SOME ASPECTS OF ORGANOPHOSPHORUS CHEMISTRY.

A thesis submitted for the Degree of

Doctor of Philosophy by M D Gray,

April 1981

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

STATEMENT

The accompanying thesis submitted for the degree of PhD entitled "Some Aspects of Organophosphorus Chemistry" is based on work conducted by the author in the Department of Chemistry of the University of Leicester mainly during the period between October 1976 and October 1979.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other University.

M D M Gray

ACKNOWLEDGEMENTS

I would like to express my gratitude to my academic supervisor, Dr D J H Smith, for his support, encouragement and optimism throughout the duration of this work.

Thanks are also due to the rest of the staff of the Department, both academic and technical, past and present, for their practical guidance and assistance. Particular thanks belong to Dr Neil Hales for many helpful and sympathetic discussions.

My thanks, too, for many valued friendships formed while a postgraduate student - Mike Webb, Sally Westlake, Andy MacPherson, Dianne Cooper, Graham Kemp and others who enlivened the Chemistry Department.

My appreciation to my industrial supervisor, Dr K P Parry, for his suggestions, and to the staff of I.C.I. Plant Protection Division, Jealotts Hill Research Station, for making my sojourn a pleasant one.

The production of this thesis owes much to my wife, Garcia, not only for drawing the diagrams, but also for her invaluable help and support at all stages of writing. Thanks go to Miss S Mangal for her typing, and to Graham Jay, Dianne Cooper and Andy MacPherson for proof-reading, and remaining on speaking terms.

Finally, I would like to thank the S.R.C. and I.C.I. Plant Protection Division for financial support, under the C.A.S.E. Award Scheme, and my family and friends for their forbearance and moral support.

CONTENTS

Part of this work has appeared as a communication in Tetrahedron Letters, 21, 859 (1980).

INTRODUCTION

As interest in organophosphorus chemistry continues to increase, more derivatives are revealed that bear structural and chemical relationships to reactive intermediates known from other areas of organic chemistry. For example, in the phosphinidene is seen the phosphorus equivalent of nitrenes, while pentacoordinate phosphoranes are akin to the SN2 transition state envisaged for nucleophilic substitution at carbon. Nitrogen and sulphur ylides have their counterpart in alkylidenephosphoranes.

That *cyclo*-hexadienyl analogues have the facility to undergo electrocylic reactions on thermal or photolytic excitation,

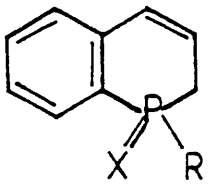
$$X = CR_2, NR, S, SO_2$$

thus, to give hexatrienyl derivatives, is well documented (Chapter 2). It was the pursuit of a similar reaction incorporating phosphorus that formed the basis of this research project. The synthesis of suitable phosphorus heterocycles was required, which with subsequent investigation of their photochemical behaviour constituted a large proportion of the work, excursions along other lines of research stemming directly from this central theme.

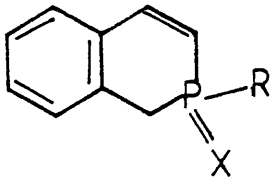
CHAPTER ONE

CHAPTER 1

In order to study the photolytic reactions of systems containing a phosphorus heteroatom within a cyclohexadienyl unit, it was necessary to have easy synthetic access to a suitable substrate. Dihydrophosphanaphthalenes, with the phosphorus in either the 1-position (1,2-dihydrophosphinolines (1)) or the 2-position (1,2-dihydroisophosphinolines (2)), possess the required structural elements. Furthermore, work



1



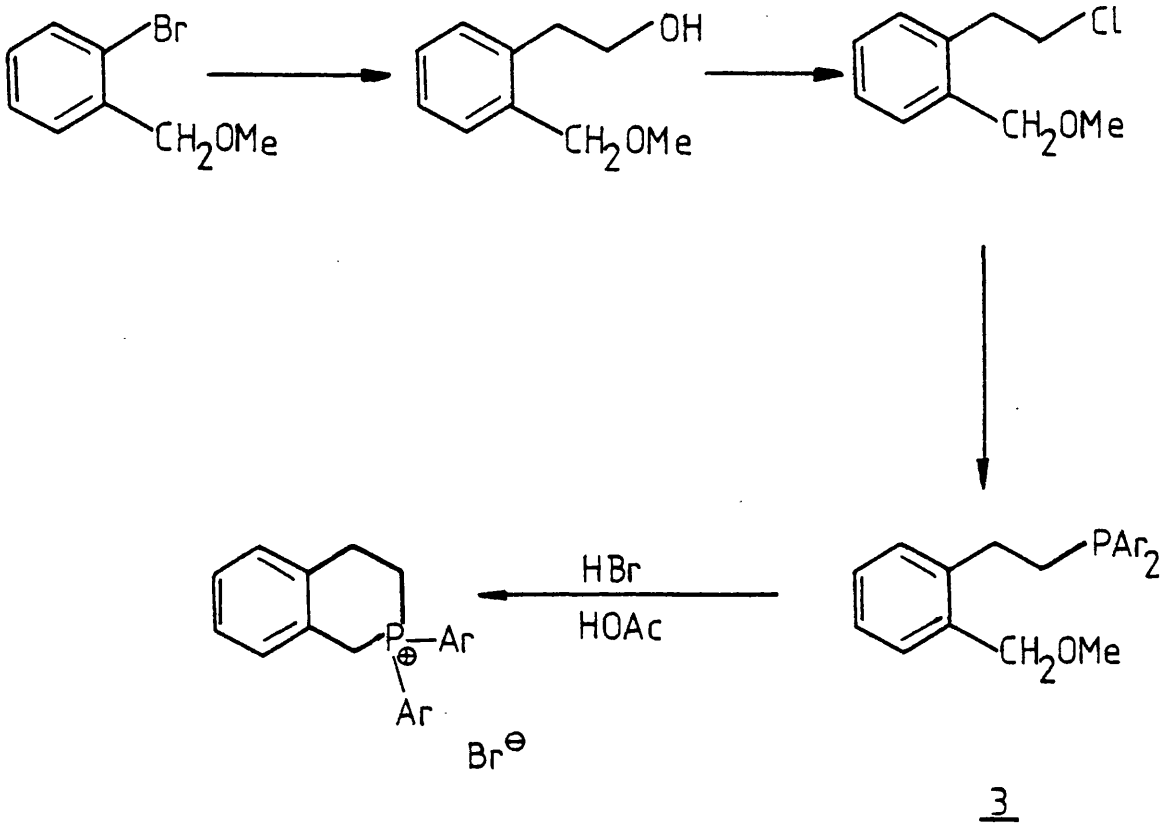
2

by Brown[10] has demonstrated the lability of these molecules under photolytic conditions. Whilst elaborating upon these studies, a novel synthesis of these heterocycles was devised, which would allow the flexibility necessary for specific substitution of the ring nucleus, with the eventual aim of elucidating the mechanism of photolytic reaction.

THE SYNTHESIS OF PHOSPHINOLINES AND ISOPHOSPHINOLINES

The first published synthesis of a phosphanaphthalene ring-system was provided by Holliman and Mann[1] in 1947. The route employed an intramolecular quaternisation of

phosphorus to achieve the crucial ring-closure leading to the bicyclic isophosphinolinium salt (Scheme 1).

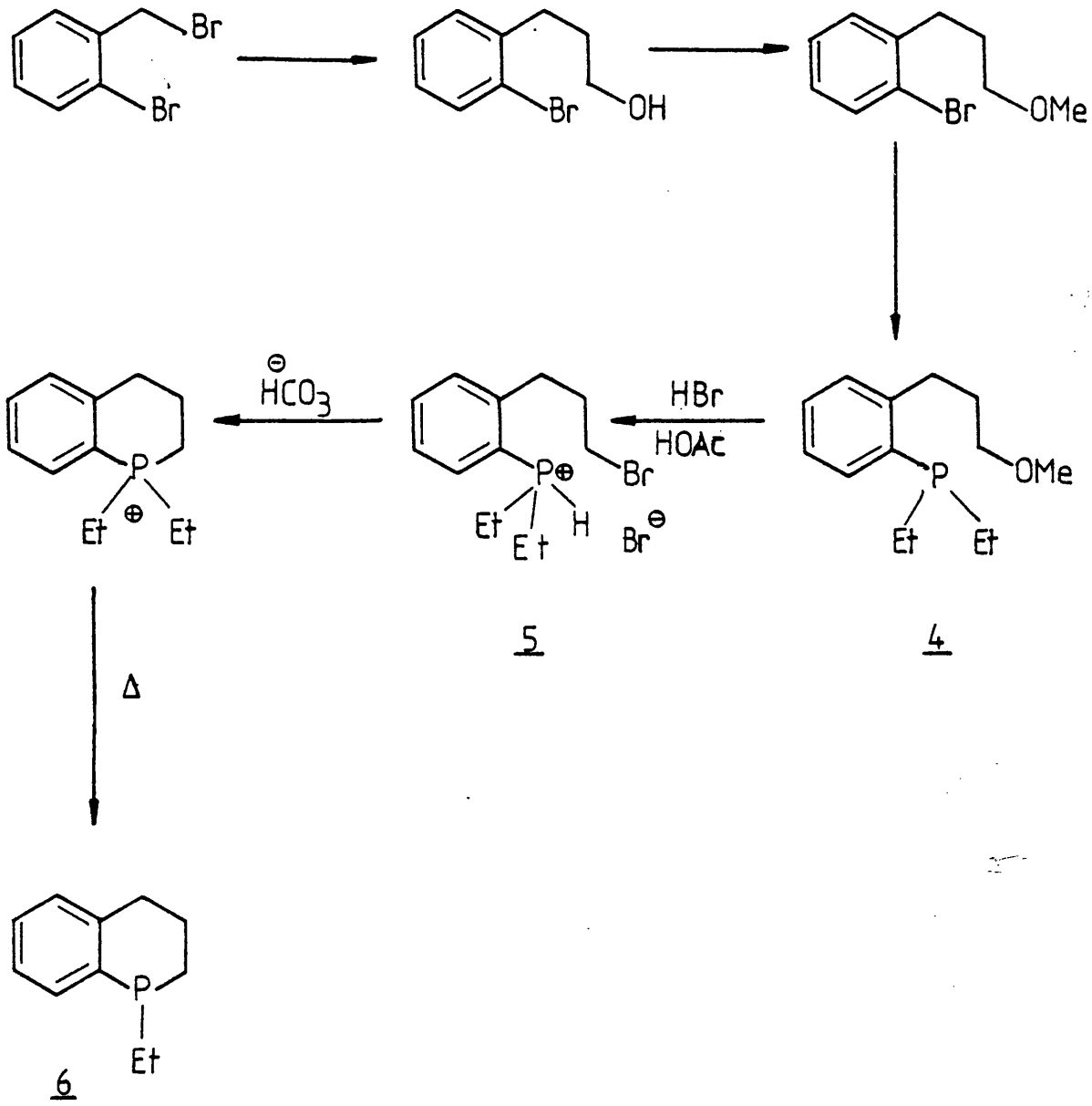


3

SCHEME 1

Acid cleavage of the methyl ether of tertiary phosphine (3) gave the corresponding bromide, spontaneously quaternising with concomitant cyclisation.

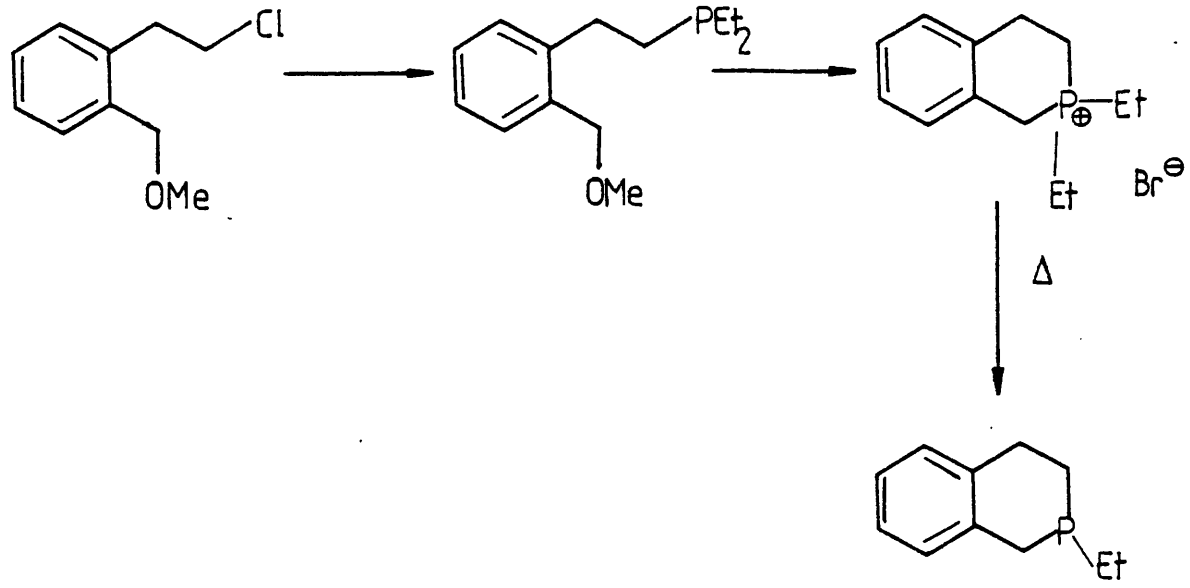
Following the success of this approach, later syntheses frequently utilised similar reactions in the construction of both phosphinoline and isophosphinoline systems. Further work by Mann[2] led to the production of 1-ethyl-1,2,3,4-tetrahydrophosphinoline (6) from 3-(*o*-bromophenyl)propan-1-ol (Scheme 2).



SCHEME 2

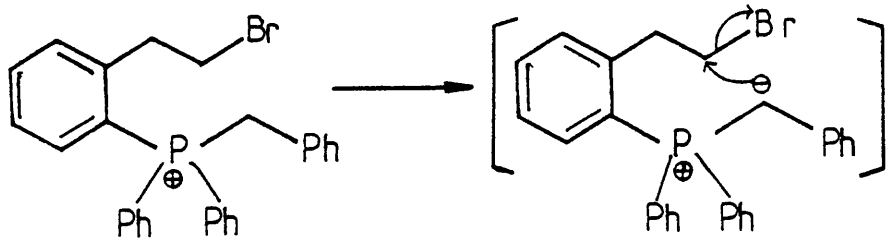
Treatment of diethyl-*o*-(3-methoxypropyl)phenylphosphine (4) with hydrogen bromide led to the aryldiethylphosphonium bromide (5), the addition of base being required to regenerate the phosphine and effect cyclisation. Thermal dealkylation of the first-formed tetrahydrophosphinolinium salt gave

phosphine (6). An analogous route has been used to synthesize the equivalent isophosphinoline[2] (Scheme 3).

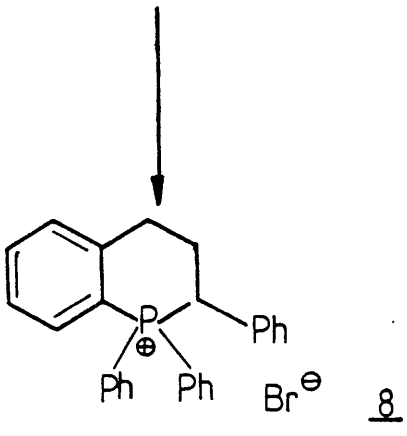


SCHEME 3

An alternative mode of synthesis uses a stabilised carbanion as an internal nucleophile. Märkl has published a route[3] involving removal of a benzylic proton from phosphonium salt (7), the resultant stabilised ylide intramolecularly displacing a bromide ion to give 1,1,2-triphenyl-1,2,3,4-tetrahydrophosphinolinium bromide (8)

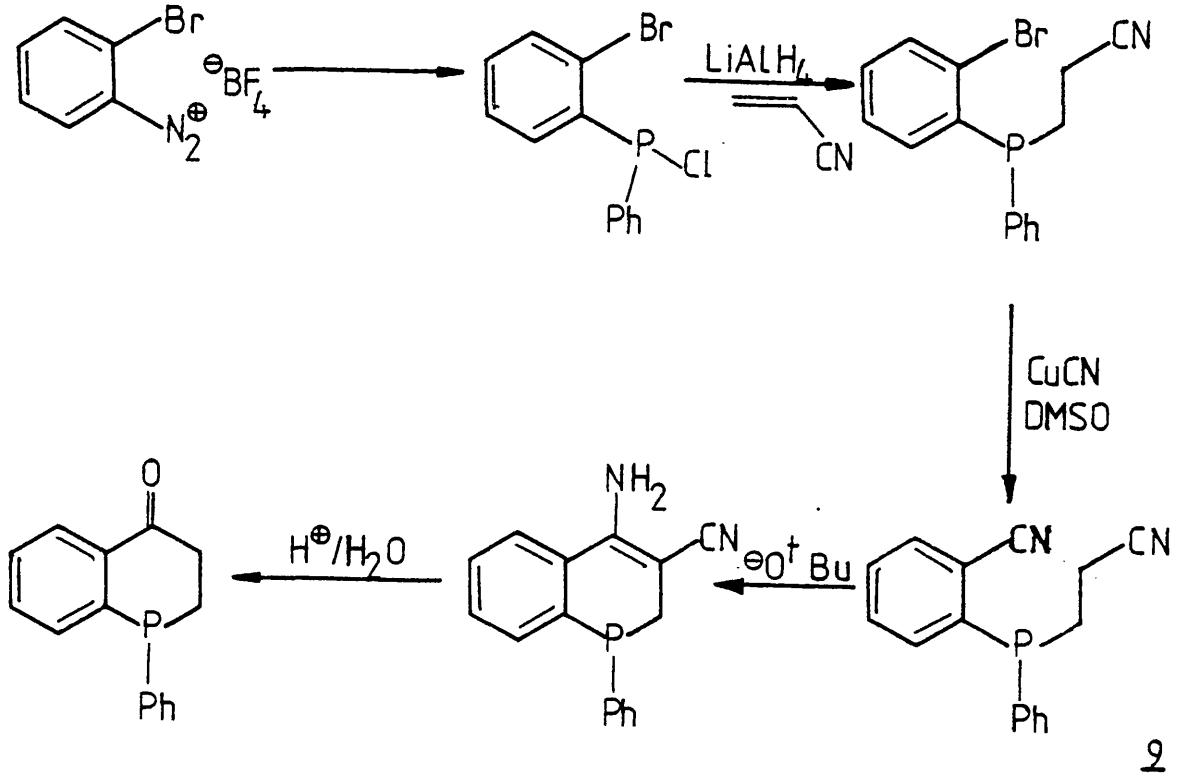


7



8

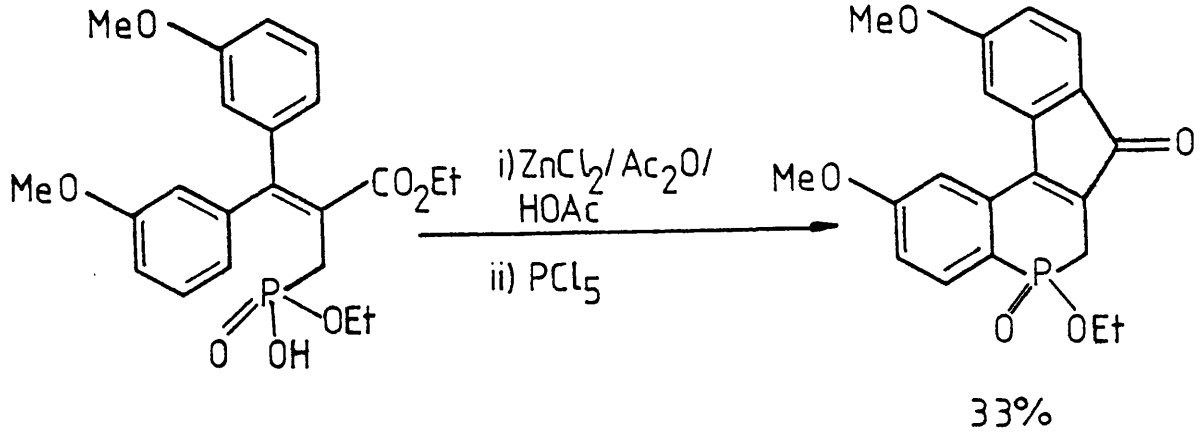
Treatment of (2-cyanoethyl)(*o*-cyanophenyl) phenylphosphine (9) with t-butoxide led to formation of a cyanoimide, hydrolysis of which gave 1-phenyl-1,2,3,4-tetrahydrophosphinoline 4-oxide[4] (Scheme 4).



9

SCHEME 4

The cyclisation of (10), gave the singular phosphinoline[5] (11).

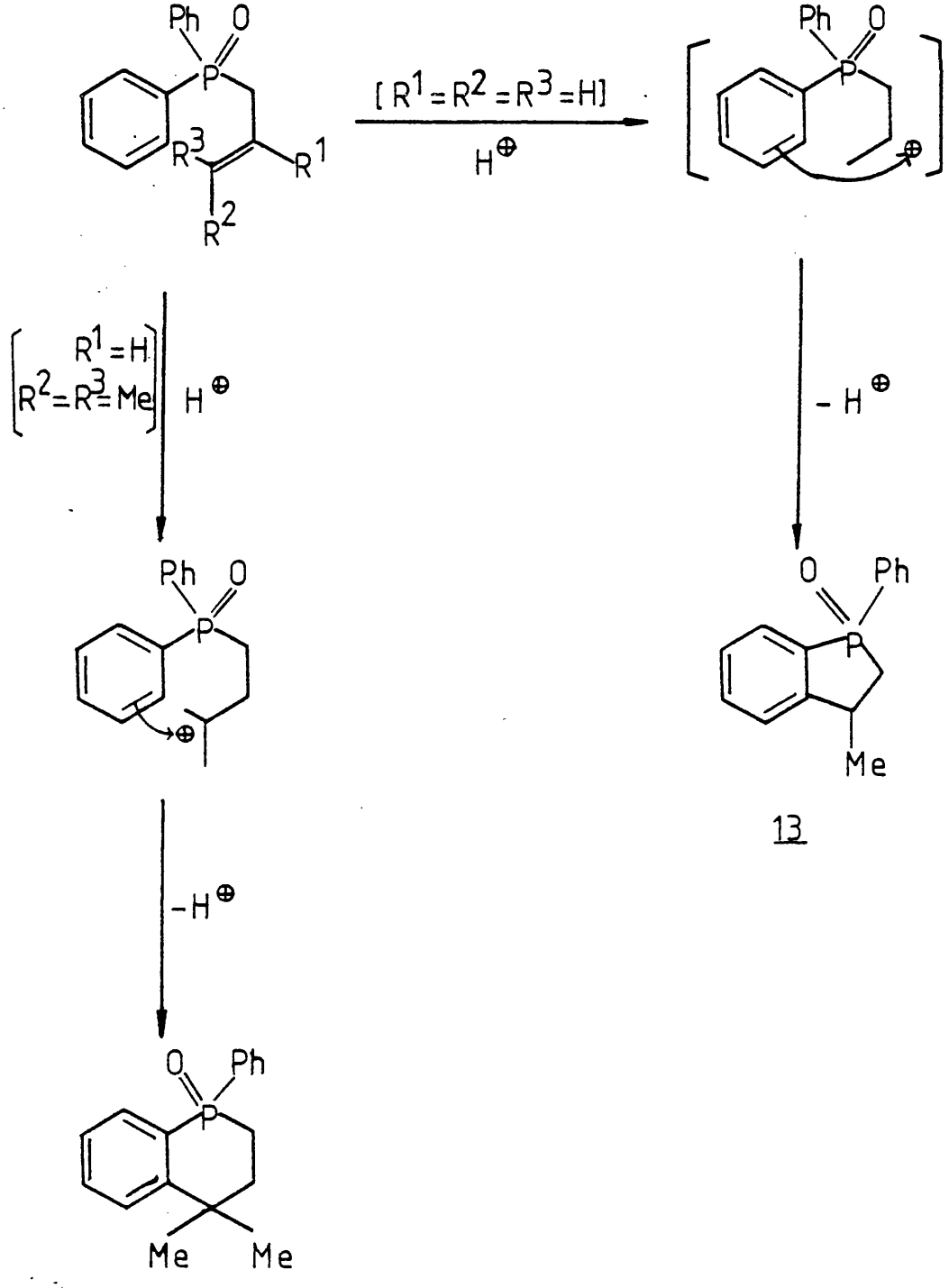


33%

10

11

Of more general significance are the acid-catalysed syntheses of phosphorus heterocycles reported by Berlin *et al*. Polyphosphoric acid (PPA) mediated ring-closure of diphenylalkenylphosphine oxides[6-8] and triphenylalkenyl phosphonium salts[9] has led to phosphinoline derivatives,

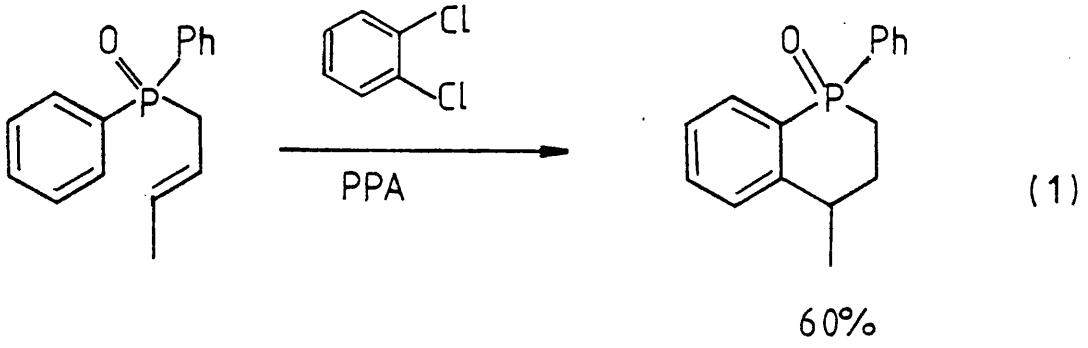


13

12

SCHEME 5

as well as fused five-membered ring-systems (phosphindolines). The size of the ring in the product is determined by the position of the most stable carbonium ion formed on protonation of the double bond (Scheme 5). Thus diphenyl(3-methylbut-2-enyl)phosphine oxide gave the six-membered phosphinoline (12), while allyldiphenylphosphine oxide cyclised to the five-membered phosphindoline (13). The original experimental procedure used in these reactions involved addition of the acyclic precursor to polyphosphoric acid preheated to 180°C in an open vessel. Further heating was followed by aqueous work-up to give the appropriate phosphorus heterocycle in up to 70% yield. That much of the 100:1 W/W ratio of PPA to phosphine oxide required was merely for dilution, to prevent polymerisation, has been demonstrated by Brown[10], who investigated the use of a solvent in PPA catalysed cyclisation reactions. He obtained yields comparable to those of Berlin[8] with a ratio of only 6:1 (PPA to phosphine oxide) by employing *o*-dichlorobenzene as the diluting solvent (equation (1)).



