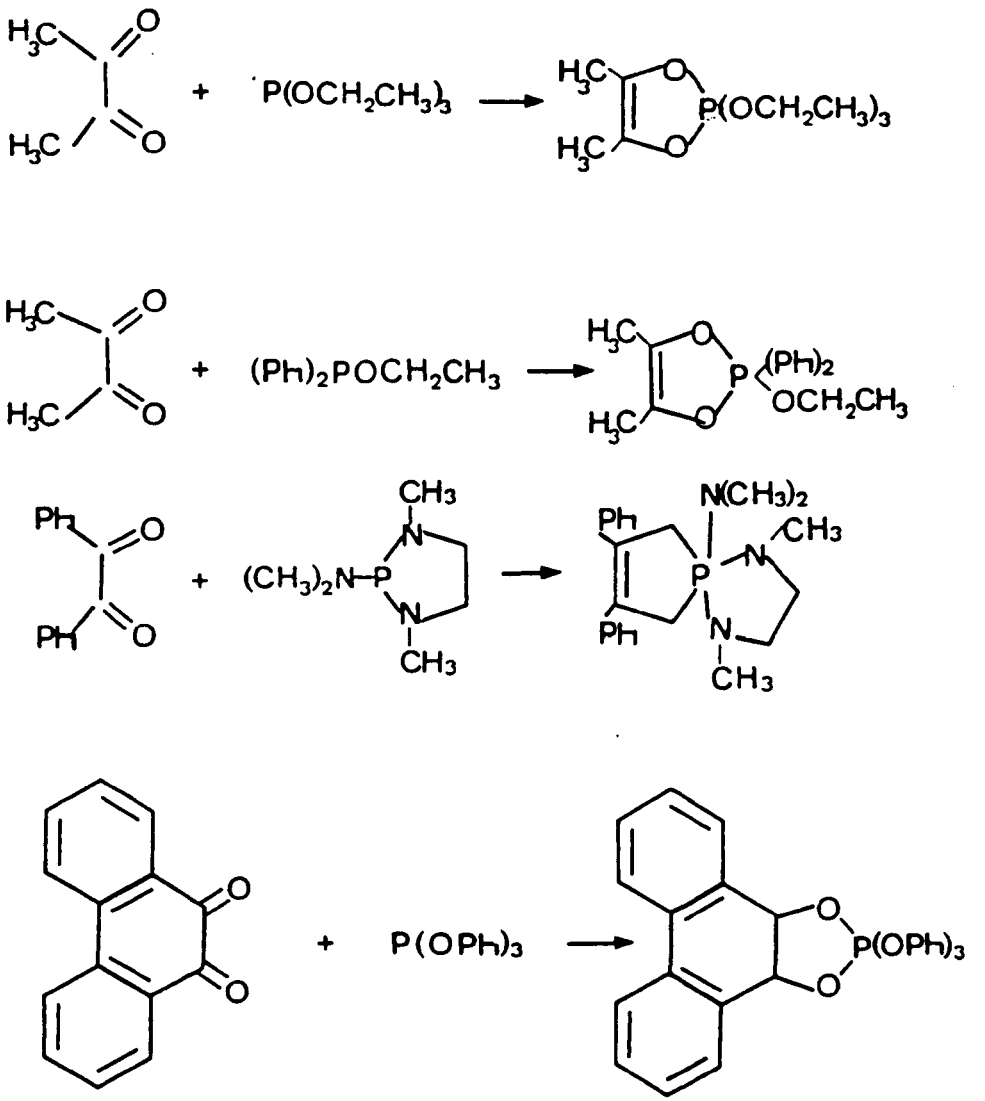
Scheme 23

1.4 Attack at Carbonyl Carbon

A) Nucleophilic attack on α-Diketones and o-quinones

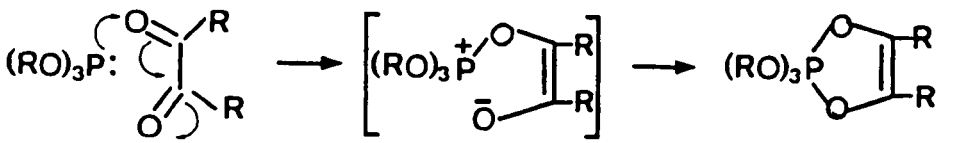
A wide range of phosphites, phosphonites, phosphinites and their amino- and thio-analogues react with α-diketones or o-quinones.

Ramirez[22,23,24] led an extensive investigation in this area reporting phosphorane formation from the above mentioned tervalent phosphorus classes. (Scheme 24).



Scheme 24

Nucleophilic attack by tervalent phosphorus on carbonyl oxygen followed by cyclisation of the zwitterion was the suggested mechanism (scheme 25).

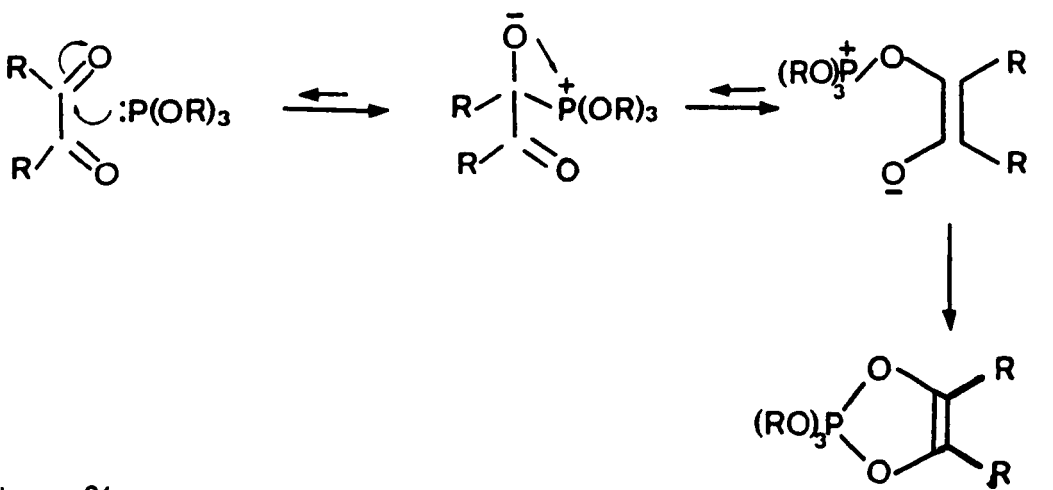


Scheme 25

However, an alternative mechanism was proposed by Ogata and Yamashita.[25] Based on their studies of the addition of trimethyl phosphite to benzil, the authors' suggestion was that the initial nucleophilic addition was on carbonyl carbon.

Further support for this came from a study of the electronic substituent effects of groups attached to the aromatic rings of benzil[26,27,28], which concluded that resonance interactions between the electron releasing or withdrawing substituents and the positive charge on the phosphorus atom, or the negative charge on the carbonyl oxygen, had little effect on the stabilisation of the transition state.

Ogata proposed the following mechanism involving initial attack by phosphorus at carbonyl carbon followed by rearrangement and cyclisation. (Scheme 26).



Scheme 26

A more recent report on the reactions of silyl phosphites adds support to the proposal attack of phosphorus on carbonyl carbon.[29] However, the authors admit that one must take into account the difference in structure between trialkyl phosphites and silyl phosphites and hence mechanistic analogies are subject to some uncertainty.

A third mechanism for the addition of tervalent phosphorus compounds to α-dicarbonyls was postulated based on the results of e.s.r. spectroscopy experiments.

Lucken[30] and then Boekestein[31,32] observed that using phenanthraquinone and certain α-diketone and α,β-unsaturated ketones as substrates, electron transfer occurs and radical intermediates result.

B) Nucleophilic attack on activated monocarbonyl compounds

Ramirez has conducted extensive studies into the reactions of a variety of tervalent phosphorus species with suitably activated monocarbonyl compounds. (Table 1).

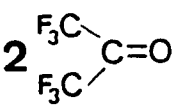
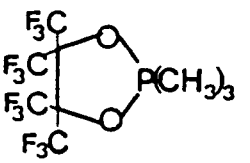
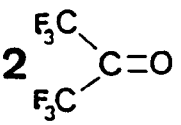
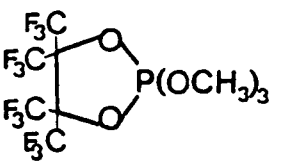
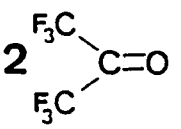
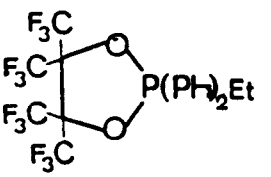
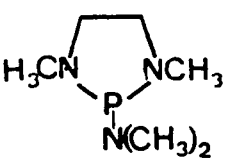
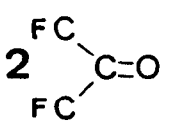
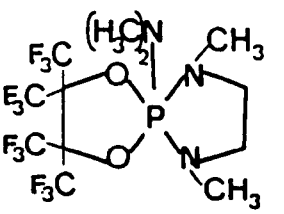
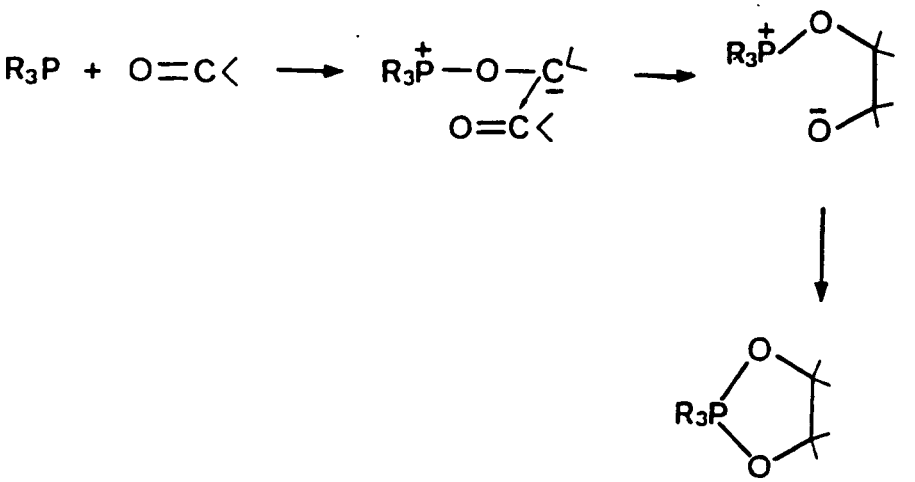
Phosphorus Reagent	Substrate	Product
$P(CH_3)_3$		
$P(OCH_3)_3$		
$P(PH)_2Et$		
		

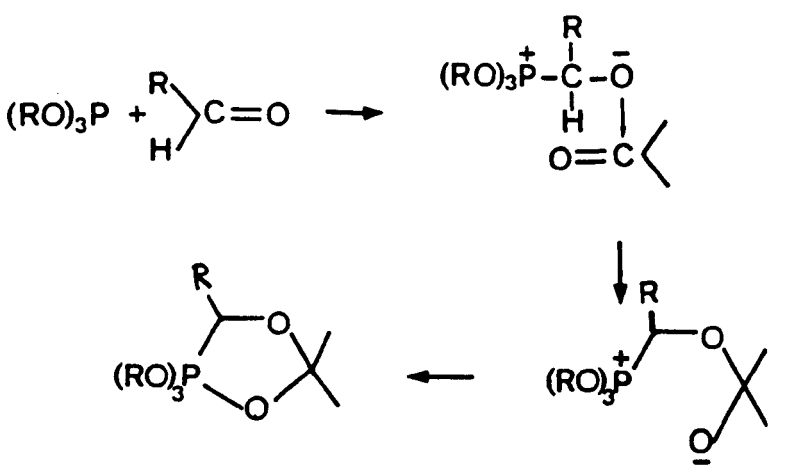
Table 1

The mechanism of these condensations involves initial attack by phosphorus on carbonyl oxygen, the negative charge so generated being stabilised by electron-withdrawing substituents on carbon such as p-nitrophenyl or trifluoromethyl. The second step involves nucleophilic addition at the carbanion to carbonyl carbon and subsequent ring closure to form the oxyphosphorane (scheme 27).



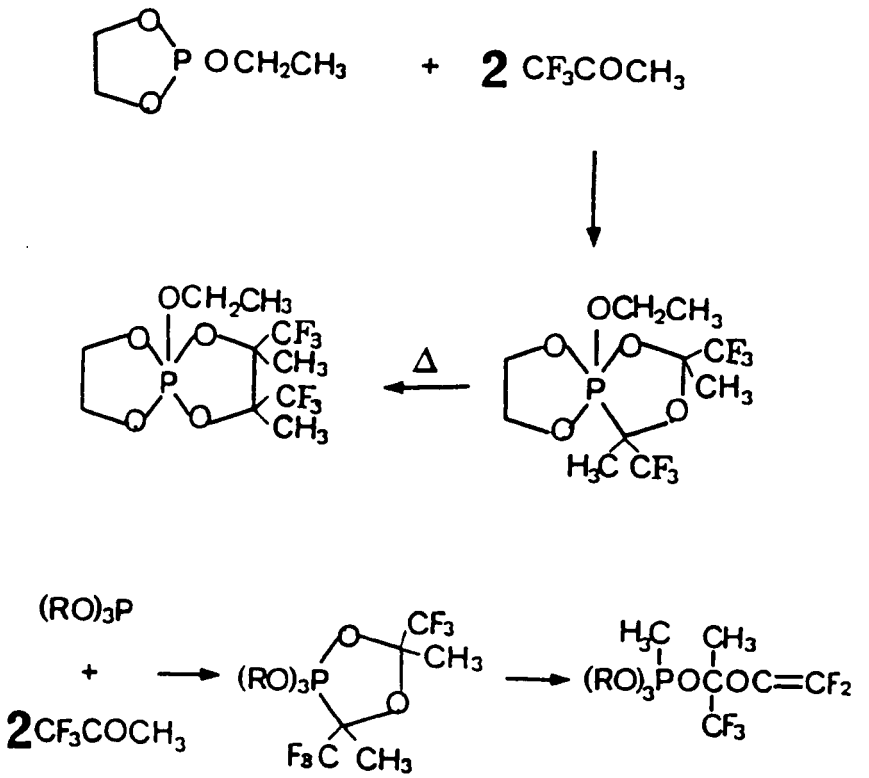
Scheme 27

In contrast, derivatives of the 1,4,2-dioxaphospholane system are formed by reactions of tervalent phosphorus compounds with unactivated aldehydes or ketone.[33] Here, initial attack by phosphorus take place at carbonyl carbon (scheme 28).



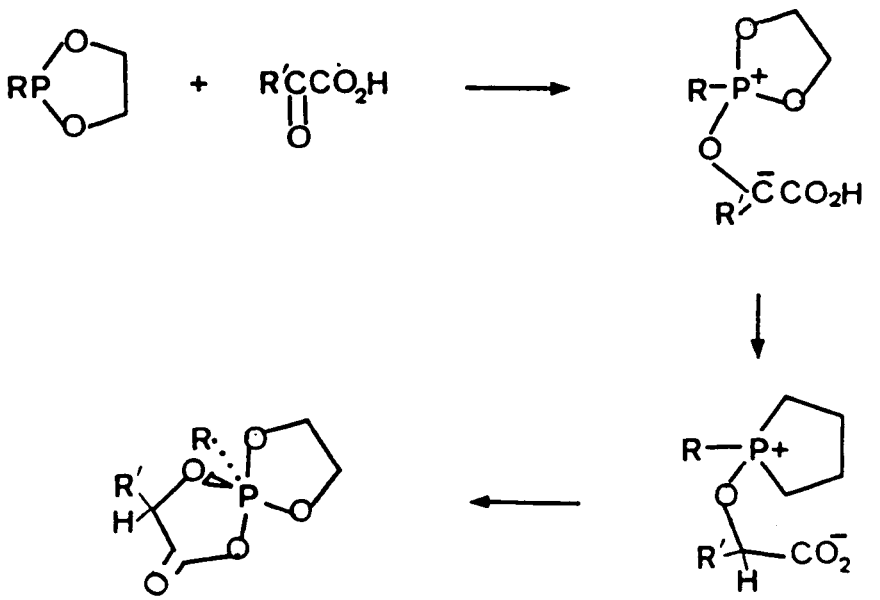
(Scheme 28)

However, two articles in the Russian literature[34,35] have reported formation of the 1,4,2-dioxaphospholane ring from the reactions of phosphites with the activated ketone 1,1,1-trifluoroacetone. (Scheme 29).



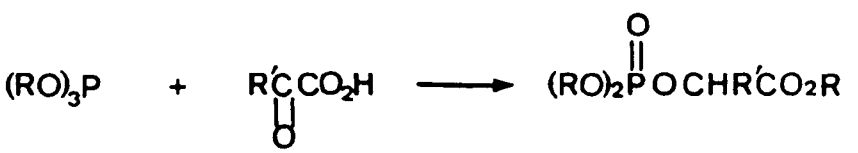
Scheme 29

Investigations into the reaction of cyclic phosphites or phosphonites with α-keto acids showed that these led to cyclic acyloxyphosphoranes[36]. The authors suggest a mechanism which involves initial attack on oxygen to form an intermediate phosphonium carbanion which undergoes an intra or intermolecular proton transfer to yield a zwitterion. Subsequent cyclisation at the latter leads to the product phosphorane (scheme 30).



Scheme 30

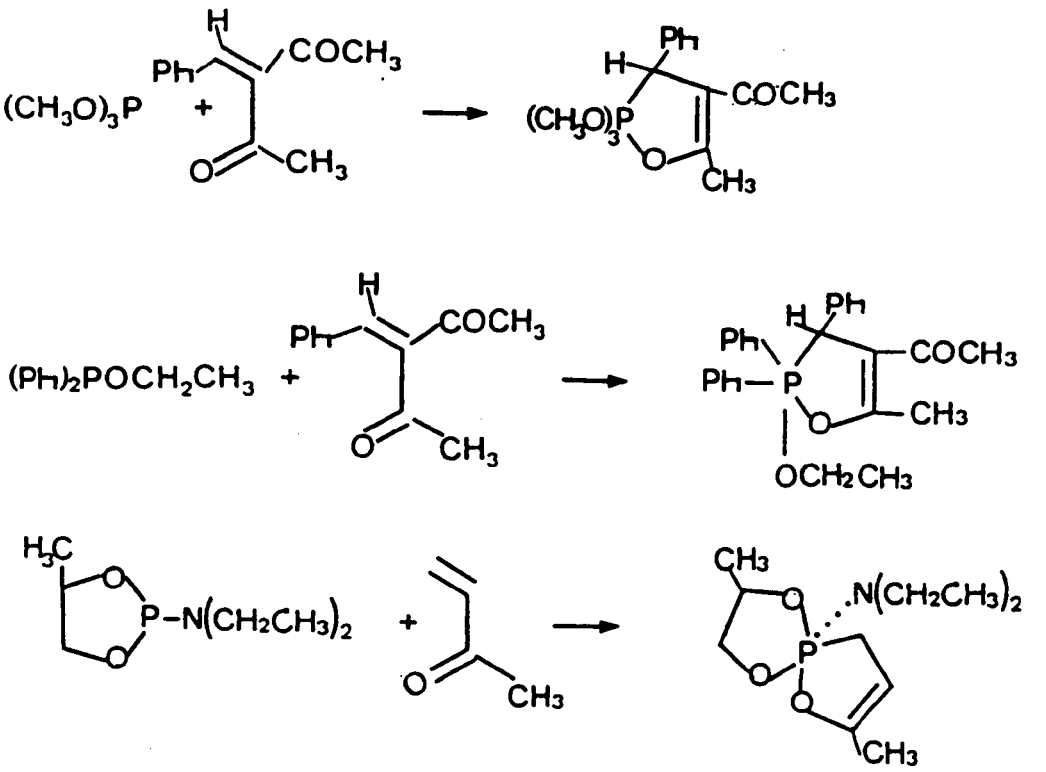
In contrast to this acyclic phosphites were found to give the Arbusov product (scheme 31).



Scheme 31

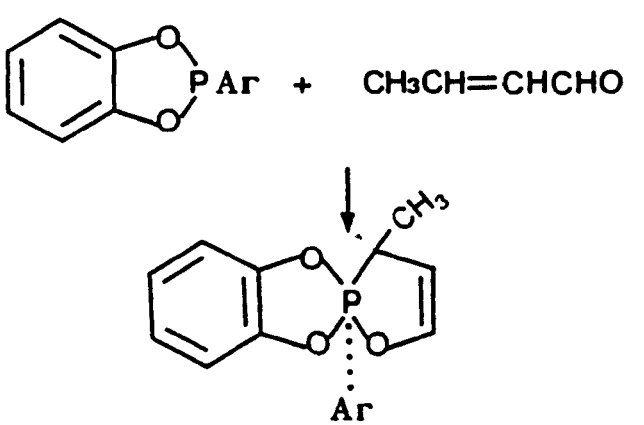
C) Nucleophilic attack on 1,3-unsaturated systems

A variety of α,β-unsaturated carbonyl compounds were found to react with phosphites, phosphonites, phosphinites and amino substituted phosphorus compounds to give oxyphosphoranes.[37,38,39] (scheme 32).



Scheme 32

Russian workers[40] have studied the kinetics of the reaction of cyclic arylphosphites with crotonaldehyde (scheme 33).

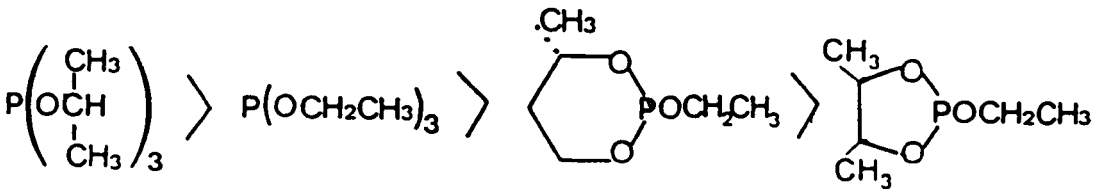


Scheme 33

A positive ρ value was obtained suggesting that the initial nucleophilic attack by phosphorus on the substrate was not rate-determining. Earlier work[41] with 3-buten-2-one indicated the contrary and the author's explanation of these contrasting results lay with the position of the methyl group in the component.

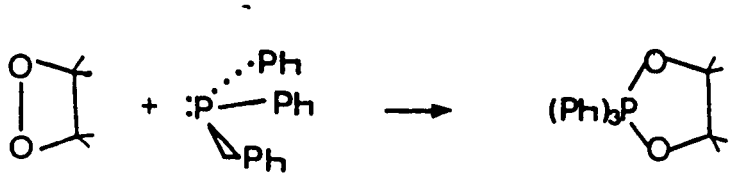
1.5 Attack at saturated oxygen (The Peroxide linkage)

The reaction of trivalent phosphorus compounds with dialkyl peroxide was, at one time,[42] thought to proceed via nucleophilic attack on oxygen by phosphorus. However, Aksnes[43] had observed that the rate of nucleophilic attack of acyclic and cyclic phosphites on ethyl iodide in the Michaelis-Arbusov reaction had the following order of reactivity:



Subsequently, Denney[44] used a similar series of phosphites for reaction with diethyl peroxide and found that the relative rate order had been totally reversed. He concluded that direct formation of the pentaoxyphosphorane and not initial nucleophilic attack was responsible for product formation.

In contrast, the initial study[45] of the reaction of the dioxetane with triphenylphosphine, diphenylphospinites and trialkoxy phosphites to form, in each case, a phosphorane containing a dioxaphospholanium ring concluded on the basis of rate studies and the lack of polar solvent effect, that the mechanism must be either concerted or homolytic in character (scheme 34).

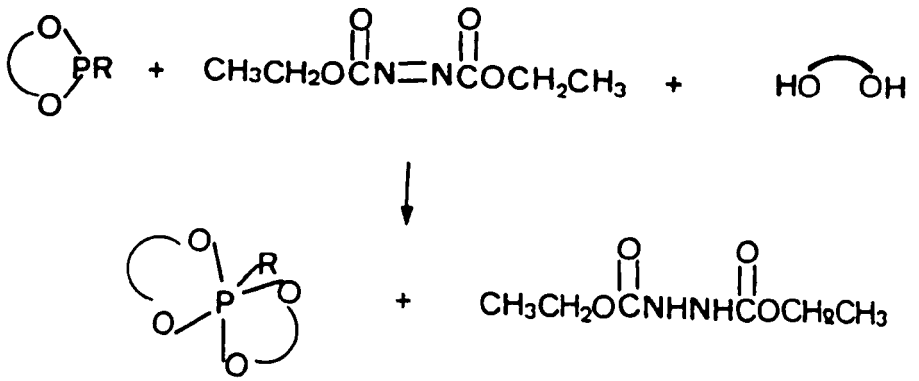


Scheme 34

In summary, we can say that the mode of cleavage of the peroxide linkage of diethyl peroxide and that of the dioxetanes by trico-ordinated phosphorus compounds has been set apart from the more classical ionic or radical mechanisms and is considered as a biphilic process in which both the nucleophilicity and the electrophilicity of the phosphorus atom are involved in the transition state.

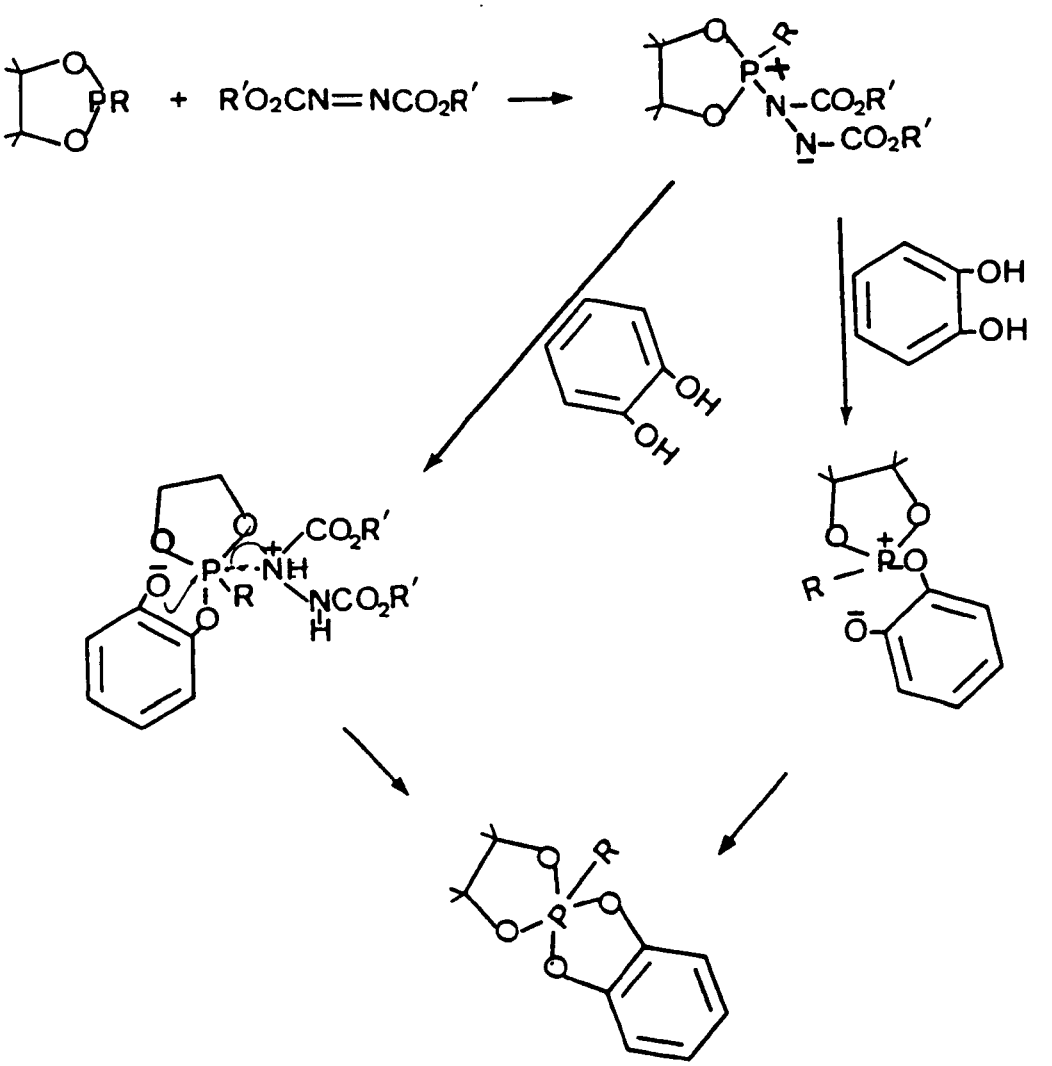
1.6 Attack at Nitrogen

Trippett and Bone[45] reported the synthesis of spirophosporanes from reaction of cyclic phosphites and 1,2 or 1,3 glycols with diethylazodicarboxylate (scheme 35).



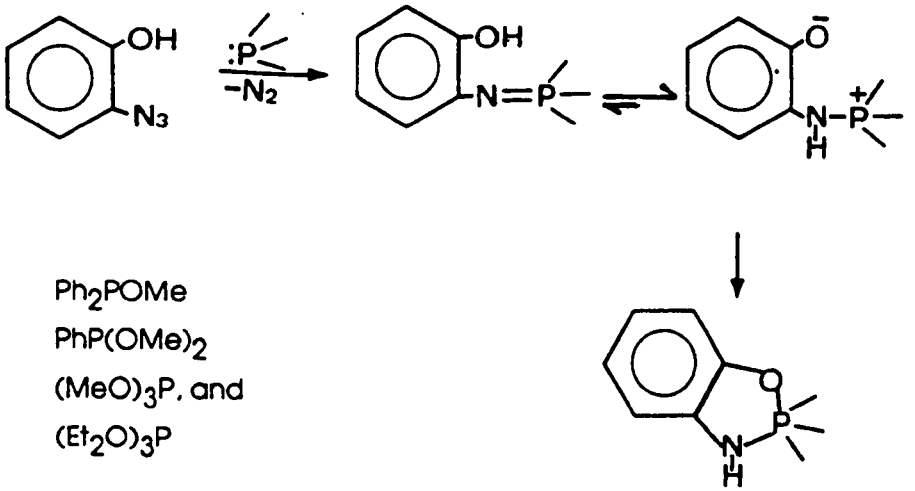
Scheme 35

The mechanism probably involves initial nucleophilic attack by phosphorus on nitrogen to form a 1,3-dipolar species. Final cyclisation may take place via substitution of pentacovalent phosphorus or through an intramolecular phosphonium alkoxide follwoed by ring closure. (Scheme 36).



Scheme 36

Azides[46] were also found to react with tervalent phosphorus compounds, methyl diphenylphosphinite, dimethylphenylphosphonite trimethyl phosphite and triethyl phosphite (scheme 37).

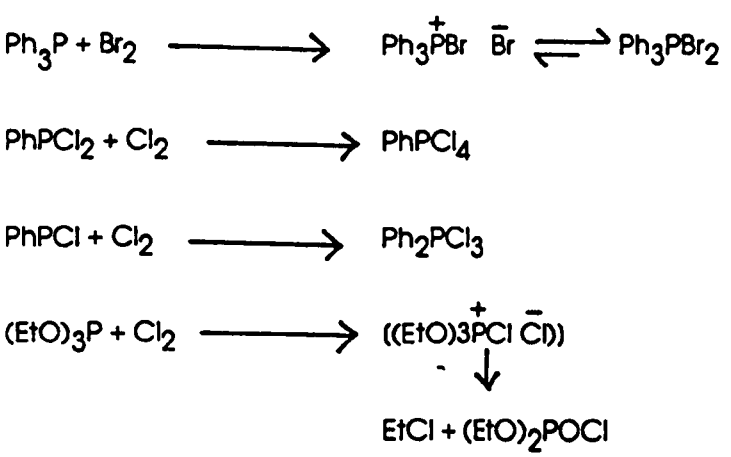


Scheme 37

Extension of this work has led to the synthesis of bicyclic spirophosphoranes.[47]

1.7 Attack at Halogen

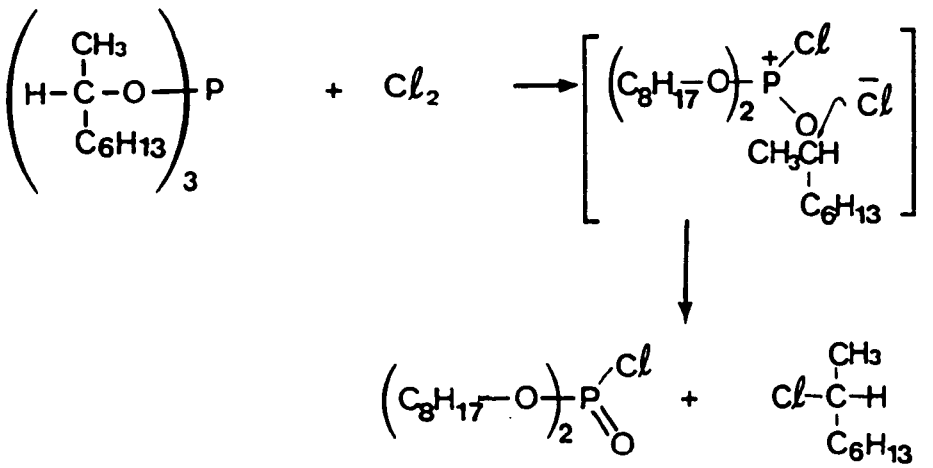
Tertiary phosphines react with halogens[48] to give dihalophosphoranes, whereas trialkyl phosphites (or mixed aryl alkyl phosphites) with chlorine form phosphonyl chlorides via an Arbusov rearrangement (scheme 38).



Scheme 38

Over thirty years ago, Gerrard and Phillp[49] studying the halogenation of optically active tri-2-octyl phosphite found that 2-chlorooctane was obtained with essentially

complete inversion. This prompted the proposal of initial nucleophilic attack on the halogen to form an intermediate chlorotrialkoxy phosphonium salt followed by S_N2 displacement by chloride ion (scheme 39).

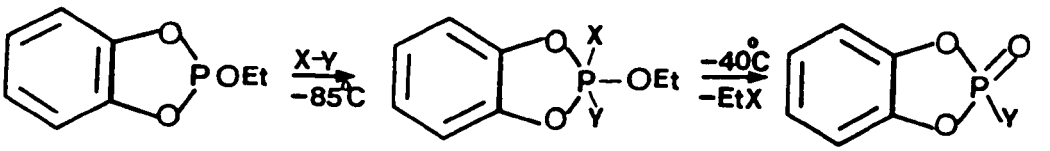


Scheme 39

However, this evidence is not sufficient to preclude the reaction via a molecular (or free radical) pathway involving a pentaco-ordinate intermediate, which ionises and dealkylates to products.