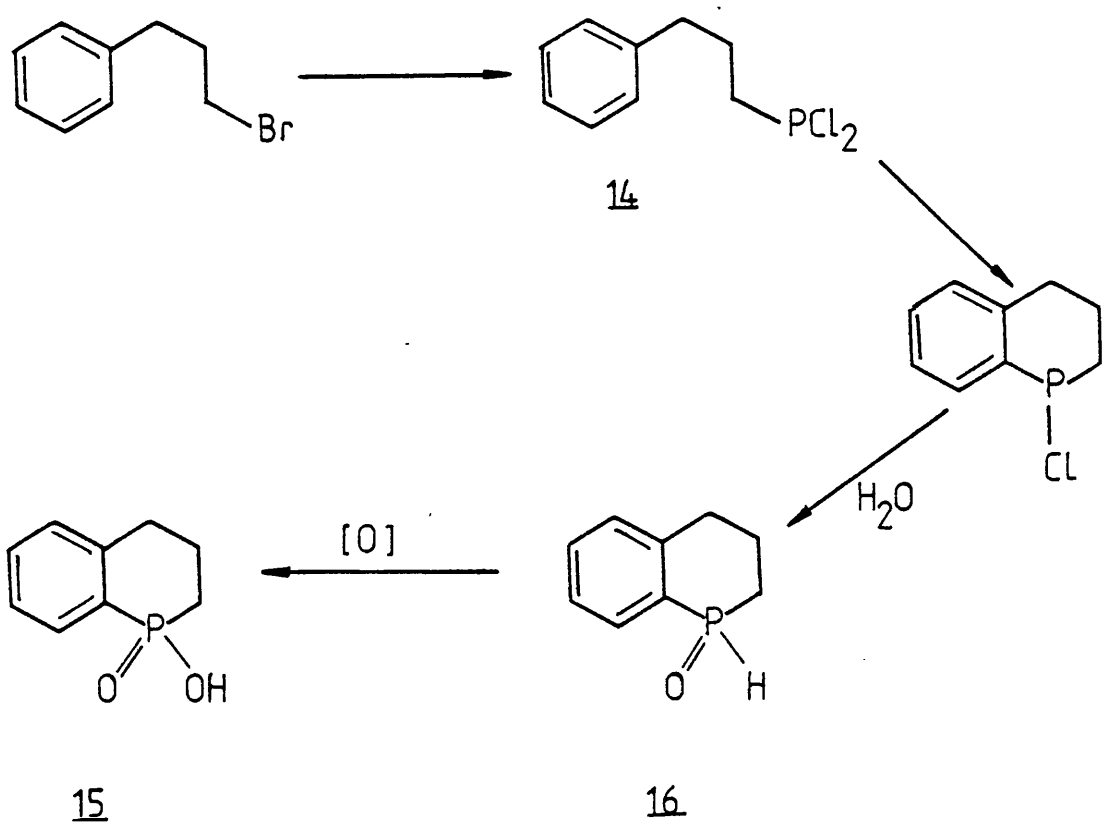
(1)

60%

Although notable for their chemistry, none of the foregoing phosphinoline syntheses possessed the versatility necessary to readily provide the variation of substitution

required, either at phosphorus or within the rest of the molecule. Even the PPA cyclisations of alkenylphosphine oxides have considerable constraints as to ring substituents, while the substitution reactions undergone by tertiary phosphines and their oxides are strictly limited.

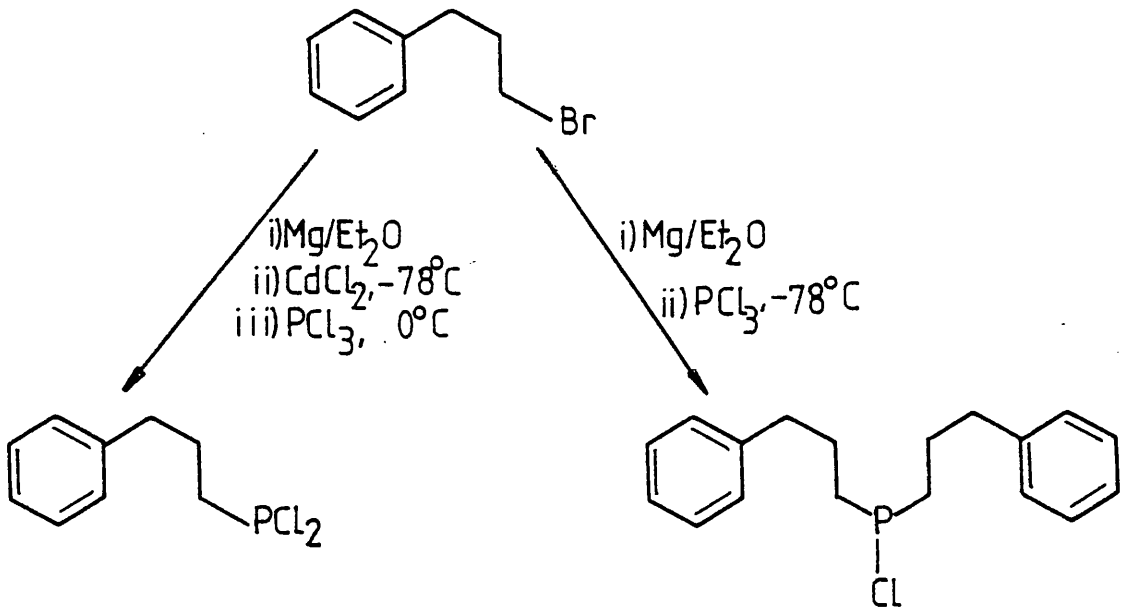
Substitution at phosphorus as a phosphinic acid facilitates manipulation at this centre, so that a synthesis of 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (15), published by Rowley and Swan[11,12], promised to provide a useful starting point (Scheme 6).



SCHEME 6

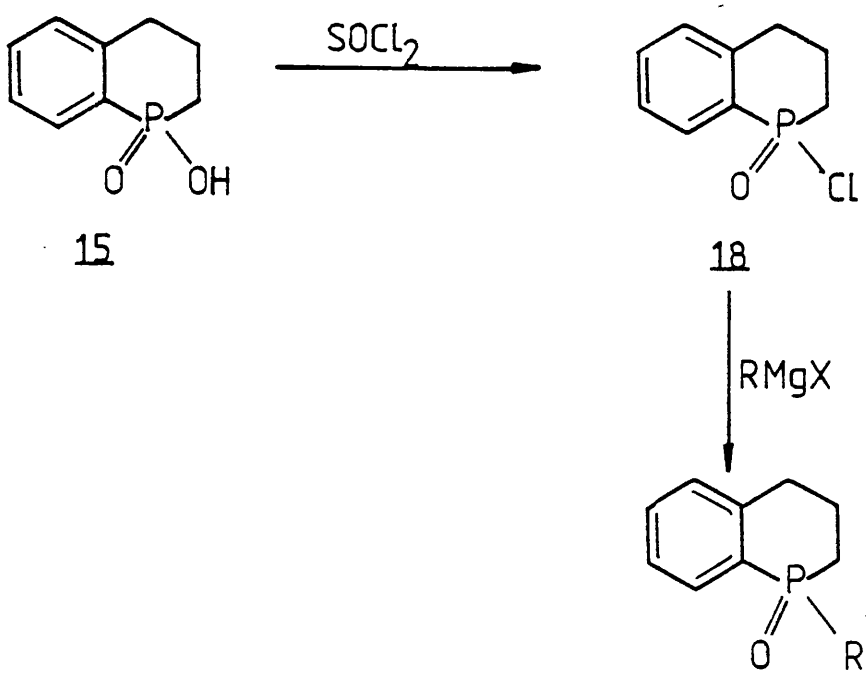
Treatment of the dialkyl cadmium, formed on reaction of 3-phenylpropylmagnesium bromide and cadmium chloride, with phosphorus trichloride at low temperature gave 3-phenylpropylphosphonous dichloride (14), isolated in 60% yield. Friedel-Crafts cyclisation onto the aromatic ring with a zinc chloride catalyst produced a chloro-tetrahydrophosphinoline, which was hydrolysed and oxidised without further purification to the phosphinic acid (15).

With an overall yield of 25% the method, although a bit long and involved, provided a viable route to the desired ring-system. While the secondary phosphine oxide (16) is, on paper, at least as attractive for modification as the acid (15), in practice its rapid oxidation[10] detracts from its synthetic potential. In an attempt to simplify the procedure described, the feasibility of eliminating the need to use an organocadmium reagent for the introduction of the phosphorus functionality was investigated. However, even at higher dilution (2.5 times that used previously), maintaining the temperature at -78 °C with a very slow rate of addition, 3-phenylpropylmagnesium bromide proved too reactive, leading only to a reasonable yield of bis(3-phenylpropyl)phosphinous chloride (17). Reversion to the original conditions described provided sufficient 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (15) to synthesize a number of dihydrophosphinolines. Alkyl substituents were introduced at phosphorus by the action of the relevant Grignard reagent with phosphinic chloride (18), 1-methyl- and 1-benzyl-1,2,3,4-tetrahydro-phosphinoline 1-oxide (19, R = Me, CH_2Ph respectively)



14 17

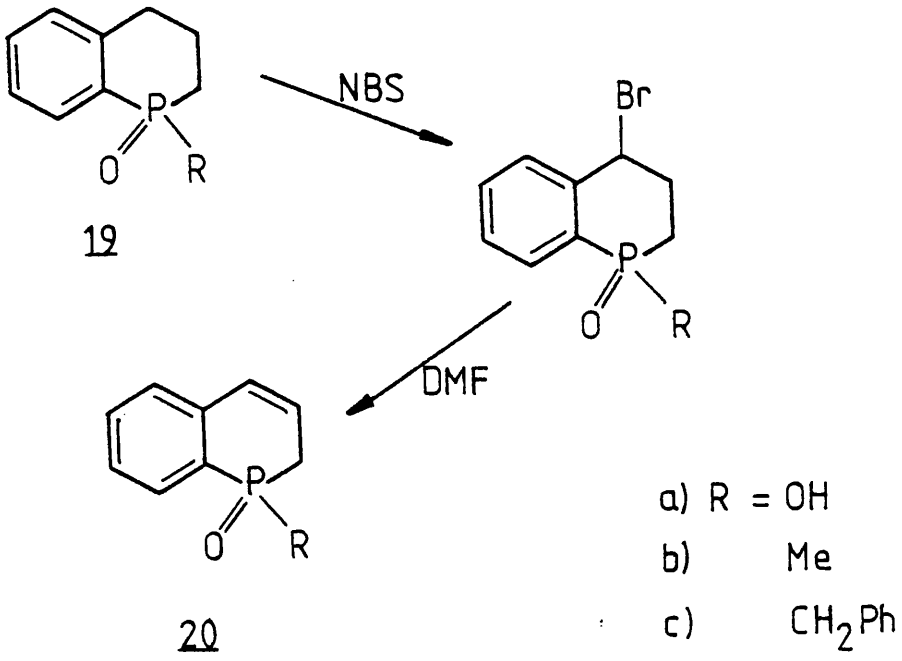
being produced in this manner.



15 18 19

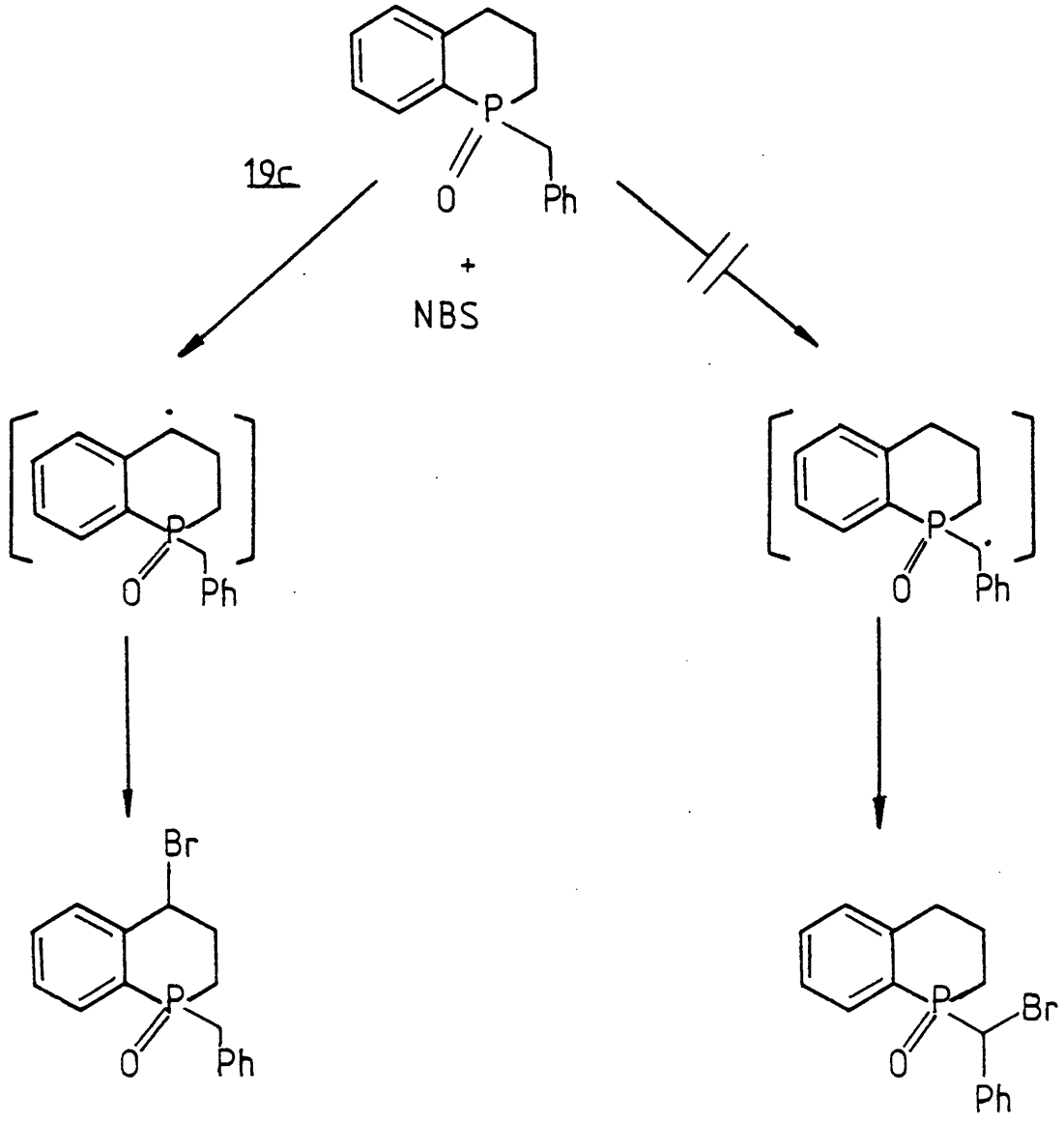
Oxidation of these compounds to the dihydrophosphinolines (20a - c) was achieved by radical bromination at the benzylic

position with N-bromosuccinimide (NBS), followed by dehydrobromination in dimethylformamide (Scheme 7).



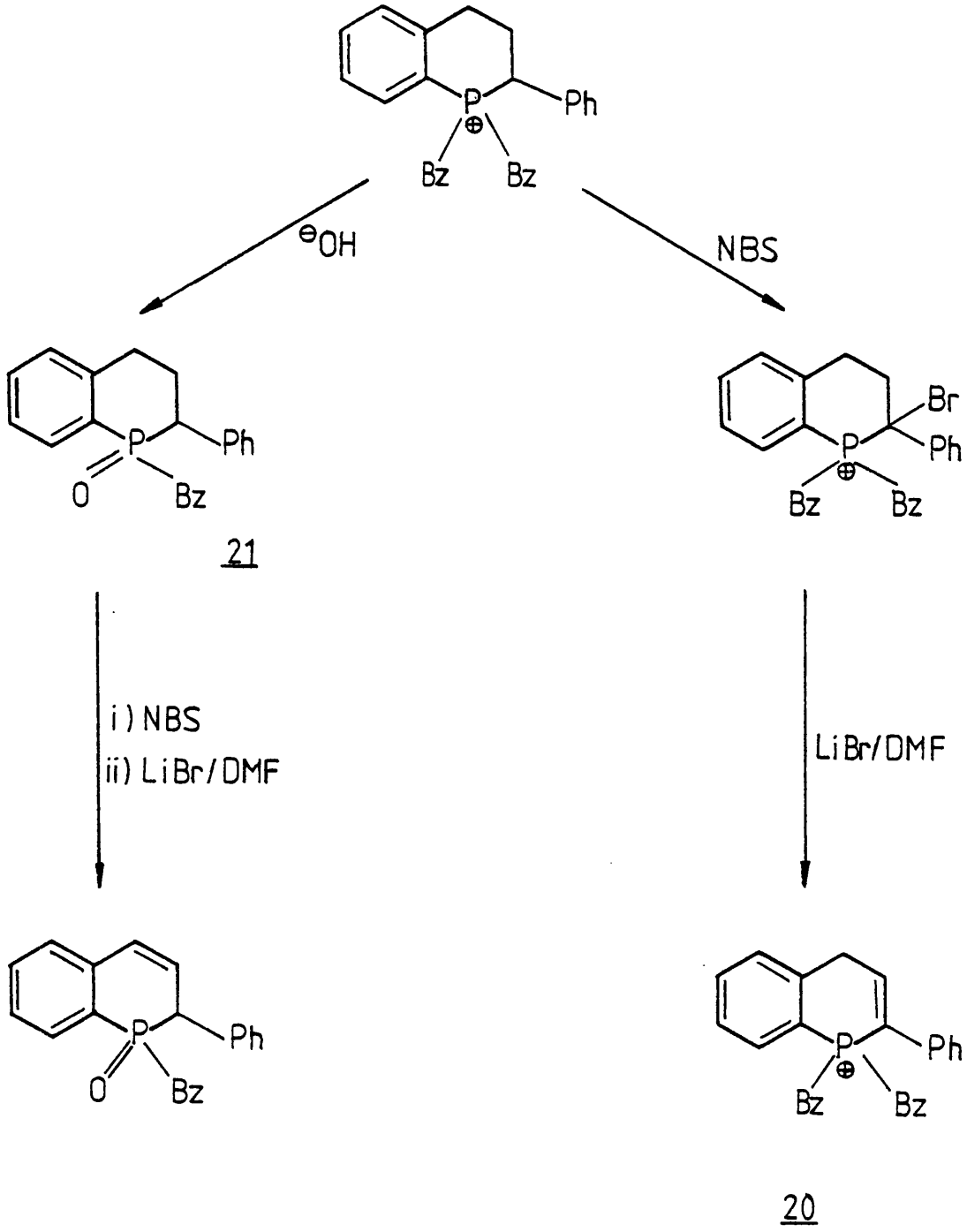
SCHEME 7

In principle, 1-benzyl-1,2,3,4-tetrahydrophosphinoline 1-oxide (19c) contained two benzylic methylene groups capable of stabilised radical reaction. The product of bromination, however, consisted entirely of the 4-bromo-1,2,3,4-tetrahydrophosphinoline, with no indication of the presence of an isomeric product (Scheme 8).



SCHEME 8

This relative reluctance to form a radical centre α to a phosphoryl group is in accord with similar observations made by Brown[10]. Märkl and Heier[13] found that 1,1-dibenzyl-2-phenyl-1,2,3,4-tetrahydrophosphinolinium bromide underwent substitution by NBS at the 2-position

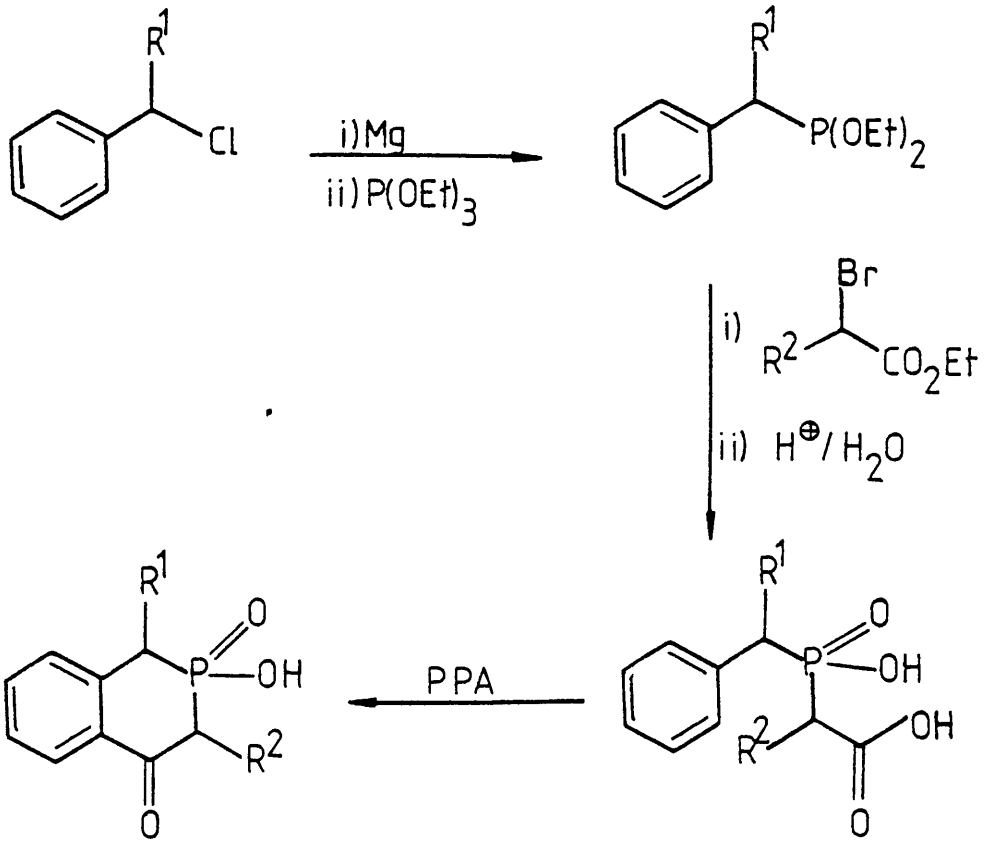


SCHEME 9

(Scheme 9), the intermediate being a tertiary benzylic radical, further stabilised by the adjacent phosphonium centre. Dehydrobromination then led to a 1,4-dihydrophosphinolinium salt (20). Hydrolysis of the original phosphinolinium salt to phosphine oxide (21) caused bromination to occur preferentially in the 4-position, all other benzylic centres being rendered unreactive by

the presence of the phosphoryl group. Dehydrobromination in this case led to a 1,2-dihydrophosphinoline 1-oxide.

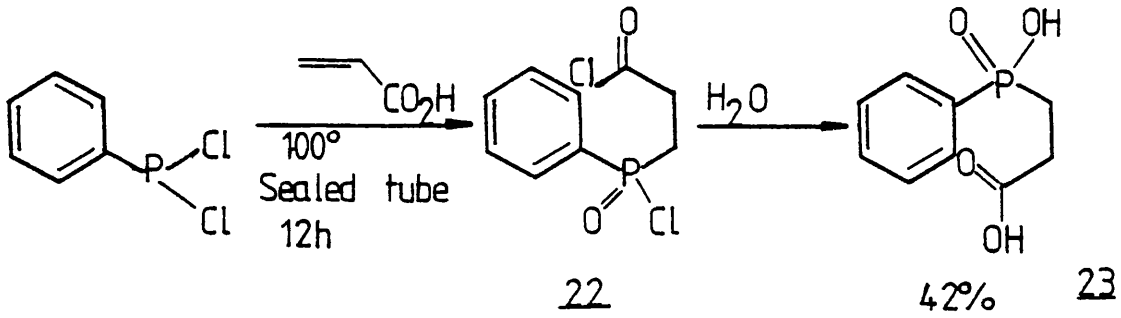
A synthesis of isophosphinolines that could fairly readily be adapted to the production of variously substituted molecules was published by Henning[17], and elaborated upon by de Graaf and Bickelhaupt[18,19]. Reaction of diethyl benzylphosphonites with an α-haloester gave, on hydrolysis, substituted benzylcarboxymethylphosphinic acids (Scheme 10). Condensation of the side-chain onto



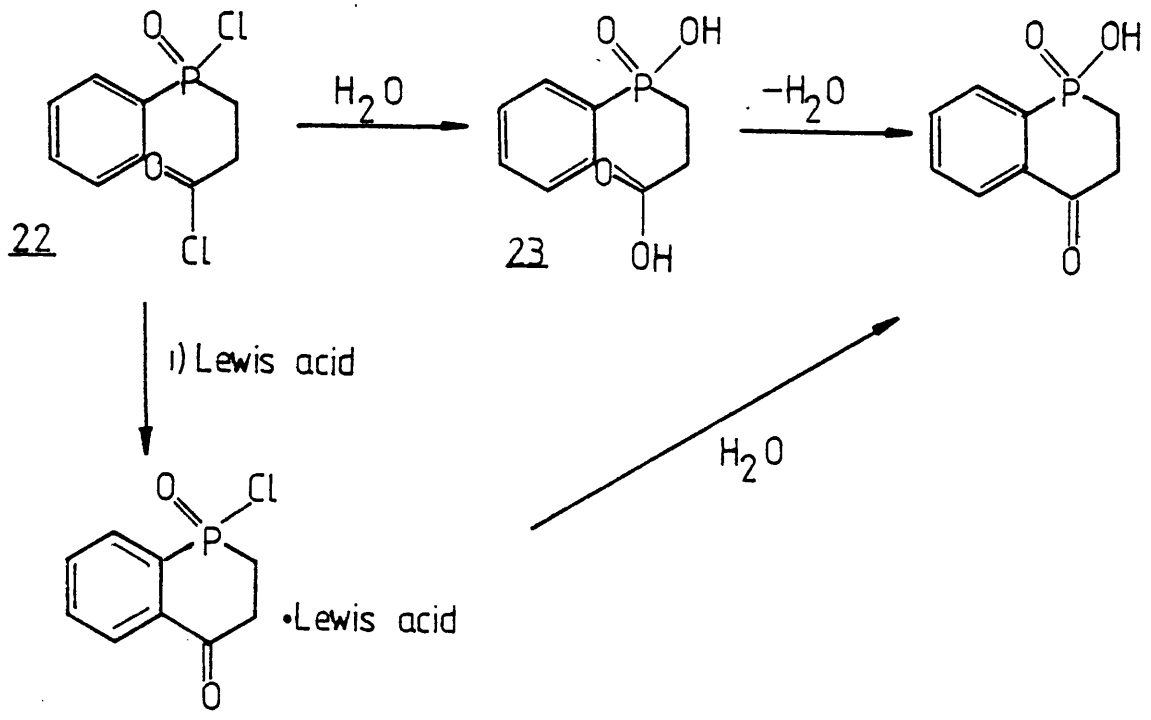
SCHEME 10

the ring with polyphosphoric acid produced the appropriate tetrahydroisophosphinoline. The reported overall yield, however, was only 15%, the majority of this loss occurring in the cyclisation step, which proved very susceptible to changes in reaction conditions[15,17].

Although ultimately successful, a simpler and cheaper route to phosphinolines than that of Swan was desirable,



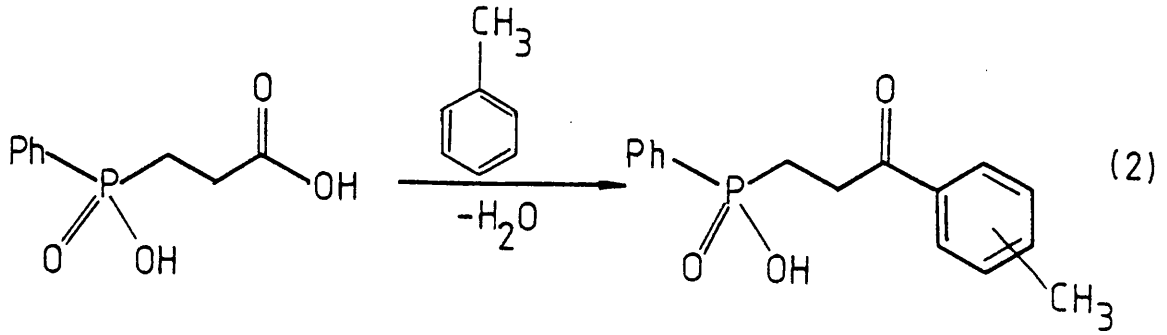
to allow larger scale preparations to be more easily handled. The ready availability of 3-(chlorophenylphosphinyl)-propanoyl chloride (22), and its hydrolysis product (23),



SCHEME 11

from the reaction between phenylphosphonous dichloride and acrylic acid[14], made it a promising candidate for cyclisation to phosphinoline derivatives (Scheme 11).

Intramolecular dehydration of (23) with a polyphosphoric acid catalyst was attempted under conditions suggested by results obtained by Berlin[6-8], Brown[10], Henning[17], and Bickelhaupt[18,19], from different proportions of neat PPA to the use of a solvent as a diluting agent. In no instance was any indication of cyclisation observed, phosphinic acid (23) being recovered in reduced quantity. That this lack of success was probably due to deactivation, by the adjacent phosphoryl group, of the ring towards electrophilic attack was indicated by an intermolecular condensation that occurred when using toluene as a solvent in the presence of PPA[15]. A similar reaction was observed during azeotropic removal of water with toluene (equation (2)).



(2)

23

No greater success was achieved with alternative dehydrating agents such as concentrated sulphuric acid, or phosphorus pentoxide in combination with either PPA or methane sulphonic acid[15].