The above paragraph is borne out in a communication reporting direct evidence by ^{31}P n.m.r. of a pentacovalent intermediate species in the Arbusov reaction of tervalent phosphorus esters.[50]

When the phosphite was added to halogen or benzenesulphenylchloride at low temperature, the corresponding phosphorane was detected. On warming to -40°C the respective oxides resulted (scheme 40).



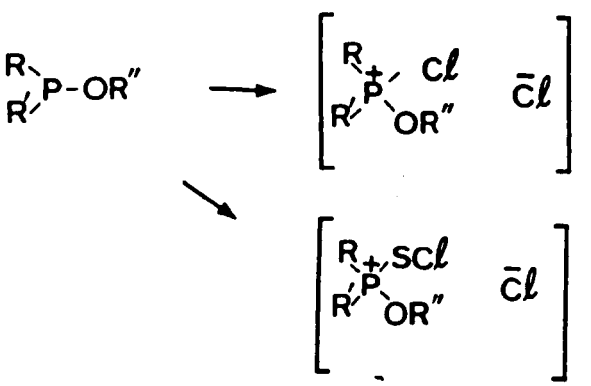
X = Y = Cl

X = Y = Br

X = Cl, Y = phS

Scheme 40

Michalski[51] while studying the reaction between phosphorus thionoesters and chlorine or sulphuryl chloride by low temperature ^{31}P n.m.r., detected phosphonium intermediates whose structure were confirmed through independent synthesis by Arbusov-type reactions (scheme 41).



(I) R = Et, R' = OEt, R" = Et

(II) R = Ph, R' = OBut, R" = Bu

Scheme 41

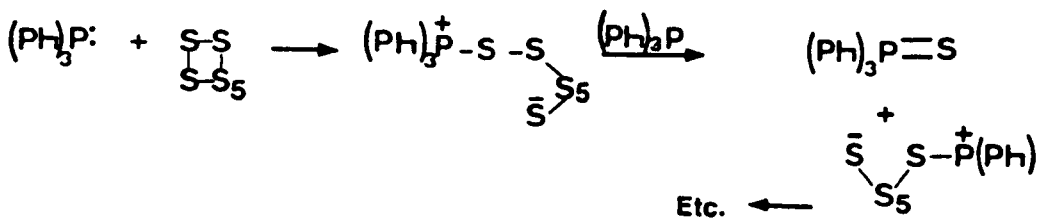
These salts were prepared by mixing the reagents in ethyl chloride solution at the temperature of liquid nitrogen and allowing the solution to warm gradually to -40°C.

1.8 Attack at Sulphur (II)

(A) Attack at Sulphur (S_8)

Trialkyl and triaryl phosphines have been found to react vigorously with octa-atomic sulphur in low polarity solvents. Bartlett[52] investigated the kinetics of the reaction of triphenylphosphine with S_8 in benzene at room temperature. He found the reaction to be second order and also observed that this system was highly sensitive to solvent polarity. The increase in reaction rate did not parallel an increase in the dielectric constant of the medium but did relate to the solvent's hydrogen-bonding power (its ability to solvate anions).

Using a variety of para-substituted arylphosphines Bartlett obtained a ρ value at -2.5 and proposed a mechanism involving initial nucleophilic displacement of sulphur by attack of the phosphorus on sulphur, opening the sulphur ring to produce a linear octasulphide derivative. The resulting dipolar ion then undergoes a series of rapid nucleophilic displacements (scheme 42).



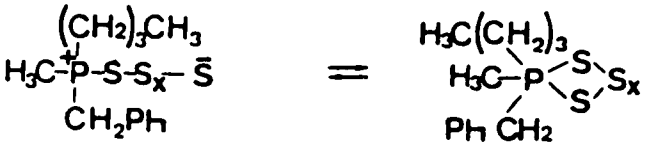
Scheme 42

The possibility arises though, that the intermediate involved during reaction may cyclise.

McEwan[53] effectively negated the existence of cyclic tautomers by reacting optically active phosphines with S_8 under similar conditions to those of Bartlett's. The reaction proceeded with retention of configuration.

If (1) is in equilibrium with the pentaco-ordinate (2) we may expect stereomutation through,

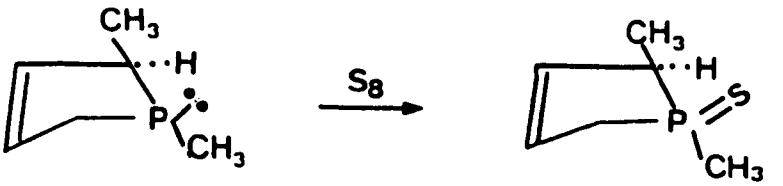
i) - basal attack/basal departure (inv.)
ii) - apical attack/apical departure (inv.)
iii) - apical attack/basal departure (ret.) (scheme 43)



(1) (2)

Scheme 43

Similarly,[54] with phospholane (3) attack on sulphur S_8 occurs with retention of configuration of phosphorus to give the cyclic phosphine sulphide(4). (Scheme44).



(3) (4)

Scheme 44

The ρ values and activation parameters for triarylphosphines, diarylphosphinites and arylphosphinites attacking octatomic sulphur have been published recently[55] and Table (2) summarises their work.

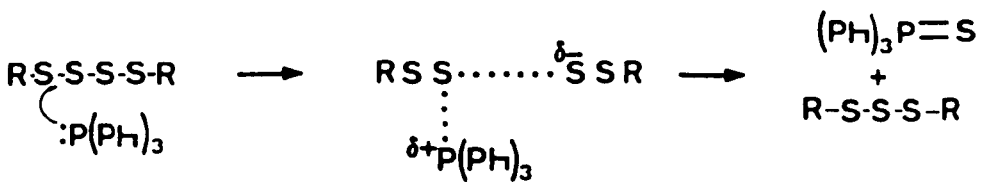
Table 2

P(111)	k_2 at parent $mol^{-1} s^{-1}$	ρ value
Ar_3P	3.5×10^{-3}	-2.25
Ar_2POPri	1.54	-3.28
$ArP(Opri)_2$	1.23	-3.34

Again, like Bartlett, the system was found to be sensitive to solvent polarity. This result, together with the high ρ values indicates that the transition state must be of a highly polar nature. The relative rates of reaction of triphenylphosphine, isopropyldiphenyl-phosphinite and di-isopropyl phenyl phosphonite with sulphur did follow the trend observed for similar trico-ordinate phosphorus compounds reacting with ethyl iodide in the classical Arbusov system.[6]

B) Attack on Tetrasulphides

Moore and Trego[56,57] have studied the desulphurisation of dialkyl and dibenzyl tetrasulphides by triphenylphosphine in dry benzene to give disulphides illustrated in scheme 45.



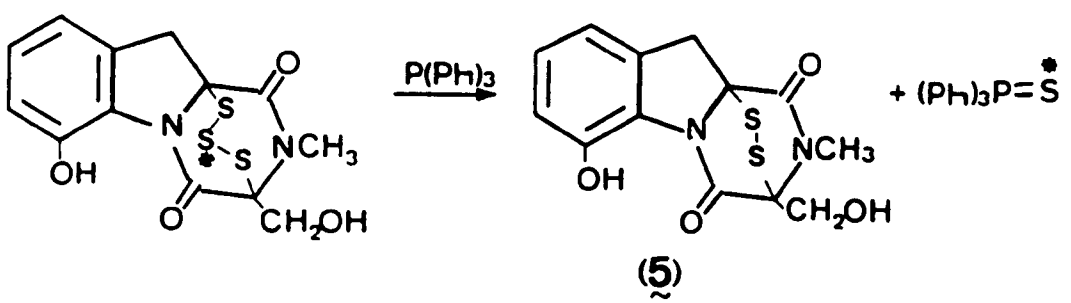
Scheme 45

The polar mechanism proposed for this reaction is consistent with the enhancement of rate observed on increasing the dielectric constant of the medium. However,

the magnitude of this effect contrasts with the considerably larger rate enhancement for the triphenylphosphine/S_8 system and for this reason char ge separation in the transition state is thought to be less pronounced.

C) Attack on Trisulphides

^{35}S radioactive tracer studies performed on the thiodehydrogliotoxin (5) showed that only the S_8 central sulphur atom was removed by triphenyl phosphine.[58] Circular dichroism experiments performed on the same compound also revealed that the reaction proceeded with retention of configuration of the asymmetric carbon atoms at both ends of the trisulphide linkage; however, Harpp believed that this molecule might constitute a special case, since terminal sulphur extension, he proposed, would appear to necessitate "front-side displacement of phosphine sulphide by mercaptide ion[59] (scheme 46)



(5)

Scheme 46

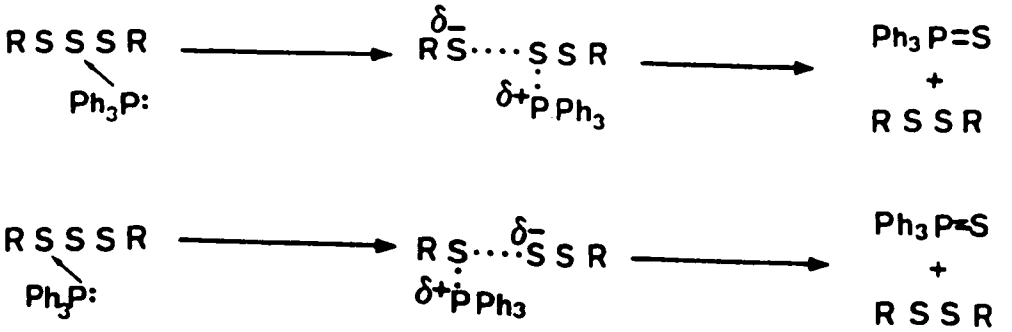
Accordingly, the same author prepared ^{35}S-labelled benzyl trisulphide and discovered that the mode of desulphurisation was highly dependent on the type of phosphine used. His results are summarised in scheme 47.

$R_3P + R'\text{-}S\text{-}\overset{*}{S}\text{-}S\text{-}R' \longrightarrow R'\text{-}S\text{-}S\text{-}R' + R_3P{=}S$

R	R'	$\%R_3P{=}S^*$
Ph	$PhCH_2$	88
NEt_2	$PhCH_2$	4
Bu^n	$PhCH_2$	72

Scheme 47

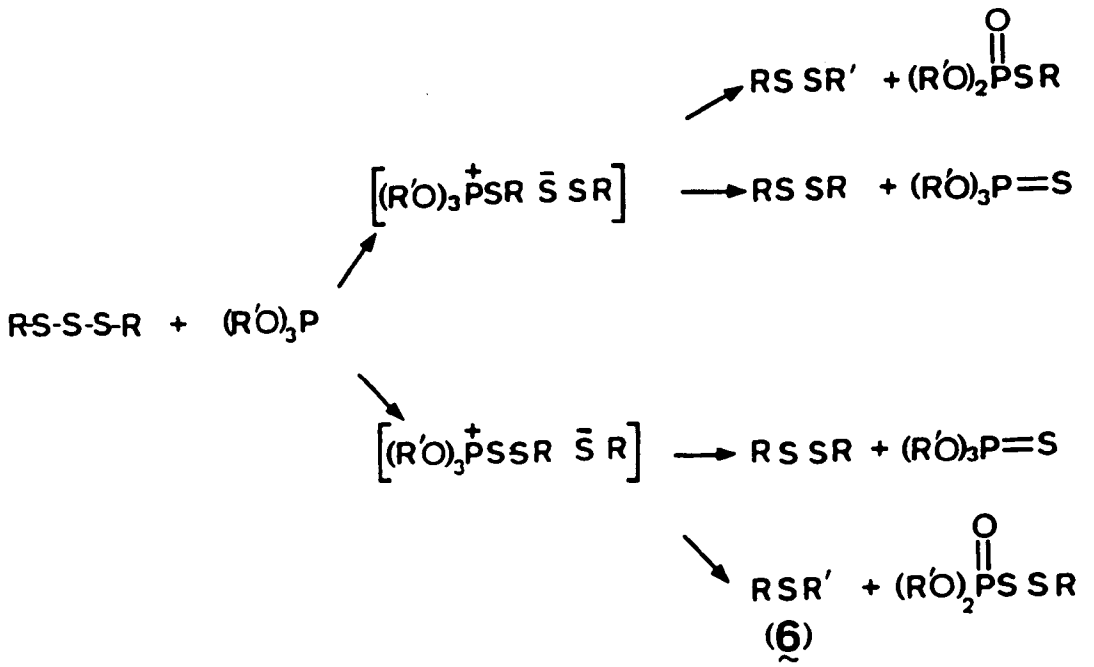
Prior to either of these investigations, Trego[57] had studied the reaction of symmetrical dialkenyl trisulphides with triphenylphosphine and proposed that two routes, leading to eventual formation of disulphide, were possible. Through structural consideration of the reaction product this author suggests again that an (intimate) ion-pair was involved in both processes (scheme 48).



Scheme 48

In more recent publications the reaction of thialkyl phosphites with organic trisulphides[60] was reported to give mixture of unsymmetrical and symmetrical disulphides, and the corresponding phosphorothioates. Here, further mechanistic complexities are implied, since ion pair formation may then result in possible dealkylation as well as in desulphurisation.

The following scheme shows four possible consequences of the phosphite/trisulphide reaction (scheme 49).



Scheme 49

In general,a mixture of(O,O,S)and(O,O,O)trisubstituted phosphorothioates was obtained, along with varying ratios of unsymmetrical (R'SSR) and symmetrical (RSSR) disulphides. In no instance was the unsymmetrical sulphide (6) observed.

The rate of reaction of dibenzyl trisulphide with trimethylphosphite was shown to be a function of solvent polarity increasing in the order.

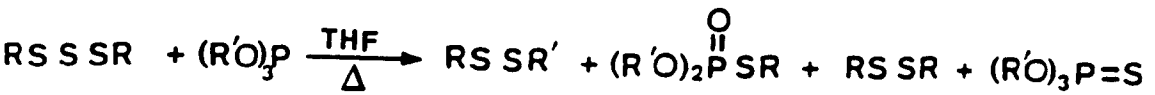
Cyclohexane < Benzene < THF < Acetone < Acetonitrile

Interestingly, the composition of the reaction products had an analogous dependence. For instance while reaction of dibenzyl trisulphide with trimethyl phosphites in either acetone or acetonitrile produced almost equal amounts of dibenzyl and benzyl methyl disulphides, use of THF as solvent, specially gave benzyl methyl disulphide and the corresponding phosphorothioate.

Some of the more relevant sulphide product's ratios ensuing from the reaction of a variety of trialkyl phosphites with trisulphides are presented in scheme 50 and the conclusions drawn by the author from a rigorous study of product composition are:

The effect of varying the trisulphides group R on reaction product composition is related to the pKa of the corresponding thiol. The more acidic RSH becomes, the higher percentage of asymmetric disulphide produced.

The ratio of disulphides RSSR'/RSSR is a function of the steric hindrance of the alkyl group of the trialkyl phosphite. More precisely, less readily dealkylated phosphonium salts yield higher percentages of symmetric disulphides and hence an excess of(O,O,O)trialkyl phosphonothioates(Scheme 50).



R	R'	R'SSR	RSSR		pKa
P-CH_3-C_6H_4	CH_3	69	31		
P-CH_3-C_6H_4	CH_3CH_2	37	63	$CH_3C_6H_4SH$	9.3
P-CH_3-C_6H_4	$(CH_3)_2CH$	19	81		
C_6H_5-CH_2	CH_3	100	0		
C_6H_5-CH_2	CH_3CH_2	81	19	$PhCH_2SH$	11.8
C_6H_5-CH_2	$(CH_3)_2CH$	74	26		

Scheme 50

Harpp[61,62] also has shown that desulphurisation of dialkyl trisulphides by triphenylphosphines results in 91-99% central sulphur removal, essentially independent of solvent (Et_2O, CH_3CN) reaction temperature (0-50°C), type of trisulphide (dibenzyl or dipropyl), and para substituents on Ar_3P (CH_3O to Cl, electron-withdrawing group may slightly increase central sulphur removal). In sharp contrast to this, desulphurisation of dialkyl trisulphides by aminophosphine results in preferential removal of a terminal sulphur atom in Et_2O, while in CH_3CN more than the statistical amount (33%) of central sulphur is removed (scheme 51).

R' = ph, R_2N in CH_3CN
(Central S removed)

R' = R_2N in ether
(Terminal S removed)

Scheme 51

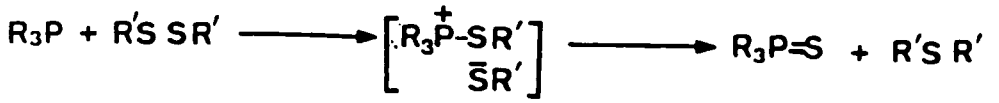
He concluded from these studies that the interaction of phosphine with a trisulphide is much more complicated than previously thought.[63] When the transition state of the two reaction steps in ionic desulphurisation are of similar energy, variation in phosphine type and reaction solvent may effect these transition states enough to alter the kinetically important step.

Therefore, for desulphurisation without inversion of an α-carbon, triphenylphosphine is quite effective as it removes almost exclusively the central sulphur atom. However, for less reactive trisulphides, tris(dialkylamino)phosphine would be required for rapid desulphurisation. In this case, desulphurisation in benzene or ether provides a disulphide with predominant inversion at one α-carbon (via terminal sulphur removal), while in acetonitrile a disulphide having predominantly retained stereochemistry at both α-carbons (via central sulphur removal) is obtained.

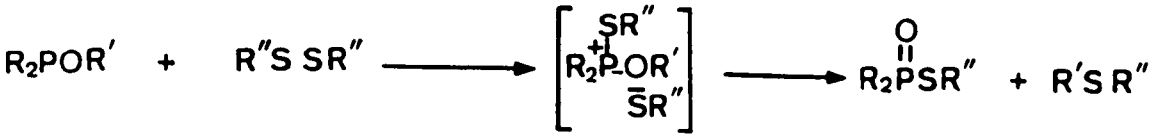
D) Nucleophilic attack on Disulphides

Since the first reported example of trivalent phosphorus reacting with the disulphide linkage in 1935, the amount of literature published in this field has been extensive. The disulphide bond is probably the only covalent permanent cross-linkage in most proteins and peptides. A recent[64] publication has reviewed the many systems studied.

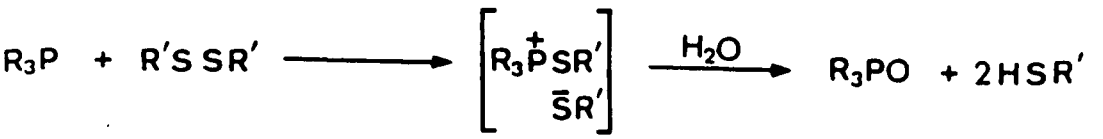
Most of the reactions between disulphides and trico-ordinate phosphorus compounds are believed to proceed through ionic pathways and one can categorise these into four main groups, desulphurisation



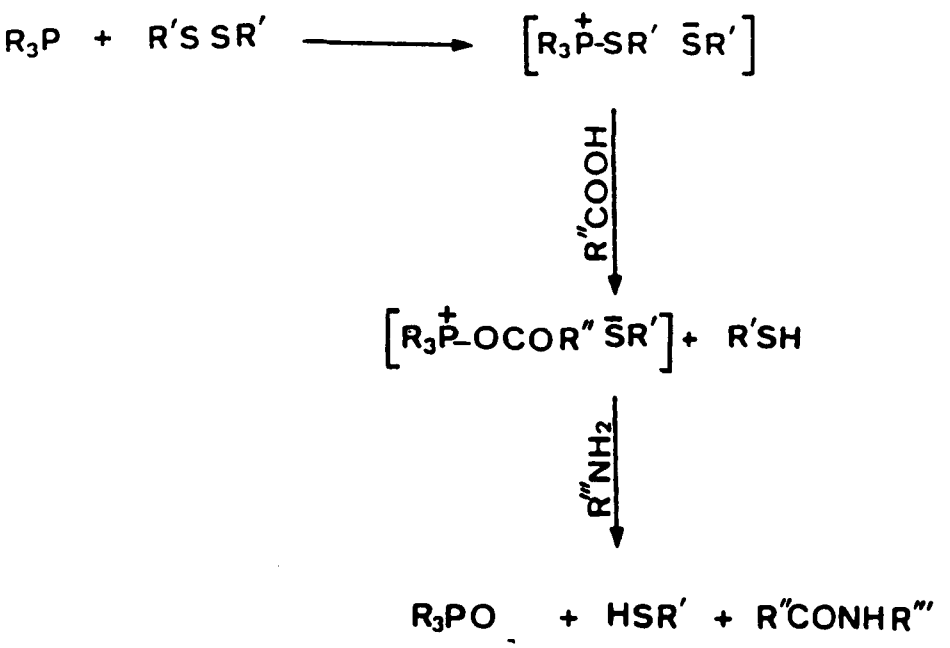
the Arbusov type reaction



reduction of Disulphides

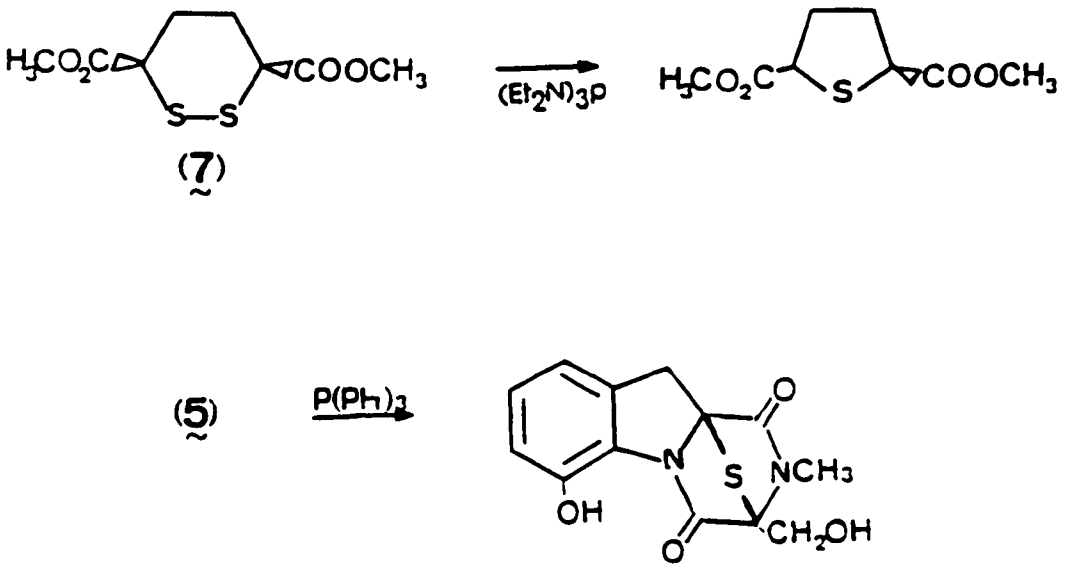


Oxidation-Reduction Condensation



In order to develop the synthetic scope and to delineate the mechanism of the phosphine/disulphide reaction, it was of crucial importance to define the stereochemical consequence of desulphurisation on the carbon α to sulphur.

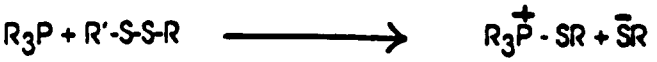
for this purpose two independent studies of the reaction of the disulphides (7), (5) with trico-ordinated phosphorus compounds were undertaken.[58,64] (Scheme 52).



Scheme 52

Whereas desulphurisation of cis-3,6-dicarbonethoxy-1,2 dithione (7) afforded a quantitative yield of the corresponding trans thiolane (implying phosphonium salt formation followed by S_N2 type decomposition), the spirodesmine (5) gave a product whose circular dichroism spectrum suggested that inversion of configuration of both asymmetric centres linking the sulphide bridge had occurred. This observation cannot be explained by assuming an S_N2 type decomposition of an intermediate phosphonium salt.

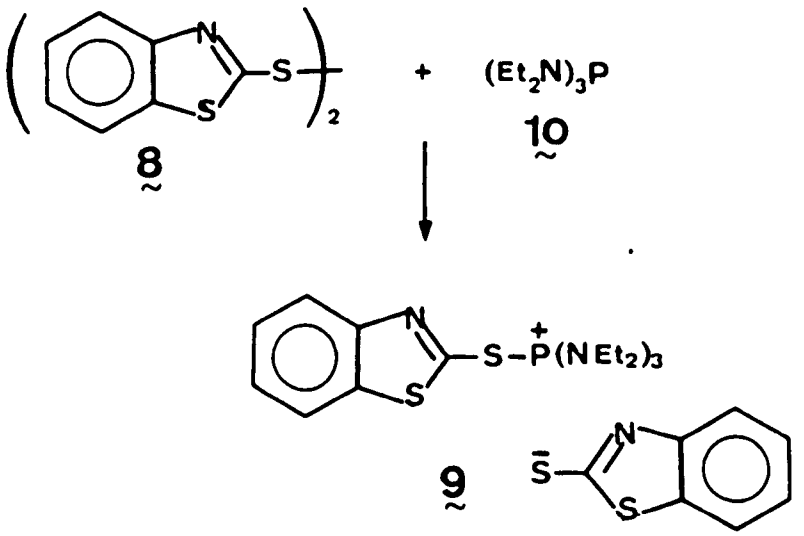
The literature generally suggests though that as long as the disulphide linkage is readily polarisable, then the first step of the reaction of disulphides with trivalent phosphorus compound is salt formation as in scheme 53.



Scheme 53

This reaction is believed to be an equilibrium process, and normally the intermediate phosphonium salts are not isolable.

Harpp and Gleason[65] however, have managed to isolate the salt (9) formed from bis(2-benzothiazoyl) disulphide (8) and trisdiethylaminophosphine (10) (scheme 54).



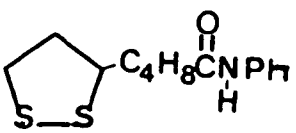
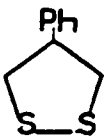
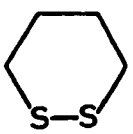
Scheme 54

The desulphurisation of disulphides can be achieved by means of tertiary phosphines, phosphites and aminophosphines. Notably in the latter case of trico-ordinates (10) has been found to be a very effective reagent, for a wide variety of disulphides which usually resist desulphurisation with tertiary phosphites.[65,66,67]

Table (3) reports some of Harpp's results in this field.

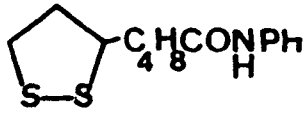
TABLE (3)

$R\text{-}S\text{-}S\text{-}R + (Et_2N)_3P \Rightarrow RSR + (ET_2N)_3PS$

Disulphide	Temp (^oC)	Time (hrs)	% yield RSR'
$(Ph_2CH_2S)_2$	80	4	92
$P\text{-}MeC_6H_4S_2CH_2PH$	RT	0.01	86
	RT	1	64
	80	4	86
	80	16	38

A kinetic study[65] of the desulphurisation led to the conclusion that it follows a second order reaction, first order each with respect to the phosphine and the disulphide. Harpp and Gleason also examined the effect of the solvent on the rates of this reaction - the rate of desulphurisation are enhanced in solvents of high polarity. The highly negative $\Delta S^{\#}$ is in accord with bimolecular reactions and is suggestive of considerable ordering in the activated complex. Solvation of a transition state in which change separation has occurred should cause a lowering of $\Delta H^{\#}$ as the solvent polarity is increased. This was observed as shown in Table (4).

TABLE (4) Desulphurisation of various disulphides with Tris(diethylamino)phosphine(10).

Disulphide	Solvent	Dielectric Constant, E	k_2.(30°C) $l\,mol^{-1}sec^{-1}$.	kr[a]	$\Delta H^{\#}$	$\Delta S^{\#}$	pKa[b,68]
$(C_5H_{11}S)_2$	Benzene	2.28	$1.6\pm1X10^{-9}$	$4X10^{-5}$			12.6
$(phCH_2S)_2$	Cyclohexane	2.02	$1.5\pm1X10^{-5}$		15.6	-24	11.8
	Benzene	2.28	$4.7\pm0.2X10^{-5}$		13.5	-24	
	Ethyl acetate	6.02	$1.2\pm0.1X10^{-4}$	1.1	10.2	-34	
	o-Dichlorobenzene	9.93	$2.1\pm0.1X10^{-3}$		9.7	-28	
	Benzene	2.28	$4.18\pm0.08X10^{-4}$	11.0			
$P\text{-}CH_3C_6H_4SSCH_2Ph$	Cyclohexene	2.02	$4.46\pm0.03X10^{-3}$				
	Benzene	2.28	$1.20\pm0.03X10^{-1}$	2800	5.4	-35	9.3
	Ethyl acetate	6.02	$6.18\pm0.03X10^{-1}$				
CH_3SSPh	Cyclohexane	2.02	$1.14\pm0.02X10^{-2}$				
	Benzene	2.28	$4.50\pm0.03X10^{-1}$	10550			8.6
	Ethyl acetate	6.02	1.51 ± 0.03				

a relative to the desulphurisation at 1,2-dithiane.

b pKa of the thermodynamically most favourable thiol.

Thus, these results strongly suggest the occurrence of a charged intermediate in the rate determining step of the desulphurisation reaction. In other words, the intermediate is likely to be a phosphonium salt and this mechanism is in accord with the stereochemical results. If the thiolate anion is displaced in the rate-determining step, the overall rate of desulphurisation should be some function of the thiolate anion stability. That is, the thiolate tends to act as a better leaving group with increasing stability and, hence, the reaction becomes faster. Table 4 also shows the pKa of the thiol corresponding to the displaced thiolate anion. The rate of desulphurisation increases by a factor of over 10^8 in accordance with the decrease by four pKa units in the pKa of the thiol.

More recent work[69] by the same author has resulted in successful selective removal of sulphur from compounds of the type R-X-S-R', using amino-phosphines. (Scheme 55).

$$R\text{-}X\text{-}S\text{-}R' + (R''_2N)_3P \longrightarrow R\text{-}X\text{-}R' + (R''_2N)_3PS$$

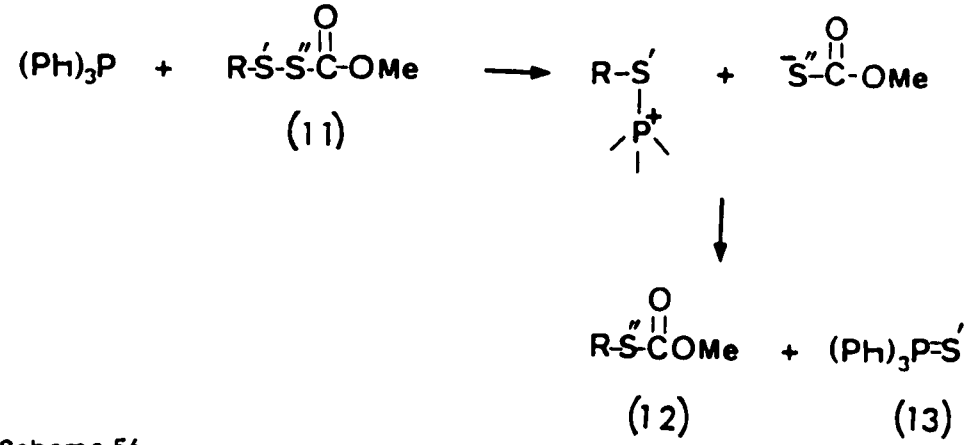
$$X = S\ ,\ -SO\ ,\ -SO_2\ ,\ -N(COCH_2)$$

$$R = R' = \text{Alkyl}\ ,\ \text{Aryl}$$

$$R'' = \text{Me}\ ,\ \text{Et}$$

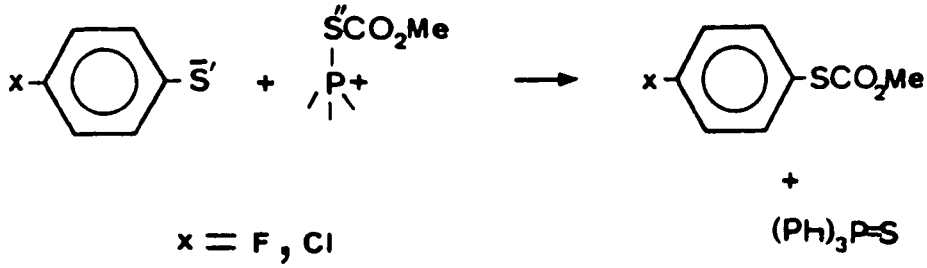
Scheme 55

A related study[70] on the nucleophilic attack by triphenylphosphine on sulphenyl thiocarbonates has been published. Careful chromatographic techniques were employed to elucidate the structure of the resulting products (scheme 56).



Scheme 56

When R is benzyl (12) and (13) are the main products whereas when R is phenyl, triphenyl phosphine oxide and phenyl mercaptan were observed as a consequence of the hydrolysis of the more stable phosphonium salt on the chromatographic column. With these experimental results Harpp concluded that the main reaction pathway involves attack at (S') but in the case of aryl derivatives, as (X) became increasingly more electronwithdrawing, a greater degree of attack was observed at the carbonyl sulphur (S") (scheme 57).

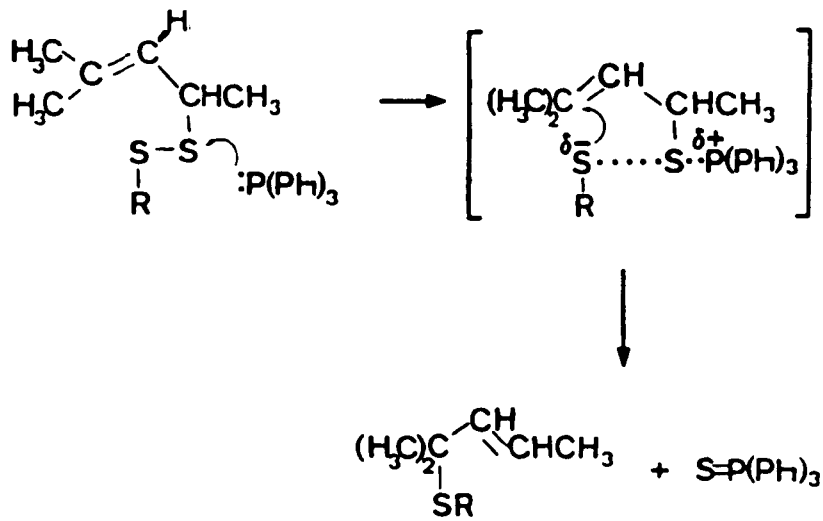


Scheme 57

Desulphurisation with tertiary phosphines has been investigated only to a small extent because of their low reactivity towards disulphides. Schonberg[71] classified various disulphides into groups according to their reaction with triphenylphosphine.