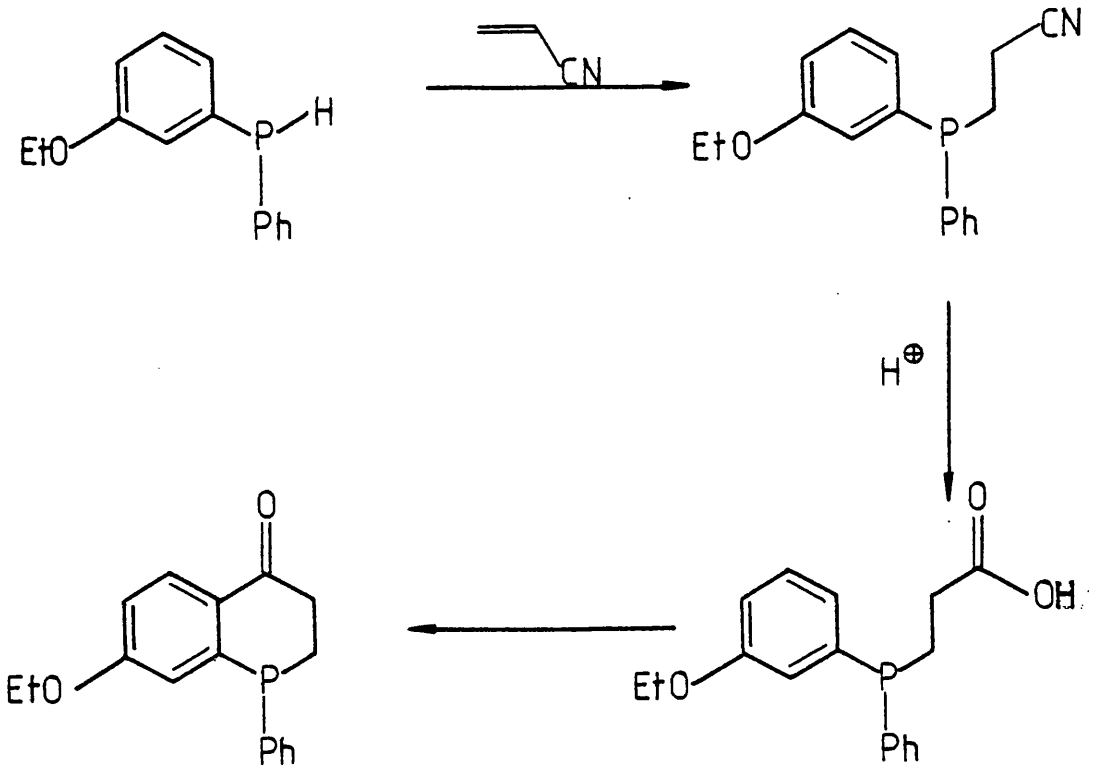
A similar reluctance to undergo intramolecular reaction was encountered with bis-acid chloride (22). The use of up to three molar equivalents of Lewis acid catalyst at temperatures up to 140°C for prolonged periods failed to induce cyclisation. Increasing polymerisation and decomposition occurred with more forcing conditions.

On observing the ^{31}P nmr during the reaction, an immediate change of chemical shift from +52.5 to +70.0p.p.m., after addition of aluminium chloride, indicated formation of a complex between the Lewis acid and (22). No significant change was observed in the signal during the reaction period, and aqueous work-up gave 3-(hydroxyphenylphosphinyl) propanoic acid (23) as the only isolated product.

Cyclisation could probably be ultimately achieved by activation of the aromatic nucleus towards electrophilic attack. A similar problem was overcome in an organo-arsenic system[25] by introduction of methoxy substituents into the ring. Mann eventually succeeded by analogy in ring-closing a diarylphosphinopropanoic acid to a phosphinoline, in very low yield, by activating one of the rings with an ethoxy substituent[16] (Scheme 12).

Alkoxyphenylphosphonous dichlorides, required for the synthesis of an activated analogue of (23), substituted in either the 3-, or 3,5-positions were not readily available, and it was felt that introducing the practical complexities that would be necessary would defeat the

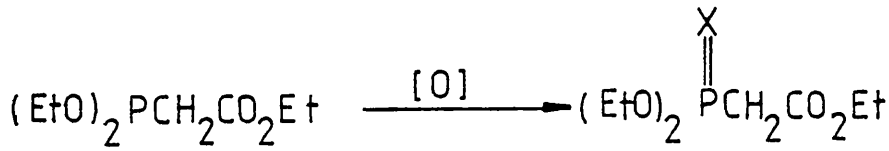
object of easy phosphinoline synthesis.



SCHEME 12

Denied a simple method of cyclisation of 3- (hydroxyphenylphosphinyl)propanoic acid derivatives, attention was concentrated on developing a route to the bicyclic phosphanaphthalene system that incorporated as much synthetic flexibility as possible. It was felt that the reagent used to incorporate phosphorus into the molecule held the key to a successful approach, and careful choice of this would allow its use in constructing a wide variety of phosphinoline derivatives.

The ethyl ester of (diethoxyphosphino)acetic acid (24) exhibits reactive centres of three different types. As a tervalent phosphorus compound, the phosphonite (24) undergoes ready oxidation to a phosphonate (equation (3)).

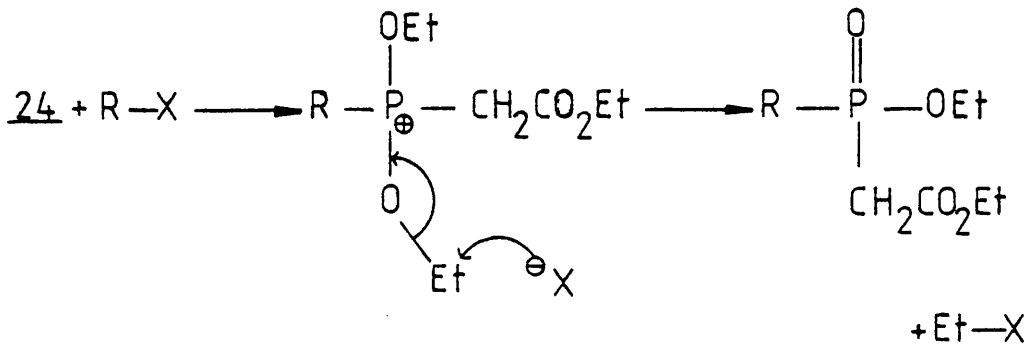


(3)

24

X = O, S.

In common with other tricoordinate derivatives, the lone-pair residing on phosphorus imparts considerable nucleophilic and, to a less important extent, basic characteristics. With alkoxy- substituents on phosphorus, use as a nucleophilic reagent would frequently lead to an Arbusov reaction, giving rise to phosphinate esters (Scheme 13).



SCHEME 13

Once oxidised to the quinquevalent state, removal of a proton from the acetate chain gives a carbanion doubly stabilised by the adjacent phosphoryl and carboxylic ester groups. With the ester group itself providing an electrophilically reactive centre, ethyl (diethoxyphosphino)acetate (24) was considered to have the desired versatility, and was accordingly synthesized.

Previously published routes involving the use of organic mercury[20] or tin[21] compounds proved to be both cumbersome and erratic in their results. Far easier was the treatment of chlorodiethylphosphite with the carbanion of ethyl acetate, generated with sodium hexamethyldisilazide [22], or experimentally simpler, lithium diisopropylamide as non-nucleophilic base (equation (4)). Carried out in ether at low temperature,

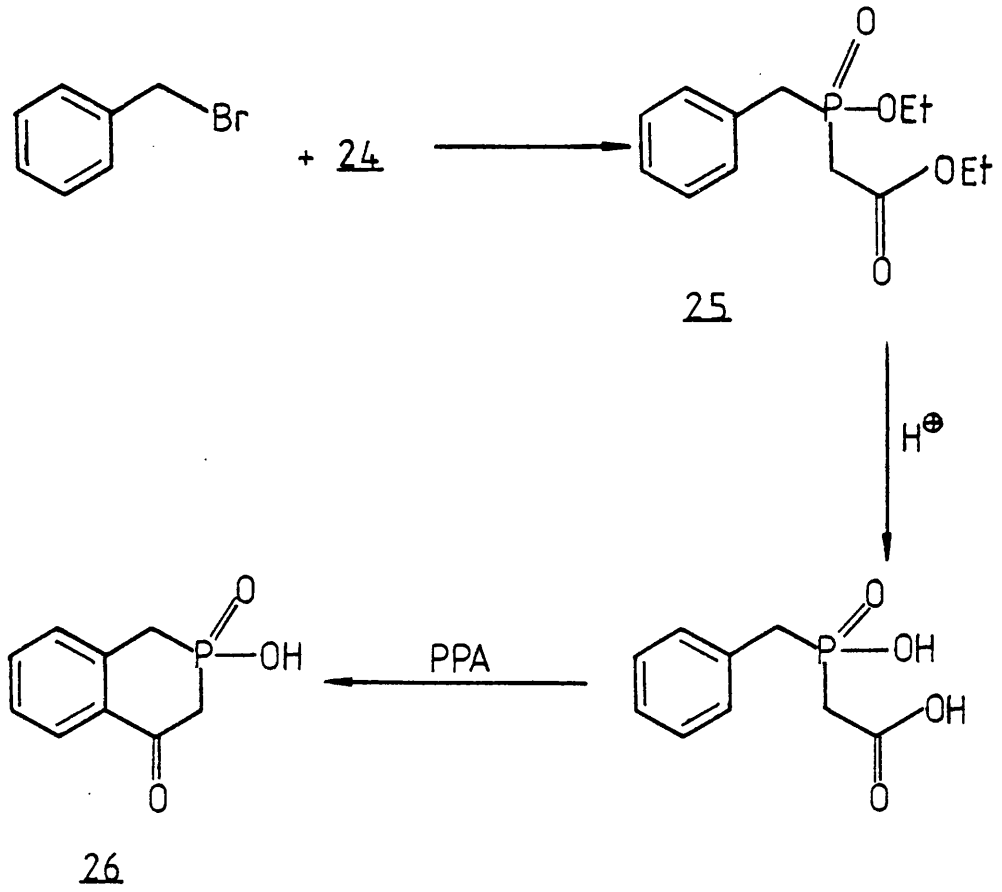
$$H_3CCO_2Et \xrightarrow[ii)\ (EtO)_2PCl]{i)\ LiNPr^i_2} (EtO)_2PCH_2CO_2Et \quad (4)$$

24

with the latter reagent as base, the reaction yielded 71% of (24), after distillation.

Evaluation of the phosphinoacetate as a synthetic reagent commenced with the production of ethyl benzyl-carbethoxymethylphosphinate (25), an open-chain isophosphinoline precursor previously reported by Henning[17], and Bickelhaupt[19]. Combination of phosphonite (24) with benzyl bromide gave a clean Arbusov reaction, allowing

the isolation by distillation, of (25) in 85% yield (Scheme 14).

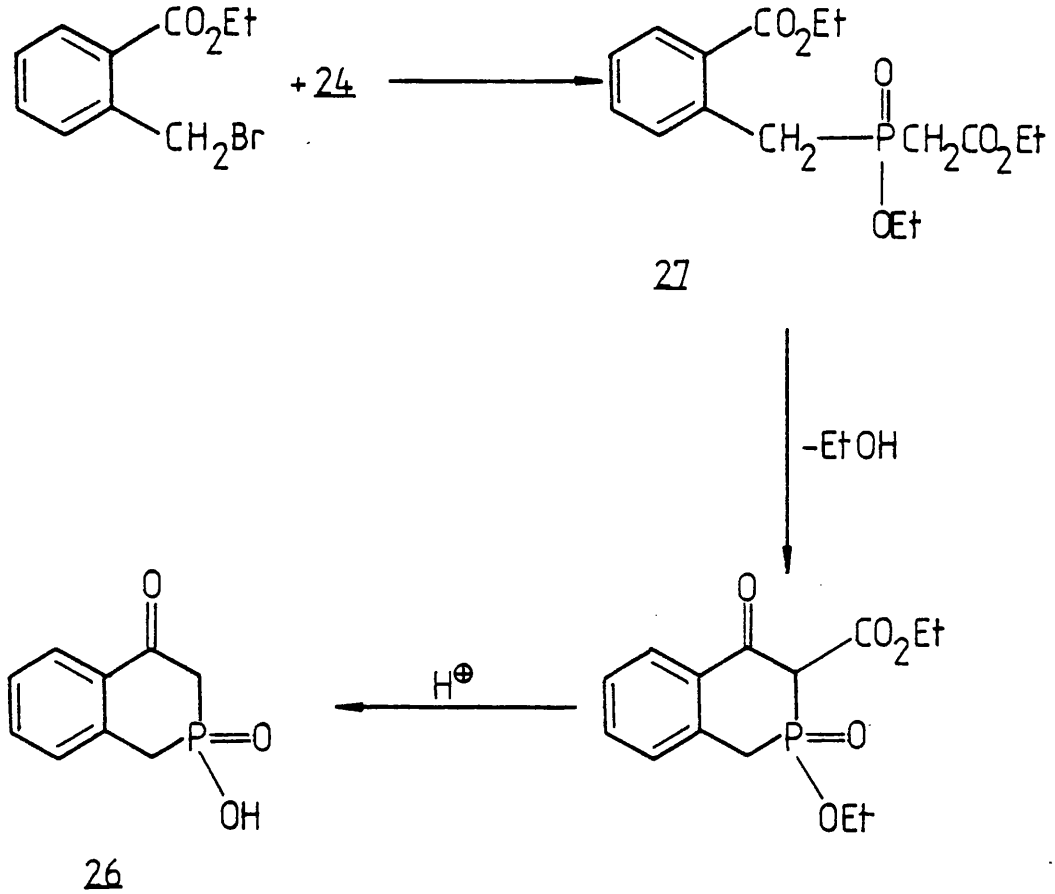


SCHEME 14

Hydrolysis and PPA-catalysed cyclisation according to published procedure[17] would have led to 2-hydroxy-1,2,3,4-tetrahydroisophosphinoline 2,4-dioxide (26).

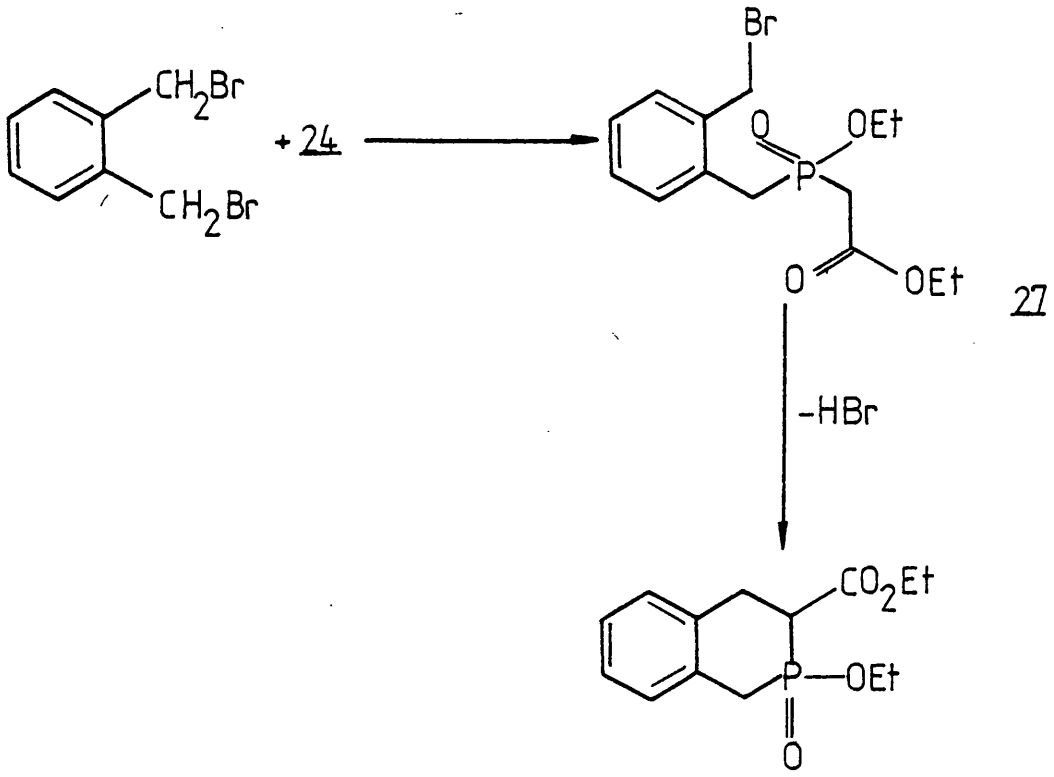
A different route leading to the same goal involved initial reaction between ethyl *o*-(bromomethyl) benzoate and phosphinoacetate (24) to form triester (27). A Dieckmann cyclisation reaction then gave 2-ethoxy-3-carbethoxy-1,2,3,4-tetrahydroisophosphinoline 2,4-dioxide. Of the

bases tried in this step sodium ethoxide in ethanol produced the best result. Purification of this cyclised product was prevented by its ready decomposition on attempted distillation or use of chromatographic techniques. Characterisation was further complicated by the mixture of diastereoisomers obtained from the reaction causing loss of spectral resolution. Hydrolysis, however, caused decarboxylation of the resultant β-keto-acid, and allowed the isolation and characterisation of 2-hydroxy-1,2,3,4-tetrahydroisophosphinoline 2,4-dioxide (26).



A similar reaction pathway may be envisaged, with cyclisation occurring by intramolecular expulsion of a

bromide ion by the stabilised carbanion formed from (27) (Scheme 15).

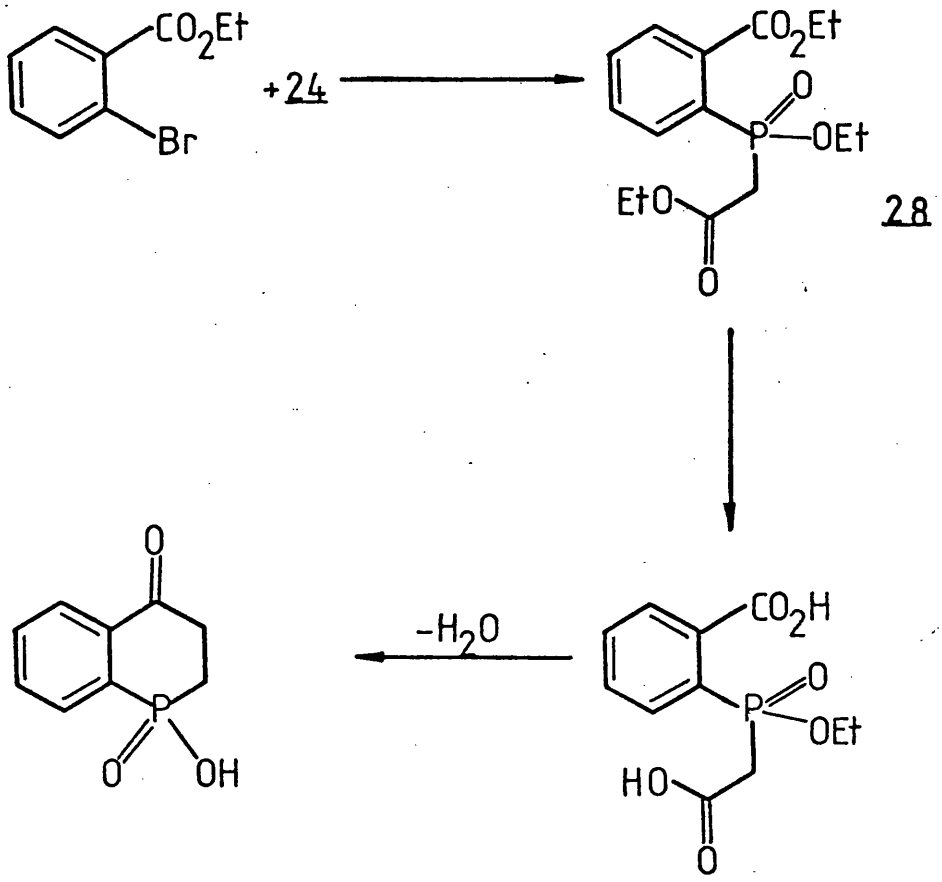


SCHEME 15

Preliminary investigation of the addition of ethyl (diethoxyphosphino)acetate (24) to α , α^1-dibromo-o-xylene indicates the feasibility of such a route, although the conditions to achieve the optimum yield of monosubstituted product remain to be developed.

A nickel halide catalysed addition of (24) to an aromatic halide[23,24] , would allow the synthesis of phosphinolines (eg Scheme 16). However despite several attempts, the phosphinic acid (28), expected from

substitution, was not isolated.



SCHEME 16

While restricted here to the production of phosphinolines, ethyl (diethoxyphosphino)acetate (24) can, in principle, be used to synthesize a much wider variety of molecules.

Particularly suited to phosphorus heterocyclic synthesis, the contribution of this reagent could be quite considerable.

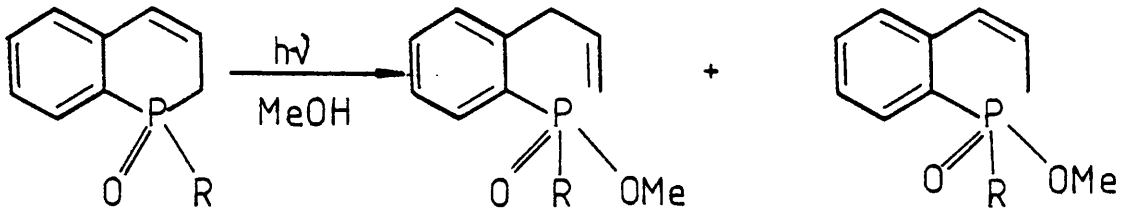
CHAPTER TWO

CHAPTER 2

THE PHOTOLYSIS OF 1,2-DIHYDROPHOSPHINOLINE 1-OXIDES

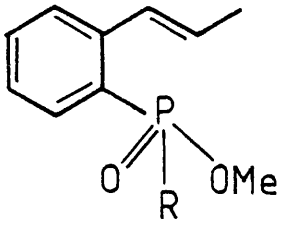
Ultraviolet irradiation of dihydrophosphinolines (20a - c) in methanol gave rise to three products, separated by gas chromatography, their relative proportions varying with the particular substrate used. Mass spectral analysis of each component showed all three to have identical molecular ions. The ^{1}H n.m.r. spectra exhibited a sharp doublet at a chemical shift of +3.7 p.p.m., characteristic of a P-OMe function. In addition to aromatic protons, the spectra of the product mixtures also showed the presence of olefinic protons in two different environments (+5.7 to 6.1 and 5.0 p.p.m.), and a fairly complex absorption pattern at +1.8 p.p.m., attributable to a methyl group attached to a double-bond. Assignment of the spectra to mixtures of the double-bond isomers of 2-propenylphenyl-substituted phosphorus esters (Scheme 17) was supported by comparison with authentic spectra of allylbenzene and β-methylstyrene[26], with only minor modifications being introduced by the phosphorus substituent. Absorptions due to benzylic protons in (29) were partially obscured by the P-OMe doublet at +3.6 p.p.m.

The course of the photolytic reaction of 1,2-dihydro-1-hydroxyphosphinoline 1-oxide (20a) in methanol was followed by monitoring the ultraviolet spectrum of the reaction mixture. After 9h, an absorption at 258nm had



20 29 56

a) R = OH
b) Me
c) CH_2Ph



57

SCHEME 17

greatly reduced in intensity, and no subsequent changes were noted. Removal of solvent gave a mixture containing predominantly methyl 2-(prop-2-enyl)phenylphosphonate (29a), the balance provided by the *cis*- and *trans*-isomers of methyl 2-(prop-1-enyl)phenylphosphonate (56a) and (57a), with no starting material remaining. Relative integration of peaks in the ^1H n.m.r. spectrum that could be assigned to the individual isomers (absorptions at+5.1 and 3.6 p.p.m. for (29a), and the methyl absorptions at +1.8 p.p.m. for the styrene derivatives (56a) and (57a)) indicated that the allylbenzene derivative (29a) accounted for 88% of the product mixture, the rest being distributed approximately equally between the other two isomers. Direct vacuum-distillation of this product mixture led to

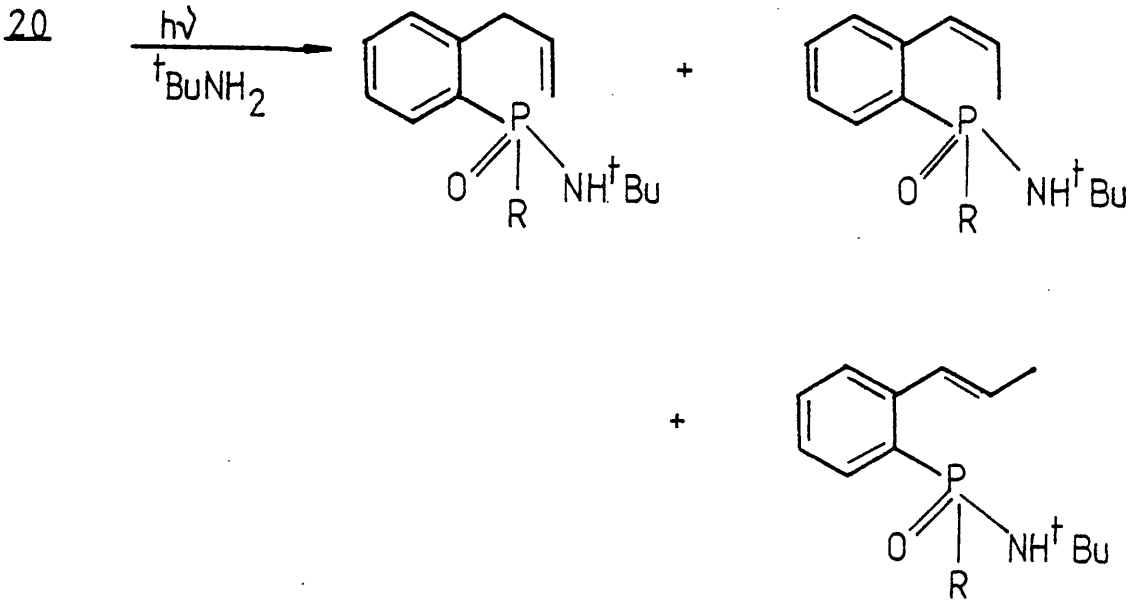
considerable decomposition, polymerisation and isomerisation, shown by gross changes in the ^1H spectrum of the condensate. Methylation of the photolysis mixture with excess diazomethane facilitated distillation, and also permitted the use of thick-layer chromatography to purify dimethyl 2-(prop-2-enyl)phenylphosphonate (29, R = OMe), although this material was never obtained completely free of contamination by the conjugated isomers (56 and 57, R = OMe), shown by their distinctive absorption at +1.8 p.p.m. in the ^1H spectrum. Whether this was due to isomerisation during the isolation procedure, or merely to their close similarity of physical properties was not ascertained.

Similarly 1,2-dihydro-1-methylphosphinoline 1-oxide (20b) photolysed in methanol to give the 2-allylphenylphosphinate (29b) as the major product. Gas chromatography (3% OV17 at 200°C) gave a product distribution of 50% (29b) to 25% each of the other two isomers. The ^{31}P spectrum showed three closely separated absorptions at +43.0, +44.2 and +44.6 p.p.m., while integration of the ^1H n.m.r. spectrum was complicated by the coincidence of the P-Me doublet and the methyl groups of (56b)and (57b). Within experimental error, however, the ratio of isomers was the same as that obtained by G.C. Preparative G.C. had previously been used by Brown[10] to separate a sample of methyl (2-allylphenyl)methylphosphinate (29b), but due to its hygroscopic nature a satisfactory elemental analysis could not be obtained. In the instance described here, however, a molecular formula of $C_{11}H_{15}O_2P$ was unambiguously assigned

to each component of the mixture by high-resolution mass spectrometry performed on the compounds separated by gas chromatography.

In the same way, integration of the ^1H spectrum obtained for the product from photolysis of 1-benzyl-1,2-dihydrophosphinoline 1-oxide (20c) in methanol indicated a slightly higher proportion of the terminal double-bond isomer (29c, 60%), with an equal contribution of 20% from each of the other two isomers.

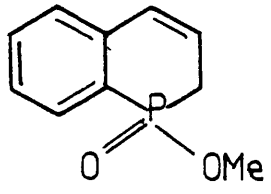
The use of t-butylamine as an alternative nucleophilic solvent during irradiation of 1,2-dihydro-1-methylphosphinoline 1-oxide (20b) led to analogous products (Scheme 18), containing amido- instead of methoxy-substituents on phosphorus.



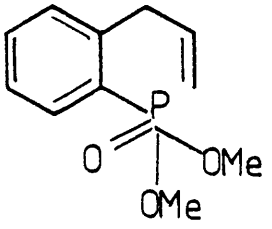
SCHEME 18

Although chromatography showed only one product in this case, the ^{1}H spectrum was again indicative of a 1:1 product distribution between the two double-bond positional isomers. With the replacement of the methoxy-group on phosphorus, the benzylic protons of the allylbenzene derivative were clearly seen as a broadened doublet of chemical shift +3.8 p.p.m. A single peak (+26.0 p.p.m.) was evident in the ^{31}P n.m.r. spectrum of the product mixture.

After similar photolytic reactions of other dihydrophosphinolines Brown[10] was able to isolate the principal product, again usually the allylbenzene derivative. 1,2-Dihydro-1-

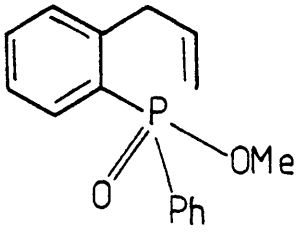


30



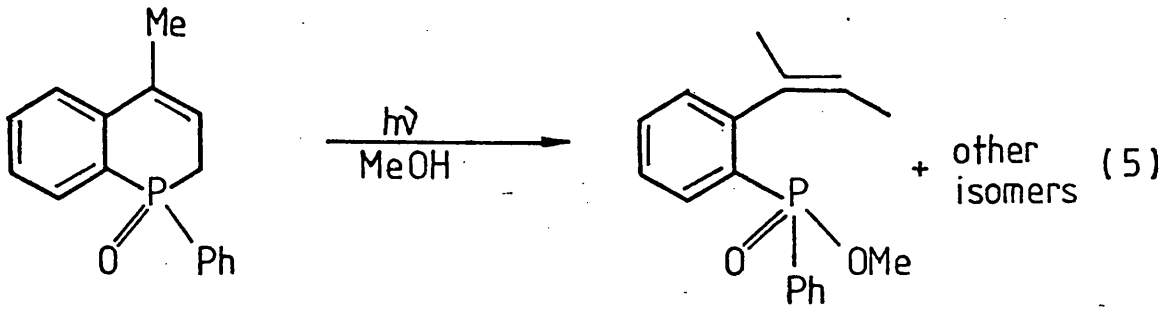
31

methoxyphosphinoline 1-oxide (30) gave rise to an 82% isolated yield of (31), following irradiation for 26h in methanol. Methyl phenyl-2-(prop-2-enyl)phenylphosphinate (32)



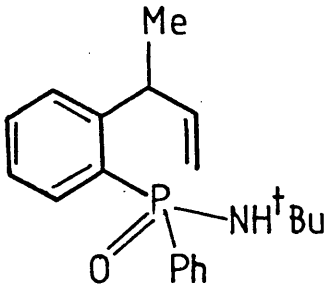
32

was isolated from the methanolic photolysis of 1,2-dihydro-1-phenylphosphinoline 1-oxide. The only instance when Brown observed a different isomer as the major product was on photolysis of a 4-methyl-substituted phosphinoline in methanol, when the conjugated alkene (33) was produced (equation (5)).

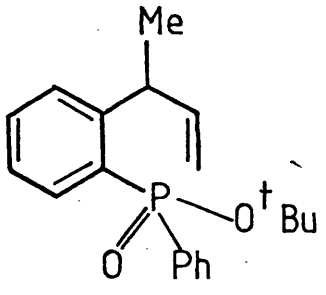


33

Using *t*-butylamine or *t*-butanol as the solvent for the reaction, however, the non-conjugated products (34) and (35) respectively were again predominant.



34



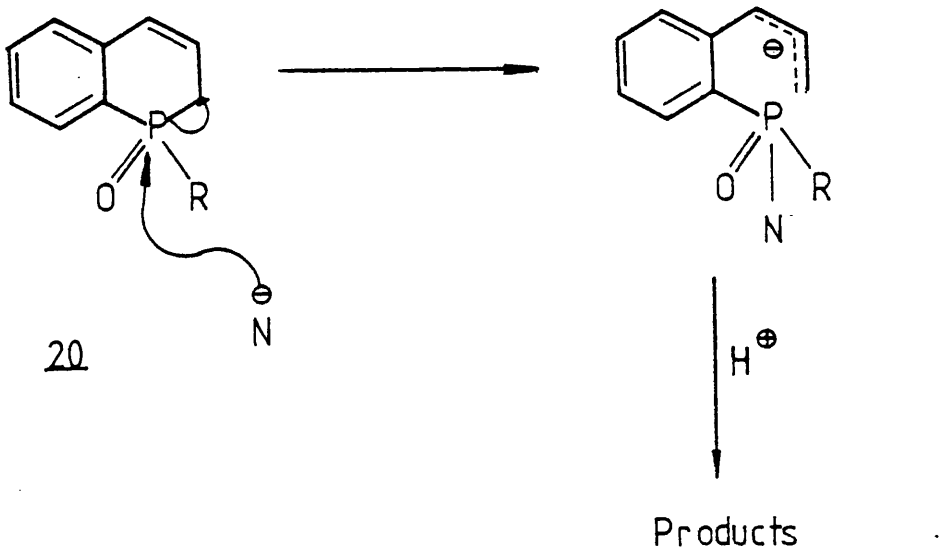
35

This result he rationalised in terms of either steric hindrance to protonation by the methyl group, or isomerisation

of the initially-formed terminal double-bond under the reaction conditions to bring it into conjugation with the aromatic ring, a process rendered less favourable by bulky substituents on phosphorus.

Interpretation of the results of photolysis of 1,2-dihydrophosphinoline 1-oxides in protic solvents can be in terms of several differing mechanisms. Ring-opening may occur by hetero- or homolytic cleavage of the phosphorus-carbon (2) bond or by a concerted, electrocyclic pathway.

It is conceivable that activation of the ring by absorption of a photon may facilitate a nucleophilic substitution, by the solvent, at phosphorus, with loss of a delocalised carbanion (Scheme 19). However, under normal conditions even a stabilised carbanion is an

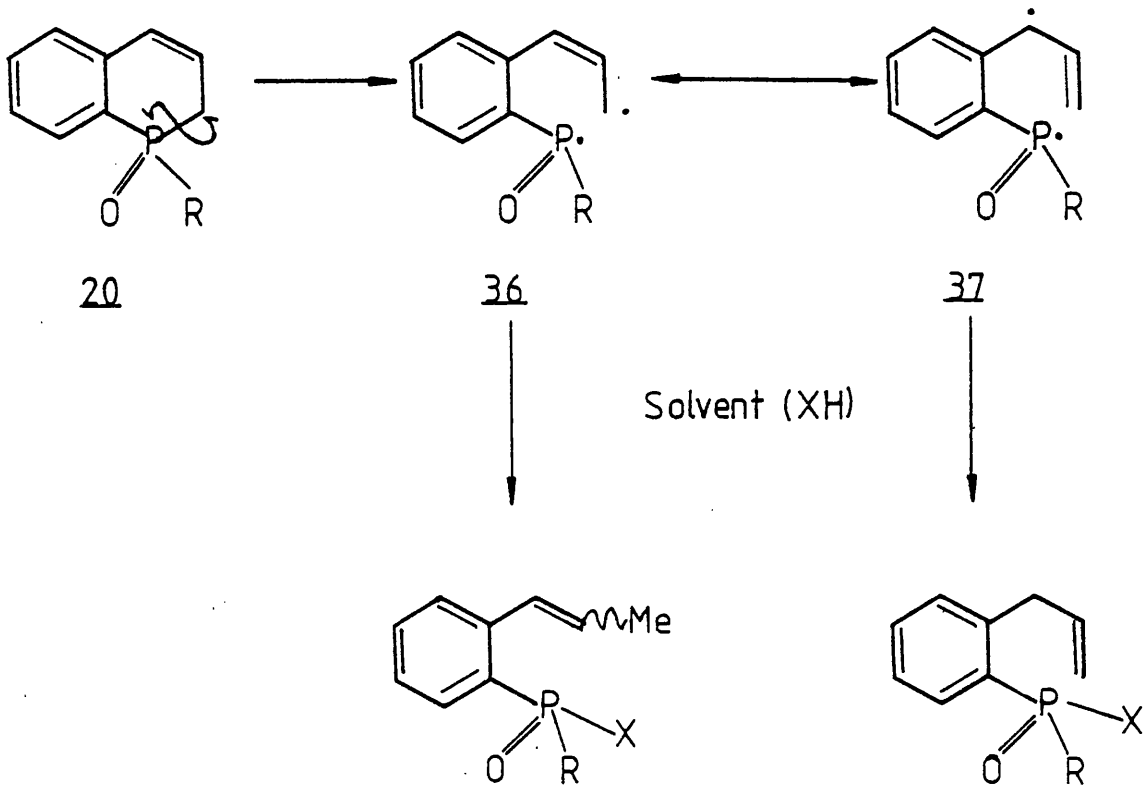


SCHEME 19

unusual leaving-group. The low electronegativity of carbon imparts the dual characteristics of unwillingness to accept electronic charge and a low apicophilicity in the pentacoordinate intermediates of bimolecular substitution at phosphorus. Thus, hydrolysis of alkylphosphinate esters would normally lead to loss of an alkoxide-, in preference to an alkyl-group[46]. Despite the presence of leaving-groups better than carbon in (20a) and (30), no evidence was found for their substitution. Neither was any indication of an equivalent thermal process observed in the comparable dark-reaction, even when heated under reflux for prolonged periods. Furthermore, although products were not identified, photolysis has been found to proceed equally well in the absence of nucleophilic species[10], indicating an unimolecular first step in the reaction.

Photo-induced homolytic cleavage of the phosphorus-carbon (2) bond of the dihydrophosphinoline would produce the diradical (36), delocalisation of the methylene radical occurring through the conjugated π-system (Scheme 20), addition of solvent leading to the products. The resultant ratio of double-bond isomers would reflect a combination of the relative contribution of each canonical form of the diradical, with the effect of steric crowding at the reaction sites. Thus, in most cases, the majority of addition of solvent is (1,4) giving an allylbenzene, but the presence of a 4-methyl-substituent gives a predominance

of (1,6)-addition (equation (5)). It is necessary to

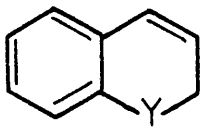


SCHEME 20

invoke either bond rotation in the diradical intermediate to give the sterically more favourable *E*-configuration to the side chain, or isomerisation of the *Z*- to the *E*-methylstyrene under the reaction conditions, in order to explain the presence of the latter in the product mixture. In either case it is difficult to rationalise the equal incidence of *E*- and *Z*-isomers.

Considerable work has been carried out on the photolysis of systems analogous to dihydrophosphinolines, and in all cases the evidence indicates a concerted, electrocyclic ring-opening to give a reactive intermediate which may

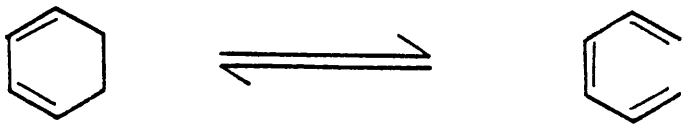
then react inter- or intramolecularly. Investigations have included dihydronaphthalene itself and equivalent heterocycles containing oxygen, nitrogen, sulphur and selenium (38a - e).



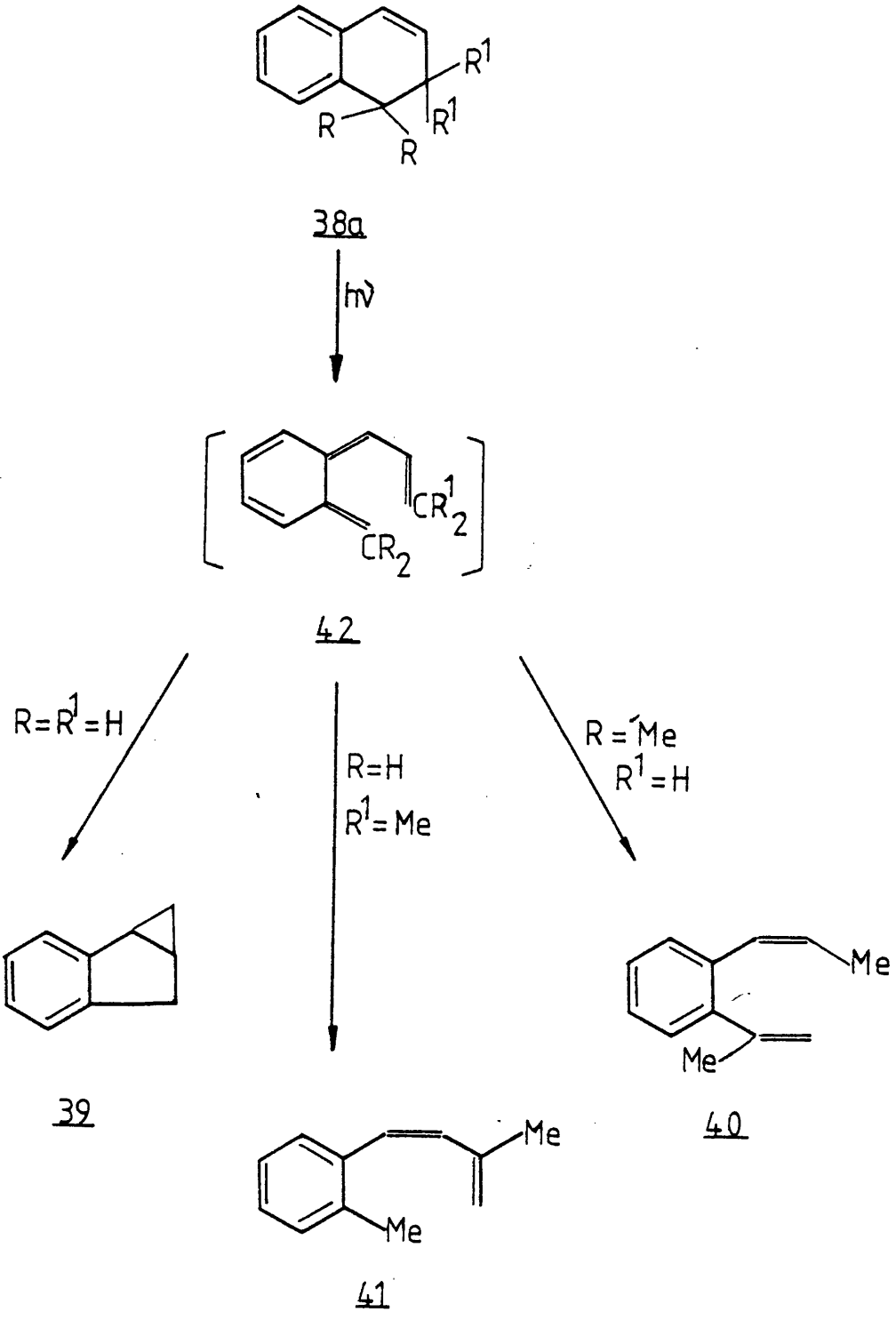
38

a) $Y = CR_2$ e) Se
b) O
c) NR
d) S

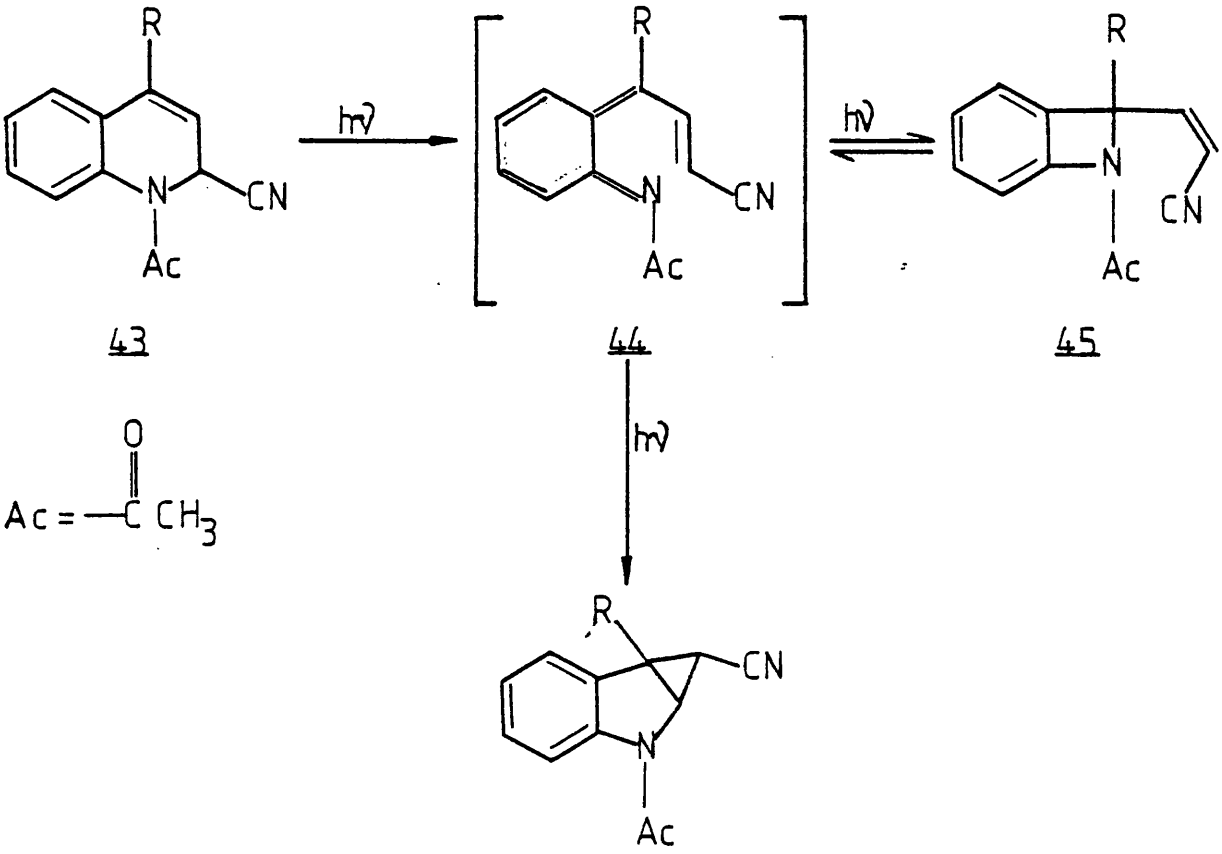
1,2-Dihydronaphthalene (38a) produces, on irradiation, the fused cyclopropane derivative (39), while methyl-substituents in the 1-position cause formation of (40) and in the 2-position give arylbutadiene (41) as the principal product[27,28]. Performing the reaction in a pentane matrix at -180°C enables the observation of an absorption at 402nm, assigned to a quinodimethane derivative (42), as the common intermediate. A photolytic $4\pi + 2\pi$ cycloaddition in the unsubstituted case gives rise to (39), while (40) and (41) are products of a (1, 7) sigmatropic rearrangement. The reaction is envisaged as a bicyclic analogue of the well-documented[29] *cyclo*hexadiene-hexatriene interconversion (equation (6)).



(6)

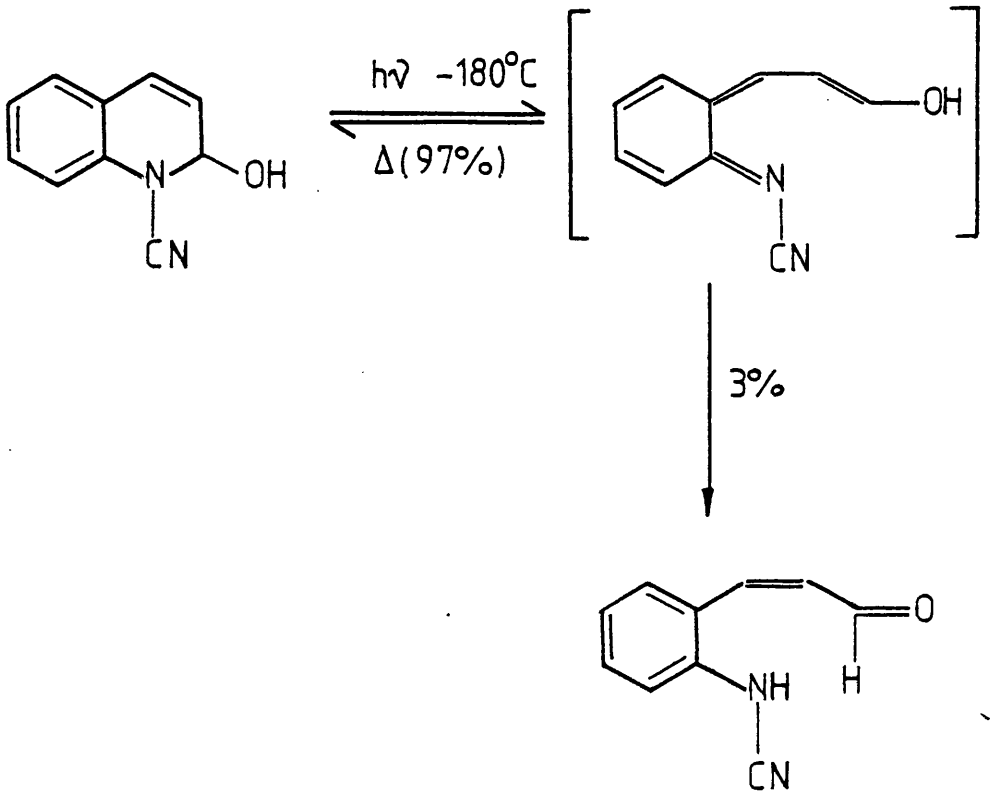

R1
R
R1
R
38a
hν
CR12
CR2
42
R=R1=H
R=H
R1=Me
R=Me
R1=H
39
Me
Me
40
Me
Me
41

Photochemical reaction of dihydroquinoline (43) is postulated to proceed by a similar reactive intermediate (44), formed on electrocyclic ring-opening of the starting material[30]. Absorption of further energy gives



products derived from intramolecular cycloaddition, either a rapid, reversible $2\pi + 2\pi$ forming benzoazetine (45), or a slower, apparently irreversible photolytic $4\pi + 2\pi$ to (46). Consequently longer periods of reaction give increased yields of (46) at the expense of (45). Reversion of the intermediate to the original

heterocycle, however, usually remains the major pathway, shown by low-temperature irradiation of a matrix containing 1-cyano-1,2-dihydro-2-hydroxyquinoline (Scheme 21),

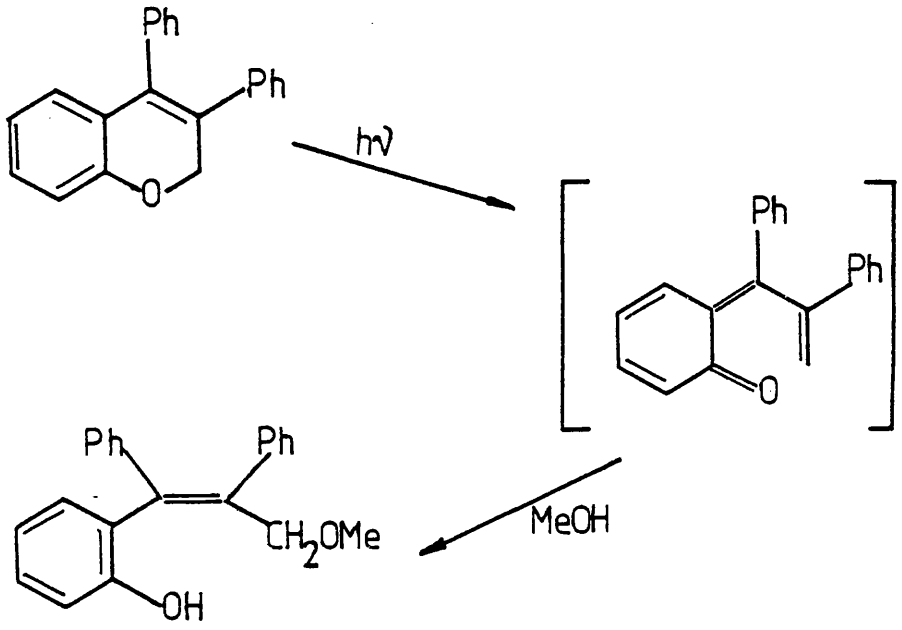


SCHEME 21

completely ring-opening to a coloured intermediate. Thermal reaction allowed a 97% recovery of starting material, with only 3% rearranging to the arylpropenal[31].

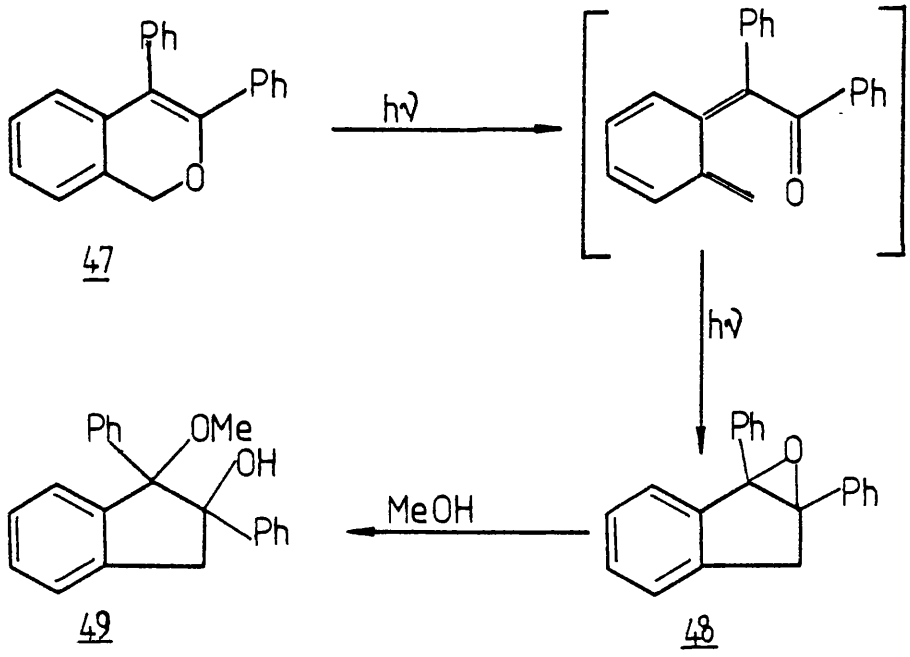
o-Quinoidal intermediates have also been proposed for photochemical reactions of chromenes and isochromenes, differences in subsequent products being attributed to the divergent characteristics of these species. A relatively reactive intermediate from the photolysis of 3,4-diphenylchromene in methanol quickly undergoes a

(1,6)-addition of solvent (Scheme 22).