1. The first group includes dialkyl, aralkyl and diaryl disulphides. These disulphides are stable towards triphenylphosphine in boiling benzene.

In contrast, Evans et al[72] has found that triphenyl phosphine could react with allyl disulphides via an allylic type rearrangement of the allyl group. (Scheme 58).



Scheme 58

On the basis of the above result, it was proposed that the reaction proceeds by a nucleophilic attack of triphenylphosphine on a sulphur atom in the disulphide followed by a reaction of the polarised complex.

2. The second group includes acyl, aryl and bis(thiocarbonyl) disulphides, which react with triphenylphosphine in boiling benzene to afford the corresponding sulphides and triphenylphosphine sulphide.

3. The third group includes only one disulphide, diphenyl disulphide, which does not react with triphenylphosphine in boiling benzene while it does react in the presence of water to give triphenylphosphine oxide and benzonethiol.

Recent reports, however, showed that when diphenyl disulphide and triphenylphosphine are fused (neat) at (250-300^{o}C) in an inert atmosphere, diphenyl sulphide and triphenylphospine sulphide are produced.[73]

$PhSSPh + Ph_3P \xrightarrow{250\text{-}300^{o}C} PhSPh + Ph_3P = S$

The author suggests nucleophilic attack of triphenylphosphine on sulphur to form a phosphonium mercaptide, followed by either nucleophilic attack of the mercaptide ion on the aromatic carbon atom bearing sulphur or formation of a phosphorane with subsequent intramolecular collapse to form products.

Tertiary phosphites have also been found to perform desulphurisation. Harvey, Jacobson and Jensen[74] found that dibenzyl disulphide reacted with triethyl phosphite exothermically to give O,O,O-triethylphosphorothioate and desulphurised product dibenzonyl sulphide, in high yields. Similarly, diacetyl disulphide was desulphurised with triethyl phosphite.[75]

Dialkyl disulphides were also desulphurised with trialkyl phosphites in the presence of appropriate initiators to afford dialkyl sulphides and O,O,O-trialkyl phosphorothioates. This reaction is considered to proceed via a radical chain mechanism.[76,77] (Scheme 59).

$RSSR + P(OEt)_3 \longrightarrow RSR + S = P(OEt)_3$

They suggested the following reaction steps.

$RS^{\bullet} + P(OEt)_3 \longrightarrow RSP^{\bullet}(OEt)_3$

$RSP^{\bullet}(OEt)_3 \longrightarrow R^{\bullet} + S = P(OEt)_3$

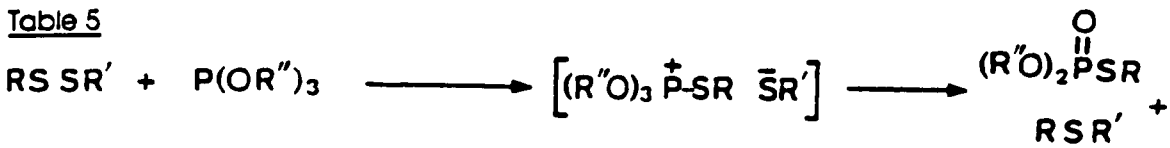
$R^{\bullet} + RSSR \longrightarrow RSR + RS^{\bullet}$

Scheme 59

However, even in the dark and in the absence of radical initiators, trialkyl phosphites can react readily with dialkyl or diaryl disulphides.[78,79] In this case, the Arbuzov-type reaction occurs and O,O,S-trialkyl or 5-aryl-O,O-dialkyl phosphorothioates are obtained in good yields (scheme 59). An example of the Arbuzov type reaction comes from a report by Harvey et al.[74] who studied the reaction of triethyl phosphite and unsymmetrical disulphides.

Depending on which sulphur atom of the disulphide linkage is attacked two sets of products are possible. However, only one set of products was observed in which the more stable thiol anion was formed (Table 5).

Table 5

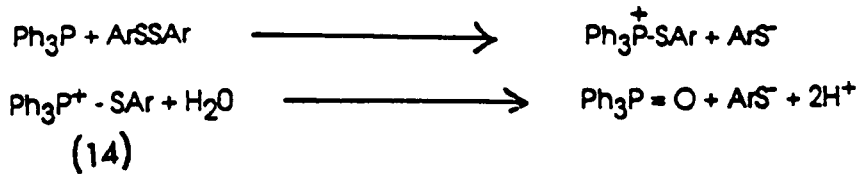


R	R'	P(III)	PRODUCT	YIELD
Me	CH_3	$P(OEt)_3$	$MeSPO(OEt)_2$	80
Me	Ph	$P(OEt)_3$	$MeSPO(OEt)_2$	71
Ph	C_6Cl_5	$P(OEt)_3$	$PhSPO(OEt)_2$	92

The rate-limiting step the authors argue is initial attack by phosphite on the disulphide linkage, with the unsymmetrical disulphides facilitating this by effective polarisation of the sulphur-sulphur bond.

Although triphenylphosphine and symmetrical disulphides will not readily result in non-aqueous media, Overman has reported an extensive stopped-flow kinetic study of the cleavage of the sulphur-sulphur bond in symmetrical aryl disulphides by triphenylphosphine using aqueous dioxane as solvent.[80]

At both low and high pH, nucleophilic attack by triphenylphosphine on the disulphide linkage to form an intermediate thioalkoxyphosphonium cation (14) was the rate-determining step. But at intermediate pH the reversal of the first step becomes important and the reaction rate equation becomes more complex. (Scheme 60).



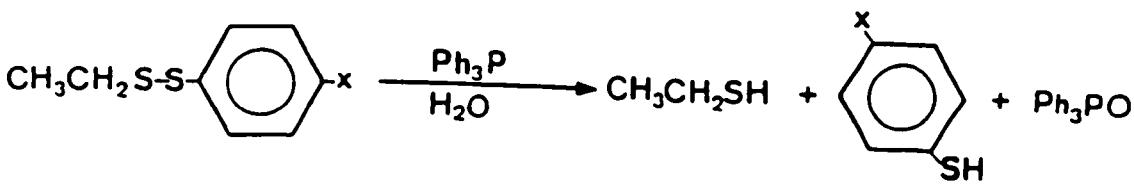
(14)

Scheme 60

A ρ value of +2.94 was obtained for variation of the substituents on the aryl group of the disulphide indicating (the expected) large sensitivity of the quaternisation step

to electronic effects. Also, the reaction was found to be extremely sensitive to solvent polarity suggesting a highly polar transition state.

Later work by the same author[81] on the reaction of triphenylphosphine with ethyl aryl disulphides under identical conditions gave a value of 1.76 implying that the transition state in this system is not of such a polar nature (scheme 61).



Scheme 61

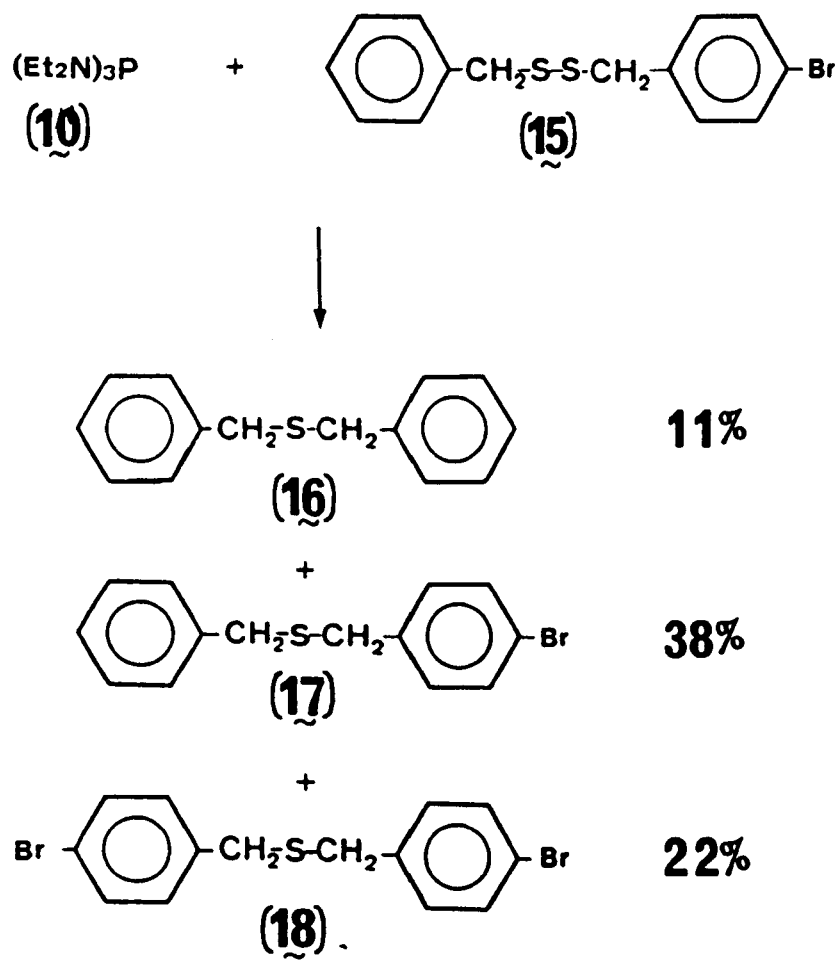
CHAPTER 2

THE REACTIONS OF UNSYMMETRICAL DISULPHIDES WITH ACYCLIC TERVALENT PHOSPHORUS COMPOUNDS

CHAPTER 2 THE REACTION OF UNSYMMETRICAL DISULPHIDES WITH ACYCLIC TERVALENT PHOSPHORUS COMPOUNDS

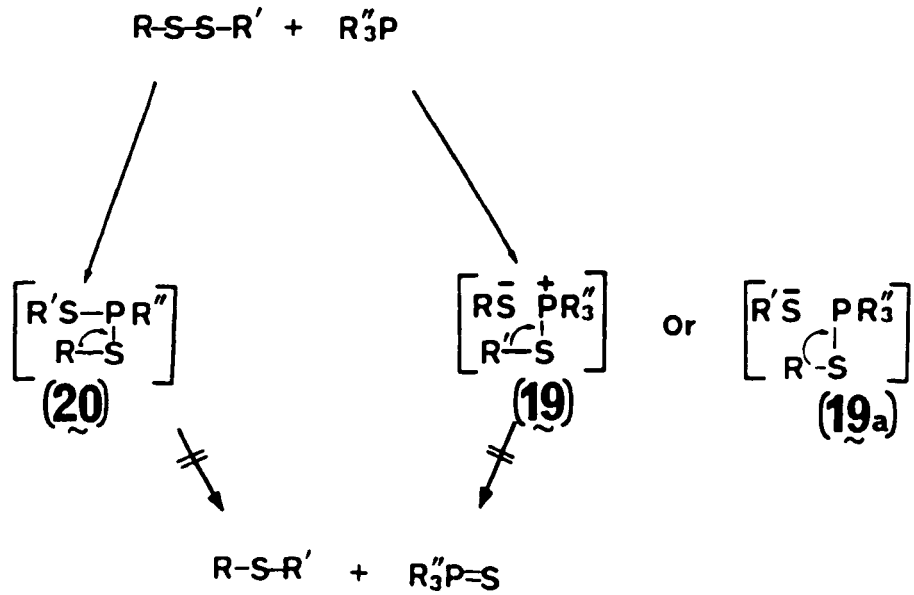
2.1 INTRODUCTION

Harpp et al. have reported that the desulphurisation of the unsymmetrical disulphide benzyl bromobenzyl disulphide (15) with the amino phosphine tris(diethylamino) phosphine (10) in benzene produced all three possible sulphides (16), (17) and (18) in the following proportions. (Scheme 62).



Scheme 62

The author suggested that if the collapse of a tight ion pair (19), (19a) or the concerted breakdown of pentacovalent species (20) were exclusively operating, only sulphide (17) would have been observed (scheme 63).



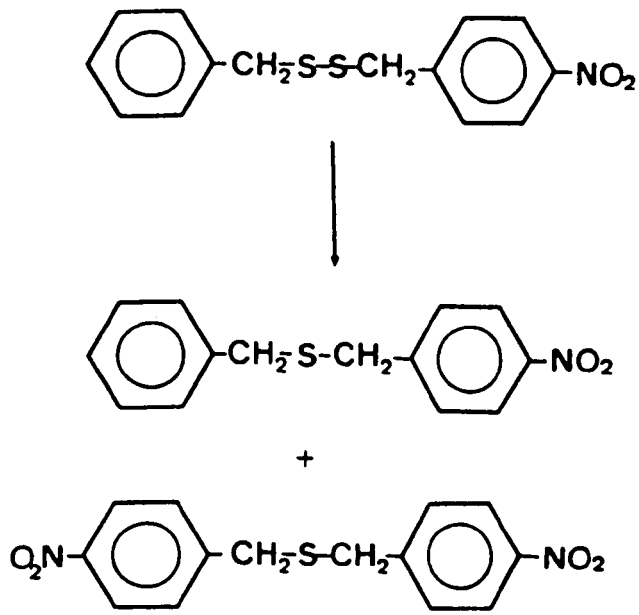
R = CH_2phBr.
R' = CH_2ph
R" = NEt_2

Scheme 63

The same author predicted that it would appear that a mixture of phosphonium salts are involved but the prior or subsequent formation of intermediate (20) cannot be precluded.

He concluded that the unsymmetrical distribution of sulphides in this reaction is difficult to rationalise.

Similar examples[82] to this type of sulphide distribution have also been reported (scheme 64).



Scheme 64

Interestingly, however, in the above reaction, only one of the two symmetrical sulphides is produced together with the unsymmetrical sulphide.

This puzzling production of one or both of the symmetrical sulphides has led the author to suggest that certain radical mechanisms could be involved, especially when the chemical literature indicates that for a number of disulphides desulphurisation proceeds via radical pathways.

A polar mechanism is, however, more likely given that these reactions are known to proceed more rapidly in polar solvents. Furthermore, there is no direct experimental evidence in the literature for radical behaviour. We were therefore inclined to look for an extension of the polar pathway illustrated in scheme 63 to provide an explanation for these unexpected results, having first eliminated the radical pathway to our satisfaction. (For details of the latter, see Chapter 3).

The present study has concerned itself with the reaction time-course of the desulphurisation of (15) in the reported conditions in order to look for any previously undetected intermediates or products.

2.2 ANALYTICAL METHODS

In order to be able to monitor such reactions, an analytical technique had to be developed to follow the reaction time course from start to finish.

HPLC has been chosen as a technique to follow the reaction because of its convenience, accuracy and reproducibility. Therefore, HPLC systems to separate sulphide isomers from each other, and from disulphide precursors have been developed. (See Chapters 3 and 4 for details). Following the successful development of an analytical HPLC method to follow this reaction a preparative method was developed which proved useful in the synthesis of unsymmetrical disulphides.

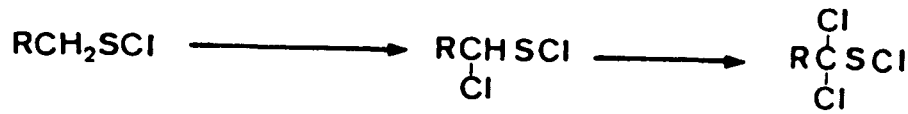
2.3 SYNTHETIC METHODS FOR UNSYMMETRICAL DISULPHIDES

The synthesis of pure unsymmetrical disulphides is often a difficult problem in organo-sulphur chemistry. While several methods of preparation are known[84,85,86,87,88] no one method suffices for all synthetic situations.

Harpp's[89] general method for preparing unsymmetrical disulphides was used to prepare the unsymmetrical disulphide (15). The method involves the chlorination of a thiol to the corresponding sulphenyl chloride. (When thiols are chlorinated with chlorine gas it first converts them into the corresponding symmetrical disulphides, which then react further to give the sulphenyl chloride.) (Scheme 65).

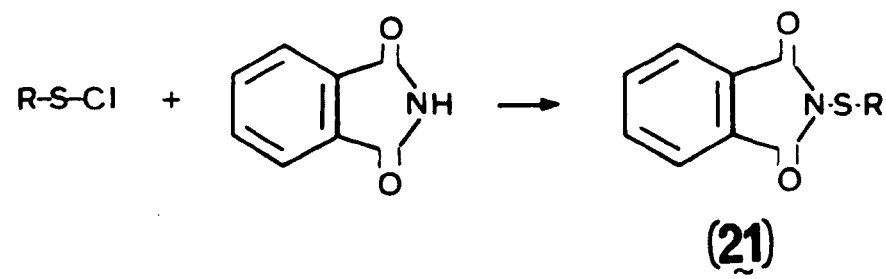
Scheme 65

Aromatic sulphenyl chlorides are known to be much more stable than the aliphatic sulphenyl chloride, as aliphatic sulphenyl chlorides have an α-hydrogen which will react with chlorine to give α-chloro sulphenyl chloride. (Scheme 66).



Scheme 66

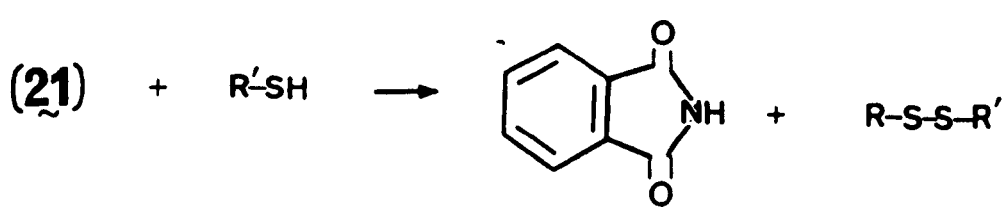
It is also known that the polarity of solvents affect the stability of these compounds. Reaction of phthalimide with the sulphenyl chloride obtained gave the thiophthalimide (21). (Scheme 67).



(21)

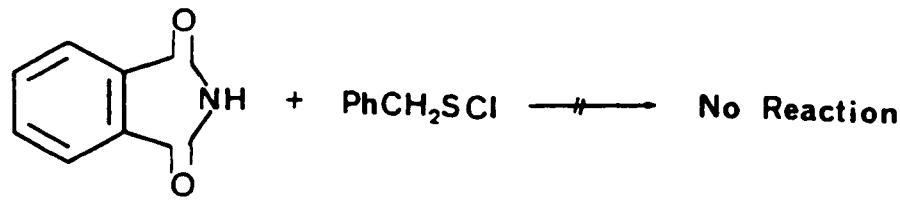
Scheme 67

Further treatment of the thiophthalimide with a second thiol should give the expected unsymmetrical disulphide (scheme 68).



Scheme 68

However, applying this method for the preparation of the unsymmetrical disulphide (15) failed to give the required disulphide, as the phthalimide failed to react with the putative phenylmethanesulphenyl chloride. (Scheme 69).



Scheme 69

The problem being the present of an α-hydrogen in benzyl thiol as described in scheme 66 above.[90]

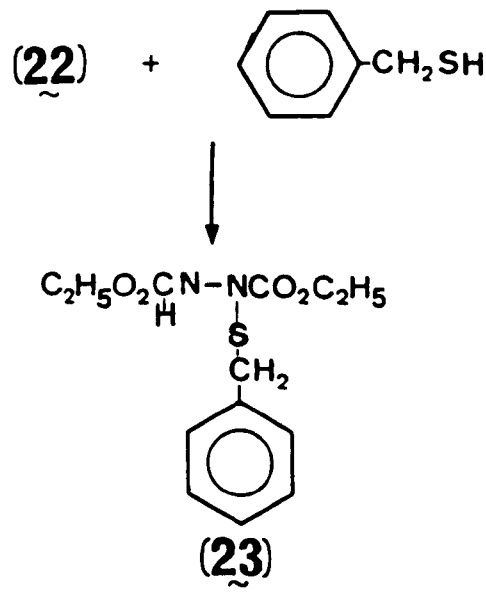
The second method employed in attempts to prepare the unsymmetrical disulphide (15) is the one described by Mukaiyama[87].

The oxidative coupling of two different mercaptans, with the formation of unsymmetrical disulphide, has been brought about by the use of diethyl azodicarboxylate (22).

$$C_2H_5O_2CN{=}NCO_2C_2H_5$$

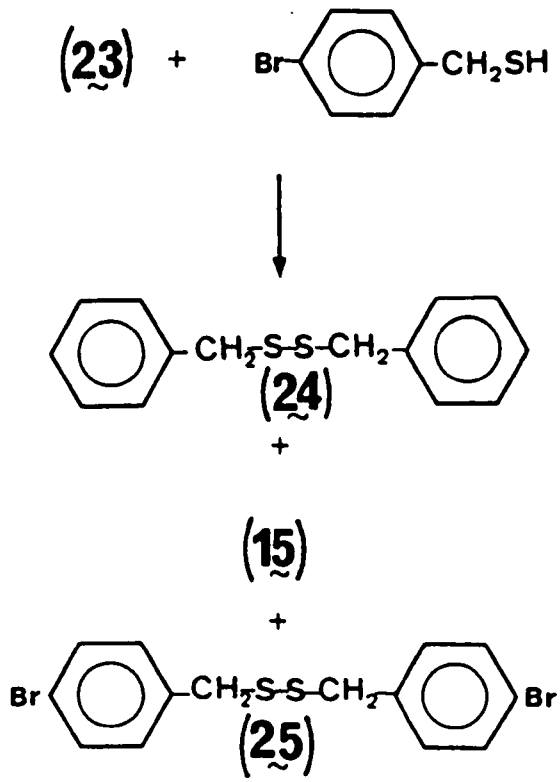
(22)

When benzyl mercaptan was allowed to react with (22) in equimolar proportions in ether at room temperature for 2 hours, the reaction mixture changed in colour from orange red, the characteristic colour of (22), to pale yellow which is that of (23). (Scheme 70).



Scheme 70

Although the adduct (23) was obtained in reasonable yield, when reacted with p-bromobenzylthiol it gave a mixture of all possible disulphides. (Scheme 71).



Scheme 71

The failure of these methods to produce the desired unsymmetrical disulphide has led this study to divert its attention to the disulphide exchange reaction.

Although the existence of unsymmetrical disulphides was reported as early as 1886 and several were prepared subsequently, it seemed that they were intrinsically less stable than symmetrical disulphides.[92] .
In fact, subsequently it was shown that disulphides undergo exchange reaction according to (scheme 72).

$$R_1SSR_1 + R_2SSR_2 \longrightarrow 2R_1SSR_2$$

Scheme 72

Several workers have investigated the kinetics and application of this reaction. Haroldson et al.[92] used gas chromatography to study the products of the exchange reaction between pairs of disulphides.

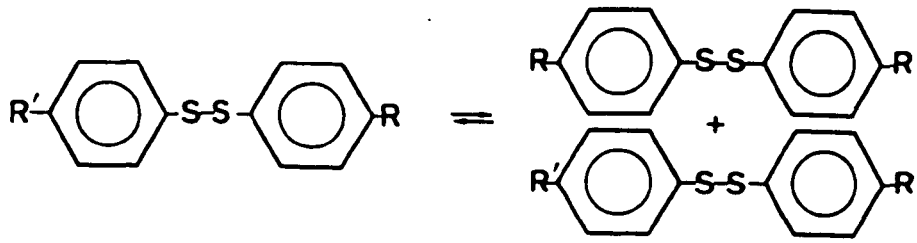
Birch[93] et al. have used it to prepare several unsymmetrical disulphides by equilibrating two symmetrical disulphides. The relative amount of unsymmetrical and symmetrical disulphides were determined by distillation. The presence of unsymmetrical disulphides at equilibrium was clearly demonstrated. The ratios of unsymmtrical and symmetrical disulphides at equilibrium are given together with the equilibrium constants of the exchange reaction (Table 6).

Table 6 - unsymmetrical disulphide ratio and the equilibrium constant at 25°C at the exchange reaction.

Disulphides	Ratio of Unsymm/Symm	Equilibrium Constant
methyl-ethyl	2/1	5.6
ethyl-n-butyl	2/1	24.5
ethyl-isobutyl	2/1	4.1
methyl-t-butyl	5/1	-

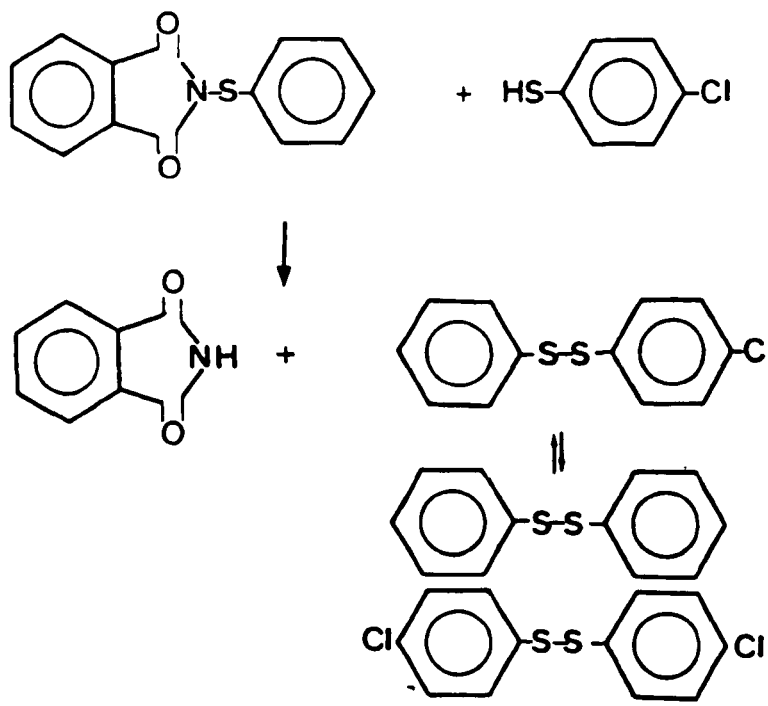
Essentially the same values were found at 60°C, showing that the heat of reaction is very small or zero.

More recently, it was found that the reverse reaction in which unsymmetrical disulphides exchange with the two corresponding symmetrical sulphides take place in polar solvent (scheme 73).



Scheme 73

Boustany et al.[94] have found that thiol with an N-aryl thiophthalimide gives the unsymmetrical aryl disulphide. The latter exchanges slowly at room temperature to give the corresponding symmetrical disulphides. (Scheme 74).



Scheme 74

More recent publications have reported that mercaptans and organic disulphides can react with one another in appropriate conditions.[95] Such reaction occurs in

diverse chemical systems and may have consequences of considerable importance: examples may be found in petroleum[96], polysulphide[97] rubber and living organisms.[98] The interchange involves three steps.[99] (Scheme 75).

$$RSH \overset{pka}{=\!=} R\bar{S} \quad \cdots\cdots\cdots \quad 1$$

$$R\bar{S} + R'SSR'' = RSSR' + \bar{S}R'' \quad \cdots\cdots\cdots \quad 2$$

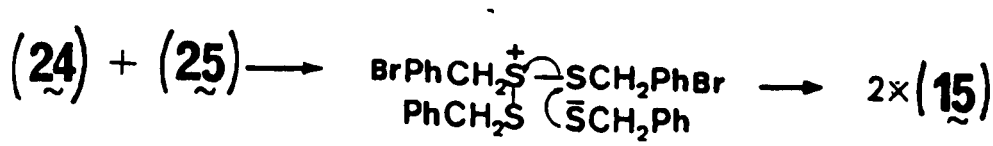
$$R''\bar{S} \overset{pka}{=\!=} R''SH \quad \cdots\cdots\cdots \quad 3$$

Scheme 75

Initially, ionisation of the thiol gives thiolate anion, this is followed by nucleophilic attack of the thiolate anion on a sulphur atom of the disulphide moiety and protonation of the product thiolate anion. All three steps are fully reversible.

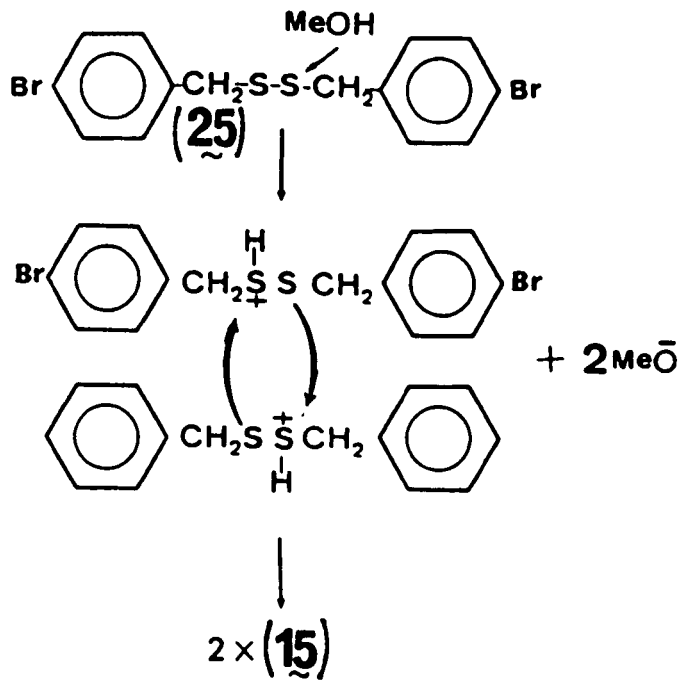
The importance of the thiol-disulphide interchange reaction to biochemistry and the remarkable ability of this reaction to effect the reversible cleavage and formation of strong, covalent S-S bonds at room temperature in aqueous solution have promoted many studies of the mechanism of this reaction.[100,101,102,103]

As will be shown in this study, disulphide exchange was only observed in high polarity solvents (methanol and acetonitrile), which suggested an ionic pathway for the reaction (scheme 76).



Scheme 76

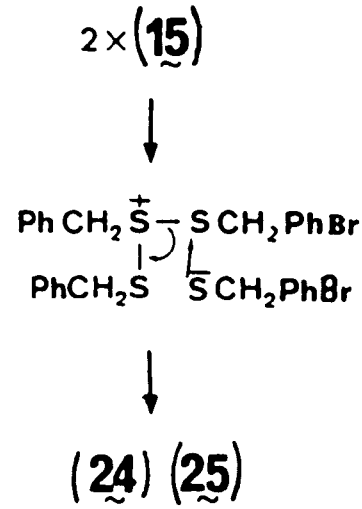
The above mechanism seems to be more credible than an alternative one which involves the initial protonation of the sulphur atom by methanol: specially when considering that this exchange mechanism also occurs in acetonitrile (scheme 77).



Scheme 77

We therefore decided that by refluxing the two symmetrical disulphides (24), (25) in methanol or acetonitrile, the rearrangement or the exchange of disulphides might enable the production of the desired unsymmetrical disulphide (15) which was to be separated by preparative HPLC. This type of rearrangement should proceed until there is an equilibrium between all three disulphides after which time further refluxing should have no effect on the composition of the reaction mixture.

In the event, the composition of the reaction mixture was found to be 1:3:1 in (24):(15):(25) respectively. Moreover, the composition of the mixture collected from refluxing the unsymmetrical disulphide alone in methanol or acetonitrile also consisted of a 1:3:1 proportion similar to the above rearrangement, as predicted by the mechanism shown in scheme 76 above. (Scheme 78).



Scheme 78

Attempts to separate these reaction mixtures by either crystallisation or distillation failed, but preparative HPLC, though rather laborious, proved very successful.

The rate of exchange of disulphides depends on sample concentration, solvent temperature and polarity.

2.4 PRODUCT ANALYSIS

Using the pure unsymmetrical disulphide (15) from the above procedure allowed us to concentrate then on treatment of (15) with the phosphorus (III) nucleophiles (10). The unsymmetrical disulphide (15) was treated with an equimolar ratio of the aminophosphine (10) in benzene at a starting temperature of 0°C, and analytical HPLC indicated the production of the two symmetrical disulphides (24) and (25) before the actual desulphurisation took place. After an hour, the benzene was brought to reflux and the composition of the reaction mixture followed by HPLC analysis of aliquots withdrawn at intervals (Figure 1).

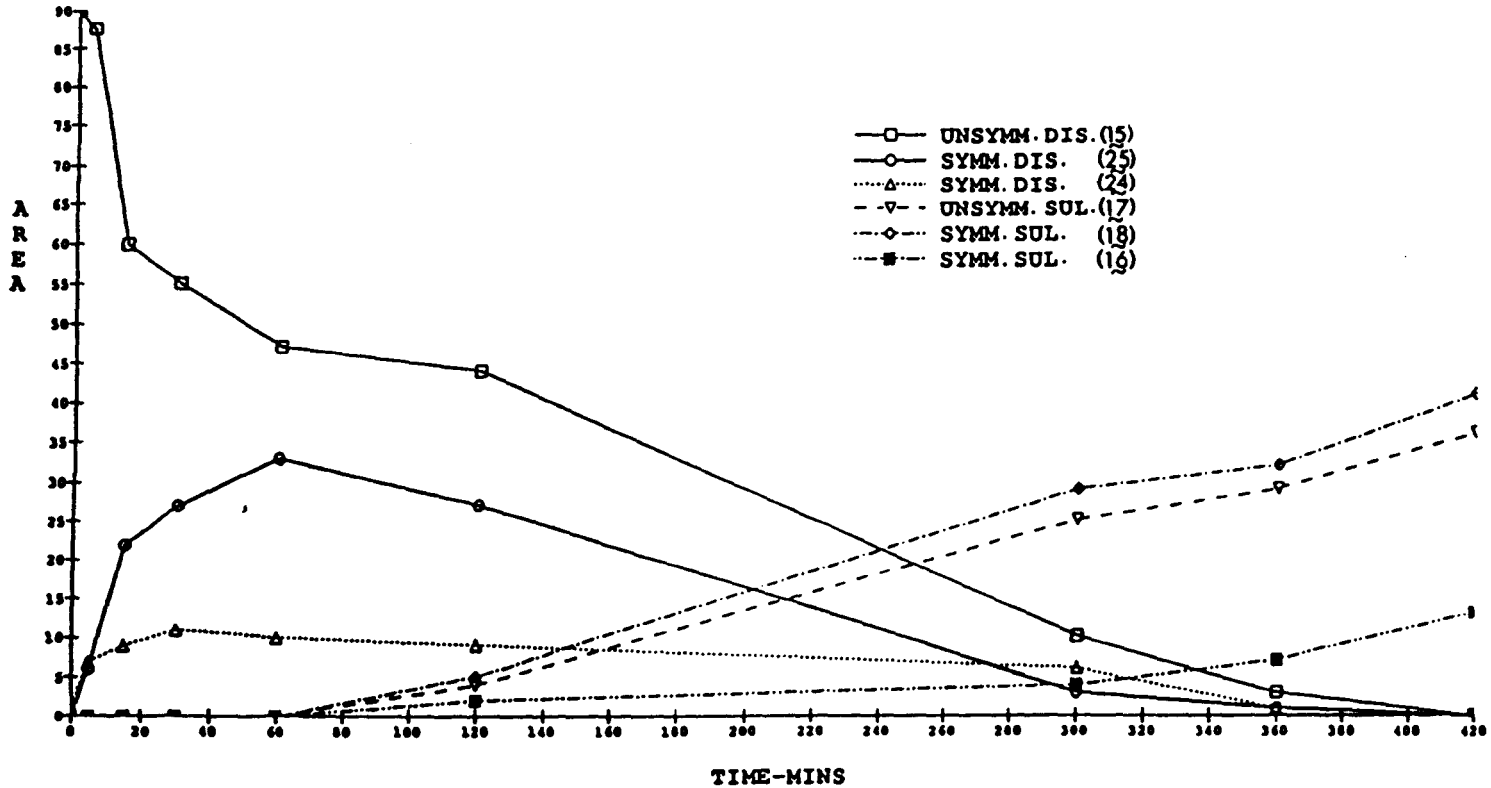
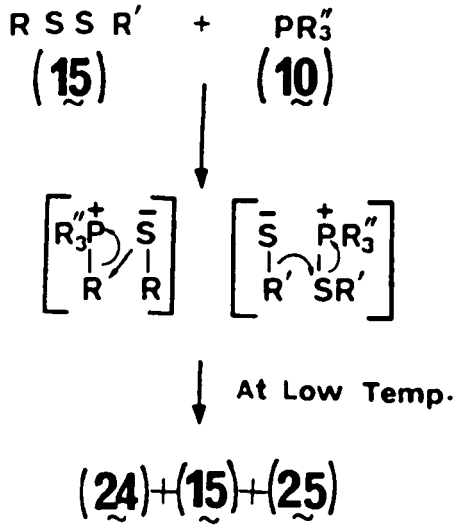


FIGURE 1

Equilibration and desulphurisation in benzene of unsymmetrical disulphide (15)

As can be seen from Figure 1, the process of equilibration is much faster than the desulphurisation reaction. It would appear therefore that the tervalent phosphorus compound (10) must be first catalysing this rearrangement of disulphides in some way before it actually desulphurises them individually via the mechanism illustrated in scheme 76 and 78 . (Direct thermal equilibration in benzene at this temperature is too slow a process to account for the observed rate of exchange). (Scheme 79).