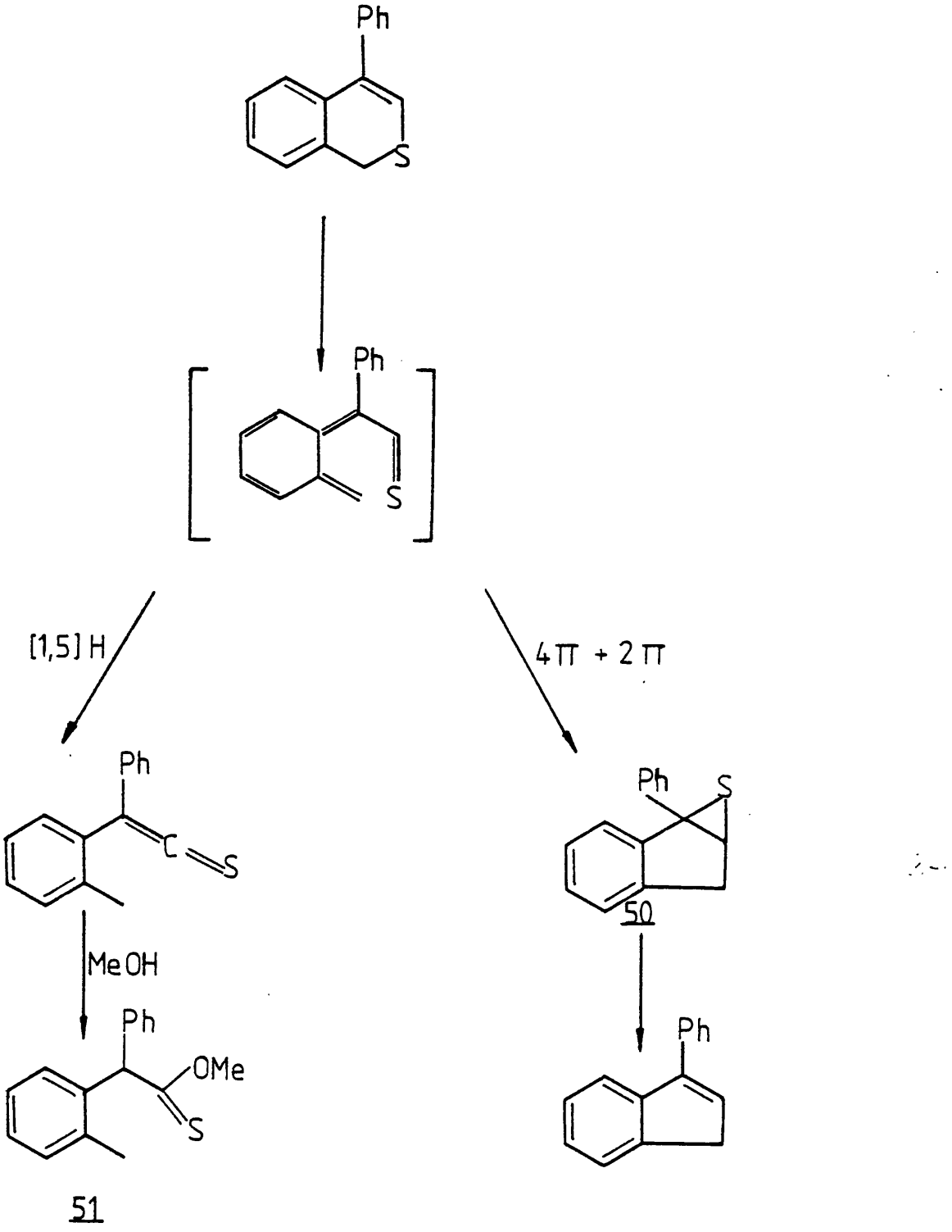
SCHEME 22

Irradiation of isochromene (47), however, gives a quinoidal intermediate sufficiently long-lived, even in methanol, to permit a photochemical 4π + 2π intramolecular cycloaddition leading to an epoxide (48) analogous to the



cyclopropyl derivative (39) obtained from dihydronaphthalenes. Addition of methanol to the epoxide gives alcohol (49)[32].

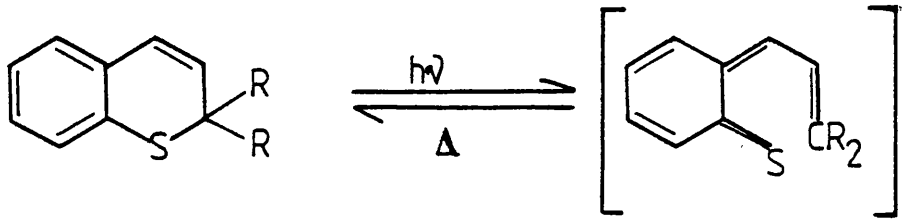
4-Phenylisothiochromene has been found to follow an entirely analogous pathway[32] (Scheme 23), leading to isolation



SCHEME 23

of 1-phenylindene after photo-induced extrusion of sulphur from episulphide (50). Alternatively, a (1,5) hydrogen shift provides a competing reaction, reforming the aromatic ring, subsequent addition of solvent giving thio-ester (51).

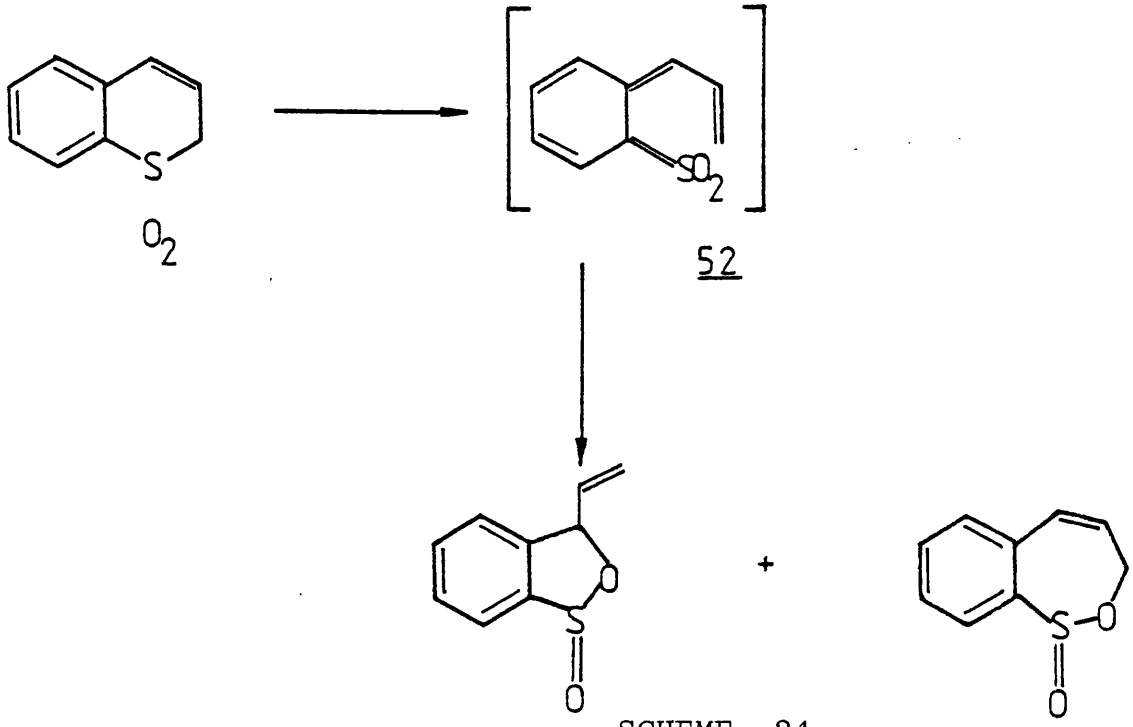
Direct observation of thio-quinoidal intermediates has been achieved by irradiation of thiochromenes in a pentane matrix at -180°C[31, 33-35] (equation (7)). Warming



(7)

caused electrocyclic reversion to starting material.

Similar ring-systems containing sulphur in a higher

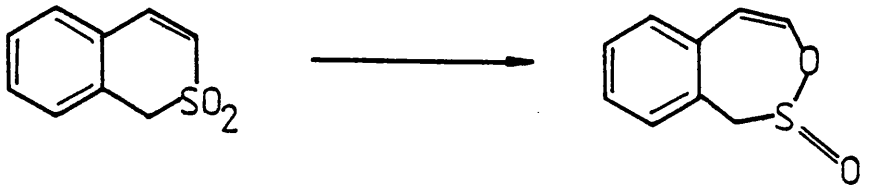


52

SCHEME 24

oxidation state also photolyse to give products explicable in terms of quinoidal intermediates. Ring-closure of (52) by addition through oxygen occurs predominantly at the 4-position to give a five-membered sulphinate ester, with some seven-membered sultine from reaction at the 6-position[36] (Scheme 24). Finlay has demonstrated a comparable thermal reaction of the system[37].

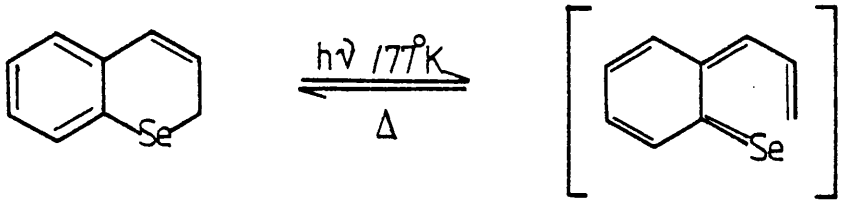
A small amount of ring-expanded product was also isolated from photolysis of (53), the majority giving



53 11%

a methanol adduct across the double bond of the thiopyran ring[38].

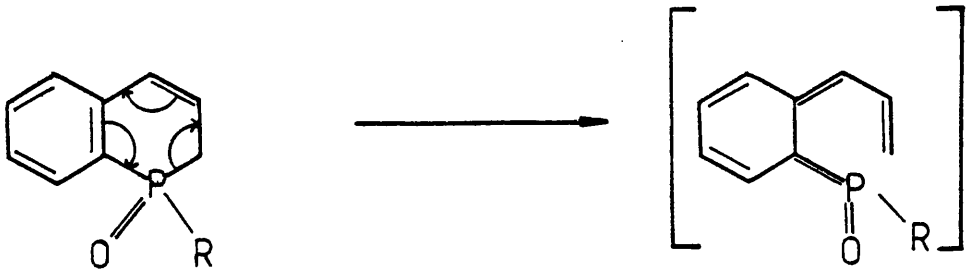
Completing the range of published photochemical reactions of dihydro-heteronaphthalenes, irradiation of the selenium analogue (38e) in an isopentane matrix at 77°K gives an intermediate postulated to be the product of electrocyclic ring-opening[39] (54). Warming the matrix



38e 54

regenerates (38e).

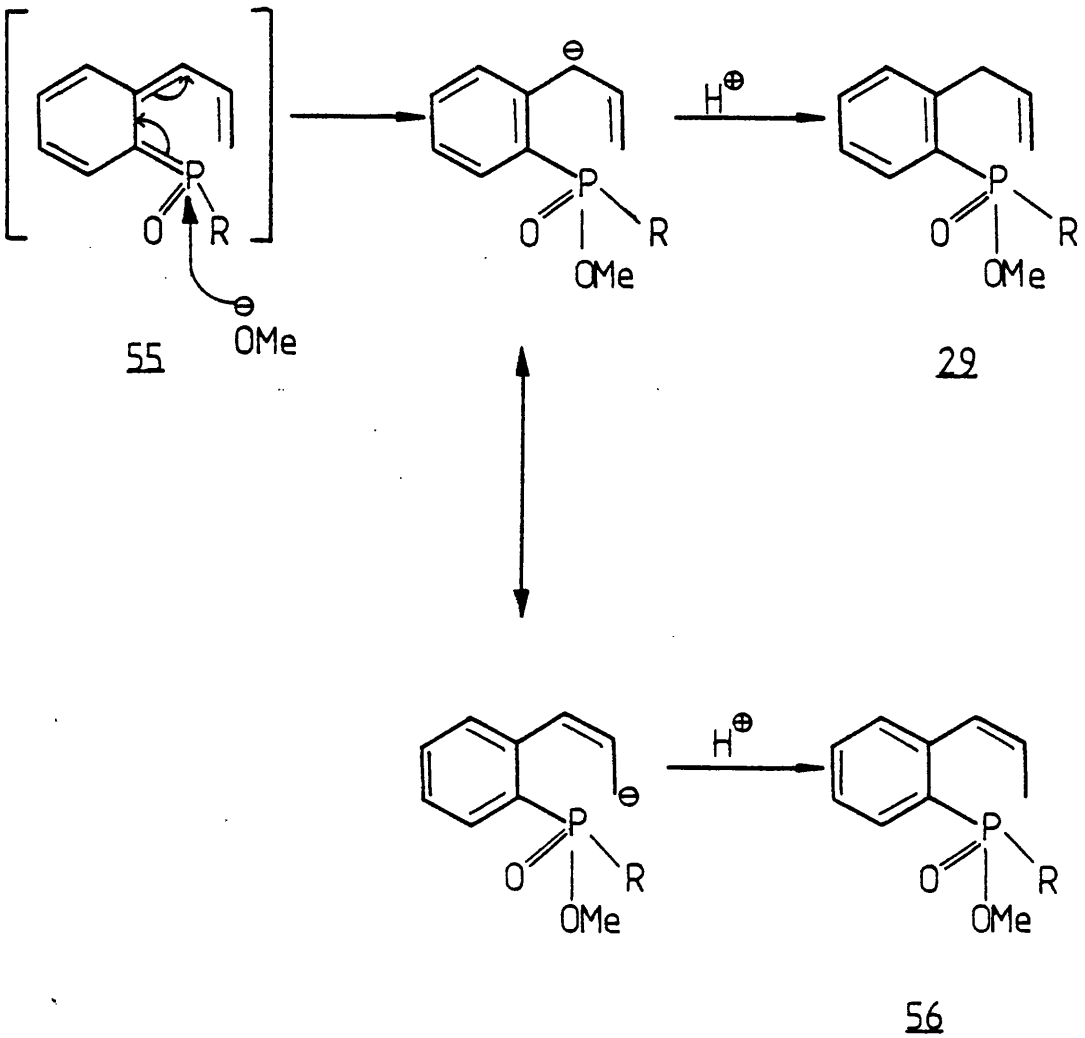
A concerted, electrocyclic ring-opening of a dihydrophosphinoline would give a reactive intermediate (55) analogous to those proposed for equivalent carbon, nitrogen, oxygen, sulphur and selenium systems (equation (8)).



(8)

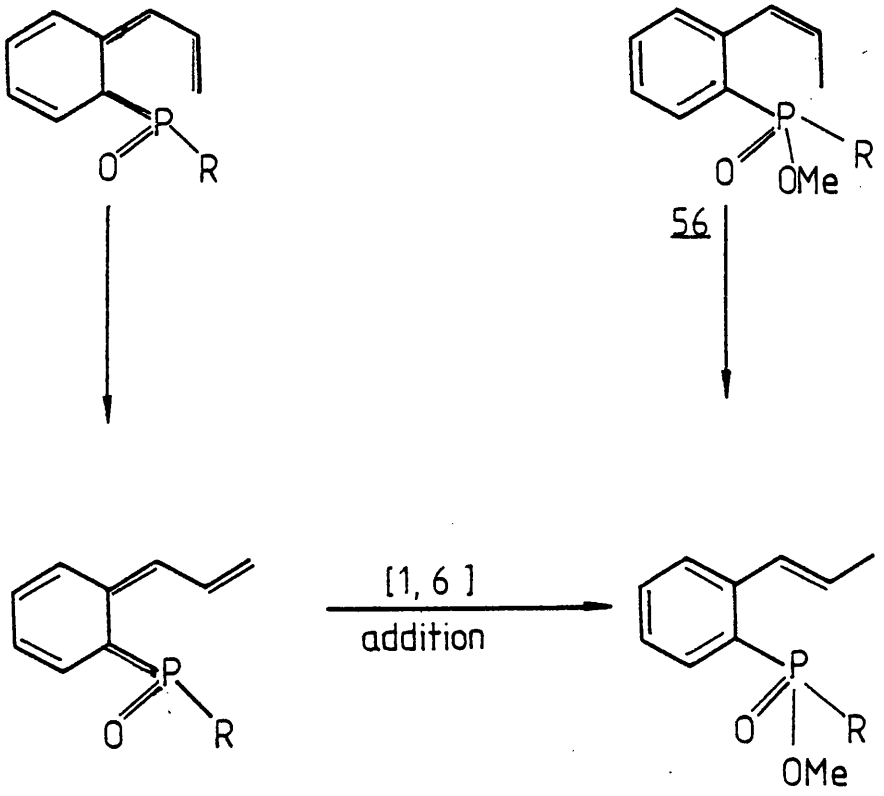
55

The electron affinity of phosphorus in such species would impart a polarisation to the π-system. Attack of a nucleophilic solvent, such as methanol, would therefore occur at phosphorus, while the site of conjugate protonation would be limited by regeneration of the aromaticity of the ring. Thus, addition of solvent could be either (1,4) giving the allyl benzene (29), or (1,6) giving the *cis*-methylstyrene (56) (Scheme 25). The *trans*-styrene (57) observed in the product mixture could arise from isomerisation of (56) under the reaction conditions, or from rearrangement of the quinoidal intermediate from a cisoid to a transoid configuration. Such isomerisations have been described for quinodimethane



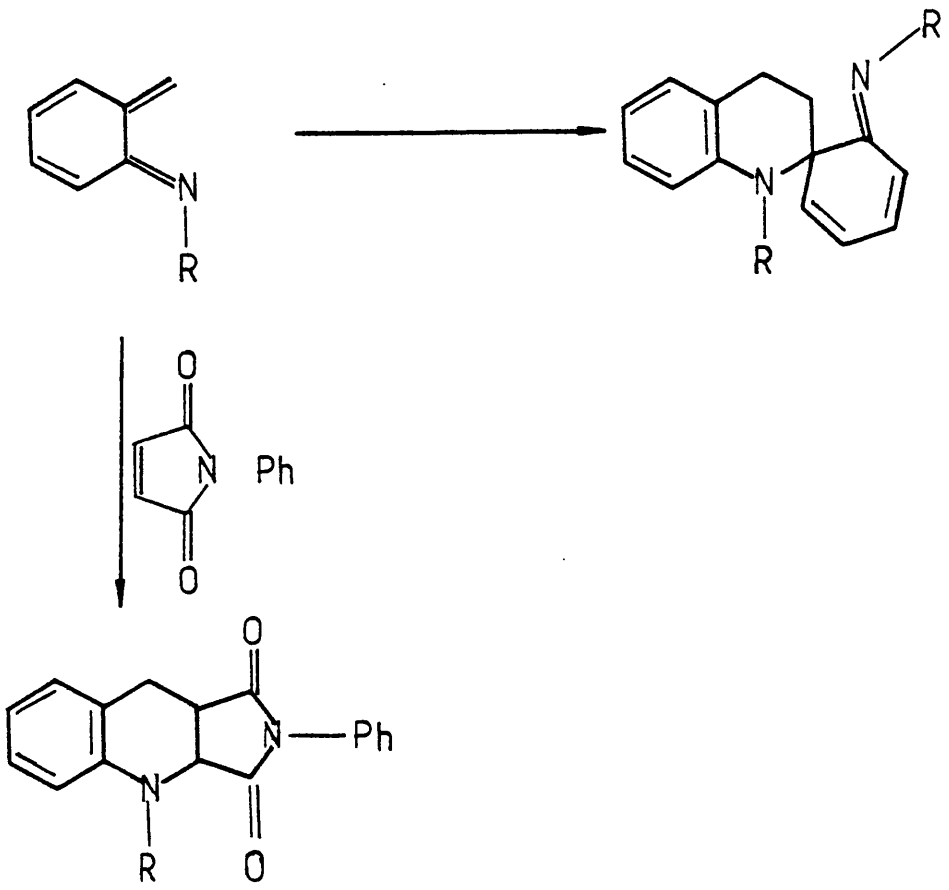
SCHEME 25

derivatives arising from the photolysis of dihydro-naphthalenes[40], and are a necessary preliminary to the $4\pi + 2\pi$ reactions leading to products containing cyclopropane (39), epoxide (48) and episulphide (50) rings. If the *trans*-methylstyrene (57) comes from the *cis*-isomer, it is difficult to explain the continued presence of this latter, energetically unfavoured



57

molecule in the product mixture. Rearrangement of the intermediate, limited in extent by its lifetime in a reactive solvent, could provide an explanation, particularly since (1, 4) addition to either configuration would lead to the allylbenzene, the major isolated product. Although no successful attempts to trap quinoidal intermediates derived from dihydronaphthalene analogues with anything but simple nucleophilic solvents have been reported[10], a similar intermediate in the nitrogen series, obtained by a different route, has been observed to undergo Diels-Alder[41] reactions (Scheme 26). In principle there is no reason why the proposed intermediates, arising from the photolysis



SCHEME 26

of phosphinolines, should not undergo similar cyclo-additions.

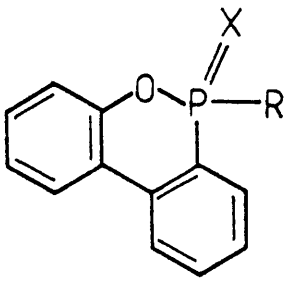
While, from the preliminary results described here, it is not possible to unequivocally decide upon the mechanism of photolytic reaction of dihydrophosphinolines, the weight of literature precedent in analogous systems lies in favour of a concerted pathway. Con-rotatory, electrocyclic ring-opening of these compounds would lead to the proposed phospha-quinoidal intermediates. Carried out at low temperature in a matrix, direct spectroscopic observation of these species may be possible, as with the carbon, nitrogen and sulphur

analogues[33-35]. Products derived from intramolecular reaction after photolysis in an inert solvent may also provide an indication of the operative mechanism.

CHAPTER THREE

CHAPTER 3

Structural modification of a molecule with demonstrable biological activity provides an insight into the relationship between cognate compounds and their physiological effects. This, in turn, may lead to the development of molecules exhibiting enhanced, or more selective activity. Through collaboration with I.C.I. Plant Protection Division, attention was directed towards compounds with potential as growth regulators for plants, so that a description of the incorporation of a fungicide (2-hydroxybiphenyl) into a phosphorus heterocycle excited interest. Since the resultant oxaphosphaphenanthrene (58) contained the *cyclo*hexadienyl unit necessary to allow a photolytic ring-opening, analogous to that observed for phosphinolines, the opportunity for further modification to novel derivatives was available.



58

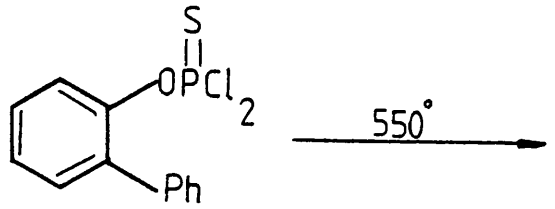
Representatives of this tricyclic system have already found application as flame-retardants[42], metal chelating agents[43], plasticisers and anti-discolourants

for polymers[44,45].

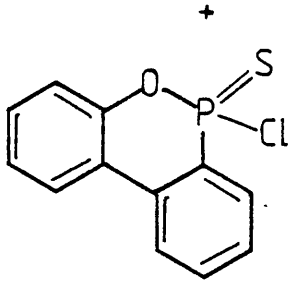
THE SYNTHESIS OF 6-CHLORO-6*H*-DIBENZ(c,e)(1,2)OXAPHOSPHORIN 6-SULPHIDE

The title thiophosphonate (59) was selected for preliminary evaluation of both the biological and chemical potential of the system.

First described as a minor product from the thermolysis of 2-biphenylylphosphorodichloridothioate[47] (60) (equation (9)), two more practicable synthetic

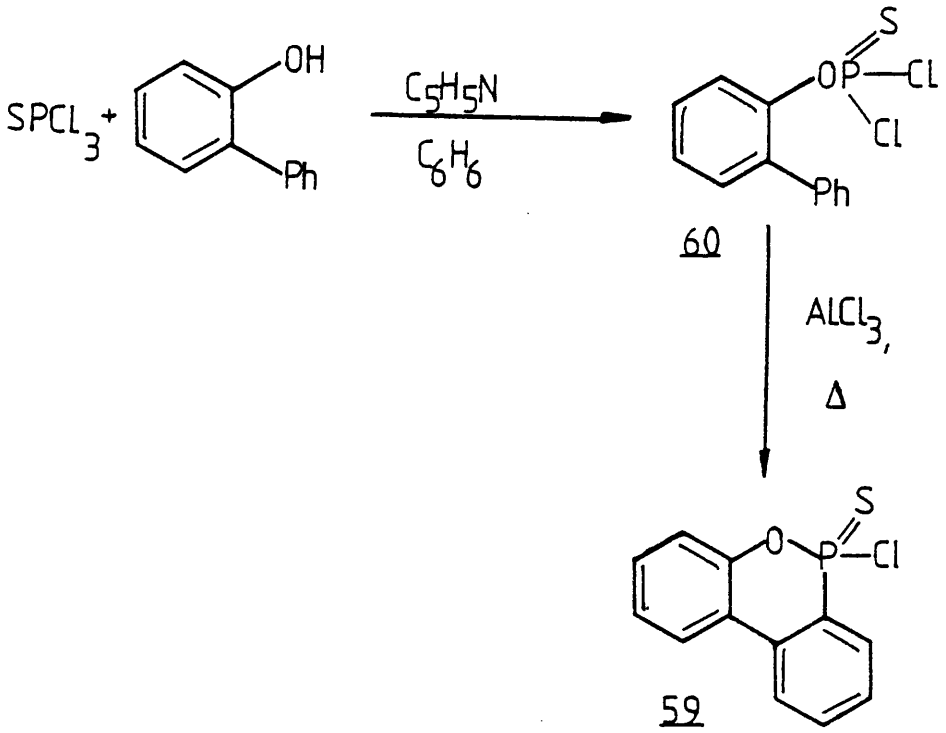


60 75% (9)



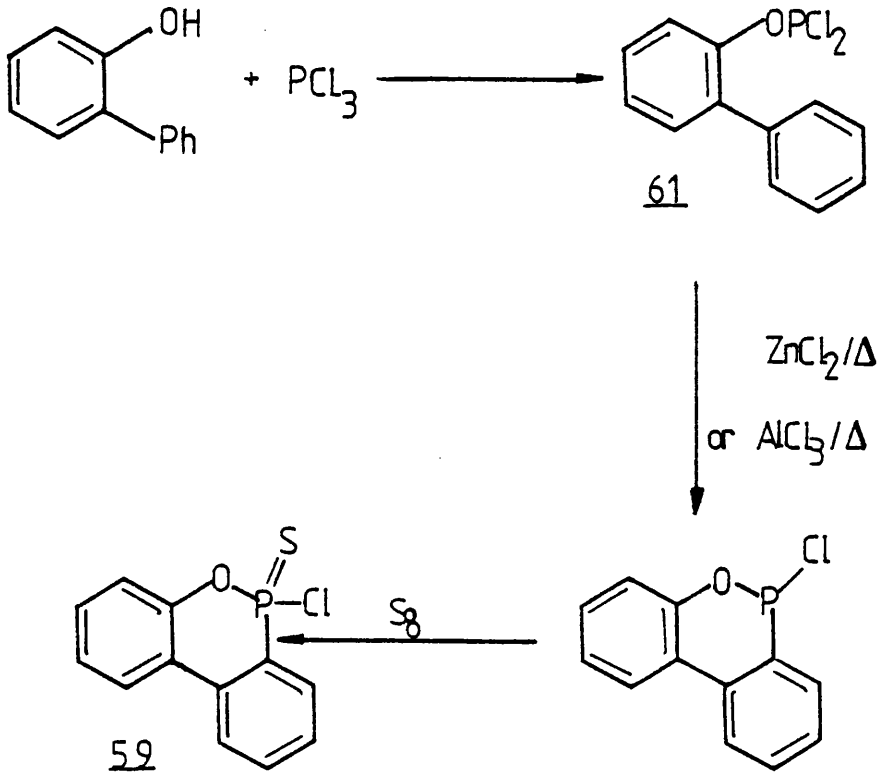
15% 59

routes have been reported. An aluminium chloride catalysed intramolecular Friedel-Crafts reaction of the same phosphorodichloridothioate[48], easily obtained by reaction of 2-hydroxybiphenyl with thiophosphoryl chloride, gives oxaphosphorin (59) directly (Scheme 27).



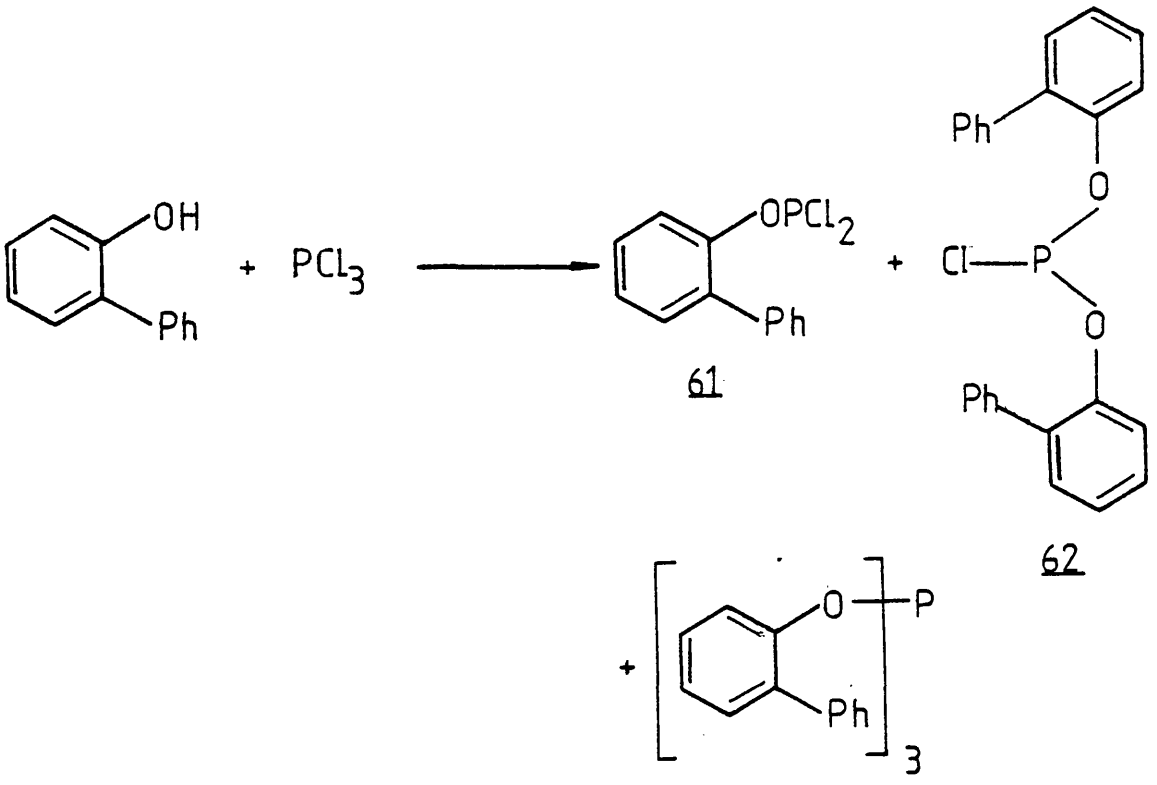
SCHEME 27

Utilising the greater activity of tervalent phosphorus halides in Lewis acid catalysed reactions[49], cyclisation of 2-biphenylylphosphorodichloridite (61), is reported to occur readily in the presence of zinc chloride[50,51]. Oxidation with elemental sulphur affords the desired product (Scheme 28). It was felt, however, that the relative ease of handling of phosphorus compounds in the quinquevalent state more than compensated for the advantage gained by any increase in reactivity of tervalent compounds, so that the chosen synthetic route to (59) was the shorter, outlined in Scheme 27.



SCHEME 28

Equimolar quantities of 2-hydroxybiphenyl and thiophosphoryl chloride, dissolved in benzene and heated under reflux in the presence of one equivalent of pyridine, reacted to give 2-biphenylylphosphorodichloridothioate (60), as a faintly pink syrup. The ^{31}P n.m.r. of this crude product showed a purity of approximately 85%, the rest being evenly distributed between three other compounds. This compares favourably with the equivalent step in the tervalent route (Scheme 28), where an excess of phosphorus trichloride is necessary to reduce the competitive formation of di- and tri-substituted products (62 and 63 respectively).



61

62

63

Attempted distillation of phosphorodichloridothioate (60) led to decomposition, so that Friedel-Crafts cyclisation, was carried out on the crude product, as recommended in the literature[48]. Addition of a small quantity of aluminium chloride to neat (60), and raising the temperature to 180°C(bath) until evolution of hydrogen chloride had ceased (6-8h), led not to the single product (59) anticipated[48], but to a 1:1 mixture of compounds, ^{31}P spectroscopy showing peaks at +73.4 and +50.0p.p.m. Column chromatography on alumina followed by recrystallisation from dichloromethane/hexane gave a small sample of 6-chloro-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-sulphide (59), showing an absorption at +73.4p.p.m. in the ^{31}P spectrum. Repetition of the reaction sequence with similar results

prompted an investigation of the conditions under which the cyclisation step was carried out.

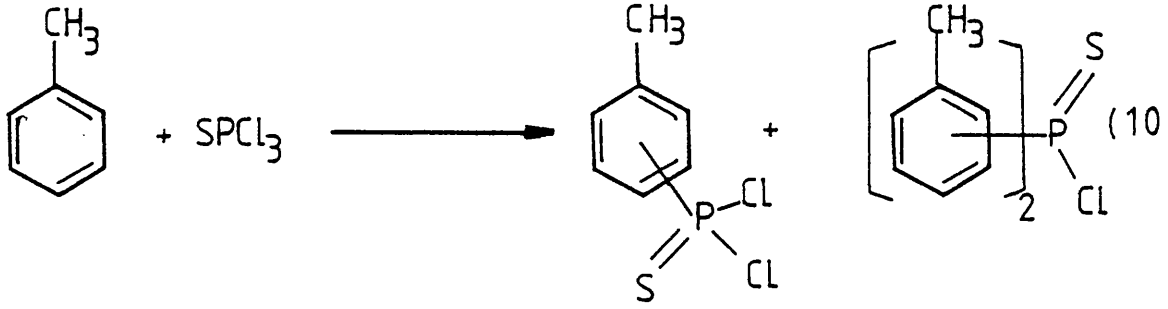
Much of the published work on the Friedel-Crafts chemistry of phosphorus halides concerns the tervalent state, relatively little information being available about the less active quinquevalent compounds[49]. Nevertheless, some general observations emerge which are equally applicable to both[52]:

(i) Yields from Friedel-Crafts reactions show a strong dependence upon the ratio of reactants, the aluminium chloride resembling a coreactant more than a true catalyst.

(ii) Both products and reactants complex strongly to the Lewis acid, requiring the development of efficient work-up procedures to avoid obtaining drastically reduced yields.

(iii) In terms of both rate and purity, the use of a suitable inert solvent often benefits Friedel-Crafts reactions involving phosphorus.

More specifically relevant are reports by Michaelis[53-55] on the formation of mono- and di-substituted products from the aluminium chloride catalysed reaction between toluene and thiophosphoryl chloride (equation (10)). A detailed investigation of the aluminium chloride catalysed reaction of thiophosphoryl chloride with benzene by Maier[56,57], explores the nature of the complex formed between the Lewis acid and the phosphorus halide. Isolation

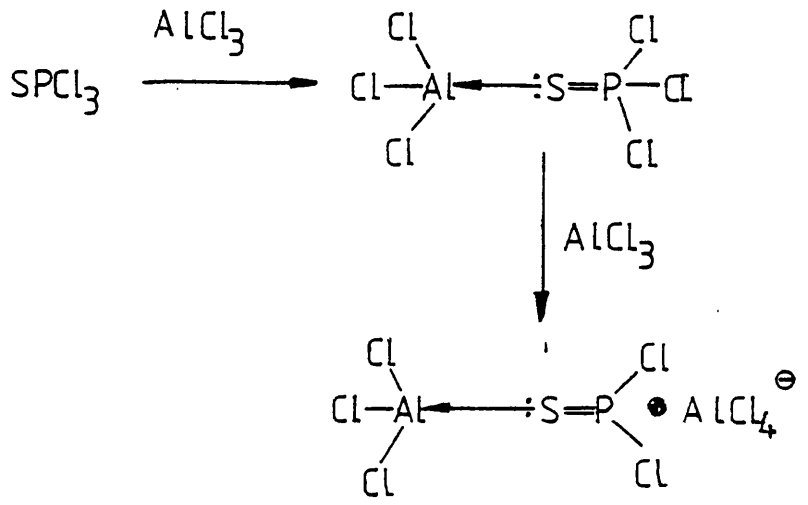


of the mono-substituted product is complicated by the ease and rapidity of further reaction under the conditions employed. Optimum conditions for the formation of phenylphosphonodichloridothioate (64) combine equimolar quantities of phosphorus halide and benzene with two equivalents of aluminium chloride (equation (11)).

$$PhH + SPCl_3 \xrightarrow{2AlCl_3} \underset{50\%}{PhP(S)Cl_2} + \underset{43\%}{Ph_2P(S)Cl} + \underset{7\%}{Ph_3PS} \qquad (11)$$

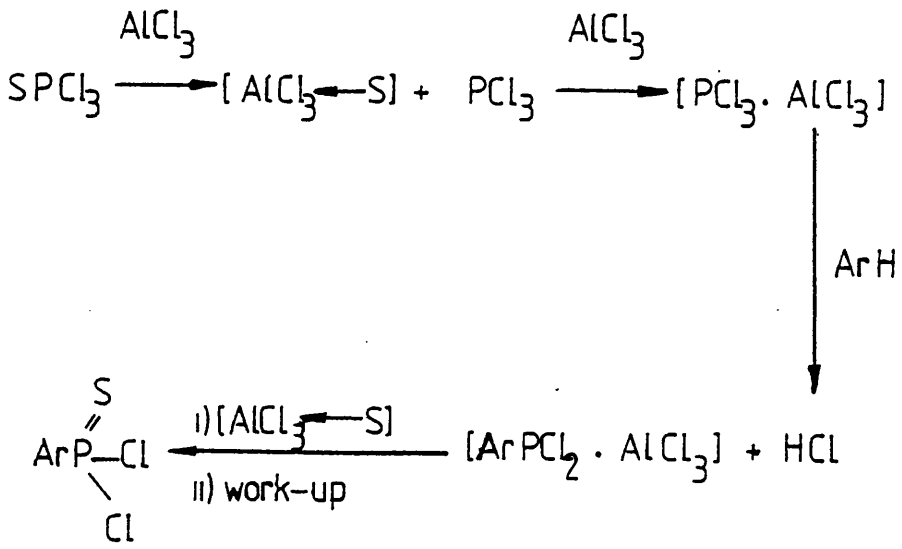
64

Strong complexation to the thiophosphoryl function holds one molecule of aluminium chloride inactive, while the second remains free to act as a chloride-ion acceptor in the Friedel-Crafts reaction (Scheme 29), activating the thiophosphoryl chloride towards nucleophiles[57]. It is



SCHEME 29

interesting to note that an aluminium chloride catalyst is utilised in the large-scale preparation of thiophosphoryl chloride[58], by the oxidation of phosphorus trichloride with elemental sulphur. From this has arisen the suggestion of a temporary, reductive dissociation of the thiophosphoryl chloride in the presence of the Lewis acid[49], followed by participation of the reactive tervalent halide in the Friedel-Crafts reaction, and ultimate reoxidation to give the products (Scheme 30). Complete removal of sulphur seems unlikely, however, since the products obtained from substituted aromatic compounds and thiophosphoryl chloride possess a different orientation to those obtained with phosphorus trichloride[59]. Further indication of at least a partial cleavage of the phosphorus-sulphur bond comes from the observation that Lewis acids active in sulphuration of phosphorus trichloride



SCHEME 30

($AlCl_3$, $AlBr_3$ and $EtAlCl_2$) also catalyse Friedel-Crafts reactions of the resultant thiophosphoryl chloride, while others such as zinc chloride or ferric chloride are not effective for either purpose[60].

Applied to the cyclisation of 2-biphenylylphosphorodichloridothioate (60) the preceding information suggested a number of modifications to the experimental procedure. The original conditions had produced a mixture of products, with no remaining starting material. The unwanted product may have arisen from either a parallel, possibly intermolecular process, or by subsequent reaction of the cyclised product. A reduction in the severity of conditions, and use of a diluting solvent should have decreased the likelihood of both these sources of side-products, and

favoured an intramolecular cyclisation. The efficiency of reaction should also have been improved by increasing the quantity of Lewis acid present, a surmise investigated in a series of experiments, summarised in Table 1.

No visible reaction occurred when 2-biphenylyl-phosphorodichloridothioate (60) was stirred at ambient temperature in an inert solvent (dichloromethane or tetrachloroethane[49]) in the presence of up to two equivalents of aluminium chloride. Observation of the ^{31}P spectrum showed no change in chemical shift commensurate with formation of a complex between (60) and the Lewis acid[57], the absorption remaining at +53.5 p.p.m. Heating the mixture under reflux in tetrachloroethane led to a gradual depletion of the phosphorus content of the solution and formation of a dark precipitate, of complexed thio-phosphate. This solid proved remarkably resistant to hydrolysis, overnight stirring in 6M sulphuric acid being necessary to obtain a poor recovery of starting material. Prolonged heating of the precipitated complex led, after work-up, to a product mixture shown by ^{31}P spectroscopy to contain a small quantity of cyclised material, together with a secondary product with a chemical shift of +50.0 p.p.m. and starting phosphorodichloridothioate (60).

In view of the difficulties of solubility, and intractibility of products in these reactions, a more detailed evaluation of a neat mixture was carried out. One

TABLE 1

SOLVENT	MOLAR RATIO ROP(s)Cl_2: $AlCl_3$	REACTION CONDITIONS	REACTION TIME	REMARKS
CH_2Cl_2	9:1	Stirred at room temperature	9 days	No reaction. Starting material recovered.
$Cl_2CHCHCl_2$	0.5:1	Stirred at room temperature	1h	No reaction, no complex formation observed.
$Cl_2CHCHCl_2$	0.5:1	Under reflux	2h	Solid complex precipitated out over period, depleting phosphorus-containing material in solution. Complex difficult to hydrolyse.
$Cl_2CHCHCl_2$	0.8:1	Under reflux	4h	Small amount of cyclised product (ca.5%) plus secondary product.
NONE	9:1	100^{o}, stirred	1h	No reaction.
NONE	9:1	200^{o}, stirred	1h	Reaction complete to give only cyclised material.

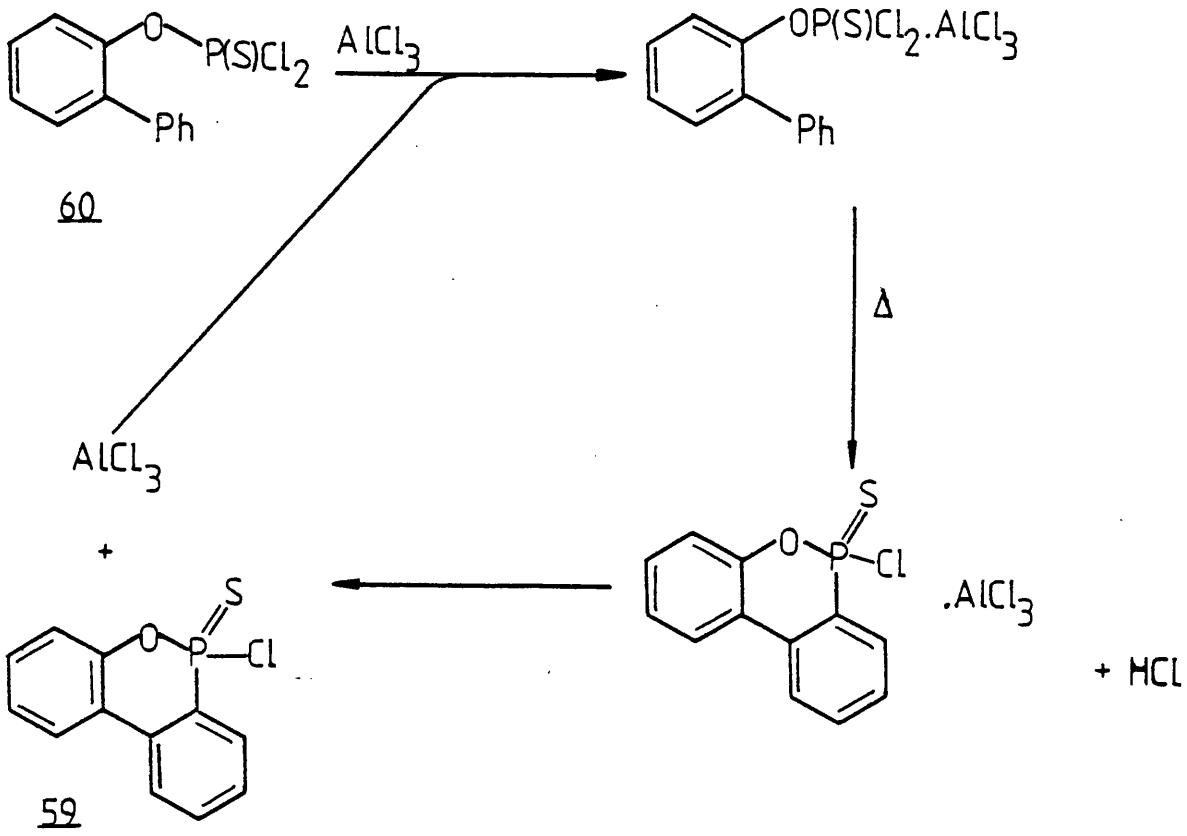
tenth of a molar equivalent of aluminium chloride was added to a sample of (60), and the temperature raised to 100°C. Investigation of an aliquot by ^{31}P n.m.r. showed no discernible reaction after 1h, and the bath temperature was gradually elevated to 200°C, when a rapid evolution of hydrogen chloride occurred. A further aliquot revealed the reaction to be complete in less than 1h, with only very minor phosphorus-containing side-products.

A standard aqueous work-up, with extraction into dichloromethane followed by recrystallisation afforded 6-chloro-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-sulphide (59) in 90% yield.

A number of inferences may be drawn from the results obtained, particularly in consideration of the departure of the optimum conditions from the published norm[49,56,57]. A considerable energy barrier to formation of a complex between (60) and aluminium chloride is apparent, requiring a temperature of 147°C for 2h. This is in contrast to unsubstituted thiophosphoryl chloride, where rapid formation of an adduct occurs at room temperature[57]. Even higher temperatures proved necessary to induce the extremely stable complex between the Lewis acid and (60) to react further.

The efficacy of a catalytic quantity of Lewis acid is indicative of a dissociation of the product-aluminium chloride adduct under the reaction conditions, allowing complexation with a further molecule of starting material,

and continuation of the catalytic cycle (Scheme 31).



SCHEME 31

Whether responsibility lies with a kinetic or thermodynamic difference between the two complexes is not possible to decide.

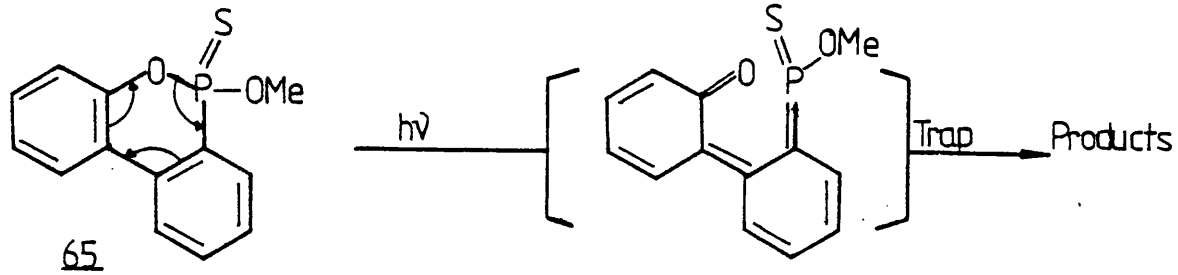
THE PHOTOLYSIS OF 6-METHOXY-6*H*-DIBENZ(c,e)(1,2)OXAPHOSPHORIN 6-SULPHIDE

Before studies of the photochemistry of the dibenzoxaphosphorin system were begun the chloro-substituent of (59) was exchanged for a less reactive methoxy-group.

Treatment of (59) with one equivalent of methoxide in methanol afforded 6-methoxy-6*H*-dibenz(c,e)(1,2) oxaphosphorin 6-sulphide (65), almost quantitatively.

An ultraviolet spectrum of this compound showed absorption to be almost at a maximum at 254nm (98% of ε_{max}), making this the preferred wavelength for irradiation.

Since the oxaphosphorin possesses a hetero-*cyclo*hexadiene unit, it was hoped that an electrocyclic ring-opening, similar to that proposed for phosphinolines, would generate a reactive intermediate, the trapping of which could lead to novel phosphorus compounds (Scheme 32).



SCHEME 32

Photolysis of a methanolic solution of (65), monitored by gas or thin-layer chromatography, proceeded extremely slowly when using a Rayonet photochemical reactor. The reaction was, therefore, transferred to a more efficient falling-curtain apparatus (Figure 1), allowing the continuous passage of a thin film of solution

FALLING-CURTAIN PHOTOLYSIS APPARATUS

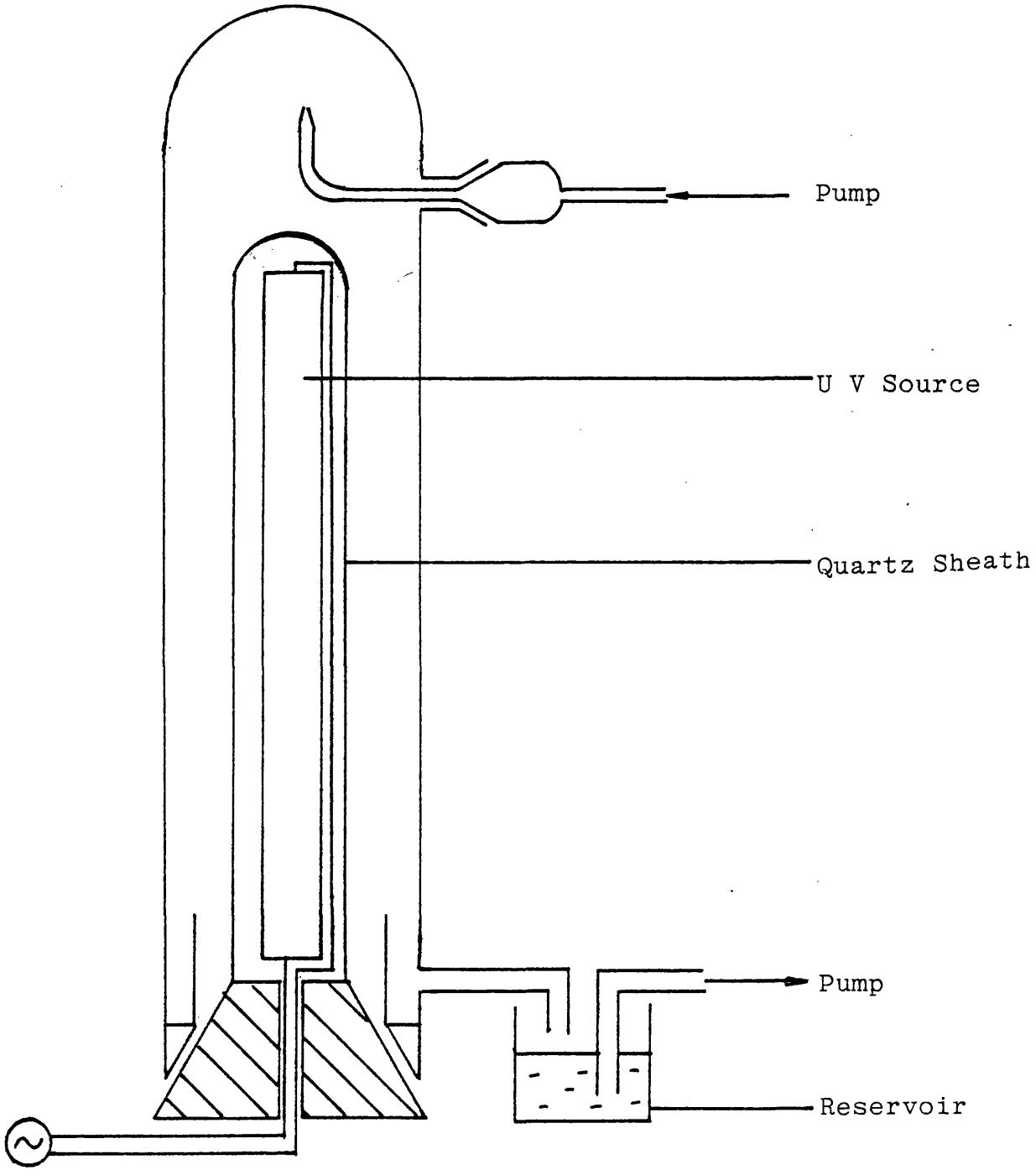


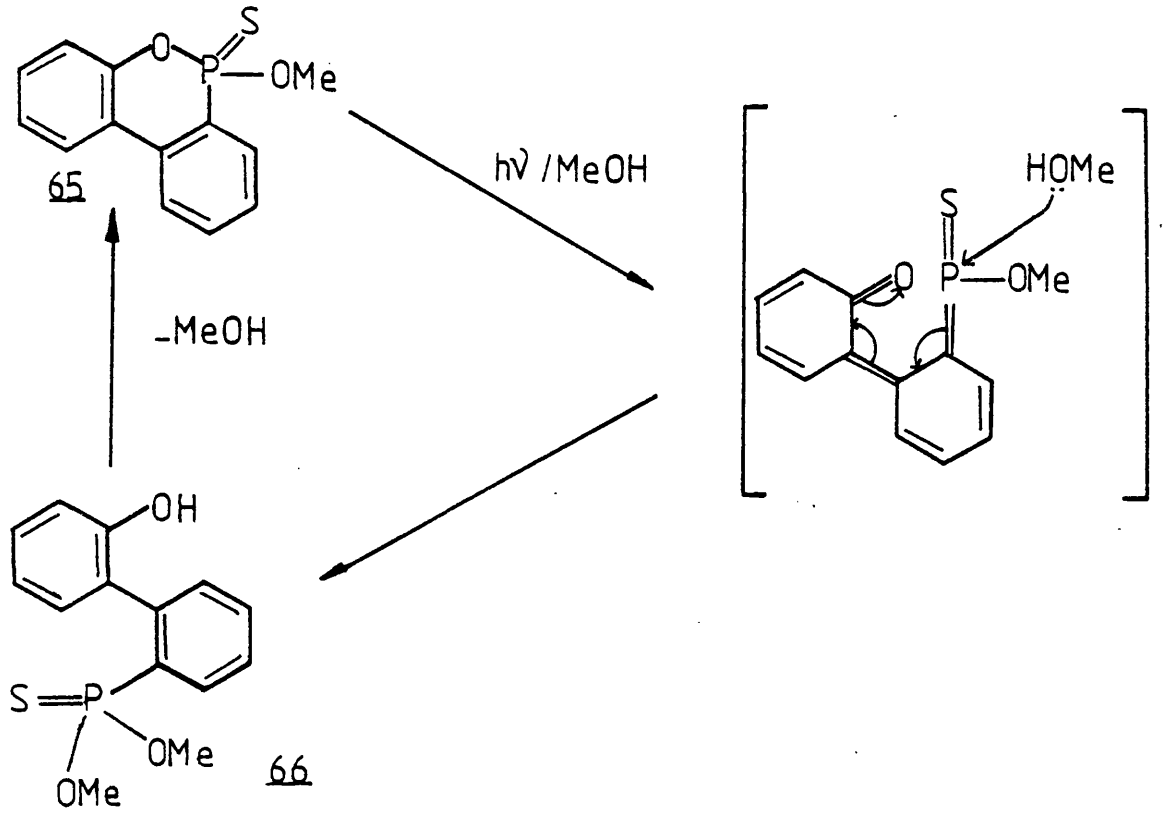
FIGURE 1

from a large reservoir over a low-pressure mercury lamp. The photolysed solution could then be collected and returned to the resorvoir for recycling.

Irradiation of the methoxyoxaphosphorin (65), in methanol, at 254 nm caused the gradual replacement of starting material by three products, all slower running by T.L.C. (silica plates eluted with chloroform). Two major absorptions appeared in the ^{31}P spectrum at +87.7, and +11.9p.p.m., and a minor peak at +20.1p.p.m., in addition to unconsumed starting thiophosphonate at +77.5p.p.m. The sharp P-OMe doublet in the ^{1}H n.m.r. spectrum of (65) was replaced by a complex absorption pattern centred around the same chemical shift of +3.7p.p.m. A D_2O-exchangeable peak at +9.0p.p.m. appeared in the product mixture, integrating to one proton relative to the aromatic absorptions.

Separation of starting material was easily achieved by column chromatography, while the photolysis products proved more difficult. Repeated elution on thick-layer plates led only to the isolation of further starting material, presumably through reversion of one or more of the products. If electrocyclic ring-opening followed by trapping with methanol had occurred, this could be explained in terms of recyclisation of the resultant phenol (66)(Scheme 33).