R = -CH_2ph, R′ = -CH_2phBr, R″ = -NEt_2

Scheme 79

The composition of the rearranged disulphides before the actual desulphurisation takes place is closely similar to that obtained by refluxing (15) in methanol or acetonitrile, indicating that the process is a catalytic one.

Similarly, Figure (2) illustrates that a mixture of benzyl disulphide (24) and p-bromobenzyl disulphide (25) and the amino-phosphine (10) in 1:1:2 molar ratio respectively in benzene at a starting temperature of 0°C, produces the unsymmetrical disulphide (15) before the actual desulphurisation at 80° took place.

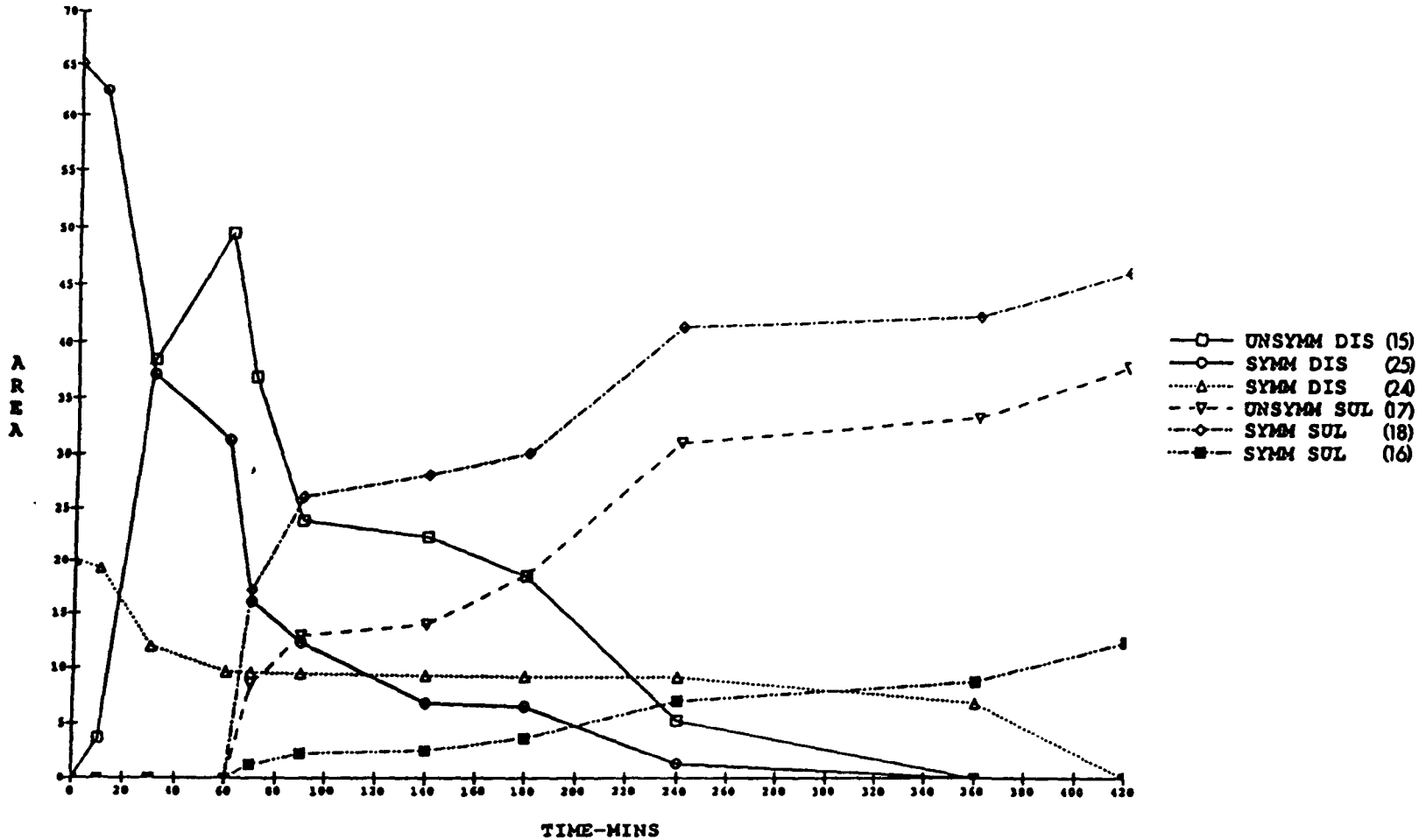
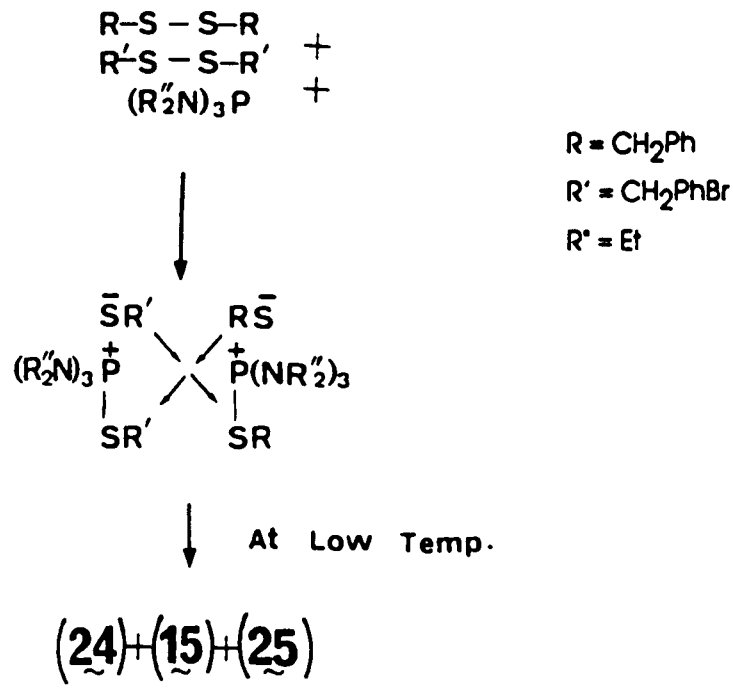


FIGURE 2

Equilibration and desulphurisation in benzene of equi-molar ratio of (24) and (25)

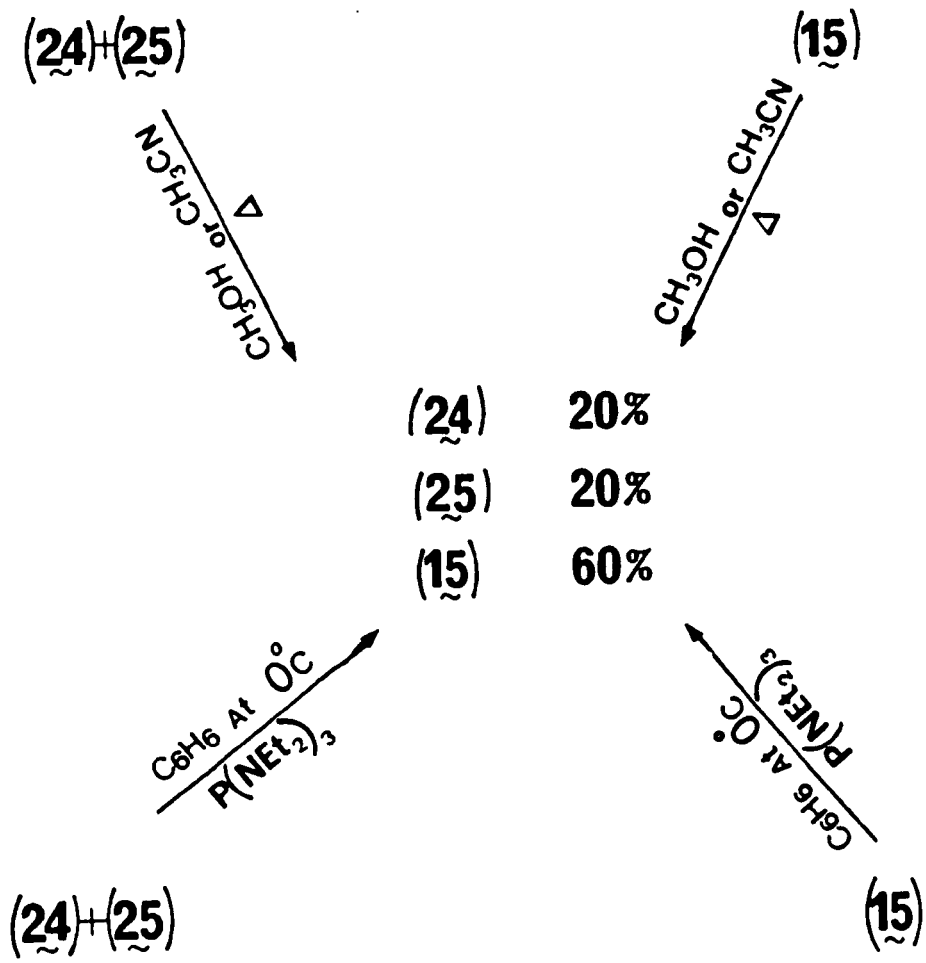
A possible mechanism for such catalysis can be understood by considering the initial phosphonium salts produced. (Scheme 80).



Scheme 80

The composition of the rearranged disulphides before the actual desulphurisation takes place is constant and similar in both experiments.

In fact, the composition of the reaction mixtures obtained from these two experiments at 0°C illustrated in Figures (1) and (2) are the same as that of mixtures obtained from refluxing either the symmetrical disulphides (24) and (25) in equal proportions or the unsymmetrical disulphide (15) in methanol or acetonitrile. (Scheme 81).



Scheme 81

B Acetonitrile

In order to monitor the pre-equilibrium of disulphides before the actual desulphurisation reaction more accurately, the reaction was followed at -40^{O} in acetonitrile solution.

Two experiments were conducted in a similar manner to those performed in benzene earlier. The results provide further evidence of the prior catalysis of disulphide

exchange by the aminophosphine (10) before the actual desulphurisation as shown in Figures (3) and (4).

The reaction mixture maintained at this temperature (-40^{o}C) contains only disulphides, with no evidence for desulphurisation. The composition of the reaction mixture finally reached its equilibrium stage at a 1:3:1 mixture of the disulphides, (24 and 25).

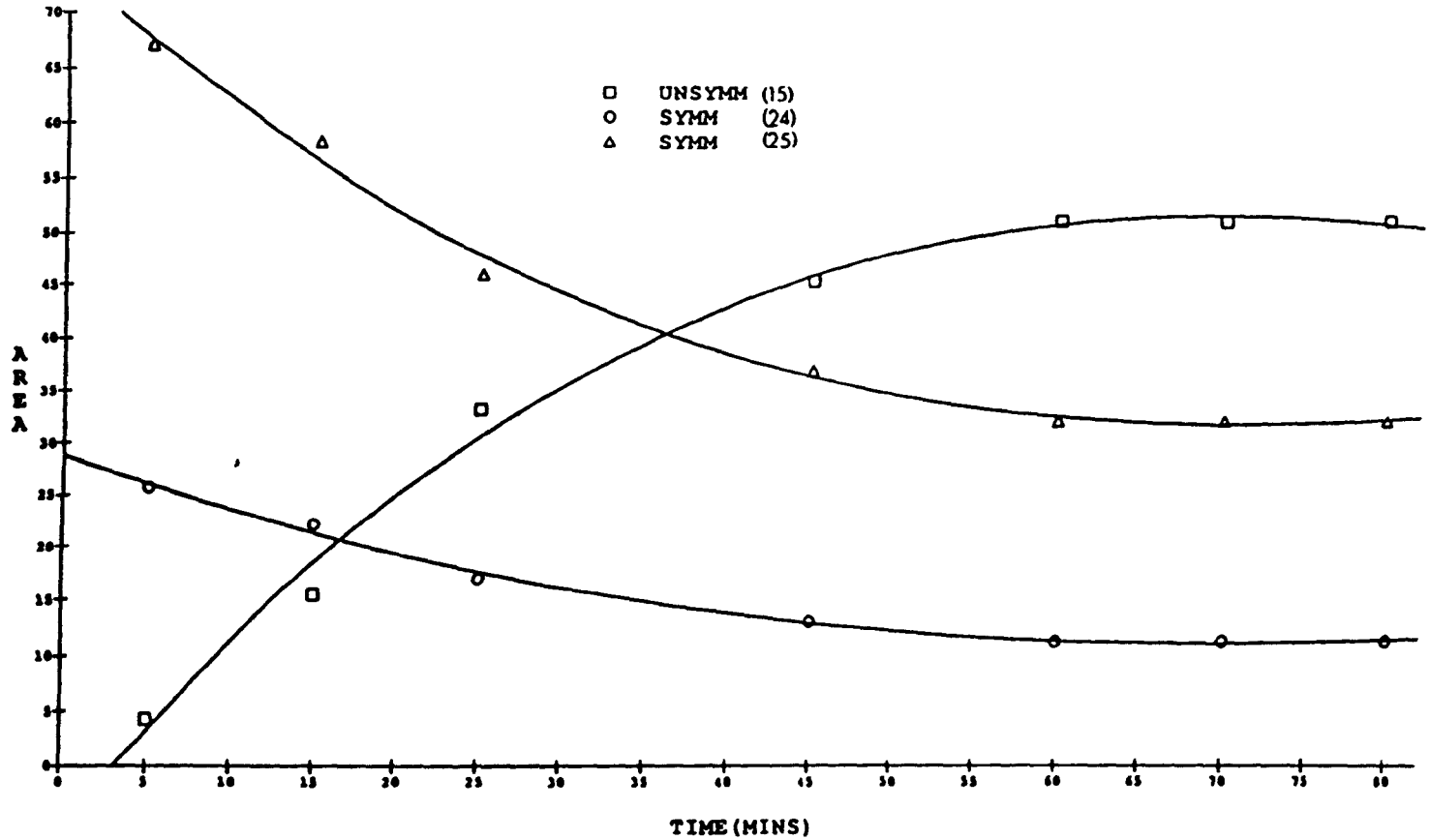


FIGURE 3

Slow equilibration of disulphides (24) and (25) in acetonitrile at -40°C

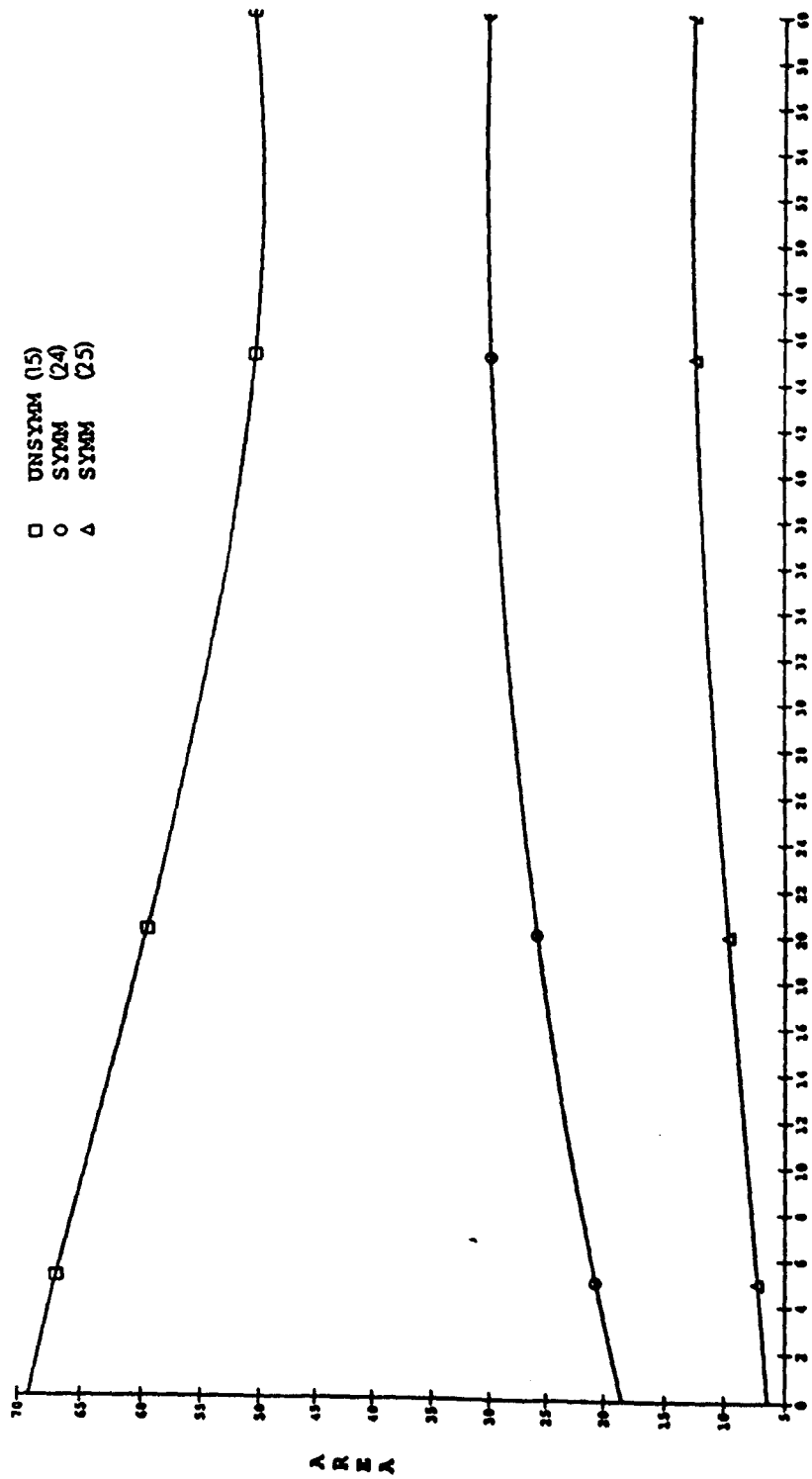


FIGURE 4

Slow equilibration of disulphide (15) in acetonitrile at -40°C

C Desulphurisation Reaction in Dry Methanol

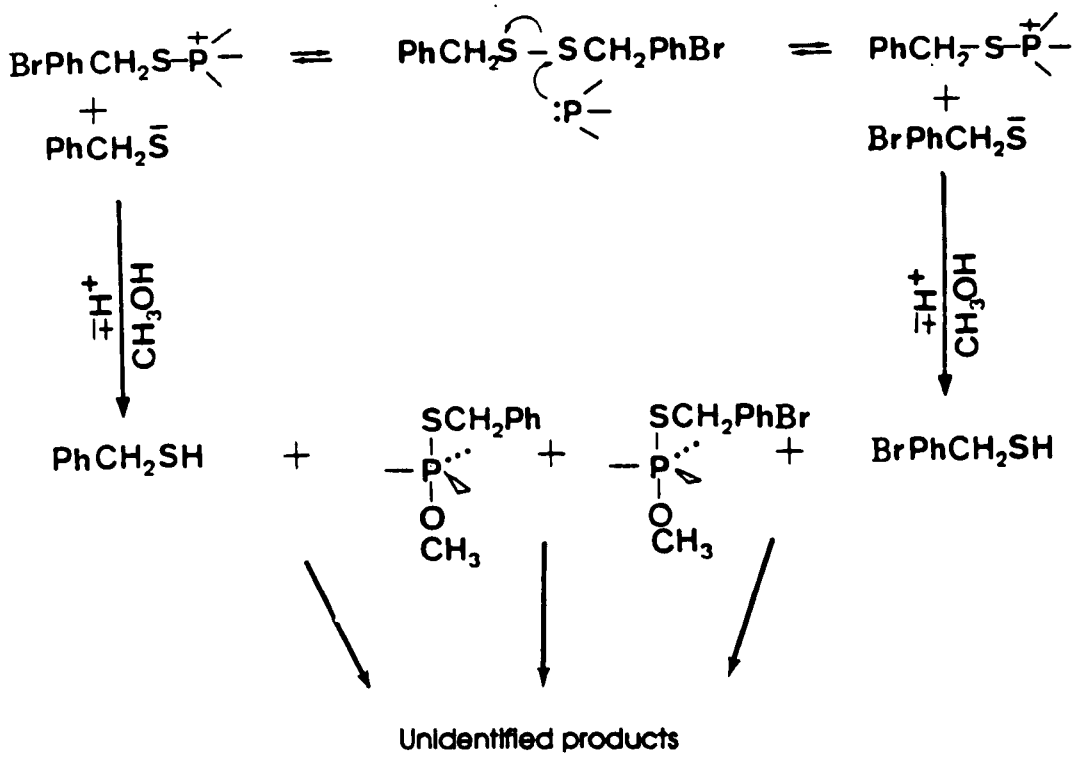
In order to examine the reaction in polar media, the unsymmetrical disulphide (15) has been allowed to react with the aminophosphine (10) in dry methanol at room temperature. HPLC analysis of the reaction mixture showed that the concentration of (15) remained unchanged through the time-course of the reaction. It was suspected that the aminophosphine might be reacting with the solvent under these conditions.

This led to a study of a blank reaction of (10) in dry methanol at room temperature. The ^{31}P n.m.r. (decoupled spectra) showed several singlets which indicated that methanol was reacting with (10) at room temperature to give a variety of phosphorus containing products.

HPLC analysis of the above reaction mixture in more carefully dried methanol at -10^{o}C showed two early eluted peaks, found to be benzyl mercaptan and p-bromobenzyl mercaptan. At that stage the concentration of (15) started to drop as these two peaks began to increase, and evidence for formation of the sulphides (16), (17) and (18) was obtained.

The only conclusion which can be drawn from this result is that in polar solvent a sulphur atom is attacking the phosphorus atom, and in the case of methanol, protonation occurs to give the free thiol. A possible mechanism to explain the formation of thiols is given in (scheme 82).

This problem is addressed in more detail in Chapter 3, using LC-MS techniques.



Scheme 82

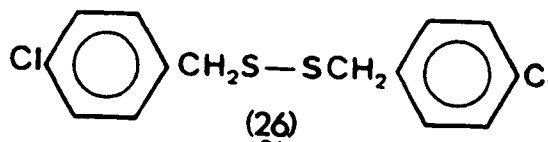
2.5 Kinetic Study of the Reaction

Having established an analytical HPLC method, and identified the products of the exchange/desulphurisation reaction, it was decided that further light might be shed on the mechanism by a kinetic study of the process.

Harpp et al[89] have studied in detail the kinetics of the desulphurisation reaction of disulphides with aminophosphines. The author concluded that the reaction follows second-order kinetics. The rates of desulphurisation are enhanced in solvents of high polarity.

In his experiments 1:1 stoichiometric amounts of phosphine and disulphide were used, and the area of the disulphide and sulphide peaks in the gas chromatograph were used in the calculation rate constants.

In the present study the second order rate constant was determined under pseudo-first order conditions, using HPLC to follow the reation. Five different concentrations of excess of the amino phosphine (10) in benzene were used. The lowest is about ten times the concentration of the initial concentration of the symmetrical disulphide p-chlorobenzyl disulphide (26). (Use of a symmetrical disulphide eliminates any complications associated with disulphide exchange).



(26)

The following procedure was adopted: a known concentration of the disulphide (26) was treated separately with the five different concentrations of the aminophosphine (10) in benzene at constant temperature (50°C). In each run, the concentration of disulphide was followed by HPLC, with dibenzyl as internal reference. The second order rate constant was calculated by plotting each pseudo-first order rate constant (k'_1, k'_2, k'_3, k'_4 and k'_5) against the original concentration of the aminophosphine. The pseudo-first order rate constants were calculated from a plot of time against the logarithm of unreacted disulphide concentration in the reaction mixture. (Figures 5, 6, 7, 8, 9).

A typical run between the aminophosphine (10) and disulphide (26) in benzene (dry) at 50°C is shown in Table 7.

Table 7 k' values and initial concentration of the kinetic runs between compounds (10) and (26)

Run No.	Amino Phosphine Concentration	Disulphide Concentration	k' Observe	Figure No.
1	0.020	0.002	k'_1 $2.23 \times 10^{-5} s^{-1}$	5
2	0.026	0.002	k'_2 $3.2 \times 10^{-5} s^{-1}$	6
3	0.035	0.002	k'_3 $4.0 \times 10^{-5} s^{-1}$	7
4	0.043	0.002	k'_4 $5.3 \times 10^{-5} s^{-1}$	8
5	0.051	0.002	k'_5 $6.00 \times 10^{-5} s^{-1}$	9

A plot of these k' against aminophosphine is shown in Figure 10. and gave a k_2 value of $1.18 \times 10^{-3} l mol^{-1} s^{-1}$. This measurement can be compared with that of Harpp for benzyl sulphide in benzene at 30°C which is $4.7 \times 10^{-5} l\ mol^{-1} sec^{-1}$.

This confirms the finding of Harpp that the overall rate of desulphurisation should be some function of the mercaptide stability. That is, the smaller the pKa of the mercaptide the better its ability to act as a leaving group and hence the faster the reaction.

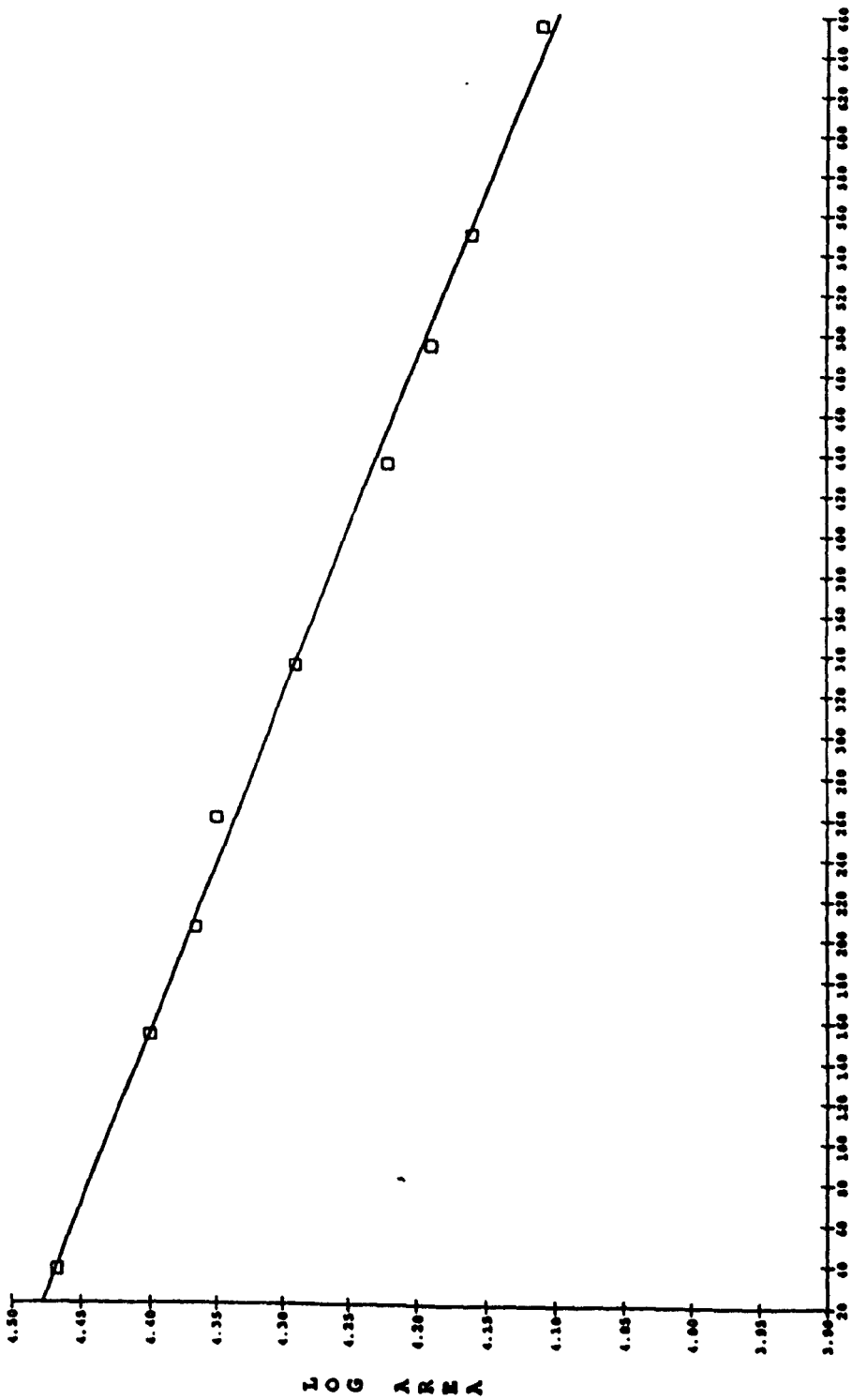


Figure 5 (Run 1)

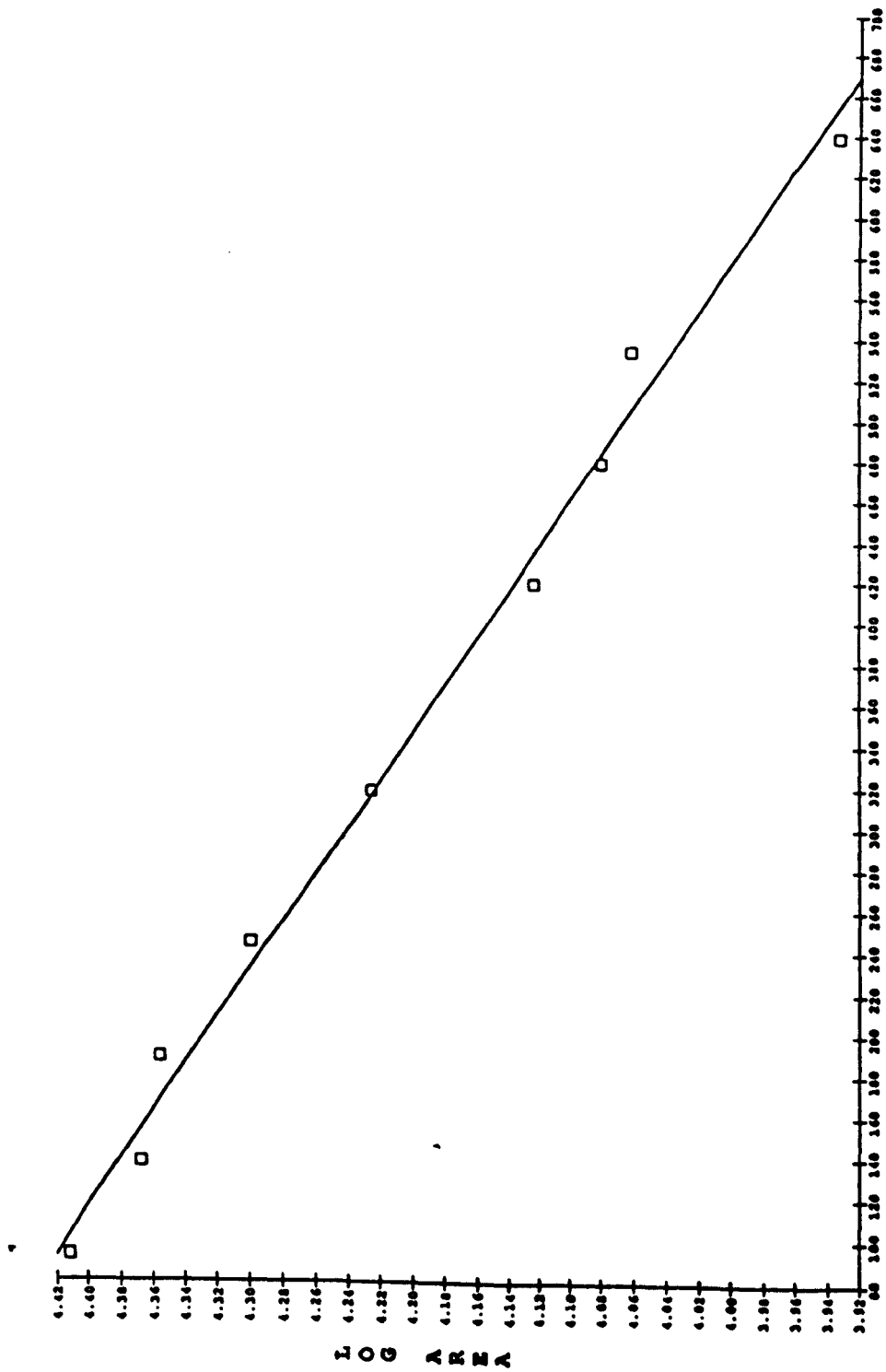


Figure 6 (Run 2)

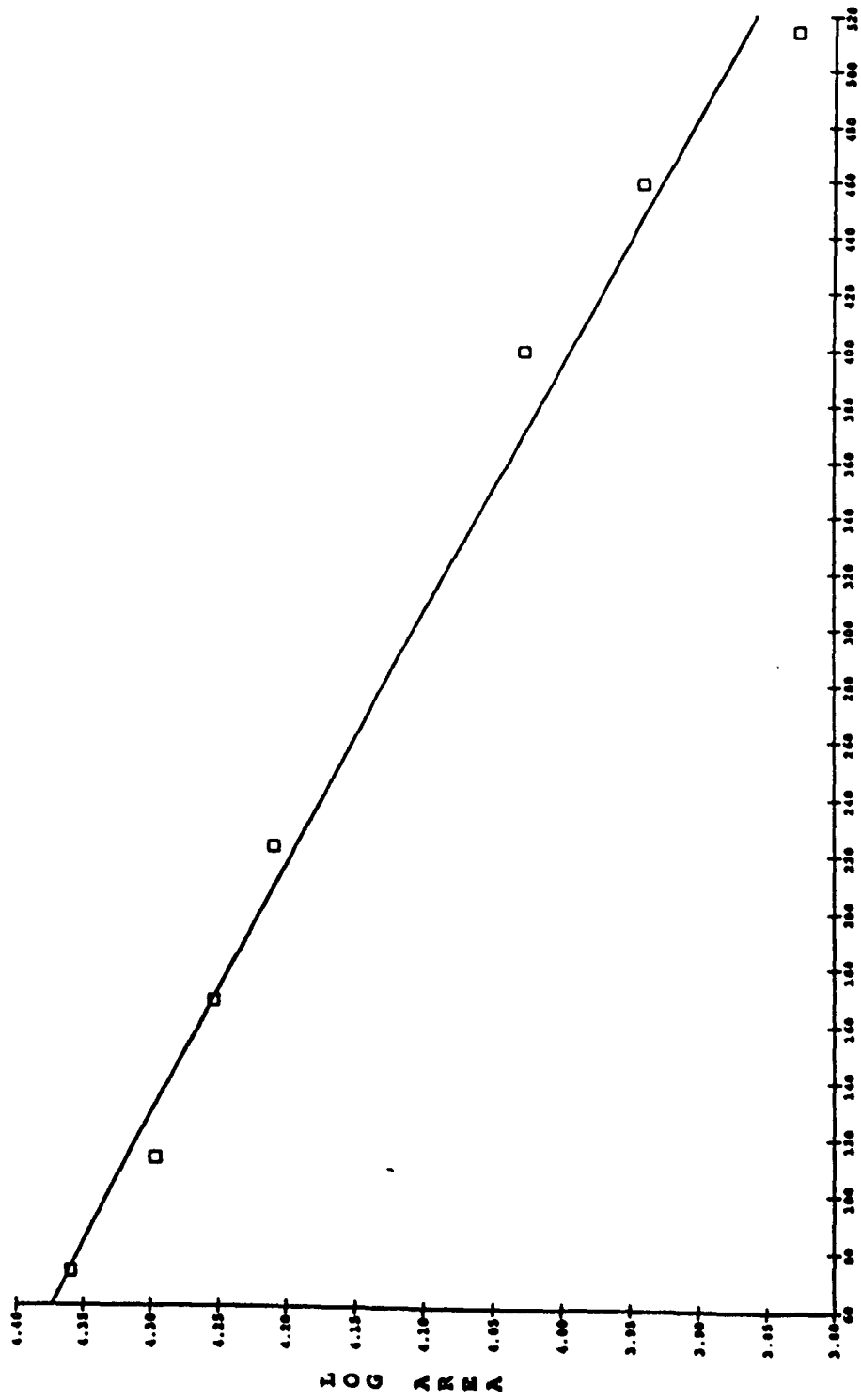


Figure 7 (Run 3)

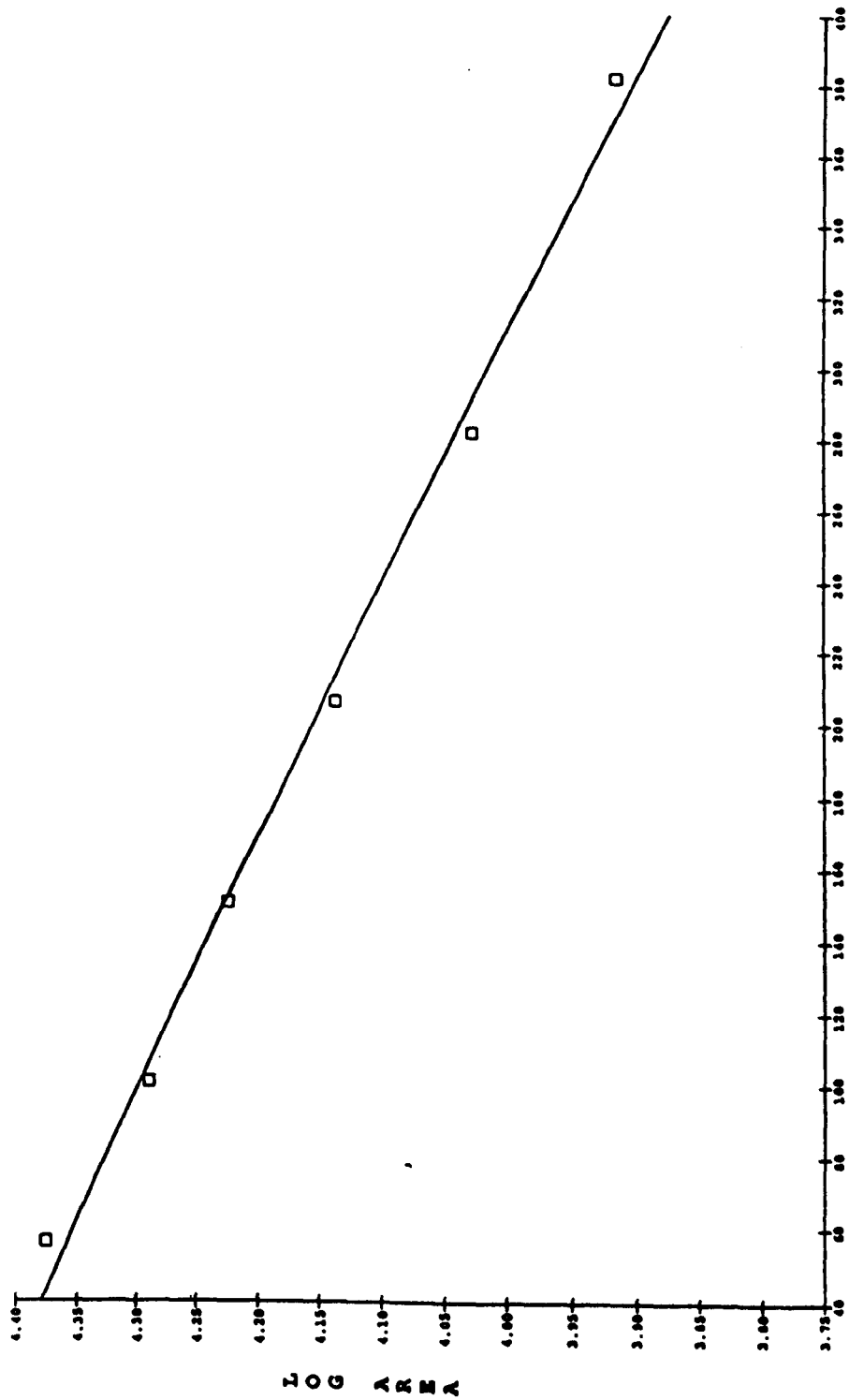


Figure 8 (Run 4)

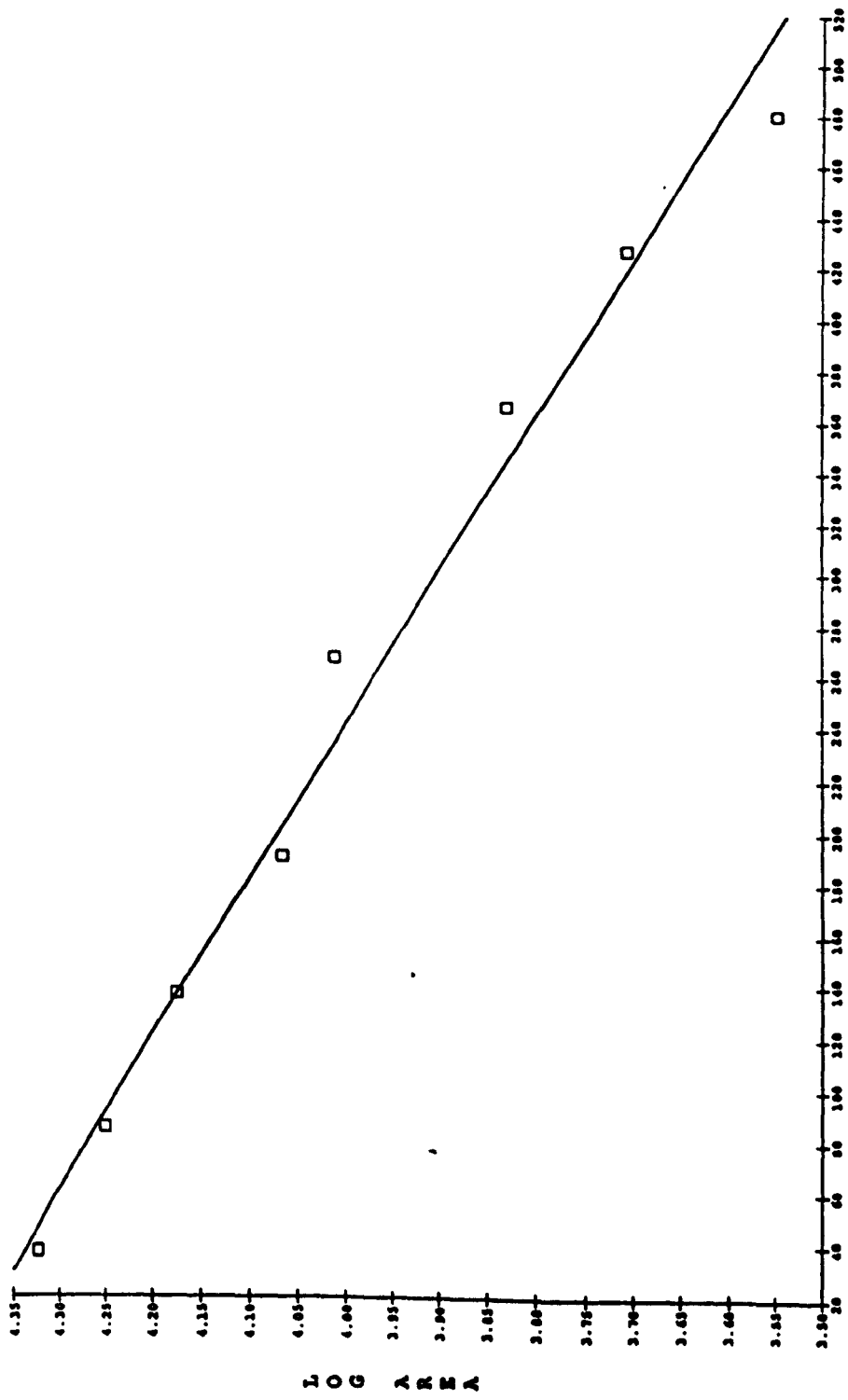


Figure 9 (Run 5)

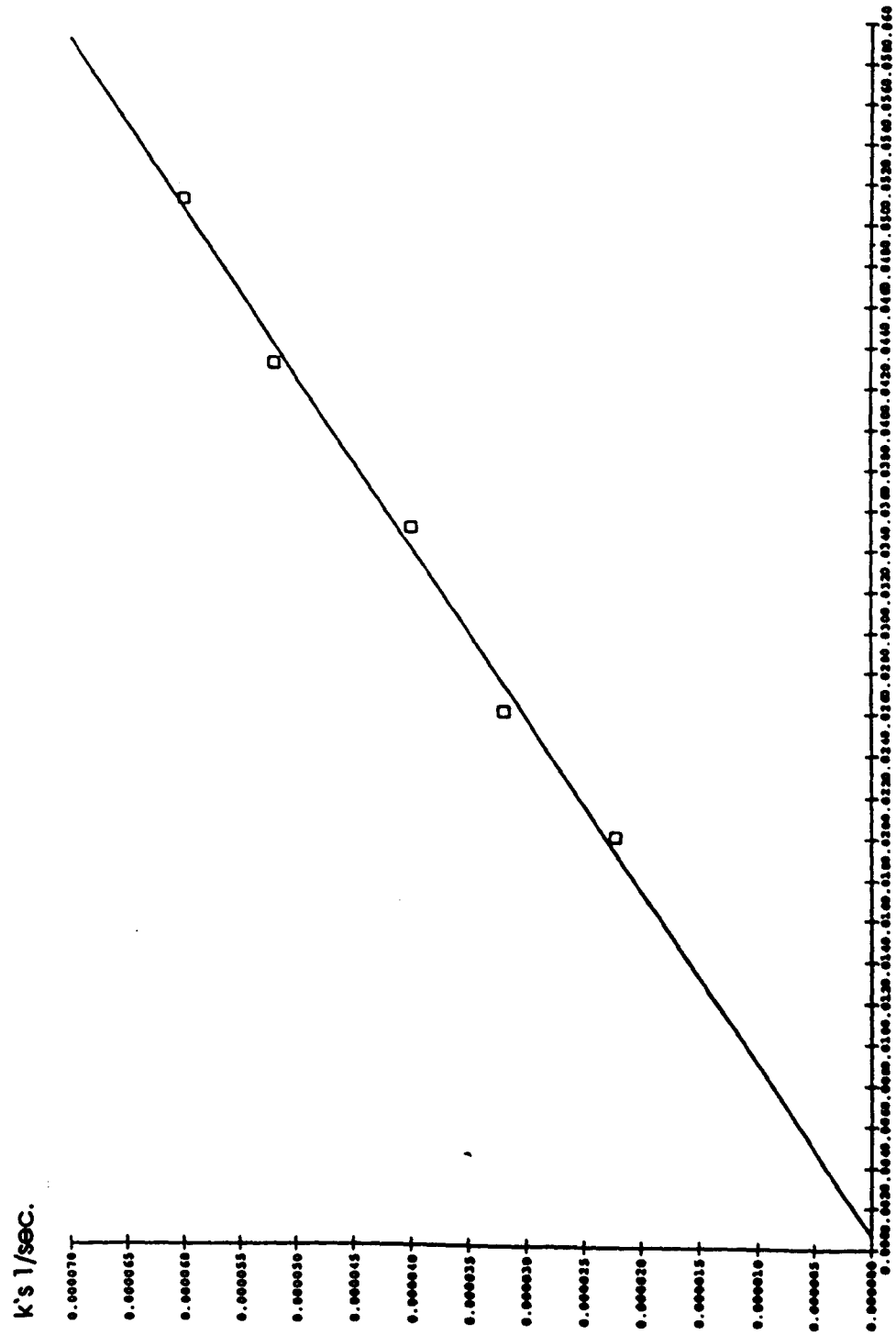


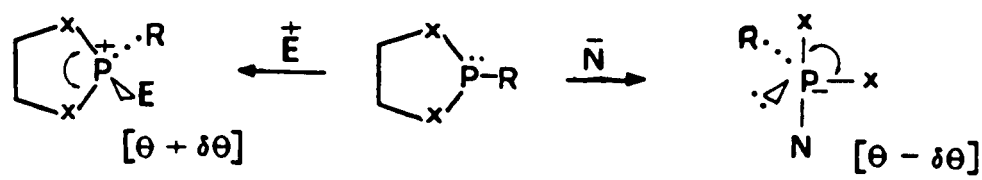
Figure 10 Plot of pseudo first order rate constant against Acyclic aminophosphine concentrations.

2.6 The Reactivity of Cyclic v Acyclic Tervalent Phosphorus Compounds

Introduction[104,105]

The natural angle of phosphines and phosphites is ca. 100°, and when phosphorus acts as a nucleophile, this should increase as a result of rehybridisation to ca. 100°. In the case of cyclic compounds, the ring strain should be increased and hence the cyclic compound should be less reactive than the acyclic analog.

On the other hand, when the reaction involves nucleophilic attack on phosphorus to give a ten-electron system, the ring angle O-P-O should decrease, leading to an enhanced reactivity for the cyclic compound, although this will depend on the transition-state configuration. (Scheme 83).

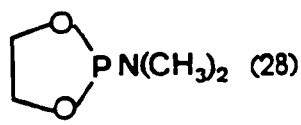
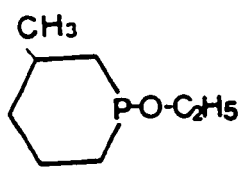
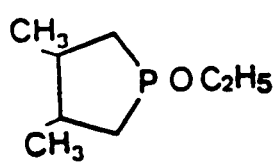
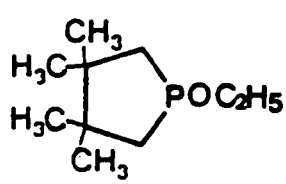


Scheme 83

Aksnes[106] has vindicated this hypothesis[107] by following the Arbusov reactions of the amide (27) and the corresponding cyclic compound (28) with methyl iodide.

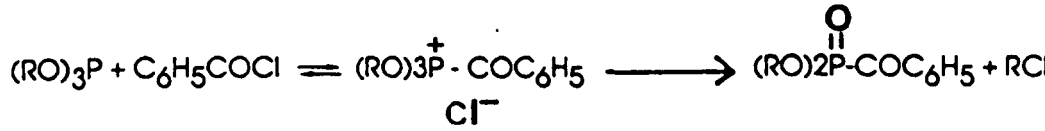
The reactions in nitrobenzene were followed by nmr. The rate constants Table (8) show the cyclic compound to be less reactive than the acyclic analog, in agreement with the above hypothesis.

Table (8) The Rate Constants of Some Arbusov Reactions

Phosphite	Alkyl halide	$10^5 k_2$. l mor^{-1} s^{-1}
$(CH_3O)_2$ P-N$(CH_3)_2$ (27)	CH_3I	0.097
 (28)	CH_3I	0.030
$(C_2H_5O)_3P$	C_2H_5I	4.80
$(C_3H_7O)_3P$	C_2H_5I	7.96
	C_2H_5I	2.7
	C_2H_5I	0.7
	C_2H_5I	1.1

Reduced steric hindrance should lead to a greater reactivity for the cyclic compound, as in the quaternisation of certain cyclic amines, e.g. pyrolidine is slightly more reactive than piperdine toward methyl iodide and acylating against[108] and aziridines and azetidines show greater increases.[109]

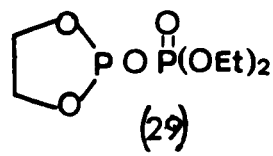
Much larger rate decreases for the acylation of cyclic phosphite have been observed by Brown and coworkers[110,111] with rate ratios of the order of 10^2, depending on the nature of the acyl halide used (scheme 84).



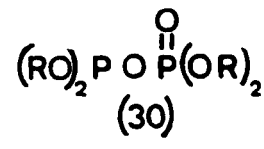
Scheme 84

Moreover, the phosphite-catalysed trimerisation of isocyanate, under pseudo-first order conditions, shows the cyclic phosphite to be ~ 30 times less reactive than the acyclic analog.

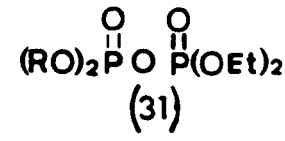
Michalski[112] has also observed greater rate differences involving acid catalysis and shown that the compound (29) is unreactive towards dialkyl phosphates whereas the acyclic analog (30) gives pyrophosphate (31) readily.



(29)



(30)



(31)

This large difference in reactivity can be understood if the initial step involves protonation of the phosphite to give a good leaving group, a process which be energetically less favourable in the case of the cyclic compound, followed by nucleophilic attack of phosphoryl phosphorus by the dialkyl phosphate anion.

A similar explanation may be put forward to account for the stability of 2-chloro-1,3,2-dioxaphospholane in the presence of free hydrogen chloride.[113]

It can be shown that the influence of strain in the cyclic compound increases with the extent of bond formation with the electrophilic reagent.

The Bronsted coefficient, β, is a convenient measure of this interaction, and from the data so far available it is found to increase regularly with relativity of cyclic and acyclic compounds. (Table 9).

Table 9 Bronsted Coefficients and Reactivity Ratios of Some Tervalent Phosphorus Compounds

Reaction	k_α/k_c	β
$(RO)_2PN(CH_3)_2 + CH_3I$	3.0	0.22
$(RO)_2P + C_6H_5NCO$	30.0	0.50
$(RO)_3P + C_6H_5COCl$	2×10^2	0.78
$(RO)_3P + H^+$	6×10^6	1.0

Another interesting rate ratio of k_α/k_c by 40 has been observed by Songstad[114] for the reaction of phosphites with isoselenocyanates, is due mainly to an unfavourable $\Delta S^\#$ for the cyclic compound. (Scheme 85).

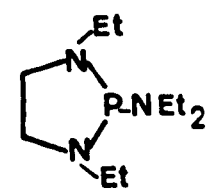
$$Ph_3CN{=}C{=}Se + (RO)_3P \longrightarrow Ph_3C\text{-}\overset{+}{N}{\equiv}\overset{-}{C} + (RO)_3P{=}Se$$

Scheme 85

Kinetics of the reaction of cyclic amino phosphines with disulphides

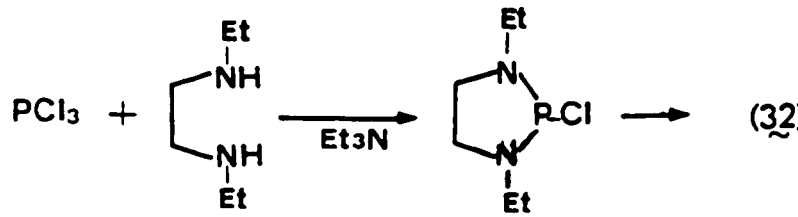
In order to compare the reactivity of cyclic phosphines with that of acyclic analogs, the kinetics of the two must be compared.

In this study, the cyclic analog prepared was (32) 2-(N-Diethylamino)-1,3 diethyl-1,3,2-diazaphospholane.



(32)

Which was prepared according to Ramirez.[114] (Scheme 86).



Scheme 86

Compound (32) had a $^{31}P-\{^{1}H\}$ nuclear magnetic resonance spectrum consisting of a single line, and gave the expected elemental analysis.

Typical kinetic runs between the cyclic aminophosphine (32) and disulphide (26) in benzene (dry) at 50°C are shown in Table (10) and (Figures 11, 12, 13, 14, 15).

Table 10 k' values and initial concentrations of the kinetics run between compounds (32) and (26)

Run No	Cyclic Phosphine Concentration	Disulphide Concentration	k' Observed	Figure No.
1	0.025	0.002	$3.93 \times 10^{-5}\ s^{-1}$	11
2	0.032	0.002	$4.86 \times 10^{-5}\ s^{-1}$	12
3	0.053	0.002	$8.52 \times 10^{-5}\ s^{-1}$	13
4	0.069	0.002	$1.14 \times 10^{-4}\ s^{-1}$	14
5	0.087	0.002	$1.45 \times 10^{-4}\ s^{-1}$	15

which gave a second order rate constant of $1.625 \times 10^{-3} l\ mol^{-1} sec^{-1}$ (Figure 16).

This measurement indicated that the cyclic aminophosphine (32) has a reactivity towards disulphides very similar to that of the acyclic analog.

This finding seems to disagree with the known behaviour of tervalent cyclic phosphorus compound mentioned in the Introduction Section of this Chapter.

However, it has to be said that the reduced reactivity for cyclic phosphorus compounds, was not investigated in cyclic phosphorus compounds containing nitrogen as a hetero-atom.

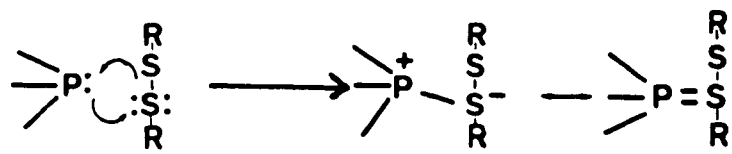
In fact, Thorstenson[105] has established that two factors can determine the nucleophilicity of phosphorus compounds.

The first being the lone-pair repulsion, the p-orbital lone pair on the nitrogen atoms are interacting with the phosphorus lone pair in a repulsive manner, raising the energy of the latter and rendering it both more basic and nucleophilic.[115]

The second being $P_N\pi$-$d_p\pi$ electronic transfer,[116,117] this type of electronic transfer should be facilitated by sp^2 hybridisation of the nitrogen lone pairs, since lone pairs in sp^3 hybrids are expected to be less effective in donating π-density to the phosphorus atom than lone pairs contained in a p-orbital. Recent X-ray structure determination of tris (morpholino) phosphine[117] indicate that the nitrogen atoms have considerable sp^2 character.

These two factors actually may well be contributing to the fact that the cyclic phosphine (32) has similar reactivity to the acyclic analog. Therefore, the ring strain is being partly or completely cancelled out by the above two factors.

An alternative explanation may involve the biphilic character of sulphur and phosphorus atoms in their lower oxidation states. Thus, each may show that both electrophilic and nucleophilic character in their reactions, leading in this case to a cancellation of the ring strain effects, illustrated below:



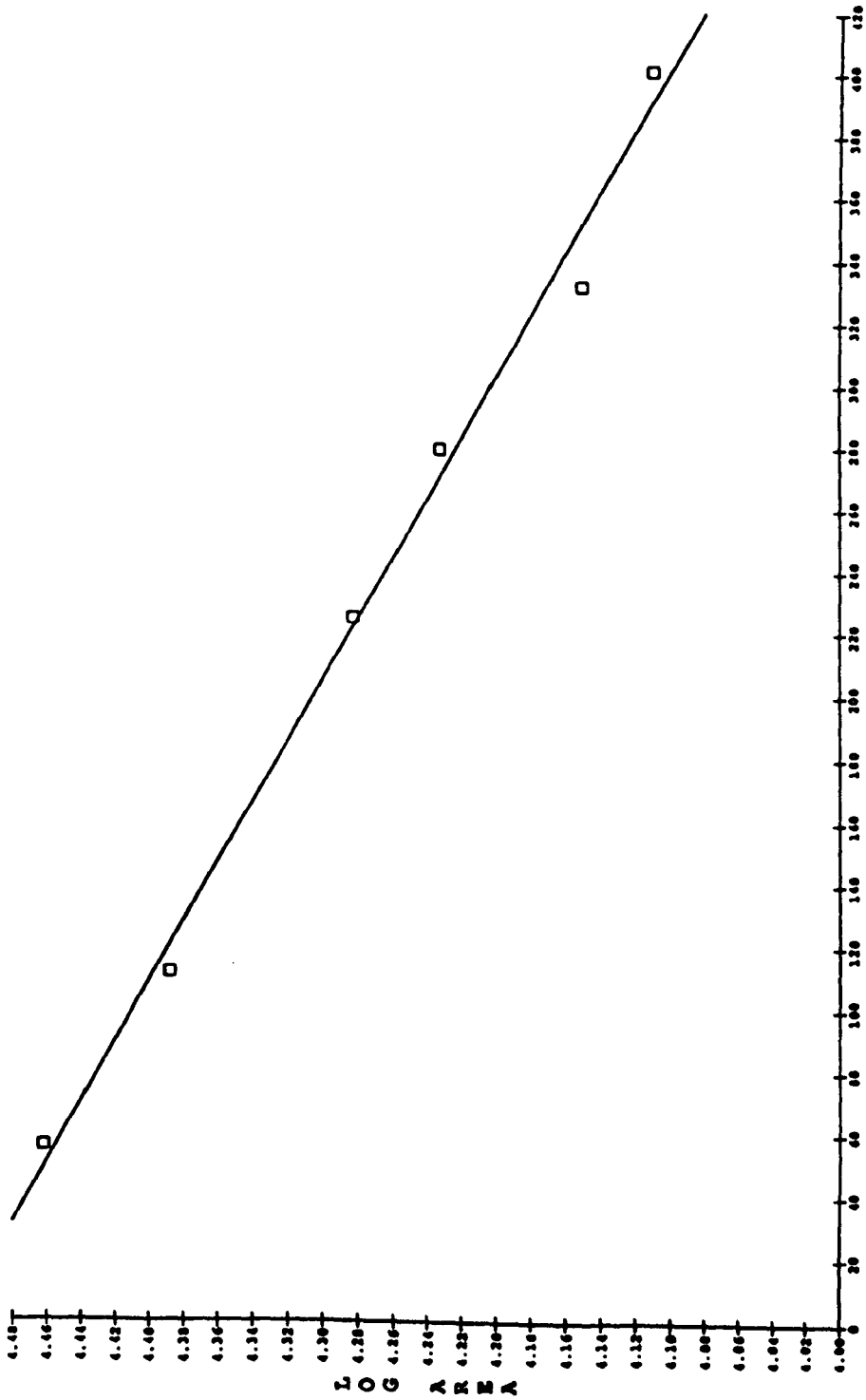


Figure 11 (Run 1)

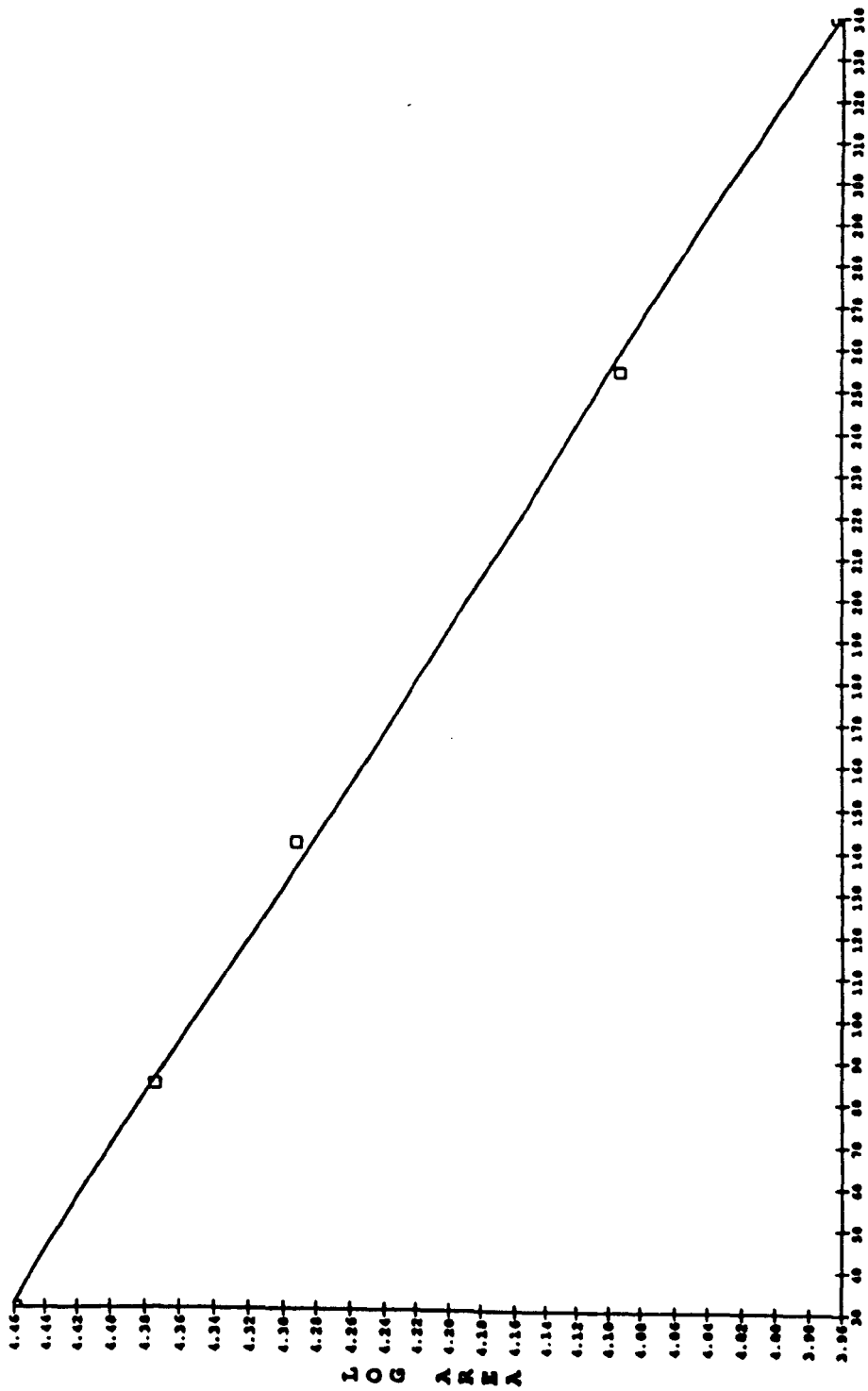


Figure 12 (Run 2)

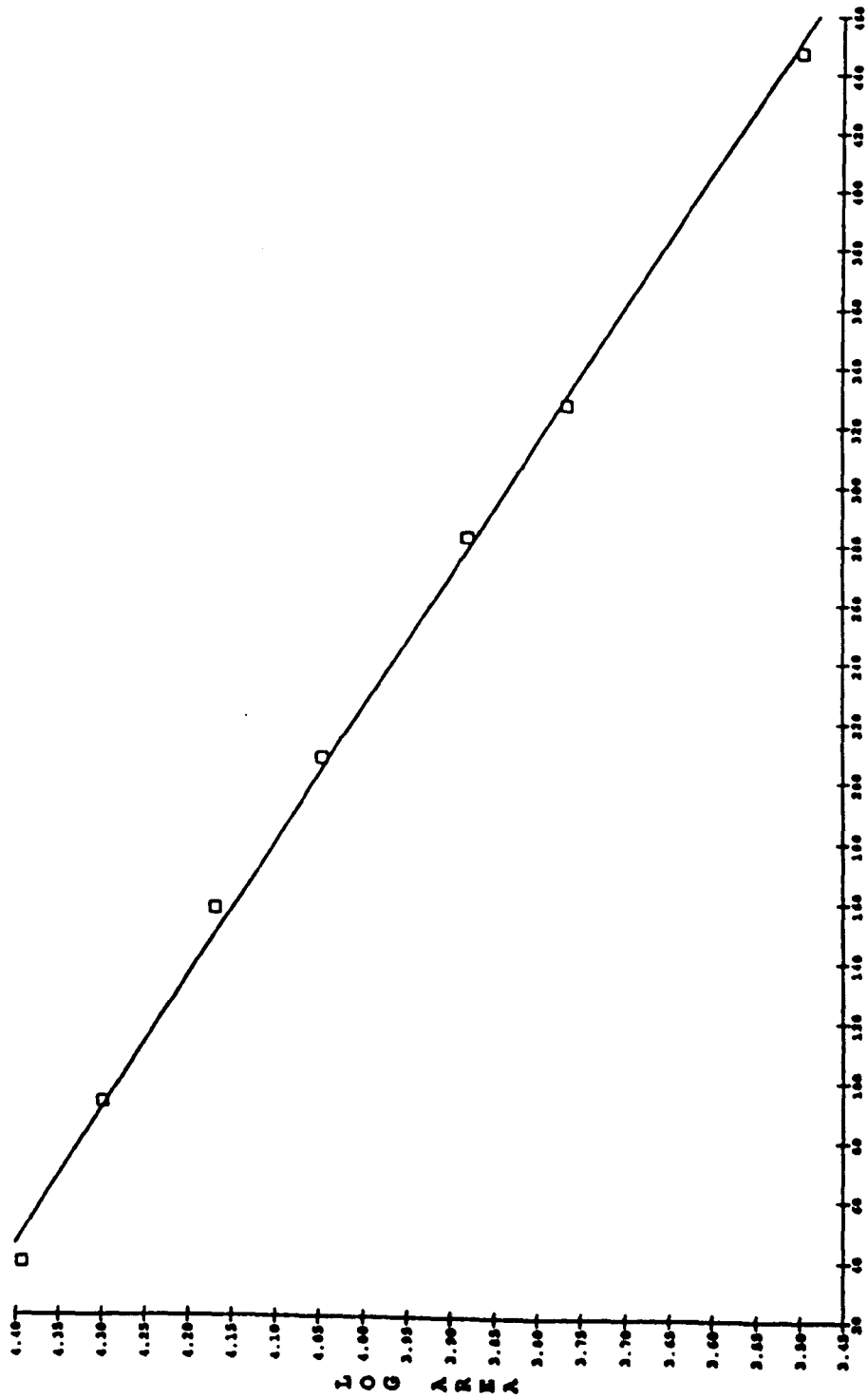


Figure 13 (Run 3)