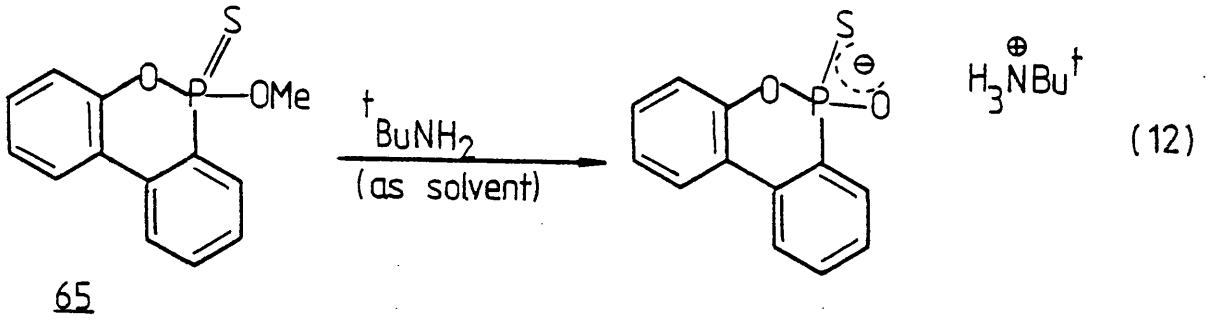
An attempt to fix any such product by methylation with diazomethane gave no discernible change in the ^{1}H or ^{31}P spectra, and led to no alleviation of the separation difficulties. Analysis by G.C. appeared promising, but



SCHEME 33

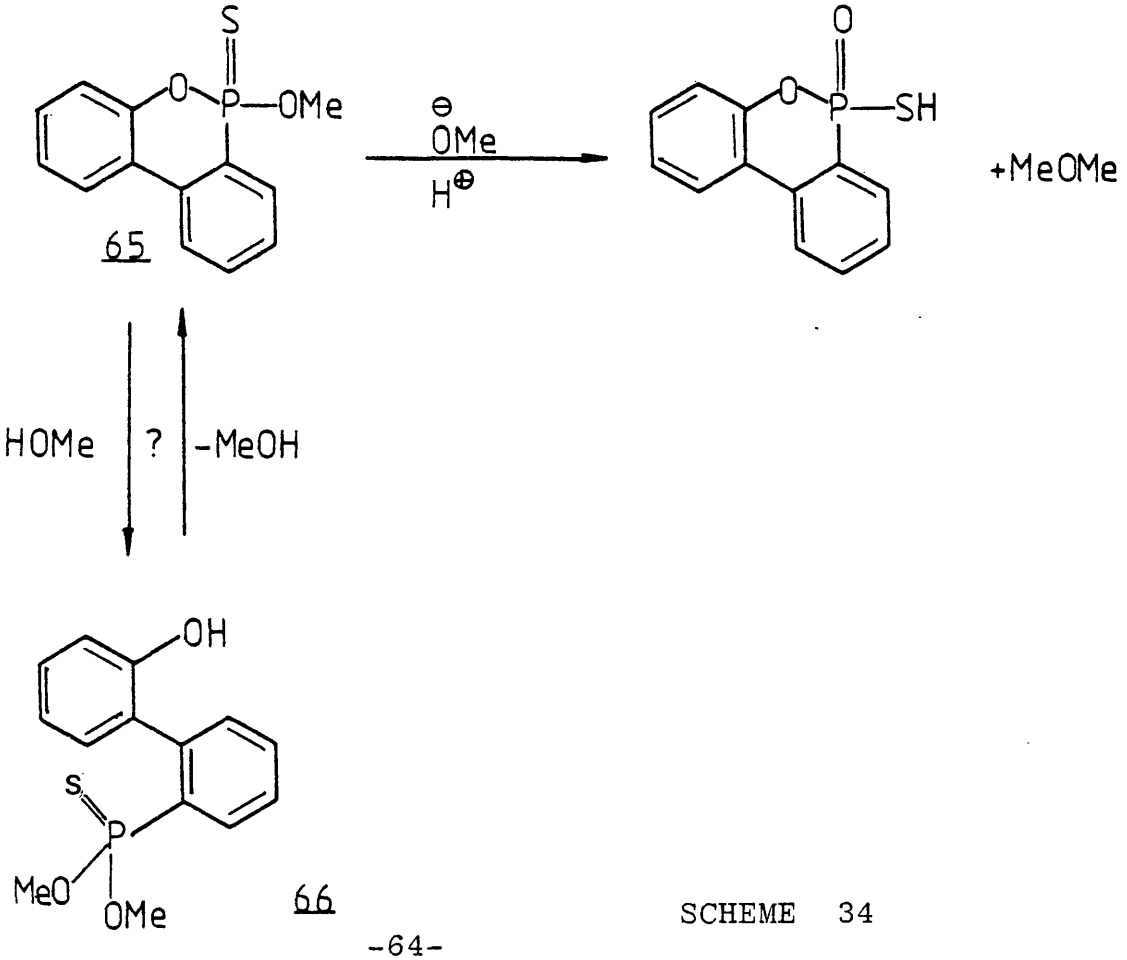
proved not to be reproducible.

Attempted use of *t*-butylamine as an alternative nucleophilic solvent led to a rapid demethylation of the thiophosphonate ester, prior to photolysis (equation (12)). This reaction was investigated more fully, and the results appear in the following Chapter.



(12)

Dealkylation was also observed after prolonged heating of (65) with methoxide in methanol, performed in the hope of ring-opening the oxaphosphorin to give a comparison sample of phenol (66). It is possible that attack of methoxide did not take place at phosphorus, or that the reverse ring-closure occurred equally readily. In either case a slow, but irreversible dealkylation to form the thiophosphonic acid and dimethyl ether (Scheme 34)



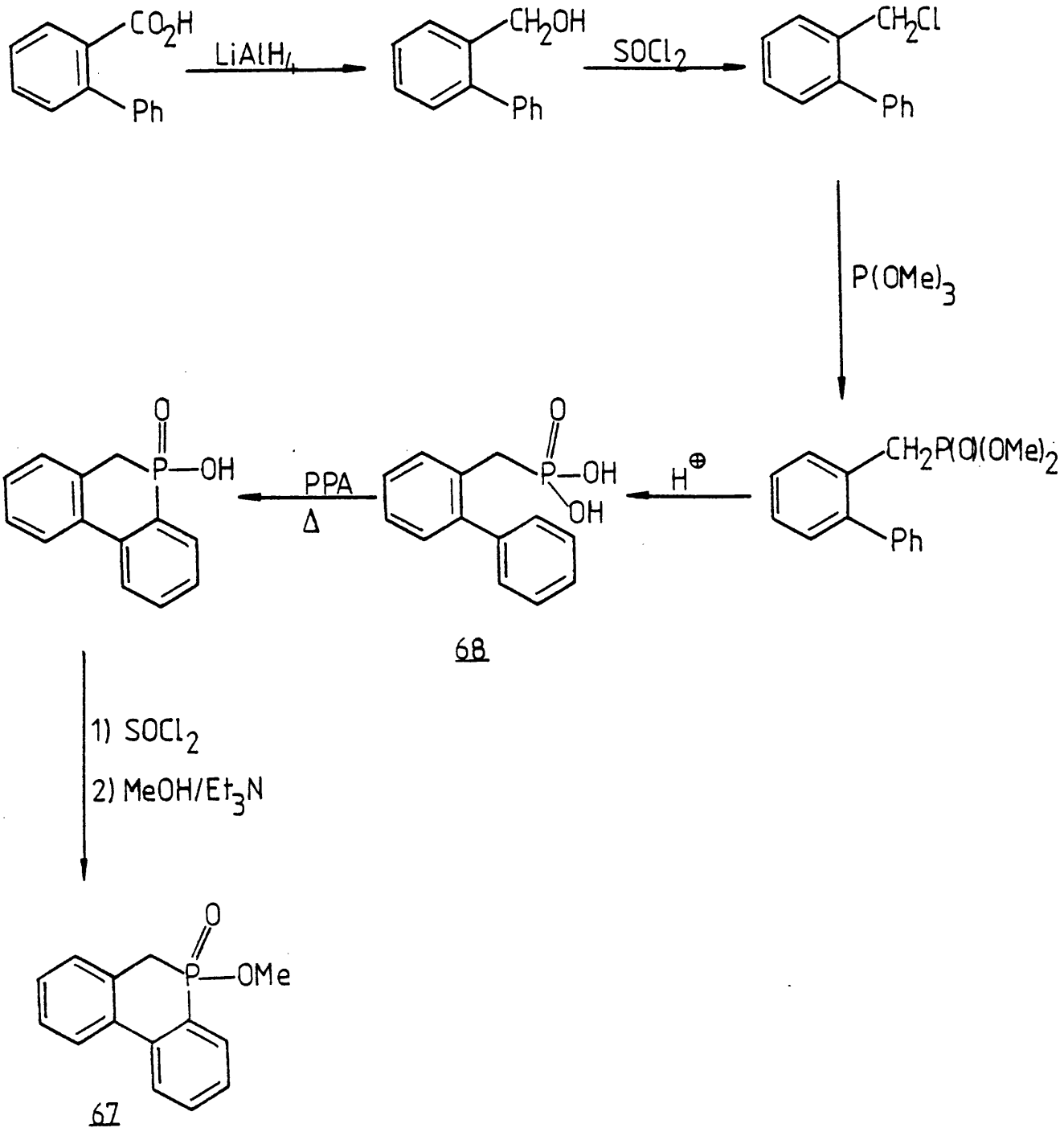
SCHEME 34

gradually consumed the starting ester (65).

With no experimental evidence for the electrocyclic generation of a quinoidal intermediate, and in view of the difficulty experienced in separating the products that were formed on photolysis of oxaphosphorin (65) in a simple, nucleophilic solvent, it did not seem reasonable to attempt more sophisticated trapping experiments. An evaluation was therefore made of an analogous system, with the ring oxygen replaced by carbon, so that photolytic products would be less inclined to recyclise, and with lower polarity be easier to separate.

THE SYNTHESIS AND PHOTOLYSIS OF 9,10-DIHYDRO-9-METHOXY-9-PHOSPHAPHENANTHRENE 9-OXIDE

9,10-Dihydro-9-methoxy-9-phosphaphenanthrene 9-oxide (67), still containing the structural elements required for electrocyclic ring-opening, was prepared by a modification of Lynch's method[61], summarised in Scheme 35. PPA-mediated cyclisation of 2-biphenylylmethylphosphonic acid (68) was found to give better yields than those obtained by Lynch for a thermal dehydration. Conversion of the cyclic acid to a phosphinyl chloride with thionyl chloride, followed by substitution with methanol gave the title ester (67) in 22% overall yield.

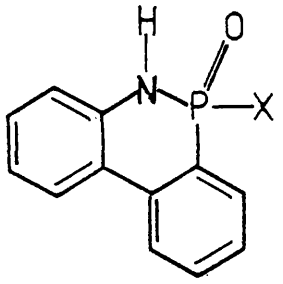


SCHEME 35

Photolysis of the methoxyphosphaphenanthrene in methanol, with 254nm wavelength light proved completely ineffective, a quantitative recovery of (67) being obtained even after 7d continuous irradiation in the falling-curtain

apparatus.

From this lack of photochemical reactivity of the phosphaphenanthrene (67), it appears likely that disruption of two aromatic systems, to give the quinoidal reactive intermediate, has too high an energy barrier to proceed under the conditions used. It is also reasonable, therefore, to conclude that the oxaphosphorin (65) does not undergo a concerted reaction, and that the products arise from alternative mechanisms. With doubt cast upon the concept of using such systems as a source of potentially biologically active, novel phosphorus derivatives, the synthesis of further analogues such as an azaphosphorin[62,63] (68) was of questionable value, the return being unlikely to balance the invested effort.

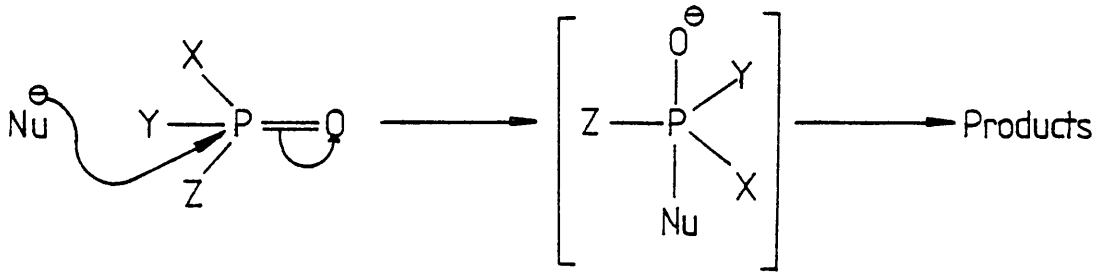


68

CHAPTER FOUR

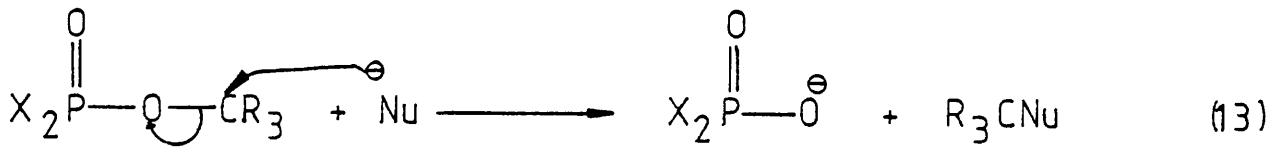
CHAPTER 4

Two centres at which nucleophilic substitution may occur are present in quinquevalent aliphatic phosphorus esters. Attack of the nucleophile at phosphorus generates a pentacoordinate intermediate[64], usually collapsing to products by ejection of a suitable leaving-group (Scheme 36). Alternatively, substitution at carbon causes loss of the anion of the appropriate phosphorus acid



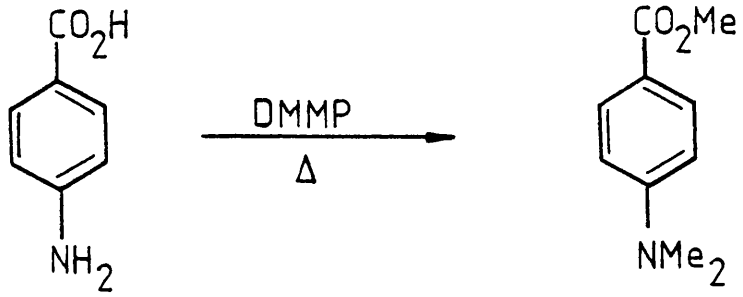
SCHEME 36

(equation (13)). This transference of an aliphatic group to the nucleophile forms the basis of the use of phosphate[65-72] and phosphonate[73-75] esters as alkylating agents for a variety of substrates, including amines, carboxylic acids, aromatic and aliphatic alcohols and thiols.



(13)

The reaction conditions normally employed cause complete alkylation of nucleophilic sites within the molecule, amino acids for example, being methylated on both oxygen and nitrogen (equation (14)) when treated with dimethyl methylphosphonate[73] (DMMP) at 180°C for 2.5h. Less severe conditions, however, allow a more selective

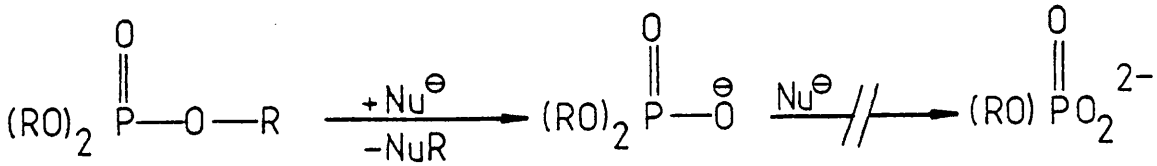


(14)

monoalkylation of adenine, and other biochemical bases[71,73].

THE DEALKYLATION OF PHOSPHORUS ESTERS

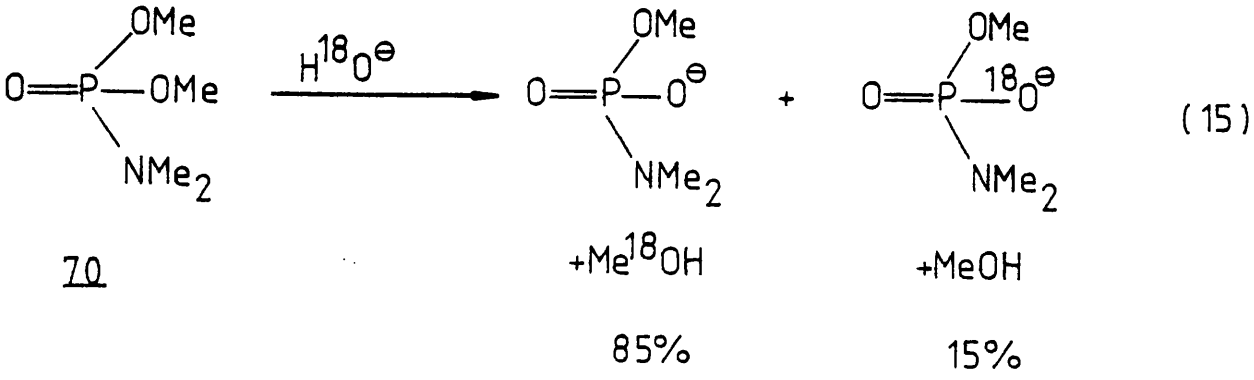
Implicit in the alkylation of nucleophiles by phosphorus reagents, is the complementary dealkylation of the ester. Investigation of the phosphorus content of the product mixture from an alkylation reaction has shown that under normal circumstances only a single alkyl group is removed[70, 76-77], the resultant anion (69) being resistant to further reaction (Scheme 37).



69

SCHEME 37

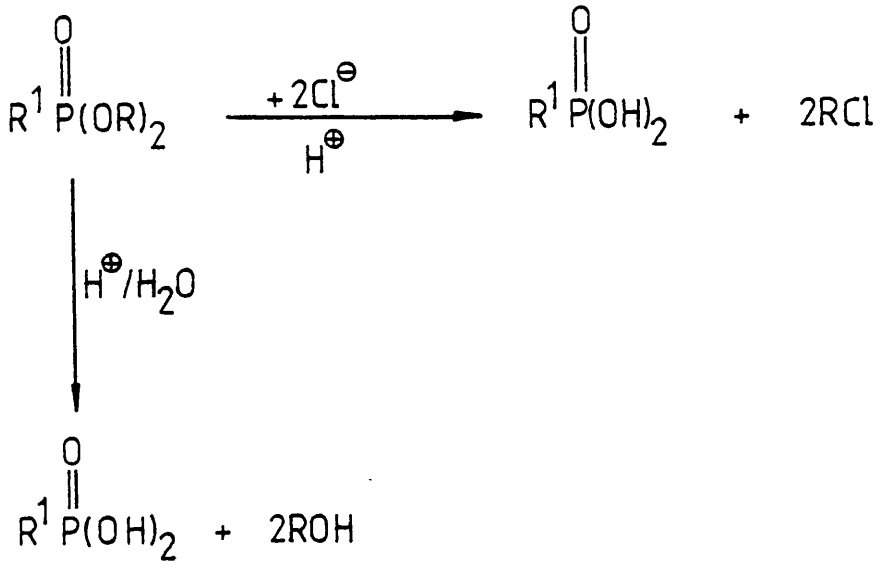
Dealkylations of this sort have been observed with a wide range of nucleophiles. Although usually found to proceed by substitution at phosphorus, the alkaline hydrolysis of phosphorus esters in some instances may include a substantial contribution from attack of hydroxide at carbon. The hydrolysis of phosphoramide (70) with ^{18}O-labelled alkali[78] shows only 15% incorporation into the phosphorus anion, 85% occurring in the liberated methanol (equation (15)), indicating preferential reaction at carbon.



70 (15)

A similar competing pathway has been reported during acid hydrolyses, particularly with hydrogen halides, where the counter-ion may attack at carbon to produce alkyl halides, in addition to the alcohol from normal hydrolysis[76] (Scheme 38).

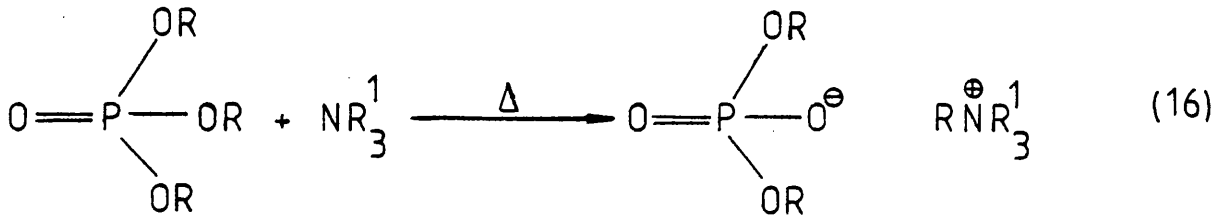
Dealkylation by halide ions also occurs under neutral conditions, the principal cause of appreciable losses of phosphonic acid diesters formed by the Michaelis-Becker reaction[79].



SCHEME 38

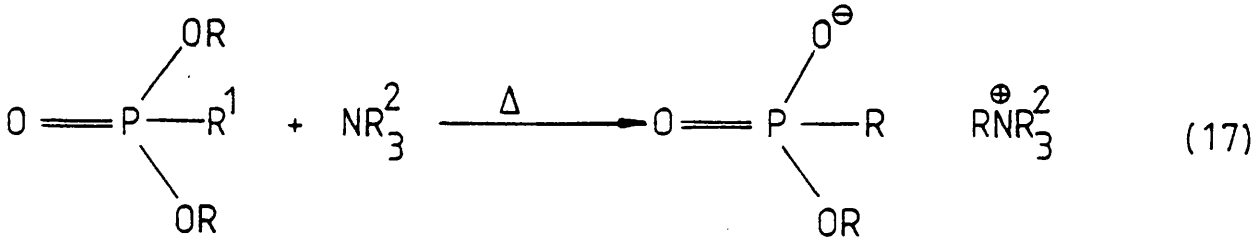
Transfer of an alkyl group from phosphorus esters has been reported for a number of other nucleophiles including cyanate, thiocyanate, thiolate anions and thiourea which, in addition to those already mentioned, are collected in a comprehensive review by Hilgetag and Teichmann[80]. Most of the literature published on this type of reaction, however, concerns the interaction of amines with phosphorus esters. In addition to the numerous descriptions of alkylation of amines[71-77,80], some attention to the phosphorus residue has provided information on dealkylation by nitrogen nucleophiles. Heating trialkyl phosphates in the presence of a tertiary amine, such as *N*-methylmorpholine or triethylamine, leads to quaternisation of the amine, with concomitant dealkylation

of the ester[81] (equation (16)).



(16)

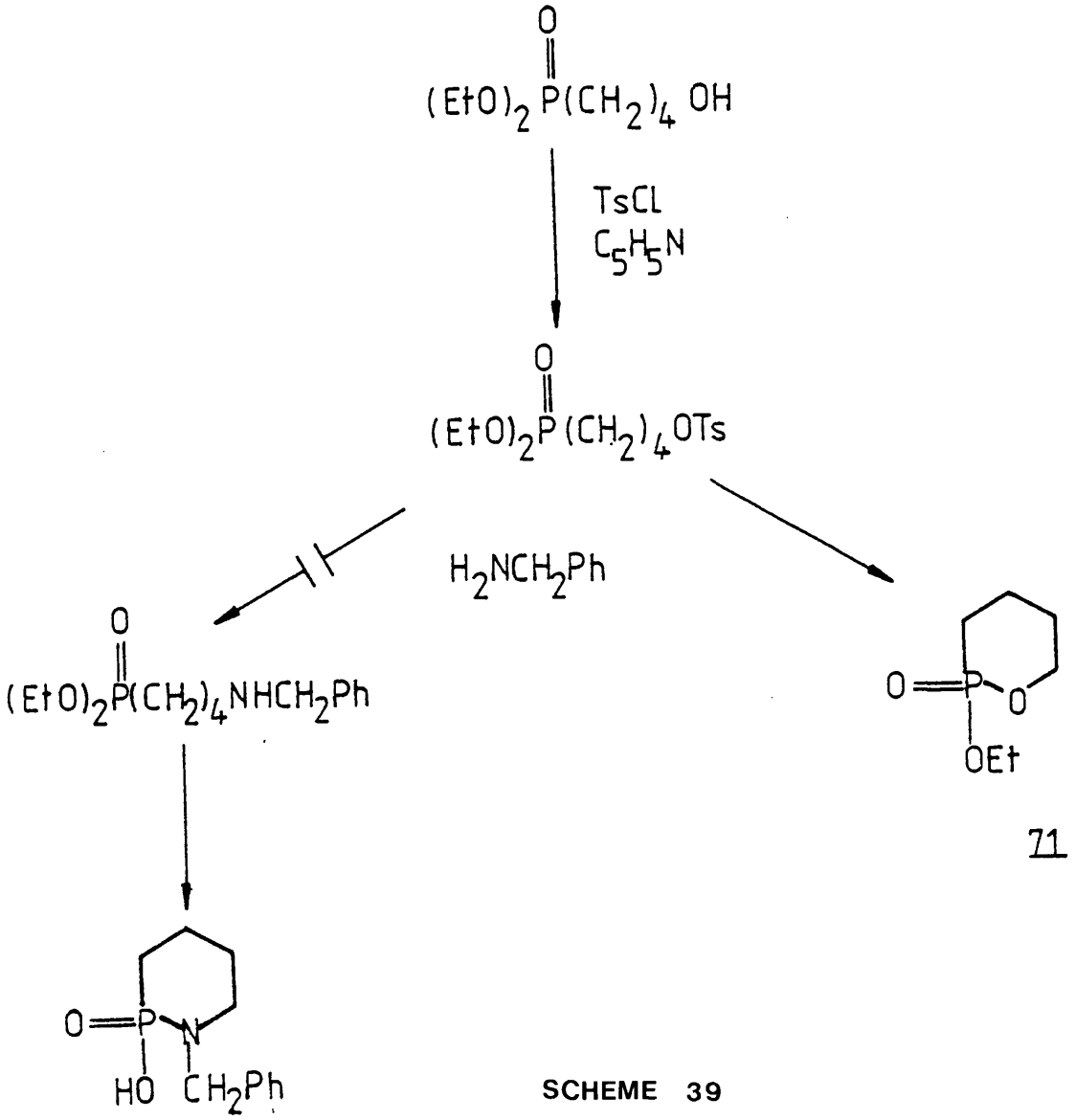
Similar ammonium salts are obtained from the action of tertiary amines on phosphonic acid diesters[76,77] (equation 17)).



(17)

Although they are the most frequently reported, dealkylations are not confined to tertiary amines, analogous reactions being observed for primary and secondary derivatives[80]. An entirely unexpected product was obtained during an attempted synthesis of a perhydro-1,2-azaphosphorin[82], through dealkylation of the phosphonate ester, and cyclisation of the resultant anion (Scheme 39) to give an oxaphosphorin (71).