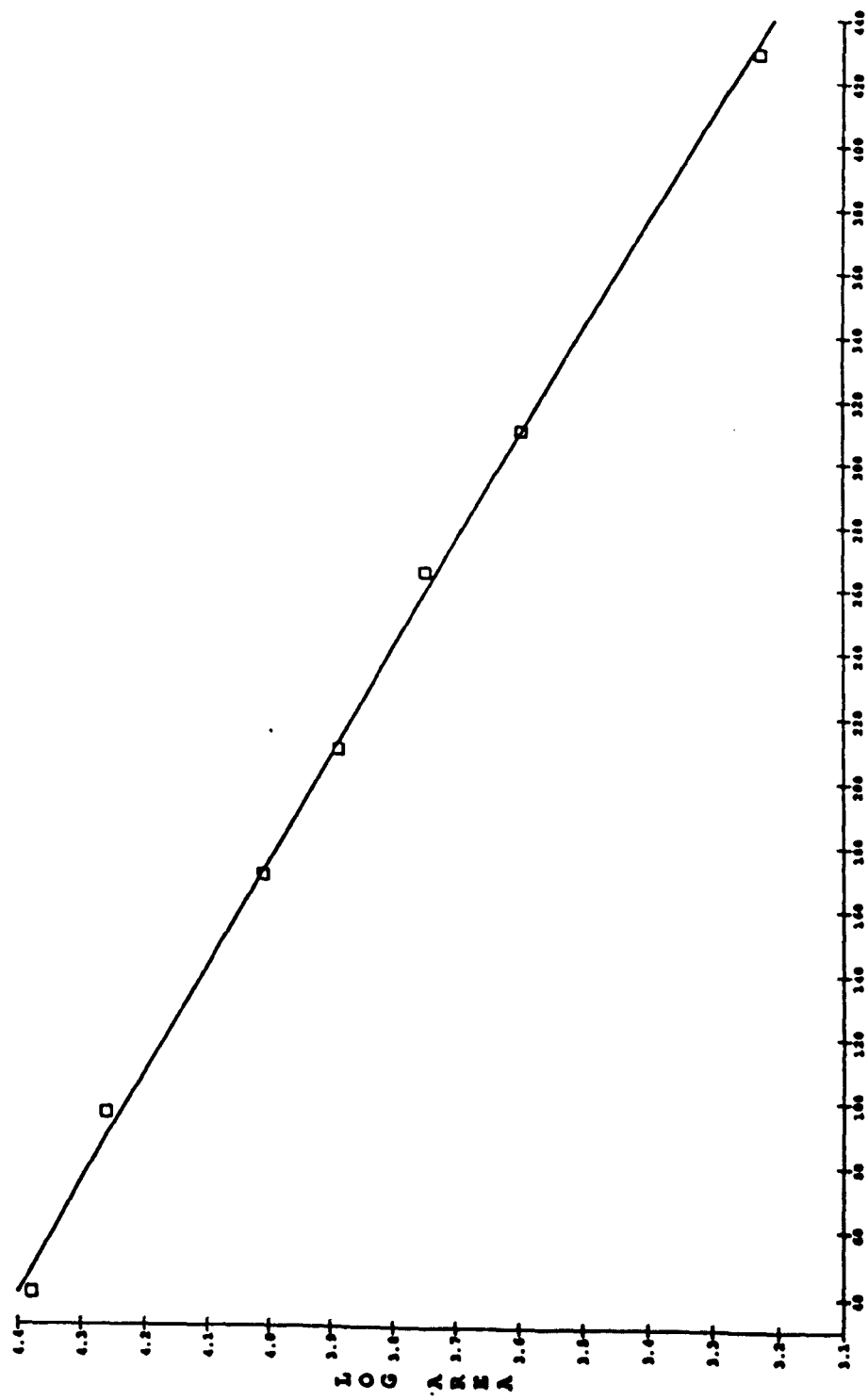


Figure 14 (Run 4)

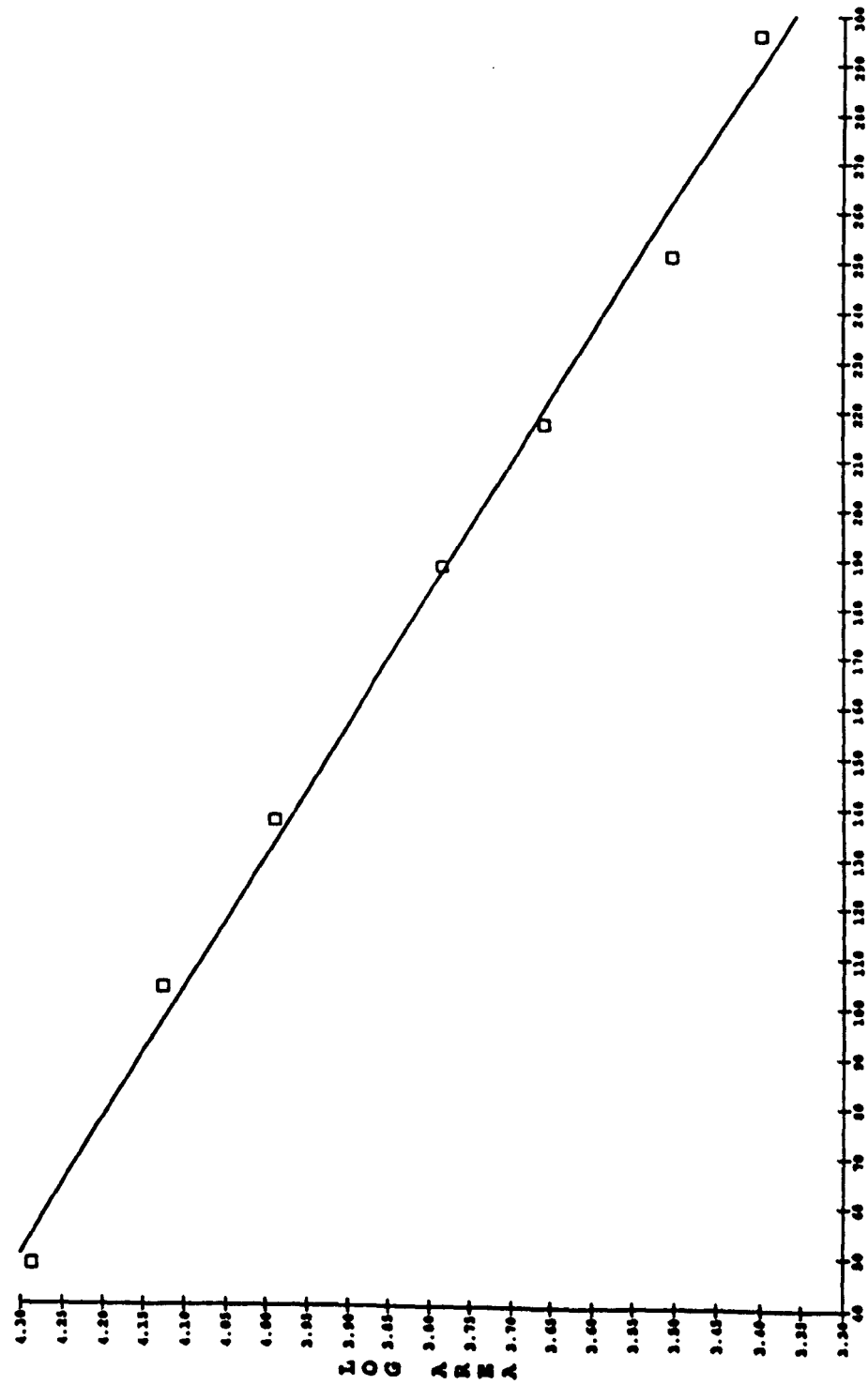


Figure 15 (Run 5)

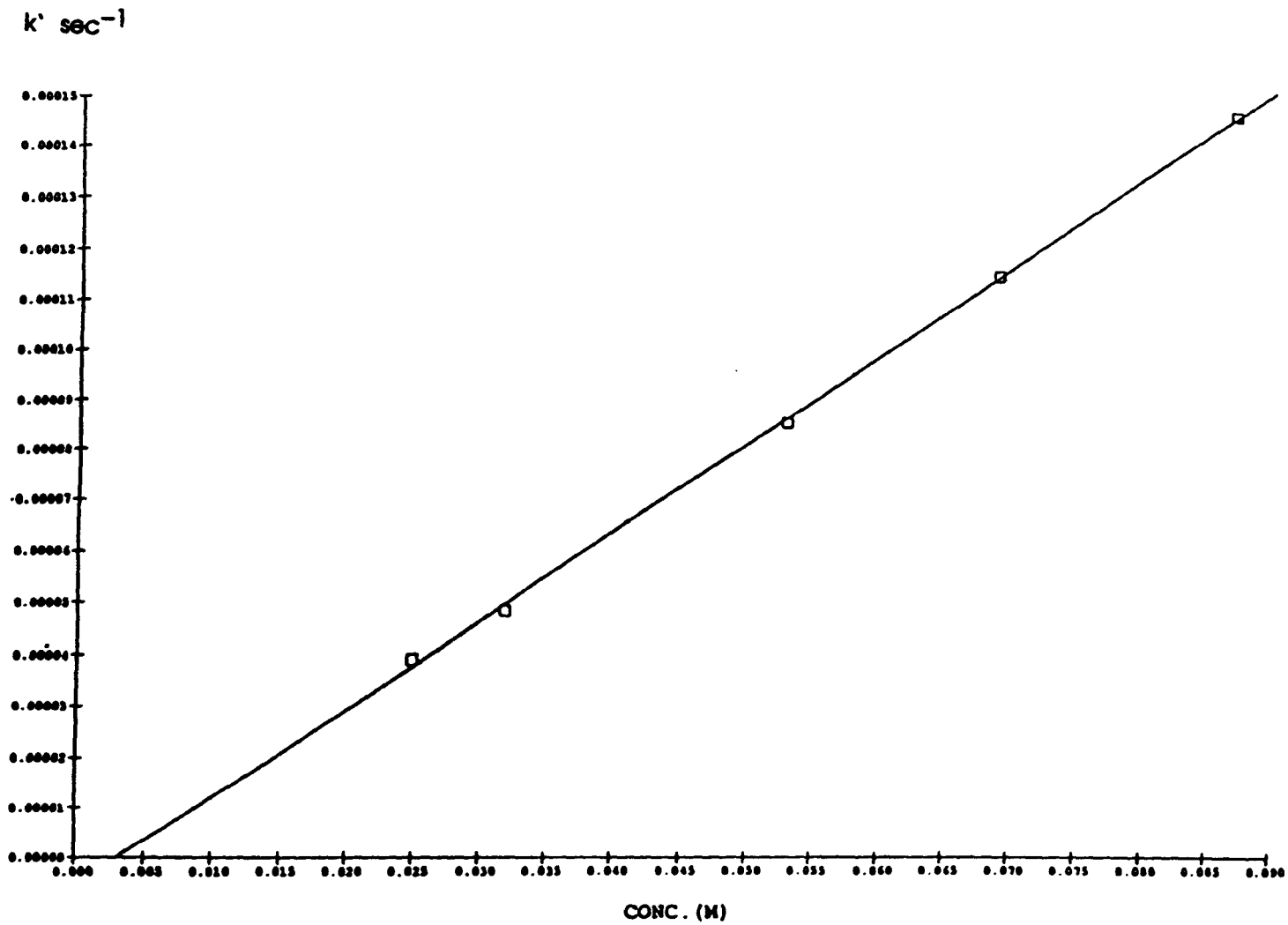


Figure 16 Pseudo-first order rate constants against the cyclic aminophosphine concentrations.

CHAPTER 3

ANALYTICAL METHODS

CHAPTER 3 ANALYTICAL METHODS

3.1 CHEMICALLY INDUCED DYNAMIC NUCLEAR POLARISATION (CIDNP)

A INTRODUCTION

ESR (Electron Spin Resonance), a commonly used technique for detecting radical species, is based generally on the energy levels of an unpaired electron. Such unpaired electrons in atoms and molecules are subject to a variety of magnetic interactions which can shift and split the simple Zeeman levels, and the effects are reflected in the e.s.r. spectrum. However, it is usually found that an e.s.r. spectrum can be described relatively simply in terms of transitions between energy levels which are eigen-function of a Hamiltonian containing only spin operators. The most common use of e.s.r. is as a qualitative method for radical detection and as such, it is a relatively sensitive technique. What e.s.r. does not do, however, is to give direct evidence of radical participation in particular reaction processes. More informative than the position of the e.s.r. lines themselves, are their intensities, and those of the nmr transition in analogous systems. Both e.s.r. and nmr lines with anomalous intensities (both absorption and emission) have been observed in chemically reacting systems. The effects have been called chemically induced dynamic electron and nuclear polarisation (CIDEP and CIDNP respectively). They arise from species (radicals in the case of esr or reaction products in the case of nmr) that are formed with non-equilibrium spin state populations, typically only from free-radical processes. The advantage of utilising the CIDNP technique is that it gives direct evidence of the nature and source of the radical species leading to diamagnetic products which produce polarised nmr spectra. More qualitatively still, the mere observation of polarised nmr spectra for a particular species can be taken as good evidence that it was formed from a radical, or radical-like precursor. A typical example of a polarised nmr spectrum is shown in Figure 17.

We decided to use this method to test the possibility, already raised in the literature[66] that the disulphide desulphurisation reaction might proceed via radical intermediates.

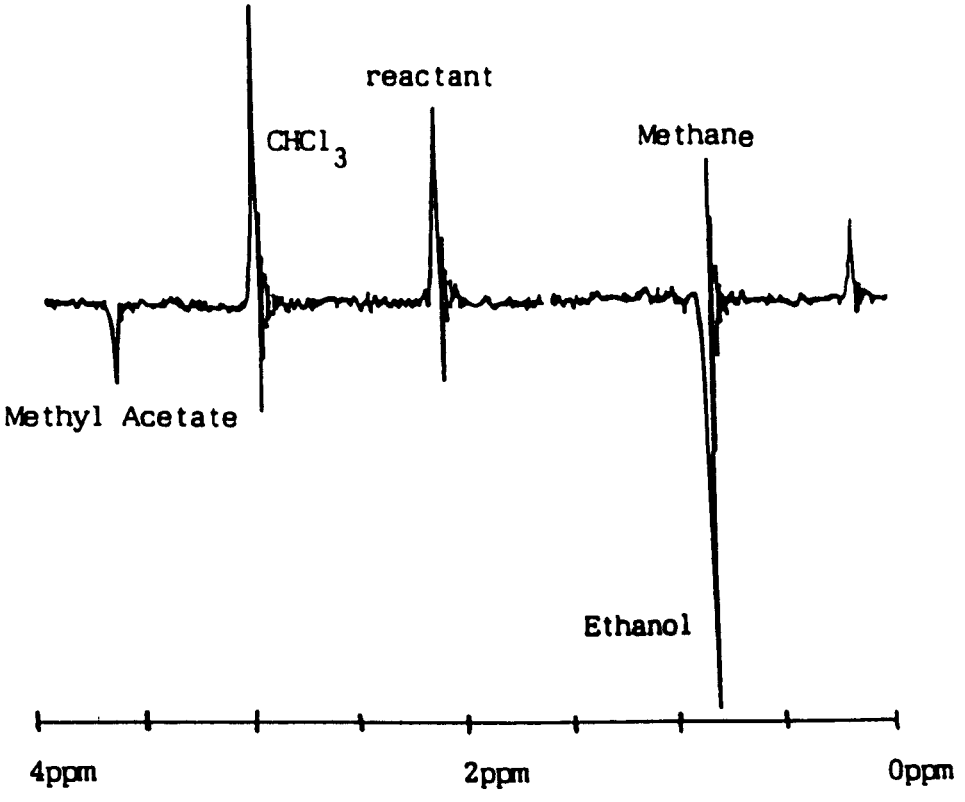
A comprehensive review of this technique can be found in reference 119.

B Results and Discussion

Two experiments were run; one in benzene solution, one in methanol, and the process followed by ^{31}P nmr. This nucleus was chosen because, apart from being intimately involved in the primary reaction process, phosphorus provides nmr spectra which are uncluttered by solvent or reagent resonances, and which can be strongly polarised in radical systems. In the event, neither experiment gave any evidence for polarised resonances, and therefore no evidence for radical processes involving phosphorus-containing species. This does not completely rule out a radical mechanism, but strongly indicates a non-radical one, given the direct involvement of the phosphorus atom.

The spectra are shown in Figures 18 and 19. The benzene experiment shows clear conversion of the aminophosphine (δp 119ppm) to the phosphine sulphide (δp 79ppm), with no anomalous line intensities. The methanol experiment is more complex, with evidence for an intermediate, (δp 63ppm), but again no polarised resonances are seen. The complex nature of the spectrum is in keeping with other observations in methanol solution (see Chapter 2).

Figure 17 Thermolysis of acetyl peroxide in hexachloroacetone in a 1.4T magnetic field, showing ^{1}H CIDNP effects.



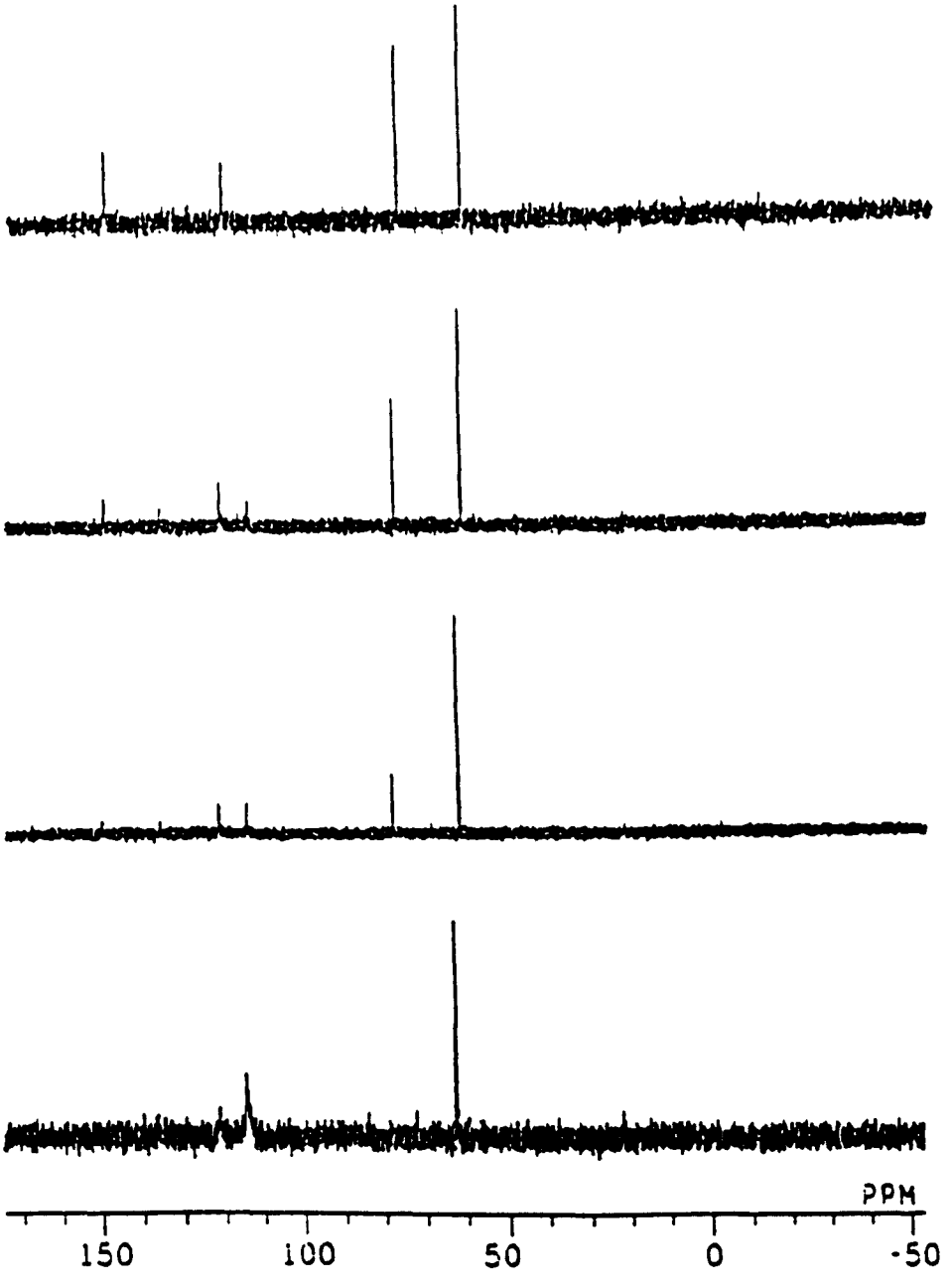


Figure 18 Reaction in methanol

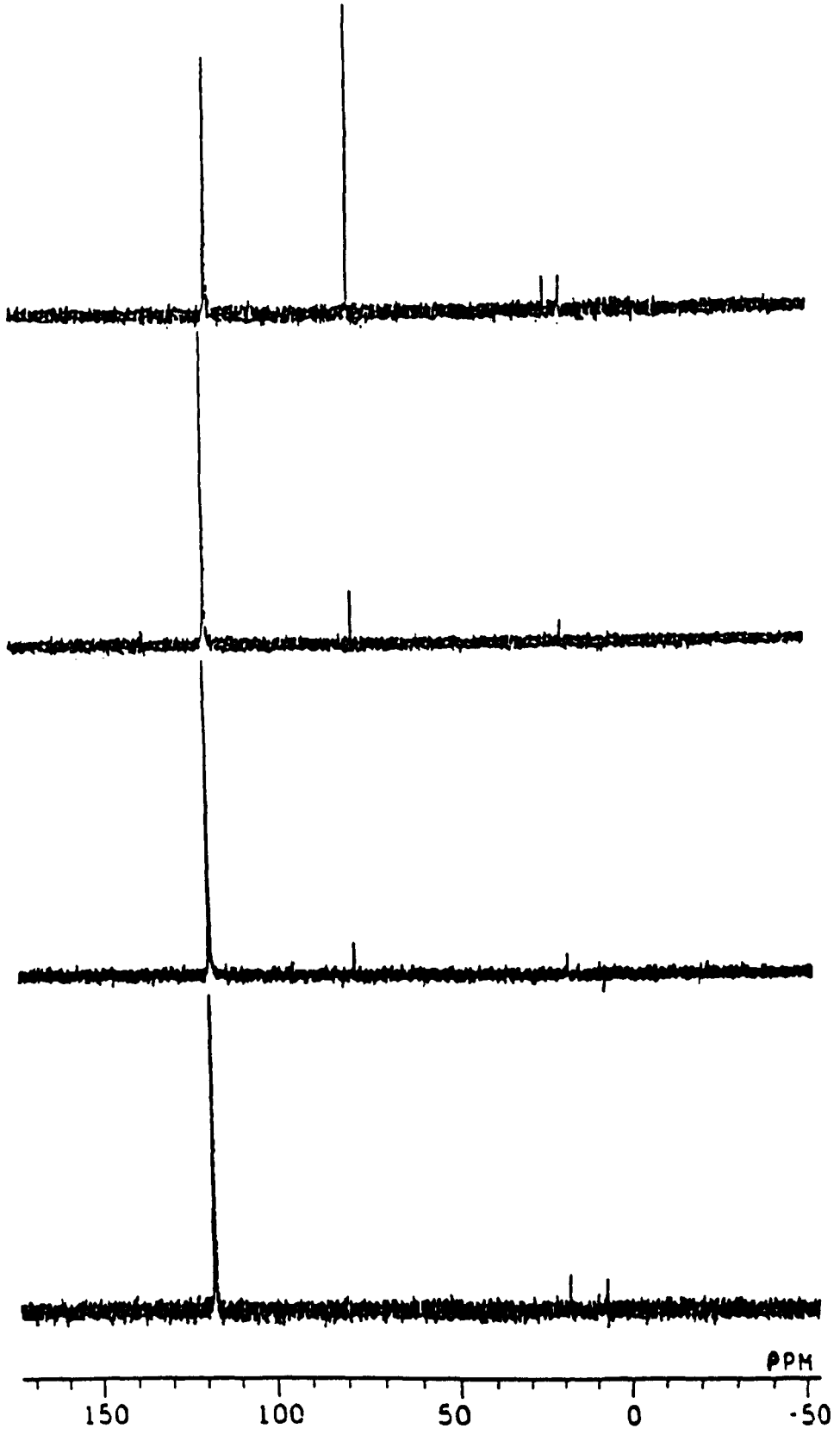


Figure 19 Reaction in benzene

3.2 HPLC (HIGH PRESSURE LIQUID CHROMATOGRAPHY)

A INTRODUCTION

Liquid chromatography is an analytical technique where different components in a sample are separated on the basis of their different speeds of transportation. This technique generally involves two phases - a stationary phase and a mobile phase.

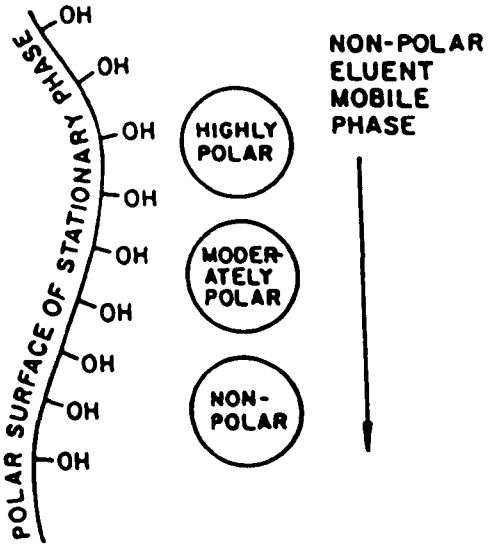
Differences in the migration speeds of the components of a mixture are caused by differences in chemical interactions between these components and the two phases. In normal phase chromatography, the stationary bed is strongly polar in nature (e.g. silica), and the mobile phase mainly non polar (such as n-hexane or tetrahydrofuran mixed with small amount of a polar solvent such as ethanol). Polar components are retained on the column longer than less polar components. In reversed-phase chromatography, the stationary bed is non polar (hydrocarbon-like in nature), while the mobile phase is a polar liquid, such as water, an alcohol or acetonitrile. In this latter case, the non polar components of a mixture are retained longer.

The diagram on the following page illustrates in a simplified manner the two types of chromatographic techniques indicating the order of elution of sample components of different polarity.

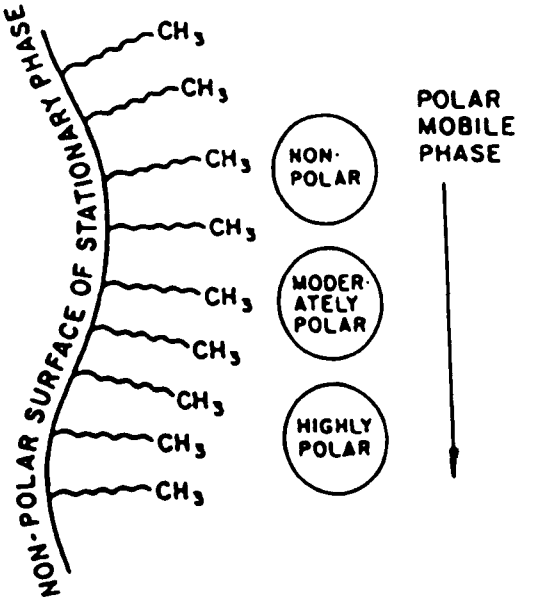
In a chromatographic separation the sample molecules partition between the mobile and stationary phases. During this process the individual substrates are retarded by the stationary phase, depending on their interaction with the mobile and the stationary phases.

This retardation is selective which means that, with a given mobile/stationary phase system the amount of retardation will be different for each sample component, this leads, therefore, to a separation of the components of a mixture passed through such a stationary/mobile two phase system.

GRAPHICAL ILLUSTRATION OF TWO TYPES OF LIQUID CHROMATOGRAPHY



Normal phase system



Reverse phase system

B RESULTS AND DISCUSSION

In the present study, a system had to be developed to resolve all six compounds (15), (25), (24), (17), (18), (16) in the same chromatogram to monitor the equilibration, desulphurisation and the kinetics involved in the conversion of disulphides to sulphides. The absorption wavelength of the detector for the chromatographic separation was set at 254nm which corresponds to the aromatic region of the compounds.

A normal phase system was first employed which consisted of hexane as a mobile phase with silica as the stationary phase. However, the above components were not retained by the stationary phase long enough to give reasonable separation. The sample components were eluted too quickly so that they were very close to the solvent front. This was due to the sample components being hydrophobic and therefore not retained by the polar stationary phase in the normal phase system.

This led us to look to a reverse phase system which consisted of a C_{18} stationary phase and a mobile phase made up of methanol:water mixtures. After experimentation an 8:2 ratio of these gave the chromatogram shown in Figure 20.

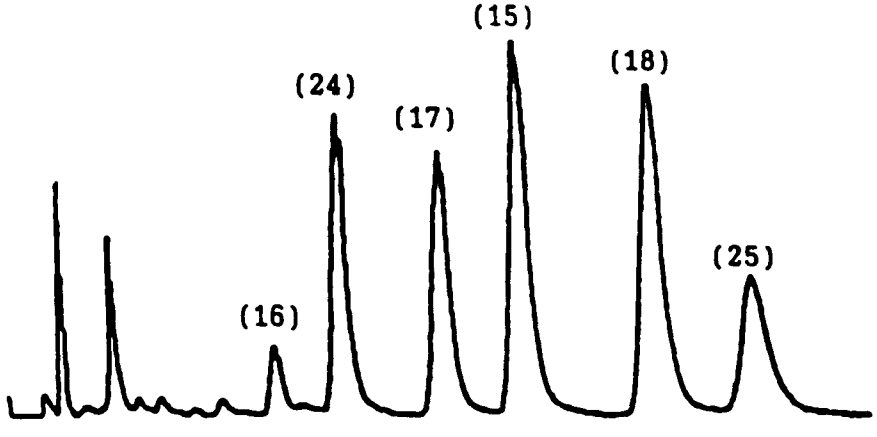


Figure 20 Reverse Phase Separation of a sample containing components (16), (24), (17), (15), (18) and (25)

This chromatograph resolved all six sample components as marked by individual number. The order of retention can be related to the hydrophobicity of the components.

Compound (16) eluted first as it is represented the least polar molecule in the mixture. This was followed by the corresponding disulphide (24). A bromine atom is more hydrophobic than hydrogen. Thus, compound (17) with one bromine was the next compound to be eluted, followed by the dibrominated components (18) and (25).

As the separation between each of the six components in the sample was so good a preparative HPLC experiment was carried out and this yielded the desired unsymmetrical disulphide (15) in good yield. This contrasts with attempts at separation of disulphide (15) from a disulphide mixture by recrystallisation or distillation were not successful.

3.3 LC/MS (LIQUID CHROMATOGRAPHY/MASS SPECTROMETRY

A INTRODUCTION

As has been stated, chromatography is not well suited to structural analysis, and needs to be combined with a suitable technique for structural elucidation.

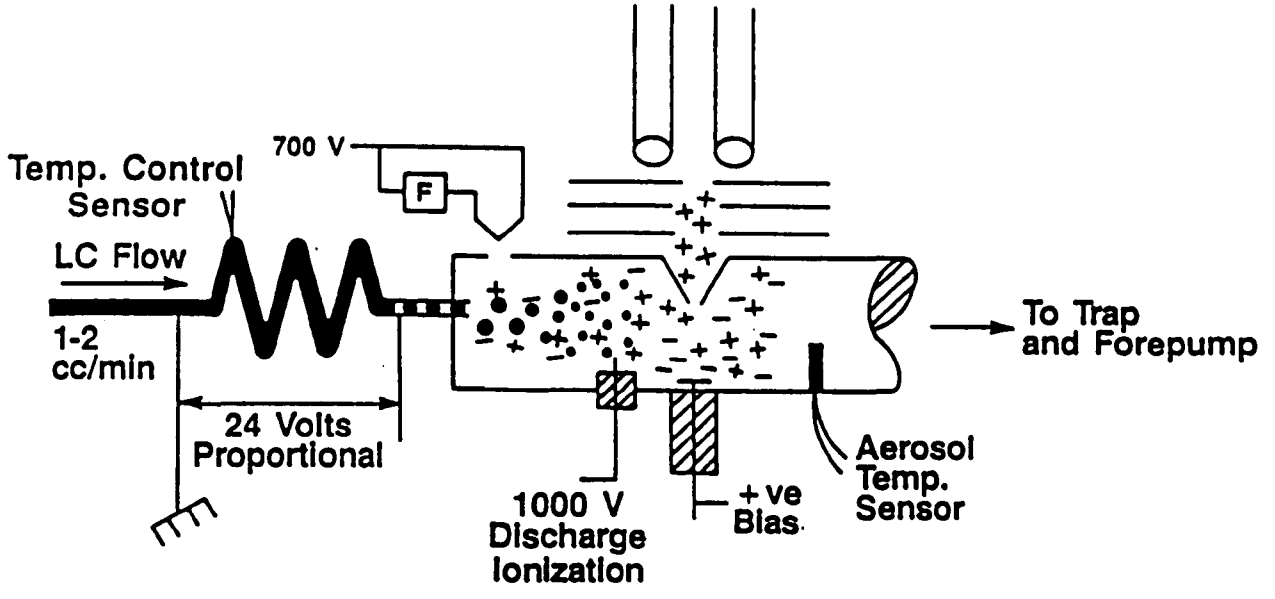
One of the most successful combinations has been gas chromatography with mass spectrometry. Such combined analytical methods are usually designated by their combined abbreviations (e.g. GC/MS or LC/MS) and are known as "hyphenated" techniques.

The development of hyphenated techniques resulted from significant increases in the scanning speeds of mass spectrometers, advances in data system technology and most importantly, the development of suitable interfaces capable of linking separation equipment to mass spectrometers.

For LC/MS the main problem is the large amount of mobile phase that must be removed at the interface to get the effluent introduced into the high vacuum at the mass spectrometer. Any techniques which can minimise such problems are desirable. Microbore columns offer one obvious solution.

Several interface devices have been developed and these include direct liquid interface, moving belt transport, thermospray, flowing FAB, particle beam and, recently, electrospray interfaces.

The thermospray interface consists of a small bore capillary tube that is heated to produce a stable, high-velocity jet consisting mostly of vapour with a small amount of mist. It not only provides an interface to the mass spectrometer, it also causes the ionisation of analytes necessary for the mass spectrometer. (Figure 21).



Interaction of Potential Fields From Discharge Electrode and Repeller Electrode Causes Ion Acceleration Producing CID.

For Most Samples, Fragmentation Occurs at Repeller Volts in Range 75-100 V

Figure 21

Thermospray is now established as a practical technique for LC/MS interfacing, and has been used for a large number of applications. Despite the obvious success of the current interfaces there remain a number of valid criticisms which clearly indicate that none of the current LC/MS interface systems can be considered to provide a universal HPLC detection system. One of the problems encountered includes the following.

Mass spectral data very often allow unambiguous determination of molecular weight, but fragmentation is either absent, insufficient or insufficiently reproducible to allow definitive identification of known compounds or offer much in the way of structure elucidation of unknown compounds.

There are ways of overcoming this problem: for example, sometimes these can be overcome using LC/MS/MS. This technique is limited to a fairly narrow range of chromatographic condition. For example, we cannot usually use phosphate buffers.

Considerable progress has, however, been made on all of these problems in recent years, and research and development is continuing to solve the remaining technical problems. In the present work a technique based on the thermospray approach was used.

B RESULTS AND DISCUSSION

It was felt that LC/MS techniques would be ideal to investigate the complex nature of the reaction in methanol.

Conventional thermospray methods were expected to be satisfactory for detection of species such as the phosphine sulphide, but not for the disulphide starting material or monosulphide product. This was in fact observed in practice. However, a variant of the conventional thermospray experiment using a source equipped with discharge electrode, in essence a type of chemical ionisation (CI) experiment (using methanol vapour as the reagent gas) did give useful results.

A typical ion current chromatogram together with the corresponding UV-detected chromatogram is shown in Figure 22: also shown are the chromatograms using detection at specific masses corresponding to starting material (26) and the expected products, the corresponding monosulphide and phosphine sulphide. It can be seen that in addition to these three species, several other compounds can be detected at both short and long retention times. Specifically, at around three minutes and

fifteen minutes retention time, both UV-detected and mass spectrally-detected species can be seen. The chromatographic data for these are shown in Figure 23. The actual mass spectra of phosphine sulphide, disulphide (26), and the corresponding monosulphide, together with those of the unknown materials of retention times three and fifteen minutes are shown in Figures 24-28.

Analysis of these mass spectra indicate that the most likely structures for these compounds are trimethyl phosphite (33) and the phosphorus-sulphur compound (34) respectively. A possible rationale for the formation of these species is shown in Figure 29. Clearly, the presence of strongly nucleophilic species is not tolerated by the aminophosphine. Direct replacement of the amino-groups by methanol is perhaps not remarkable, but the generation of the phosphorus-sulphur derivative (34) requires thiolate ion, or perhaps free thiol. This is in keeping with the ion-pair mechanism shown, ion-pair separation, with or without protonation by the methanol, being facilitated by this polar solvent.

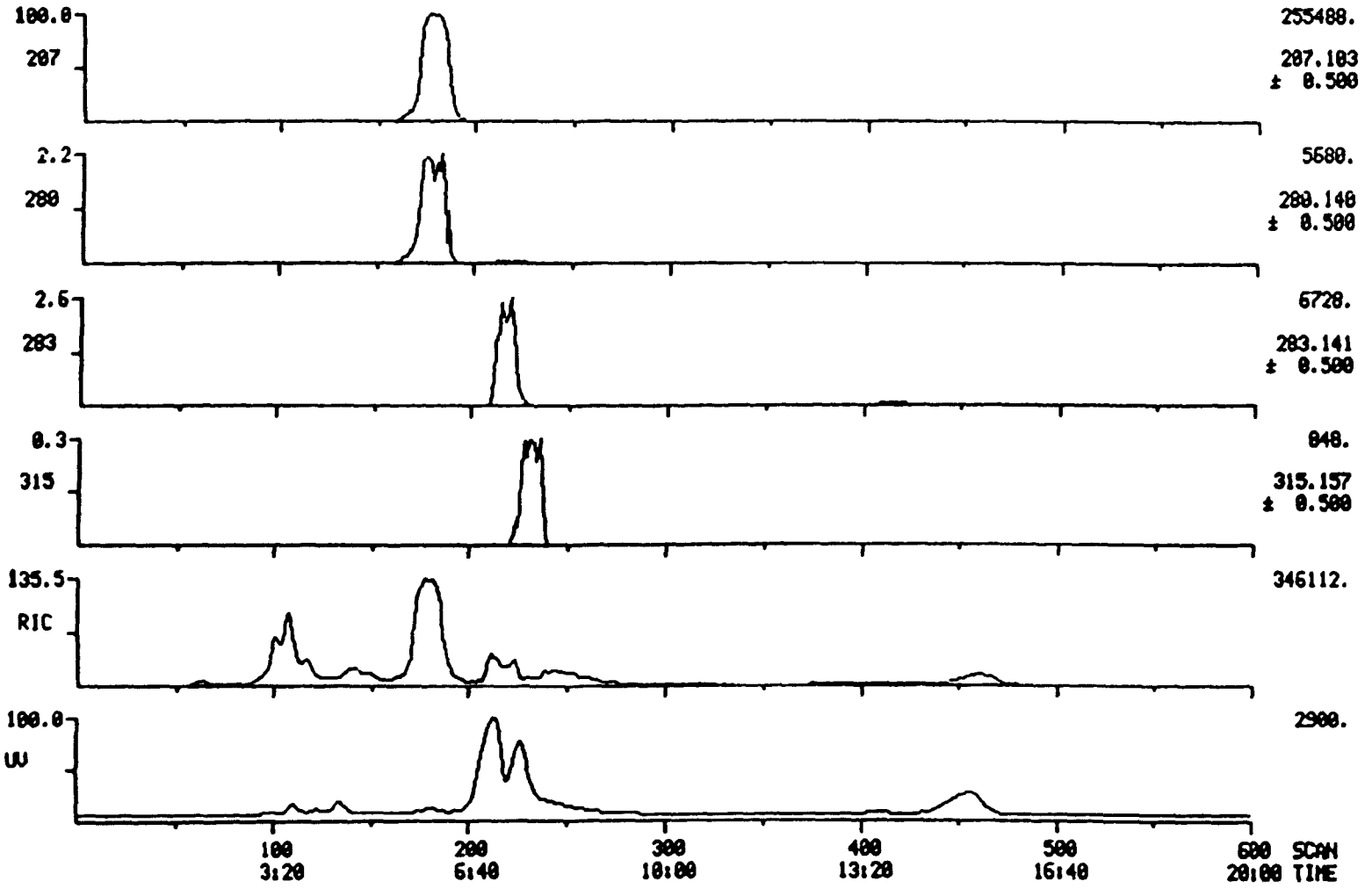

100.0
207
255488.
207.103
± 0.500
2.2
280
5680.
280.140
± 0.500
2.6
283
6728.
283.141
± 0.500
0.3
315
848.
315.157
± 0.500
135.5
RIC
346112.
100.0
UV
2900.
100
3:20
200
6:40
300
10:00
400
13:20
500
16:40
600
20:00
SCAN
TIME

Figure 22

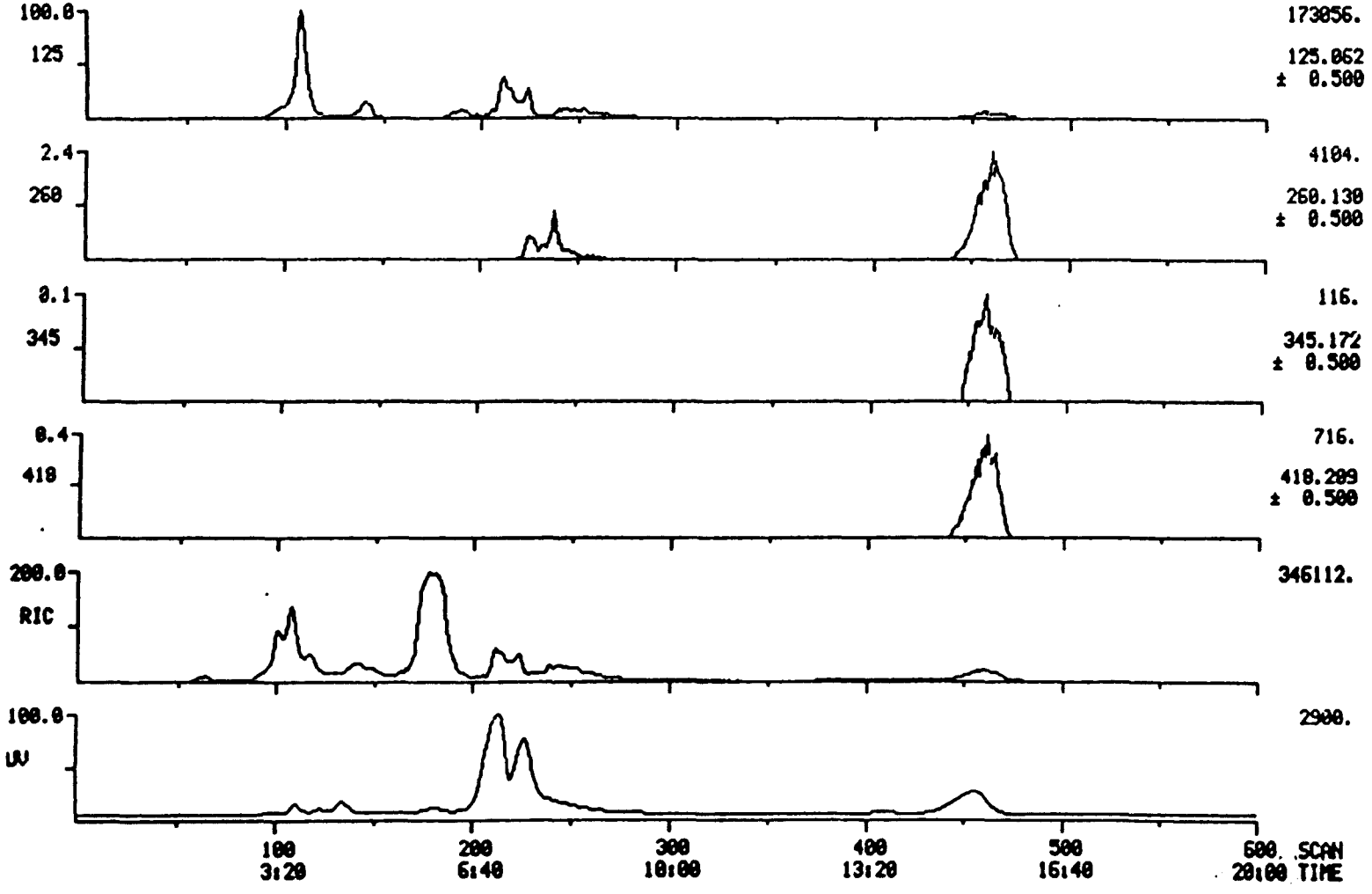

100.0
125
173856.
125.062
± 0.500
2.4
260
4104.
260.130
± 0.500
0.1
345
116.
345.172
± 0.500
0.4
418
716.
418.289
± 0.500
200.0
RIC
346112.
100.0
UV
2900.
100
3:20
200
6:40
300
10:00
400
13:20
500
16:40
600
20:00
SCAN
TIME

Figure 23

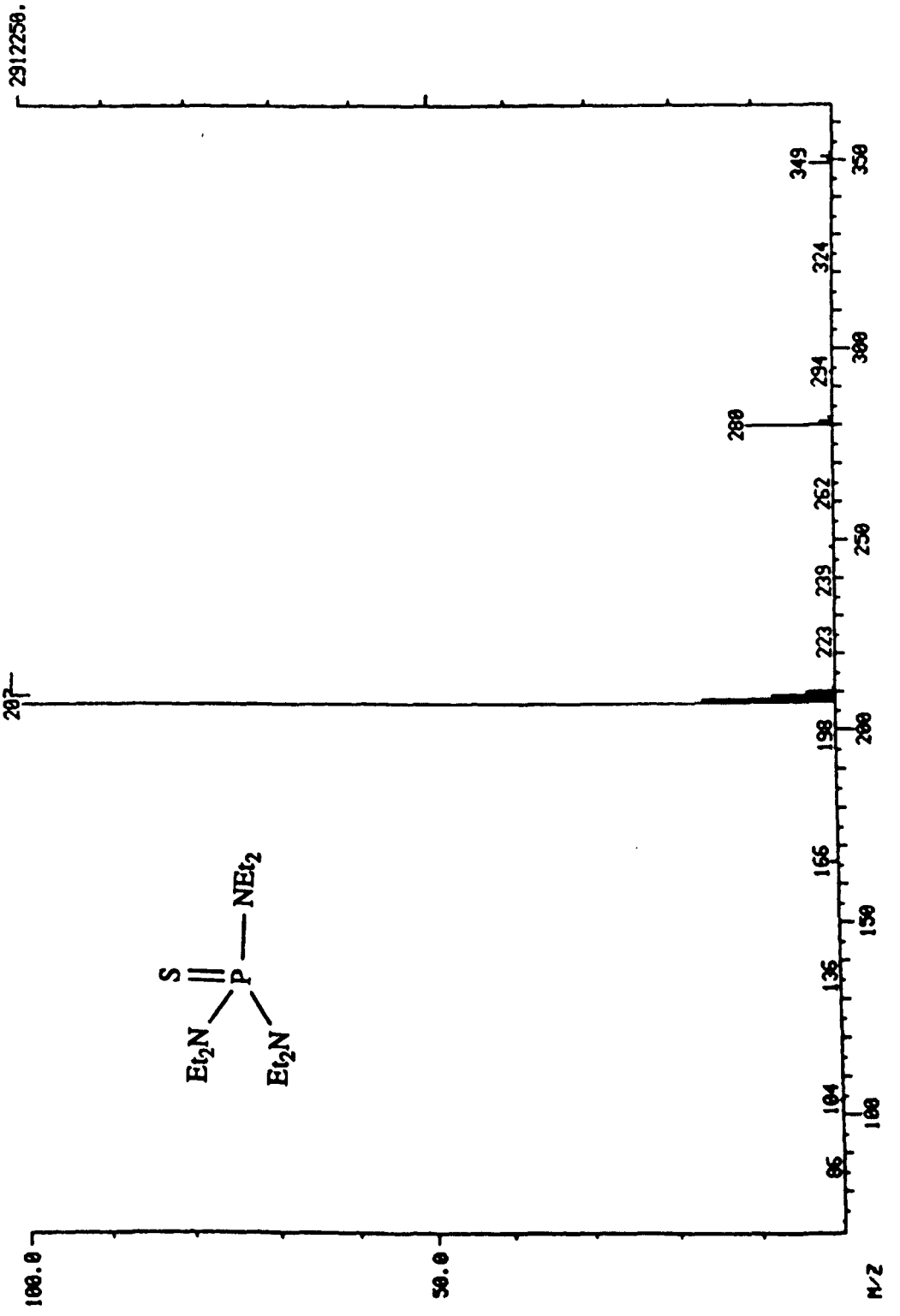

2912256.
207
280
100.0
50.0
M/Z
86
104
108
136
166
198
223
239
262
294
324
349
350
300
250
200
150
S
P
NEt2
Et2N
Et2N

Figure 24

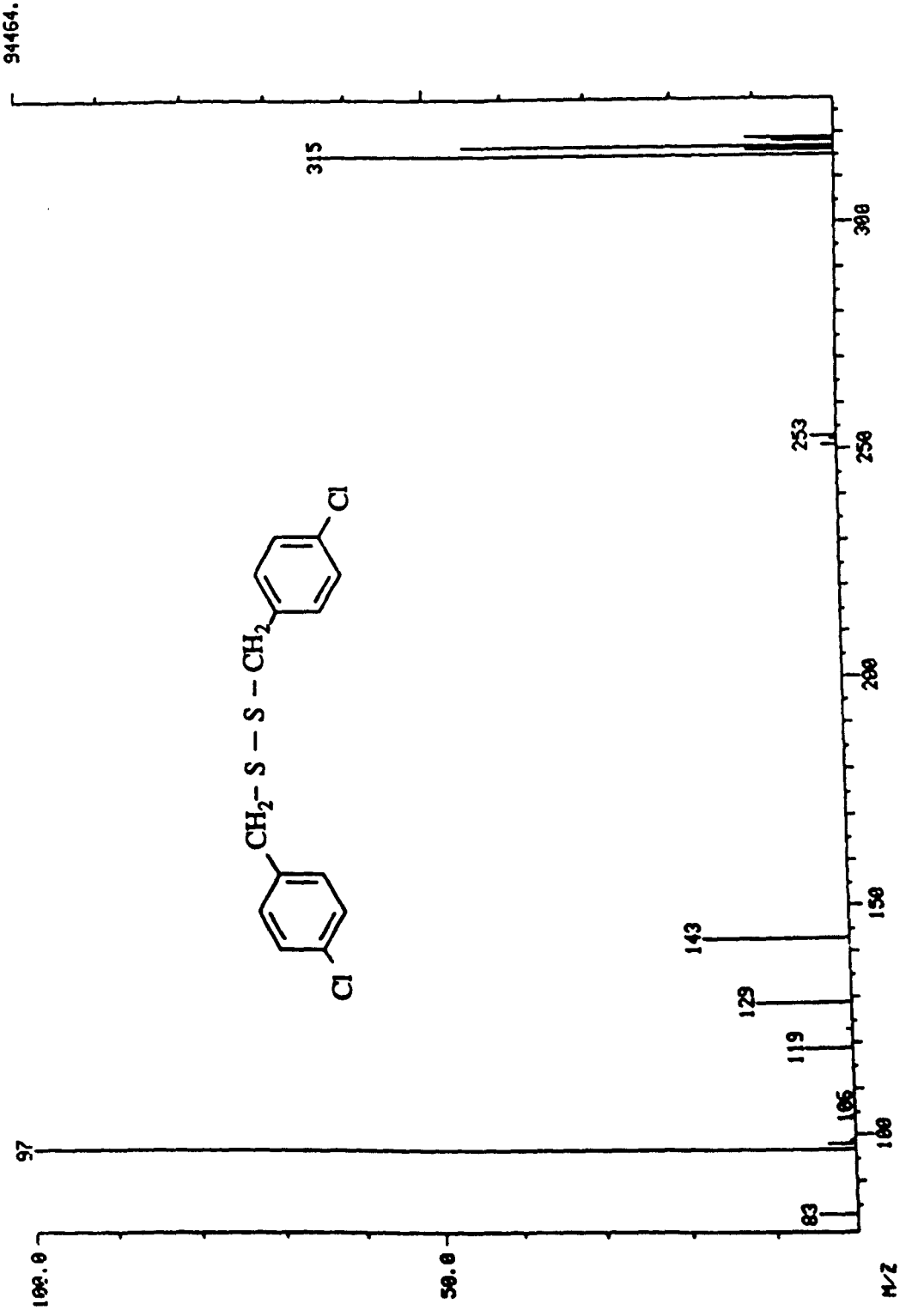


Figure 25

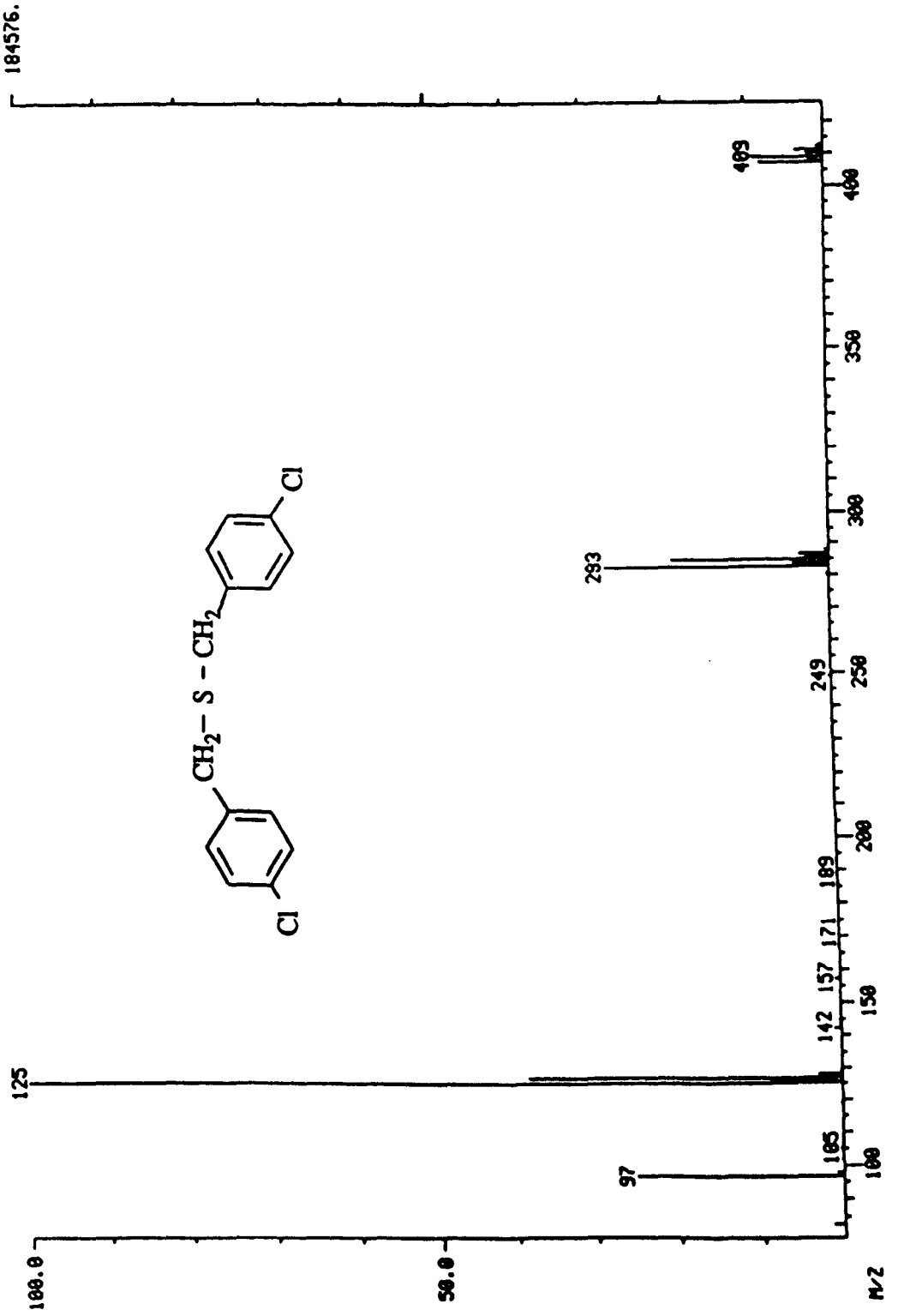

184576.
100.0
50.0
M/z
125
97
105
142
157
171
189
249
293
403
Cl
Cl
CH2 – S – CH2

Figure 26

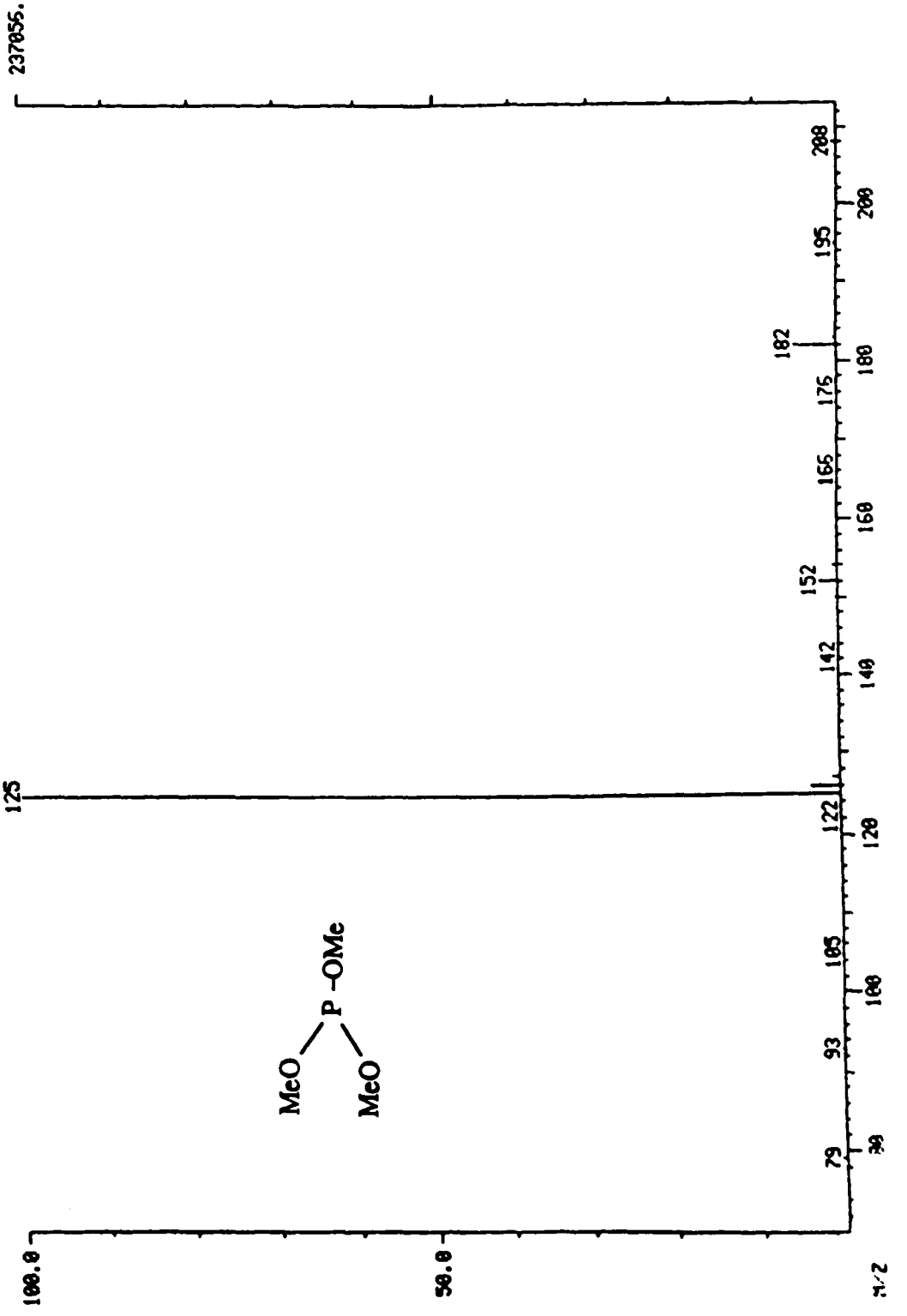

237855.
125
MeO
P
OMe
MeO
100.0
50.0
M/Z
79
93
105
122
142
152
182
208

Figure 27

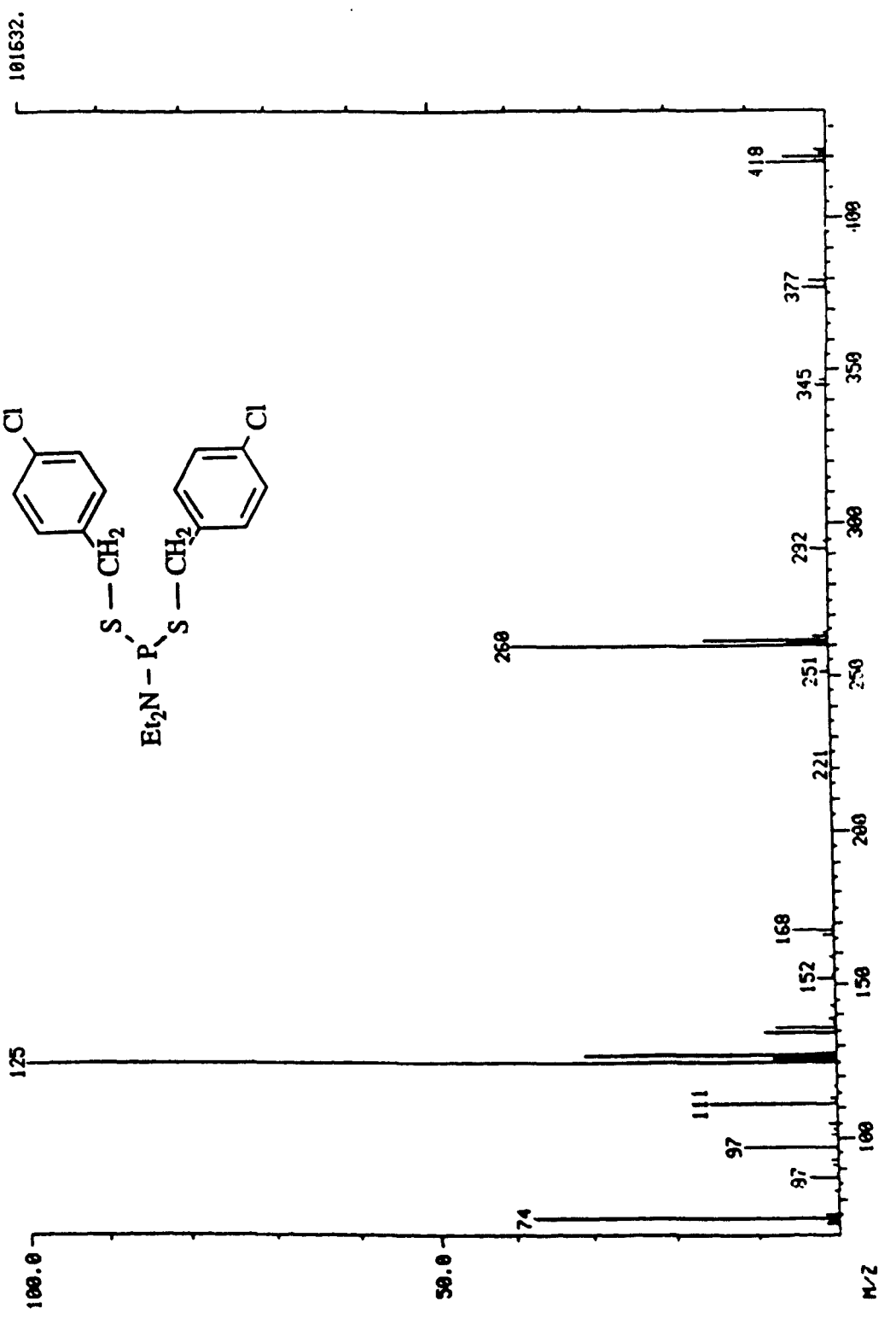

101632.
Cl
CH2
S
P
S
CH2
Cl
Et2N
125
111
97
97
74
168
152
260
232
251
221
418
377
345
100.0
50.0
M/Z

Figure 28

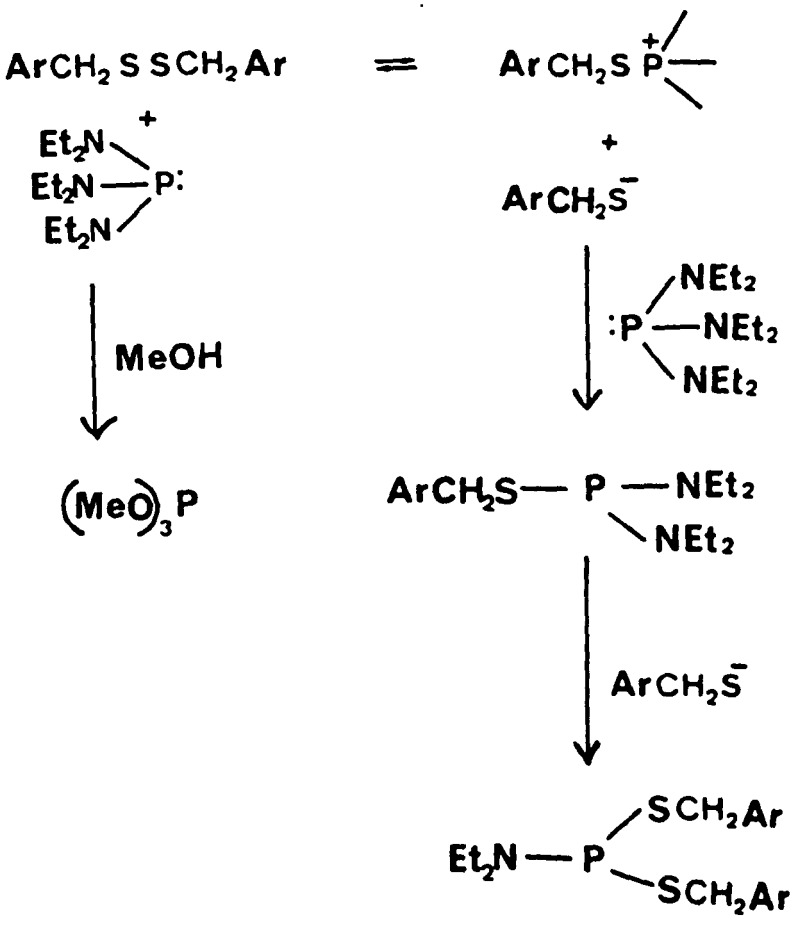

ArCH2 S SCH2 Ar
Et2N
Et2N P:
Et2N
MeOH
(MeO)3P
ArCH2 S P
ArCH2S
NEt2
:P NEt2
NEt2
ArCH2S P NEt2
NEt2
ArCH2S
SCH2Ar
Et2N P
SCH2Ar

Figure 29

CHAPTER 4

EXPERIMENTAL

CHAPTER 4 EXPERIMENTAL

4.1 General Considerations

Hexaethylphosphorus triamide was commercially available from Aldrich Chemical Company, the aminophosphine was distilled before use and kept at $0^{o}C$ in an atmosphere of nitrogen.

All b.p.s. and m.p.s. are uncorrected and the m.p.s. were carried out on a Reichert hot stage melting point apparatus.

NMR spectra were measured using JEOL PS-100MZ and GX-270MZ spectrometers. The solvent used was deuterochloroform and the internal standard for H and ^{13}C spectra was TMS. For ^{31}P spectra, the standard used was phosphoric acid.

The elemental analyses were performed on a Carlo Erba 1106 Elemental Analyser.

Benzene was refluxed over calcium chloride for six hours then stored over sodium wire.

Methanol (Analytical Grade) was filtered through 0.45µm membrane before being used as a mobile phase for HPLC.

Acetonitrile was dried over activated silica gel.

TMS - Tetramethyl silane

4.2 HPLC Methods

The HPLC system consisted of a double pistoned pump (Pye-Unicam LC-XPD) with a flow rate of 1.5ml/min for analytical runs and 4ml/min for preparative runs.

A Pye-Unicam LC-UV detector with an absorption wavelength of 254nm, (photo cell) pathlength of 10mm for analytical runs and 1mm for preparative runs was used.

A computing integrator (Pye-Unicam PU4810), which enabled the accurate measurement of peak area and percentage was employed. Several columns were

used; most effective were a C_{18} µM Bondapak (4.2mm diameter, 25cm length) for analytical runs and a C_8 Zorbax (9.4mm diameter, 25cm length) for preparative runs. (See Chapter 3).

The mobile phase consisted of 8:2 doubly distilled methanol:water mixtures, which were filtered before use. The injection loops had a capacity of 0.2ml for analytical loading and 2ml for preparative loading.

4.3 Synthetic Procedures

Attempted Synthesis of p-bromobenzylbenzyldisulphide (15)

Chlorine gas was bubbled through a stirred solution of benzyl mercaptan (0.2mol, 24.8g) in n-heptane (150ml) at 0°C.

Assay of the orange colour solution indicated the consumption of all the thiol. The sulphenyl chloride was added dropwise to a solution of phthalimide (0.2mol, 29.4g) in dimethyl formamide (120ml), in the presence of Triethylamine (0.27mol, 27.0g). After stirring for 0.5hr the reaction mixture was transferred to a larger beaker and cold water (1.5L) was added with stirring. Upon filtration and drying 30g of a whitish solid was collected.

Analysis of the solid obtained indicated mainly starting material i.e. phthalimide.

m.p. 225-227°C. (lit m.p. for phthalimide 234-236°C).

Another attempt in carbon tetrachloride also failed to produce the N-(benzylthio)phthalimide.

Second Attempted Synthesis of p-bromobenzyl Benzyl Disulphide (15)

Benzyl mercaptan (5g, 0.04mol) was mixed with Diethylazodicarboxylate (10) (6.96g, 0.04mol) in an atmosphere of nitrogen for 24hr at room temperature.

The resulting pale yellow viscous liquid was refluxed in benzene (50ml) together with p-bromobenzyl mercaptan (8.12g, 0.04mol) for 3hr, then allowed to stand for several hours.

White crystals started to form which were filtered and found to be diethyldihydroate dicarboxylate. Evaporating benzene off gave an oily residue which quickly solidified (12.5g). Recrystallisation from methanol-water mixture gave a white solid (11.9g).

Analysis of the product indicated a 1:2:1 mixture of benzyl disulphide (24), p-bromobenzyl benzyl disulphide and p-bromobenzyl disulphide respectively (25).

Separation of p-bromobenzyl, benzyl disulphide from an equilibrium mixture

The failure at the previous two attempted syntheses of the above unsymmetrical disulphide have given an indication of the problem connected to the preparation of unsymmetrical disulphides.

Benzyl disulphide (5g, 0.02mol) was mixed with p-bromobenzyl disulphide (8g, 0.02mol) in methanol (25ml), and refluxed for 12hr.

The resulting solution was analysed by HPLC and found to contain a mixture of all three disulphides: benzyl disulphide (24), p-bromobenzyl benzyl disulphide (15) and p-bromobenzyl disulphide (25).

Separation of the desired unsymmetrical disulphide was effected by using a high performance liquid chromatography preparative column.

The column was a C8 ZORBAX reversed phase system, using an 8:2 methanol-water mixture as mobile phase with a flow-rate of 4.0ml/min.

The 2ml injection loop made it possible to load the column with ~ 75mg of mixture each time and obtain about 25mg of pure unsymmetrical disulphide from each collection.

Evaporation of the mobile phase under reduced pressure and keeping the solution temperature during collection and evaporation below 5°C, gave the unsymmetrical disulphide m.p.55–56°C. (lit. m.p.54–55°C)[120].

$\delta H(CDCl_3)$. 3.53 (2H, S, CH_2Ph), 3.70 (2H, S, $CH_2C_6H_4$), 7.14 (2H, d, H_6), 7.35 (5H, S, ph) 7.50 (2H, d, H_8); $\delta C(CDCl_3$. 42.44 (C_1), 43.45 (C_2) 121.40 (C_{10}), 127.53 (C_9),

128.57 (C_5), 129.42 (C_8), 131.05 (C_6), 131.59 (C_7), 136.35 (C_3), 137.35 (C_4); (Found: C, 51.68; H, 4.17. $C_{14}H_{13}BrS_2$ requires C, 51.69; H, 4.02%).

Preparation of p-bromobenzyl disulphide (25)

p-bromobenzyl thiol (10g, 0.05mol) was mixed neat with dimethyl sulphoxide (50g), and stirred for 8hr at 80-90°C. The reaction mixture was then decolourised with charcoal and cooled to room temperature, before being poured into a tenfold volume of ice-water. The precipitate was collected after the solution had been left to stand for 3h, washed three times with water and dried to give 9.2g (91%) of a white solid. m.p.76–77°C. (lit. m.p.78–79°C)[121].

δH($CDCl_3$). 3.63 (4H, S, CH_2), 7.14 (4H, d, H_3), 7.51 (4H, d, H_4). δC($CDCl_3$), 42.56 (C_1), 121 SO_2 (C_5), 131.01 (C_3), 131.66 (C_4), 136.32 (C_2); (Found: C, 41.39; H, 2.93 $C_{14}H_{12}Br_2S_2$ requires: C, 41.6; H, 3.00%).

Preparation of benzyl disulphide (24)

Neat benzyl mercaptan (10g, 0.08mol) was mixed with dimethylsulphoxide (50g) and stirred for 8hr at 80-90°C. The reaction mixture was then decolourised with activated charcoal and allowed to cool to room temperature. The cooled reaction mixture left standing for 3hr after being poured into a tenfold volume of ice-water. The precipitated disulphide was collected by filtration, washed three times with water and dried to give 9g (91%) of pure disulphide. m.p. 66-68°C (lit. m.p.71–72°C)[121].

δH($CDCl_3$). 3.58 (4H, S, CH_2), 7.27 (10H, S, Ph) δC($CDCl_3$) 43.28 (C_1), 127.41 (C_5) 128.48 (C_3), 129.40 (C_4), 137.36 (C_2); (Found: C, 68.49; H, 5.60 $C_{14}H_{14}S_2$ require:C, 68.22; H, 5.73%).

Preparation of p-chlorobenzyl disulphide (26)

A similar procedure to the one above gave 90% yield of compound (26).m.p.55–56°C. (lit. m.p.56–57°C)[121].

δH($CDCl_3$). 3.56 (4H, $\underline{CH_2}$), 7.13 (4H, d, H_3) 7.28 (4H, d, H_4) δC($CDCl_3$) 42.49 (C_1), 128.67 (C_4), 130.65 (C_3), 133.39 (C_2), 135.81 (C_5); (Found: C, 53.42; H, 3.76 $C_{14}H_{12}Cl_2S_2$ require:C,53.33;H,3.83%).

Preparation of p-chlorobenzyl sulphide

p-Chlorobenzyl mercaptan (2g, 0.012mol) in absolute methanol was added to a stirred solution of sodium hydroxide (0.5g, 0.012mol) in absolute ethanol (15ml). The p-chlorobenzyl chloride (2.1g, 0.012mol) in methanol (10ml) was added to the previous solution after ensuring all sodium hydroxide has dissolved. Stirring for 4 hours at room temperature followed by washing with water three times and extraction with ether gave a white precipitate 3g (88%). Recrystallised from methanol.m.p.41–42°C. (lit. m.p.42–43°C)[121].

δH($CDCl_3$). 3.53 (4H, S, $\underline{CH_2}$), 7.18 (4H, d, H_3). 7.26 (4H, d, H_4) δC($CDCl_3$) 34.87 (C1), 128.66 (C_4), 130.28 (C_3) 132.86 (C_2), 136.37 (C_5); (Found: C, 59.14; H, 4.30. $C_{14}H_{12}Cl_2S$ requires C, 59.37; H, 4.27%).

Preparation of p-bromobenzyl sulphide (18)

p-bromobenzyl thiol (5g, 0.024mol) in absolute ethanol, was added to a stirred solution of sodium hydroxide (1.2g, 0.024mol) in absolute ethanol (15ml). p-bromobenzyl bromide (6g, 0.024mol) in methanol (10ml) was added to the previous solution after ensuring all sodium hydroxide has dissolved. Stirring for 6 hours at 40°C, followed by washing with water and extraction with ether gave a white precipitate, which was recrystallised from methanol to give 7.5g (84%) of white solid.

m.p.51–52°C. (lit. m.p.53–54°C)[122].

δH($CDCl_3$). 3.52 (4H, S, $C\underline{H_2}$), 7.14 (4H, d, H_3) 7.44 (4H, d, H_4). δC($CDCl_3$) 34.884 (C_1) 120.902 (C_5), 130.633 (C_3) 131.606 (C_4), 136.860 (C_2); (Found: C, 44.86; H, 3.15 $C_{14}H_{12}Br_2S$ require:C,45.16;H,3.25%).

Preparation of benzyl sulphide (16)

A similar procedure to that used in previous preparations of symmetrical sulphides gave the product as colourless crystals in 86% yield m.p. 48-49°C. δH($CDCl_3$). 3.55 (4H, S, $\underline{C}H_2$), 7.26 (10H, S, Ph). δC($CDCl_3$). 35.468 (C_1), 126.887 (C_5) 128.379 (C_3), 128.930 (C_4), 138.061 (C_2); (Found: C, 78.7; H, 6.34 $C_{14}H_{14}S$ require C, 78.45; H, 6.58%).

Preparation of p-bromobenzyl, benzyl sulphide (17)

Benzyl mercaptan (5g, 0.04mol) in absolute methanol (30ml) was added to a stirred solution of sodium hydroxide (2.4g, 0.04mol) in ethanol (30ml).

p-bromobenzyl bromide (10g, 0.04mol) in methanol (10ml) was added with stirring to the previous solution at room temperature and kept stirring for 3hr.

The reaction mixture was washed with water, extracted with ether, dried and concentrated to give crude oil 13.2g.

The oil was distilled to give 10g (85%) of a colourless liquid b.p. 150°C-155°C-0.2mm.

δH($CDCl_3$). 3.51 (2H, S, $C\underline{H}_2$-PhH), 3.57 (2H, S, $C\underline{H}_2$PhBr), 7.10 (2H, d, H_6), 7.26 (5H, S, ph), 7.50 (2H, d, H_7). δC($CDCl_3$ 34.722 (C_1), 35.419 (C_2), 120.627 (C_{10}) 126.919 (C_9), 128.362 (C_5), 128.833 (C_8), 130.552 (C_6) 131.363 (C_7), 137.055 (C_3), 137.671 (C_4); (Found; C, 57.60; H, 4.39 $C_{14}H_{13}BrS$ requires C, 57.30; H, 4.47%).

Preparation of 2-(N-Diethylamino)-1,3 diethyl-1,3,2-diazaphospholane (32)

Phosphorus trichloride (5.9g, 0.04mol) in dry diethyl ether (50ml) was treated at -78°C under an atmosphere of nitrogen, with a solution of diethylethylenediame (4.6g, 0.04mol) in dry ether (40ml) over a period of 15 min.

Then, triethylamine (8.6g, 0.08mol) was added at once and the reaction mixture was allowed to warm to room temperature. Filtration at the aminehydrochloride gave an ether solution containing crude 2-chloro-1,3 dimethyl-1,3,2-diazaphospholane.

The crude solution was added to diethylamine (5.84g, 0.08mol) in dry diethyl ether (40ml) at -78°C under an atmosphere of nitrogen.

Filtration at the aminehydrochloride and evaporation of the ether layer gave a yellowish liquid.

Distillation of the crude material gave 60% pure yield at 55°C 0.1mm.

δH (C_6D_6). 1.1 (12H, 4T, $CH_2\underline{CH_3}$), 1.9 (4H, S, -$\underline{CH_2}$-$\underline{CH_2}$-) 2.65 (8H, m, $\underline{CH_2}CH_3$). δC (C_6D_6) 15.11, 15.22, 15.50, 15.53 (4$\underline{C}H_3$), 49.23, 49.36 ($\underline{C}H_2$-$\underline{C}H_2$), 39.34, 39.63, 42.16, 42.53 (4$\underline{C}H_2$-). δp(C_6D_6) with decoupling Singlet 111.101; (Found: C, 54.91; H, 11.02; N, 19.37. $C_{10}H_{24}N_3P$ requires C, 55.27; H, 11.13; N, 19.34%). m/e 217 (8), 145 (100), 88 (15) 74 (17), 29 (25).

4.4 Equilibration Experiments

Equilibration and desulphurisation of the unsymmetrical sulphide

p-Bromobenzyl, benzyl disulphide (20mg, 0.06mmol) was dissolved in dry benzene (10ml) and chilled to ~ 0°C under an atmosphere of nitrogen.

The resulting solution was treated with acyclic amino phosphine, hexaethylphosphorus triamide (15.5mg, 0.05mmol) with stirring and then analysed by HPLC.

Samples were taken from the reaction flask by syringe and transferred directly to a small sample tube containing elemental sulphur (S_8) to quench all the amino phosphine.

A similar procedure was followed when the reaction mixture allowed to warm up to the boiling point of benzene after 1hr at 0°C. These samples were injected into the HPLC. After evaporation of the solvent under high vacuum and dissolving the remaining residue in chilled acetonitrile.

Equilibration and desulphurisation of a 1:1 mixture of symmetrical disulphides

Benzyl disulphide (10mg, 0.04mmol) and p-bromobenzyl disulphide (17.1mg, 0.04mmol) were dissolved in dry benzene (10ml) and chilled to ~ 0°C under an atmosphere of nitrogen.

The resulting solution was then treated with acyclic aminophosphine, hexaethylphosphorus triamide (20mg, 0.08mmol) with stirring and then analysed by HPLC system.

Samples were taken from the reaction flask by syringe and transferred directly to a small sample tube containing elemental sulphur (S_8) to quench all the amino phosphine.

A similar procedure was followed when the reaction mixture allowed to warm up to the boiling point of benzene after 1hr at 0°C. These samples were injected into the HPLC in known time intervals after evaporation of the solvent under high vacuum and dissolving the remaining residue in chilled acetonitrile.

Equilibration of the unsymmetrical disulphide in acetonitrile

p-Bromobenzyl, benzyl disulphide (20mg, 0.06mmol) was dissolved in freshly distilled acetonitrile (10ml) and chilled to ~ -40°C in a dry CO_2/CCl_4 bath.

The resulting solution was then treated with the acyclic aminophosphine, hexaethyl phosphorus triamide (15.5mg, 0.06mmol) with stirring and then analysed by HPLC.

Aliquots of the reaction mixture were syringed into small sample tubes containing elemental sulphur to quench the aminophosphine.

The solvent (HPLC mobile phase) was cooled down to ~ 5°C in order to maintain low temperature environment, and also to eliminate any equilibration which could occur by solvent effect.

Acetonitrile acts in a manner similar to that of methanol as far as equilibration is concerned. Leaving unsymmetrical disulphide or 1:1 mixture of two symmetrical disulphides in acetonitrile even at room temperature leads to the formation of the equilibrium mixture.

Equilibration of 1:1 mixture of two symmetrical disulphides

Benzyl disulphide (10mg, 0.04mmol) and p-bromobenzyl disulphide (17.1mg, 0.04mmol) were dissolved in dry freshly distilled acetonitrile (10ml) and chilled to -40°C in dry CO_2/CCl_4 bath.

The resulting solution was treated with acyclic aminophosphine, hexaethylphosphorus triamide (20mg, 0.08mmol), with stirring and then analysed by HPLC.

Aliquot samples were syringed into small sample tubes containing elemental sulphur to quench the aminophosphine.

The solvent was kept cool and was not removed from the aliquot content as was benzene because it does not interfere with the HPLC analysis.

4.5 Kinetics Experiments

p-chlorobenzyl disulphide (10mg) was placed in a (12ml) volumetric flask and dissolved in dry benzene, and four more flasks were made up in the same way.

Bibenzyl (10mg) was then added to each flask as an internal standard, and five volumetric flasks were incubated in a water bath controlled by thermostat at 50°C.

To each flask acyclic aminophosphine (Hexaethylphosphorus triamide) was added in the following amounts: 60mg, 78mg, 105mg, 129mg, 151mg, and each was shaken vigorously after each addition.

Each flask was labelled and the time of each addition was taken accurately.

The flask contents were then as follows:

Flask	Disulfide (mg)	Phosophine (mg)	Bibenzyl
1	10	60mg	10mg
2	10	78mg	10mg
3	10	105mg	10mg
4	10	129mg	10mg
5	10	151mg	10mg

Aliquots sample were then taken from each flask and injected as soon as possible into the analytical HPLC.

A large number of aliquots were taken from flask 4 and 5, as the reaction was fast, in order to obtain enough data points before the end of two half-lives.

The decrease in relative disulphide concentration was measured by computing integrator connected to the UV detector, from the ratio of the disulphide and internal standard peaks.

Kinetics analysis of the desulfurisation of a symmetrical disulfide with cyclic aminophosphine

A similar experiment was carried out using the cyclic aminophosphine (2-(N-Diethylamino)-1,3-diethyl-1,3,2-diazaphospholane). The quantities used are summarised in the table below.

Flasks	Disulfide (mg)	Cyclic phosphine (mg)	Bibenzyl
1	10	65mg	10mg
2	10	83mg	10mg
3	10	138mg	10mg
4	10	180mg	10mg
5	10	227mg	10mg

4.6 LC/MS Experiments

1. HPLC System

A Hewlett-Packard 1090L HPLC system was used delivering a flow at $1 ml min^{-1}$. The mobile phase used to perform the separation consisted of an 80:20 methanol:water mixture. A Waters 6000A solvent delivery pump provided $0.8 ml min^{-1}$ of 0.1M ammonium acetate containing 20% of methanol as a make up flow. The separation column was a Waters Bondapak 25cm C_{18} column.

2. Mass Spectrometry

The analyses were carried out on a Finnigan MAT TSQ46 equipped with Nova 4X super Incos data system and fitted with a Finnigan MAT thermospray interface. The vaporiser temperature was 115°C and the jet temperature was 280°C with a repeller voltage at 130V.

4.7 CIDNP Experiments

p-chlorobenzyl disulphide (0.035g) was placed in a 10mm n.m.r. tube, dissolved in dry methanol (4ml) then cooled down to -10°C in dry ice. Hexaethylphosphorus triamide (0.05g) was added and the tube shaken vigorously before being placed in a ^{31}P NMR probe pre-heated to 50°C. (Capped tubes were separately tested in a 50° thermostat bath behind a safety screen to ensure that caps were not ejected, or tubes shattered before insertion in the spectrometer) $^{31}P-\{^{1}H\}$ spectra were then recorded (60 transients per spectrum) at two minute intervals.

A similar experiment was carried out using benzene as solvent at a probe temperature of 80°C.

CHAPTER 5

REFERENCES

1. A. Michaelis and R. Kachne, Chem. Ber. (1898), 31, 1048.

2. A. E. Arbusov, J. Russ. Phys. Chem. Soc. (1906), 38, 687.

3. A. I. Razumov, O-A. Mukhacheva and Sim-Do-Khan, Izv. Akad. Nauk SSSR, utd Khim. Nauk (1952), 894, Chem. Abstr. (1953), 47, 10466.

4. A. I. Razumov, Zh. Obshch. Khim., (1959), 1609, Chem. Abstr. (1960), 54, 8608.

5. W. Gerrard and W. J. Green, J. Chem. Soc., (1951), 2550.

6. G. Aksnes and D. Aksnes, Acta Chem. Scand., (1964), 38, 18.

7. M. A. Shaw and R. S. Ward "Addition reactions of tertiary phosphorus compounds with electrophilic olefins and acetylenes." Topics in Phosphorus Chemistry. Wiley Interscience, New York (1972), 7, 11.

8. C. D. Hall and J. Emsley, "The Chemistry of Phosphorus", Harper and Row, (1976), Chapter 4.

9. R. D. Gareev, G. M. Loginova and A. N. Pudovik, J. Gen. Chem. USSR (Engl. transl.) (1976), 46, 1843.

10. H. Teichmann, W. Thierfelder and E. Schafer, Tett. Lett. (1977), 2889.

11. W. E. Krueger, M. B. Mclean, A. Rizwanink, J. R. Maloney, G. L. Beheifer and B. E. Boland, J. Org. Chem. (1978), 43, 2877.

12. M. A. Shaw, J. C. Tebby, R. S. Ward and D. H. Williams, J. Chem. Soc. (C) 1969, 1100.

13. N. E. Waite, J. C. Tebby, R. S. Ward and D. H. Williams, J. Chem. Soc. (C) 1969, 1100.

14. N. E. Waite, D. W. Allen and J. C. Tebby. Phosphorus 1971, 1, 139.

15. D. V. Griffiths and J. C. Tebby, J. Chem. Soc. Chem. Comm. (1981), 607.

16. P. J. Butterfield, J. C. Tebby and D. V. Griffiths, J. Chem. Soc., Perkin Trans. 1 (1978), 1237.

17. P. J. Butterfield, J. C. Tebby and D. V. Griffiths, J. Chem. Soc., Perkin Trans. 1 (1979), 1189.

18. W. Zeiss and H. Henjes, Chem. Ber., 1978, 111, 1655.

19. A. Schmidpeter, J. H. Weinmaier and E. Glaser, Agnew Chem., Int. Ed. Engl., (1977), 16, 549.

20. J. I. G. Cadogan, R. A. North and A. G. Rowley, J. Chem. Res. (S) (1979), 1.

21. R. Burgadan, Y. Leroux and Y. O. Elkhochnich, Tett. Lett. (1980), 925.

22. F. Ramirez, C. P. Smith, A. s. Gulati and A. V. Patwardhan, Tett. Lett. (1966), 2151.

23. F. Ramirez, A. V. Patwardhan, H. J. Kugler and C. P. Smith, Tett. Lett. (1966), 3053.

24. F. Ramirez, C. P. Smith, J. F. Pilot and A. S. Gulati, J. Org. Chem., (1968), 33, 3787.

25. Y. Ogata and M. Yamashita, J. Am. Chem. Soc., (1970), 92, 4670.

26. Y. Ogata and M. Yamashita, Tetrahedron, (1971), 27, 3395.

27. Y. Ogata and M. Yamashita, Tetrahedron, (1971), 27, 2725.

28. Y. Ogata and M. Yamashita, J. Org. Chem., (1971), 36, 2584.

29. M. Sekine, M. Nakajima and T. Hata, J. Org. Chem., (1981), 46, 4030.

30. E. A. C Lucken, F. Ramirez, V. P. Catto, D. Rhum and S. Dershowitz, Tetrahedron, (1966), 22, 637.

31. G. Boekestein, W. G. Voncken, E. H. J. M. Jansen and H. M. Buck, Recl. Trav. Chem. Phys. Bar (1974), 93, 69.

32. G. Boekestein and H. M. Buck, Phosphorus Sulfur (1981), 9, 343.

33. F. Ramirez, Pure Appl. Chem. (1964), 9, 337.

34. A. M. Kibardin, T. Kh. Gazizov, P. I. Gryaznov and A. N. Pudovik, Bull. Acad. Sci. USSR, Div. Chem. Sci. (1979), 1303.

35. A. M. Kibardin, T. Kh. Gazizov, Yu-Ya Etremov, V. N. Zinin, R. Z. Musin and A. N. Pudovik, Bull. Acad. Sci. USSR, Div. Chem. Sci. (1980), 656.

36. T. Saegusa, S. Kobayashi, Y. Kimura and T. Yokoyama, J. Am. Chem. Soc. (1976), 98, 7843.

37. F. Ramirez, O. P. Madan and S. R. Heller, J. Am. Chem. Soc. (1965), 87, 731.

38. F. Ramirez, J. F. Pilot, O. P. Madan and C. P. Smith, J. Am. Chem. Soc. (1968), 90, 1275.

39. A. Kh. Voznesenskaya, N. A. Razumova and A. A. Petrov, J. Gen. Chem. USSR (Engl. Transl.) (1969), 39, 1004.

40. V. V. Vasilev and N. A. Razumova, J. Gen. Chem. USSR (Engl. Transl.) (1978), 48, 1361.

41. V. V. Vasilev, N. A. Razumova and L. V. Dogadova, J. Gen. Chem. USSR (Engl. Transl.) (1976), 46, 461.

42. A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus", Elsevier, New York (1969).

43. G. Aksnes and R. Eriksen, Acta Chem. Scand., (1966), 20, 2463.

44. D. B. Denney and D. H. Jones, J. Am. Chem. Soc. (1969), 91, 5821.

45. S. A. Bone and S. Trippett, J. Chem. Soc., Perkin Trans 1 (1976), 156.

46. J. I. G. Cadogan, N. J. Stewart and N. J. Tweddle, J. Chem. Soc., Chem. Comm. (1978), 182.

47. J. I. G. Cadogan, I. Gosney, E. Henry, T. Naisby, B. Nay, N. J. Stewart and N. J. Tweddle, J. Chem. Soc., Chem. Comm. (1979), 189.

48. B. Miller, "Reaction Between Trivalent Phosphorus Derivatives and Positive Halogen Sources", Topics in Phosphorus Chemistry, Wiley Interscience, New York (1965), 2, 133.

49. W. Gerrard and N. H. Philip, Research (London), (1948), 1, 477.

50. A. Skowronska, J. Mikolajczak and J. Michalski, J. Chem. Soc., Chem. Comm. (1975), 791.

51. J. Michalski, J. Mikolajczak and A. Skowronska, J. Am. Chem. Soc. (1978), 100, 5386.

52. P. D. Bartlett and G. Meguerian, J. Am. Chem. Soc. (1956), 78, 3710.

53. D. P. Young, W. E. McEwen, D. C. Valez, J. W. Johnson and C. A. Vandwerf, Tett. Lett. (1964), 359.

54. C. Symmes (Jnr.) and L. D. Quin, J. Org. Chem. (1976), 41, 1548.

55. J. R. Llyod, N. Lowther, G. Zsabo and C. D. Hall, J. Chem. Soc., Perkin Trans 2, (1985), 11, 1813.

56. C. G. Moore and B. R. Trego, Tetrahedron (1962), 18, 205.

57. C. G. Moore and B. R Trego, Tetrahedron (1963), 19, 1251.

58. S. Safe and A. Taylor, J.C.S., Chem. Comm., (1969), 1466.

59. D. N. Harpp and R. A. Smith, J.C.S., Chem. Comm., (1976), 811.

60. D. N. Harpp and R. A. Smith, J. Org. Chem., (1979), 44, 4140.

61. D. N. Harpp, D. K. Ash and R. A. Smith, J. Org. Chem., (1980), 45, 5155.

62. D. N. Harpp and R. A. Smith, J. Am. Chem. Soc., (1982), 104, 6045.

63. B. J. Walker, 'Organophosphorus Chemistry', ed. D. W. Hutchinson and J. A. Miller (Specialist Periodical Reports), The Royal Society of Chemistry, London, (1982), 13, 86.

64. T. Makaiyama and H. Takei, 'The Reaction of Disulphides with Trivalent Phosphorus Compounds', Topics in Phosphorus Chemistry', Wiley Interscience, New York, 1976, 8, 587.

65. D. N. Harpp and J. G. Gleason, J. Am. Chem. Soc., (1971), 93, 2437.

66. D. N. Harpp, J. G. Gleason and J. P. Snyder, J. Am. Chem. Soc., (1968), 90, 4181.

67. D. N. Harpp, J. G. Gleason, J. Org. Chem., (1970), 35, 3259.

68. D. Dmuchorsky et al., J. Org. Chem., (1966), 33, 13.

69. D. N. Harpp, J. Adams, J. G. Gleason, D. Mullins and K. Stellon, Tett. Lett., (1978), 3989.

70. D. N. Harpp and A. Granata, J. Org. Chem., (1980), 45, 271.

71. A. Schonberg and M. Z. Bonakat, J. Chem. Soc., (1949), 893.

72. M. B. Evans, G. M. C. Higgins, C. G. Moore, M. Porter, B. Saville, J. F. Smith, B. R. Trego and A. A. Watson, Chem. Ind. (London), (1960), 897.

73. D. L. Middleton, E. G. Svamsel and G. H. Wiegand, Phosphorus and Sulphur (1979), 7, 339.

74. R. Harvey, H. I. Jacobson and E. V. Jensen, J. Am. Chem. Soc. (1963), 85, 1618.

75. C. G. Moore and B. R. Trego, J. Chem. Soc., (1962), 4205.

76. C. Walling and R. Rabinowitz, J. Am. Chem. Soc., (1957), 79, 5326.

77. C. Walling and R. Rabinowitz, J. Am. Chem. Soc., (1959), 81, 1243.

78. D. E. Allman, J. Org. Chem., (1965), 30, 1074.

79. R. S. Davidson, J. Chem. Soc., C, (1967), 2131.

80. L. E. Overman, D. Matzinger, E. M. O'Connor and J. D Overman, J. Org. Chem. Soc., (1974), 96, 6081.

81. L. E. Overman and S. T. Petty, J. Org. Chem., (1975), 40, 2779.

82. D. N. Harpp and J. G. Gleason, J. Am. Chem. Soc., (1968), 90, 4181.

83. D. N. Harpp and J. G. Gleason, J. Am. Chem. Soc., (1971), 93, 2437.

84. I. B. Douglass, T. T. Martin and R. J. Adder, J. Org. Chem., (1951), 16, 1297.

85. R. G. Hiskey, F. I. Carroll, R. M. Babb, R. M. Bledsoe, R. T. Puckett and B. W. Roberts, J. Org. Chem. (1961), 26, 1152.

86. L. Field, H. Harle, T. C. Owen and A. Ferretti, J. Org. Chem. (1964), 29, 1632.

87. T. Mukaiyama and K. Takahashi, Tett. Lett., (1968), 5907.

88. K. S. Boustany and A. B. Sullivan, Tett. Lett., (1970), 3547.

89. D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwing and W. F. Vanhorn, Tett. Lett., (1970), 3551.

90. M. Behforouz and J. E. Kerwood, J. Org. Chem., (1969), 34, 51.

91. E. E. Reid, "Org. Chem. of Bivalent Sulphur", Vol III, Chem. Publ. Co. New York, NY (1960), pp 362, 406-411.

92. L. Haraldson, C. J. Olander, S. Sunner and E. Varde, Acta Chem. Scand. (1960), 14, 1509.

93. S. F. Birch, T. V. Cullum and R. A. Dean, J. Inst. Petrol. (1953), 39, 206.

94. A. B. Sullivan and K. Boustany, Int. J. Sulphur Chem., A., Vol. 1, No. 2, (1971).

95. G. Dalmen, J. McDermed and G. Gorin, J. Org. Chem. (1964), 29, 1480.

96. E. E. Reid, 'Org. Chem. of Bivalent Sulphur', Chemical Publishing Co., NY, (1958), Vol 1, pp 16-18.

97. E. M. Fettes, J. S. Jorczakin and C. E. Schildknecht, Interscience Publishers, NY (1956), pp 475-498.

98. R. Cecil and R. McPhee, 'Polymers Processes' (1959), 14, 296.

99. J. Houk and G. M. Whitesides, J. Am. Chem. Soc. (1987), 109, 6825.

100. R. P. Szajewski and G. M. Whitesides, J. Am. Chem. Soc. (1980), 102, 2011-2026.

101. G. M. Whitesides, J. E. Lilburn, R. P. Szajewski, J. Org. Chem., (1977), 42, 332-338.

102. G. O. Bizzigotti, J. Org. Chem. (1983), 48, 2598-2600.

103. T. Ozawa and A. Haraki, Chem. Pharm. Bull. (1981), 29, 1101.

104. R. F. Hudson and C. Brown, Acc. Chem. Res. (1972), 5, 204.

105. T. Thorstenson and Songstad, Acta Chem. Scand. (1976), 781-786.

106. G. Aksnes and R. Eriksen, Acta Chem. Scand. (1966), 20, 2463.

107. R. F. Hudson and R. Greenhalgh, Chem. Commun. (1968), 1300.

108. H. K. Hall, J. Org. Chem. (1964), 29, 3539.

109. L. R. Fedor, T. C. Bruice, K. L. Kirk and J. Meinwald, J. Am. Chem Soc. (1966), 80, 108.

110. C. Brown and R. F. Hudson, Tett. Lett. (1971), 3191.

111. C. Brown, R. F. Hudson, V. T. Rice and A. R. Thompson, Chem. Commun. (1971), 1255.

112. J. Mikolajczyk, J. Michalski and Zwierzak, Chem. Comm. (1971), 1257.

113. H. J. Lucas, F. W. Mitchell and C. N. Scully, J. Am. Chem. Soc., (1950), 72, 5491.

114. B. A. Songstad, Private Comm.

115. F. Ramirez, A. V. Patwardham, H. J. Kugler and C. P. Smith, J. Am. Chem. Soc. (1967), 89, 6276.

116. R. Dorschrer, G. Kanfmann, Inorg. Chim. Acta (1975), 15, 71.

117. R. D. Kroshevsky and J. F. Verkade, Inorg. Chem. (1975), 14, 3090.

118. M. G. Labarre, D. Voigt, S. Senges, M. Zentil and R. J. Wolf, J. Chim. Phys. Phys. Chem. Biol. (1971), 1216.

119. L. T. Muus et al., 'Chemically Induced Magnetic Polarisation', D. Reidel, U.S.A., 1977.

120. J.G.Gleason,Ph.D. Thesis,McGill University,1970.

121. C.N.Yiannios,J.V.Karabinos,J.Am.Chem.Soc.(1963),28,3246.

122. M.G.Voronkov,A.N.Pereferkovich,S.V.Mikhailova,Zh.Prikl.Khim.(Laningrad),(1969),42,1155.