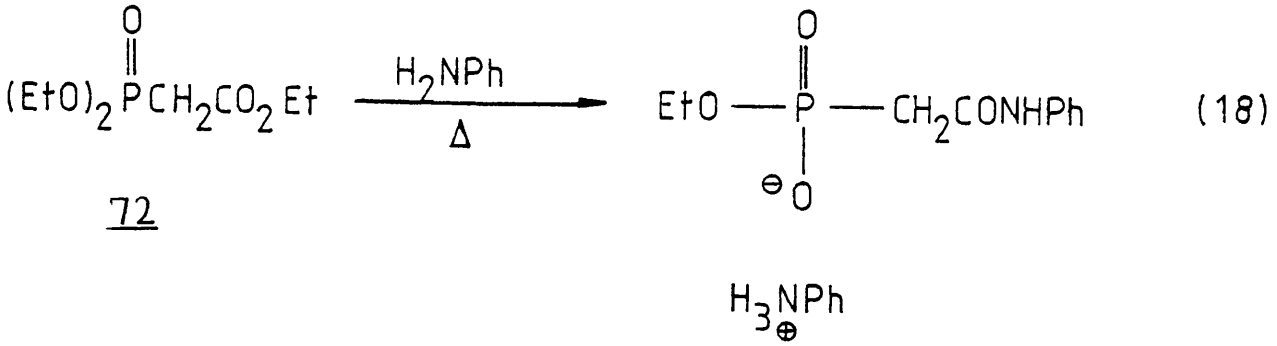
Generally the conditions employed during reactions of this type cause concurrent amination of any other susceptible centre within the molecule. In this way triethyl phosphonoacetate (72) not only forms the anilinium phosphonate when heated with aniline, but the carboxylic



71

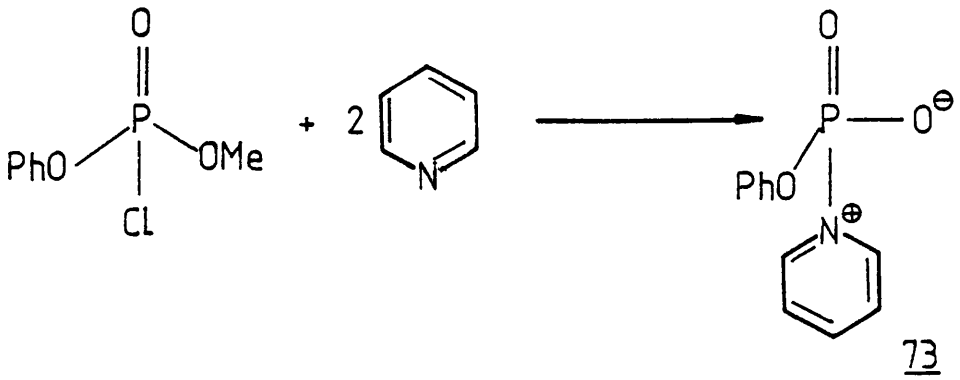
SCHEME 39

ester in the side-chain is converted to an amide[83] (equation (18)). Methyl phenyl phosphorochloridate reacts



72 (18)

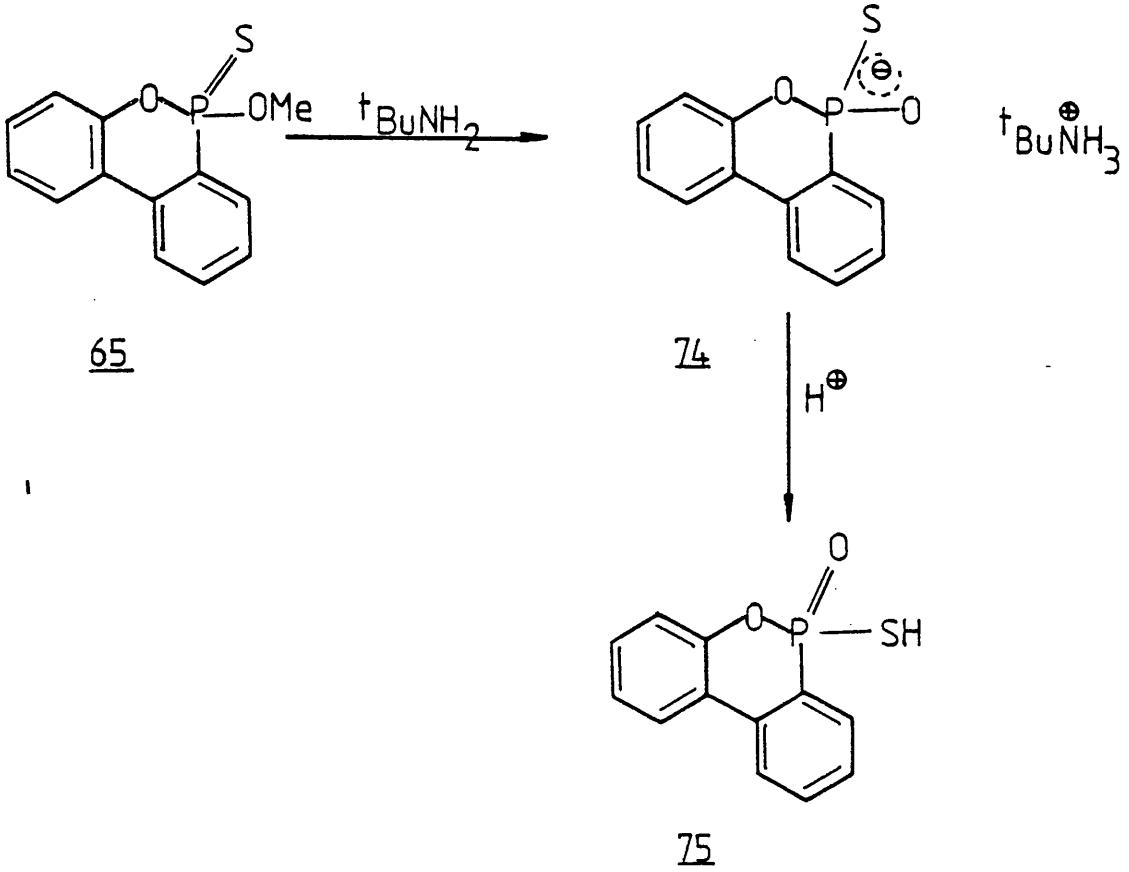
with pyridine both at phosphorus and carbon, giving rise to (73)(equation (19)), utilised as a phosphorylating agent[84].



73 (19)

In principle, therefore, it was not surprising when dissolution of 6-methoxy-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-sulphide (65) in *t*-butylamine, prior to photolysis (p. 63), led to precipitation of a white, crystalline compound, characterised as the *t*-butylammonium salt (74). What was noteworthy was the rapidity with which the reaction occurred, being complete within 30 min. at room temperature with the quantitative crystallisation of a product of high purity. As confirmation of the assigned structure, acidification of (74) gave the thiophosphonate (75), possessing spectral and analytical data comparable with that of an authentic sample of this acid. Explained in terms of dealkylation of the ester by *t*-butylamine, followed by proton exchange within the solvent to give the precipitated *t*-butylammonium salt (74), *t*-butylmethylamine remained in the mother liquor. This secondary amine was detected by comparison of the GC of the reaction solution with a sample of amine synthesised independantly,

separation being achieved on a Pennwalt 223 column at 40°C. A peak in the ^{1}H n.m.r. spectrum of the mother liquor, 1.05 p.p.m.downfield of the *t*-butyl absorption



corresponded closely to the chemical shift of the *N*-methyl of the authentic sample.

The mildness of the conditions necessary to effect a rapid dealkylation indicated either that the particular ester was an extremely good methylating agent, or that *t*-butylamine was an especially effective reagent for this type of transformation.

6-Methoxy-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-sulphide (65) was used as a standard substrate for the comparison

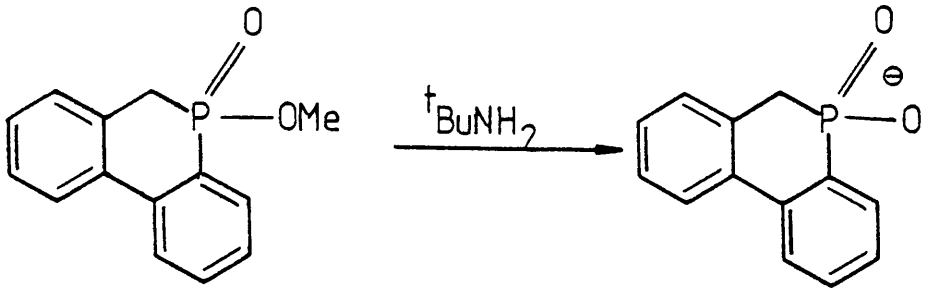
of demethylation by a number of amines, the results of which are summarised in Table 2. In each case a sample of (65) was dissolved in excess amine, the product being separated by filtration or decantation.

TABLE 2: THE DEMETHYLATION OF (65) BY AMINES

AMINE	REACTION		REMARKS
	TEMPERATURE	TIME	
t-$BuNH_2$	20 °C	30 min	White, crystalline product precipitated
$C_6H_{11}NH_2$	130°	1 h	Product precipitated on cooling
i-Pr_2NH	84°	3 h	Reaction incomplete
Et_3N	88°	6 h	Secondary products present. Separated from mother liquor as oil

Although clean demethylation occurred with *t*-butyl-, *cyclo*-hexyl- and di*iso*propylamine, reaction with triethylamine gave a colourless oil, which exhibited two major absorptions in the ^{31}P n.m.r. spectrum, at chemical shifts of +53.8 and +54.8 p.p.m. Two minor products were also evident. Reaction became slower with increasing substitution of nitrogen, and of the two primary amines used, *t*-butylamine proved most rapid.

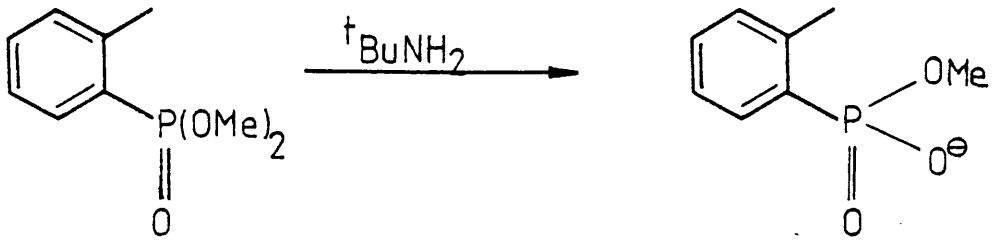
That this facility of dealkylation by *t*-butylamine was not entirely peculiar to the oxaphosphorin was proven by reaction with methoxyphosphaphenanthrene (67), to give a *t*-butylammonium phosphinate (equation (20)).



(20)

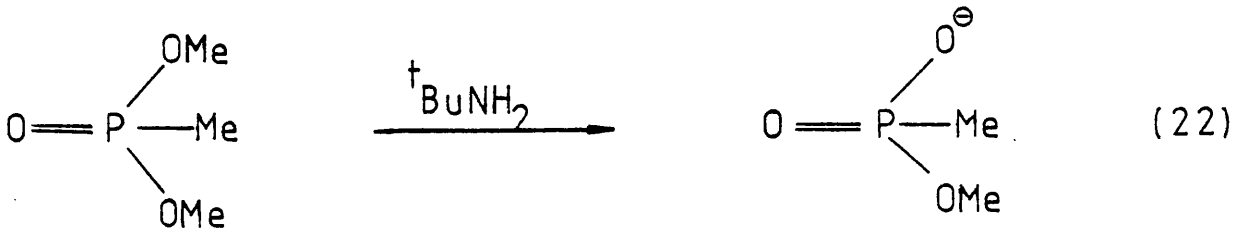
67

Similar dealkylation of dimethyl 2-methylphenylphosphonate to the monoester (equation (21)) showed that the tricyclic structure was also incidental. Successful

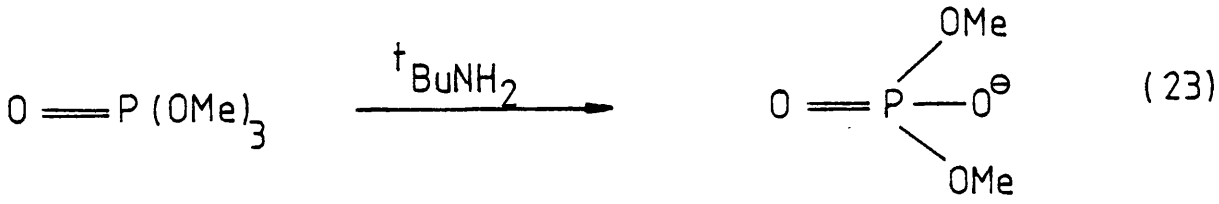


(21)

repetition of the reaction with dimethyl methylphosphonate and trimethyl phosphate, giving the monoester (equation (22)) and diester (equation (23)) respectively, eliminated further possible constraints upon the structure of the ester. Although somewhat slower than the dealkylation of (65) the reactions appeared equally clean, the crystalline products exhibiting a single peak in the



(22)



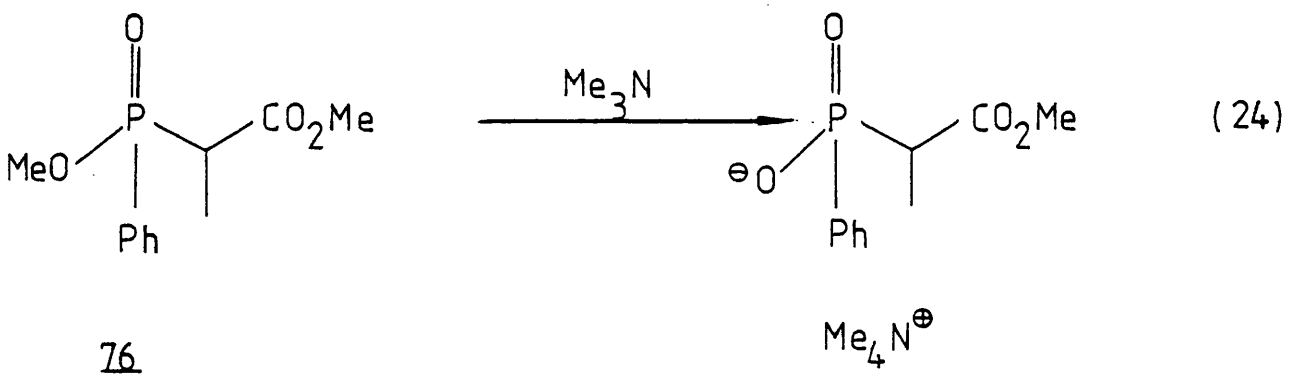
(23)

^{31}P n.m.r. spectrum. The ^{1}H spectrum, however, indicated the presence of up to 10% of excess amine of crystallisation by integration of the *t*-butyl absorption at 1.15 p.p.m.

Dealkylation of trimethyl phosphate was also achieved in inert solvents (benzene, dichloromethane or dioxan), with just one equivalent of *t*-butylamine, although the procedure was not as efficient, in terms of both rate of reaction and ease of product isolation, as that utilising the amine as the solvent. The high volatility of *t*-butylamine (b.p. 46°C) and the low solubility of most of the products lent itself to simple work-up procedures. In cases when quantitative precipitation did not occur, removal of excess amine gave the solid product.

The Selective Dealkylation of Phosphorus Esters

A number of instances are described in the literature of the selective dealkylation of phosphorus esters in the presence of other potentially reactive functional groups. Treatment of methyl 2-(methoxyphenylphosphinyl)propanoate (76) with trimethylamine causes dealkylation of the phosphinate ester, while the carboxylic ester remains intact (equation (24)), in contrast



(24)

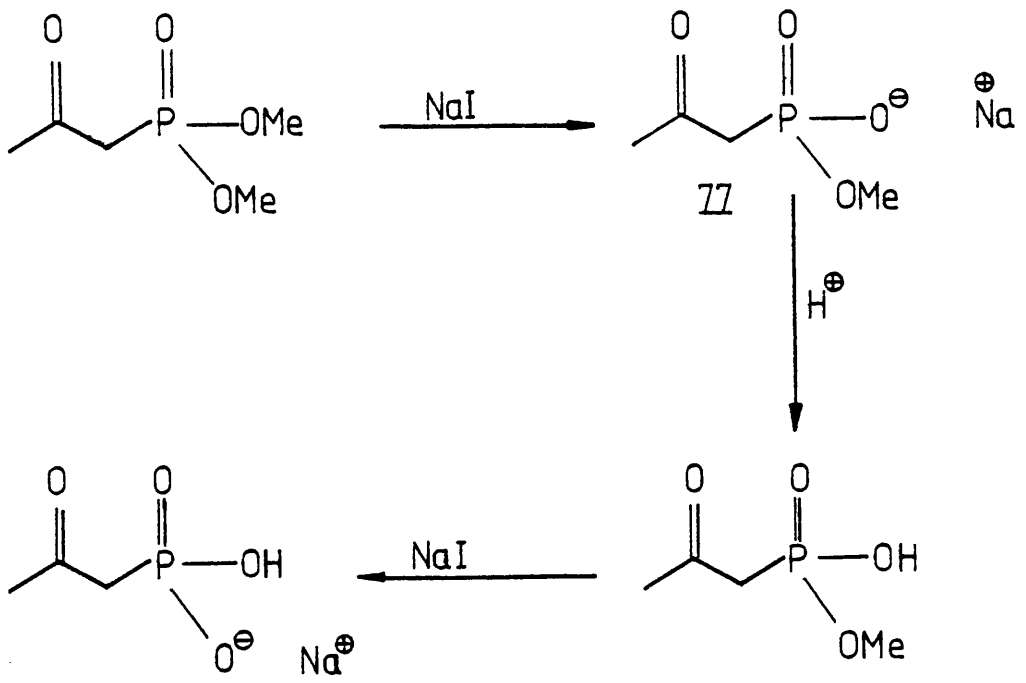
76

to the similar reaction with aniline (equation (18)).

With sodium iodide in refluxing acetone[86], monodealkylation of ketophosphonate esters is complete after 24h (Scheme 40).

Protonation of the salt (77), followed by a further treatment with sodium iodide results in complete dealkylation.

Chlorotrimethylsilane has been employed to effect similar complete, selective dealkylations of phosphorus

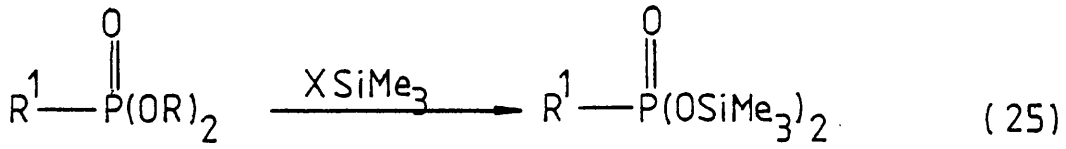


SCHEME 40

esters in a single step[87], but has recently been largely superseded by its more reactive relatives. Iodotrimethylsilane is used to avoid the need for extended reaction times, and occasionally disappointing yields reported for the chloro-analogue[88,93], but itself suffers from the disadvantages of a difficult preparation, and short shelf-life. These were largely overcome by generation of the reagent *in situ* by the action of sodium iodide on chlorotrimethylsilane[89,90], at the cost of a small degree of selectivity[92]. Bromotrimethylsilane, by virtue of its position midway between the chloro- and iodo-analogues, is reported to combine most of the advantages

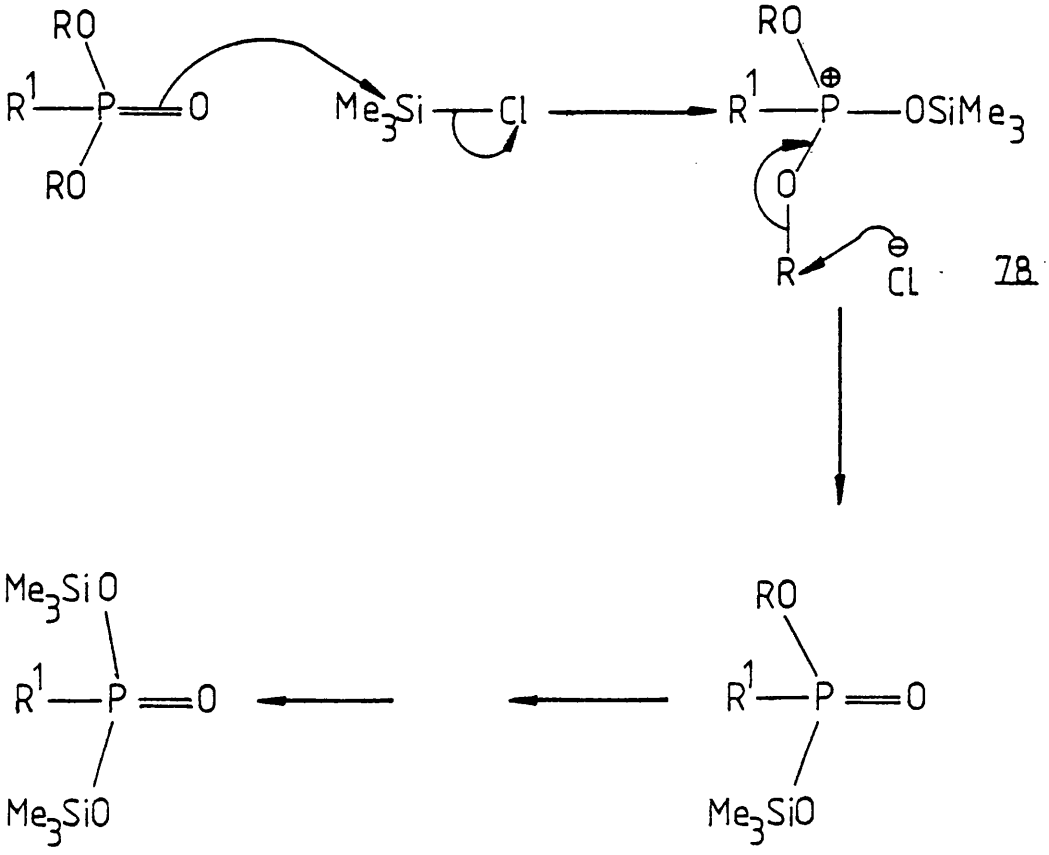
of both[91,92], being considerably more reactive than chlorotrimethylsilane, and easier to prepare and store than iodotrimethylsilane.

Characteristic of the action of halotrimethylsilanes is the complete dealkylation of phosphorus esters, to give silylated derivatives (equation (25)). The reaction



(25)

is thought to proceed by attack of the phosphoryl group at silicon[87], with ejection of a chloride ion which subsequently removes the alkyl portion of the greatly activated ester of pseudophosphonium salt (78) (Scheme 41).

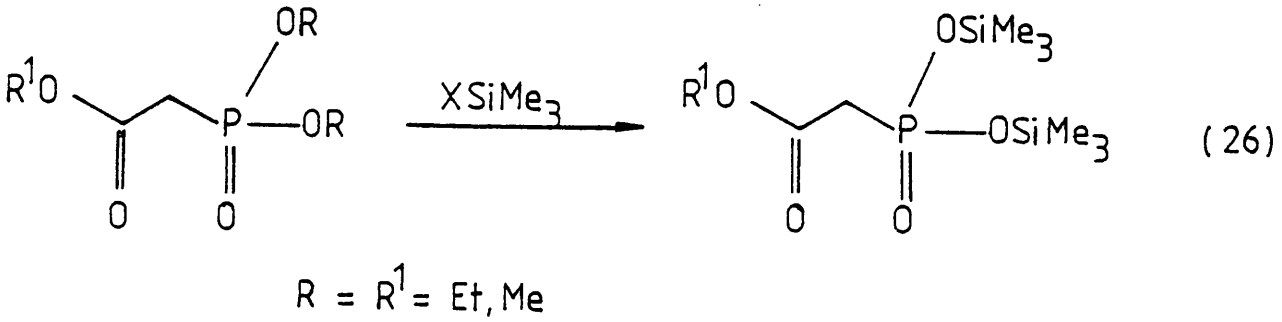


78

SCHEME 41

Since no phosphorus acid anion is involved, it is possible for the monodealkylated product to react further.

Halotrimethylsilanes in general, but iodo-[94] and bromosilanes[91,92] more particularly, exhibit a high degree of selectivity in their reactions with phosphonate esters. Although carboxylic esters will undergo silylation quite readily[123], the reaction has a sufficiently high energy barrier that a molecule containing both phosphonic and carboxylic esters undergoes exclusive dealkylation at phosphorus[92] (equation (26)).



$R = R^1 = Et, Me$ (26)

Similar phosphonate ester cleavage occurs in the presence of amide-, keto-, and haloalkyl-substituents or carbon-carbon multiple bonds in the side-chain[92].

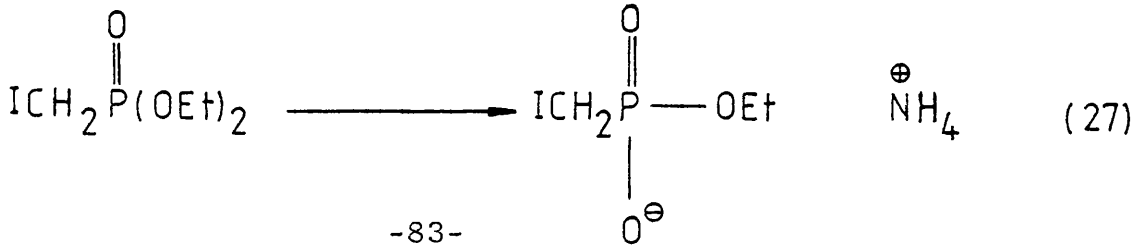
The selectivity of *t*-butylamine for dealkylation of phosphorus esters was investigated in a series of experiments, summarised in Table 3.

Methyl 3-(methoxyphenylphosphinyl)propanoate (79), on heating under reflux in *t*-butylamine for 48h, underwent demethylation to the phosphinate anion. During this

period, a peak at +43.5 p.p.m. in the ^{31}P spectrum corresponding to the starting ester (79), was replaced by the anion at +27.5 p.p.m. Comparison of the respective ^{1}H spectra showed the disappearance of the P-OMe doublet at a chemical shift of +3.6 p.p.m., while the three-proton singlet assigned to the carboxylate ester persisted.

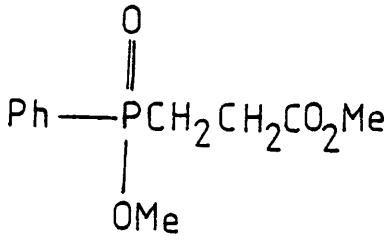
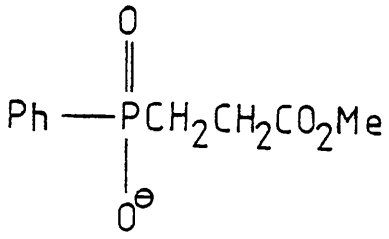
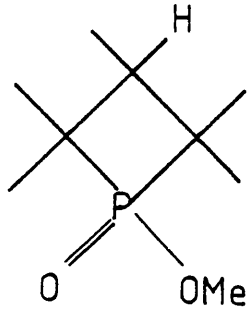
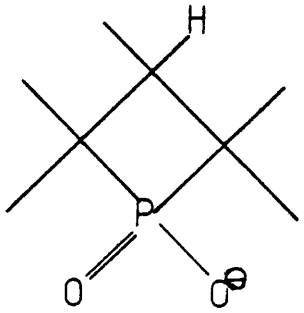
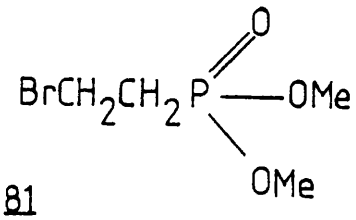
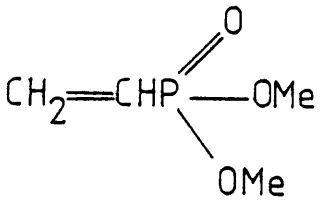
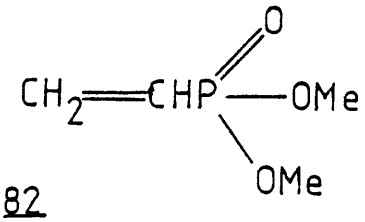
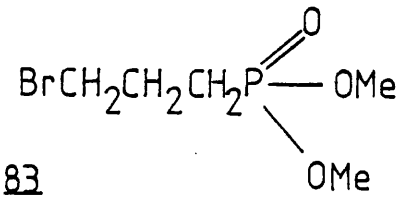
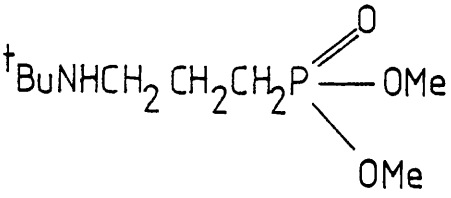
Heating phosphetan (80) in ^{t}-butylamine for 6h gave a white precipitate, whose ^{1}H spectrum had lost the P-OMe doublet at +3.7 p.p.m., but retained the distinctive pattern of the pentamethyl-substituted 4-membered ring. The ^{31}P spectrum showed a corresponding change from two closely separated peaks of chemical shift +59.5 and +57.7 p.p.m. (the two epimers of the starting phosphetan (80))to a single absorption at +49.2 p.p.m. for the salt. Despite a known enhancement of the rate of nucleophilic attack at phosphorus in a small ring[124], there was no indication of any ring-opened products, in contrast with the reaction of (80) with bromotrimethylsilane[93], where dealkylation was accompanied by products of ring-cleavage.

It has already been observed[95] that aqueous ammonia will produce phosphonate salts when reacted with α-halo-phosphonates, in preference to substitution of the side-chain (equation (27)), but whether this occurs by



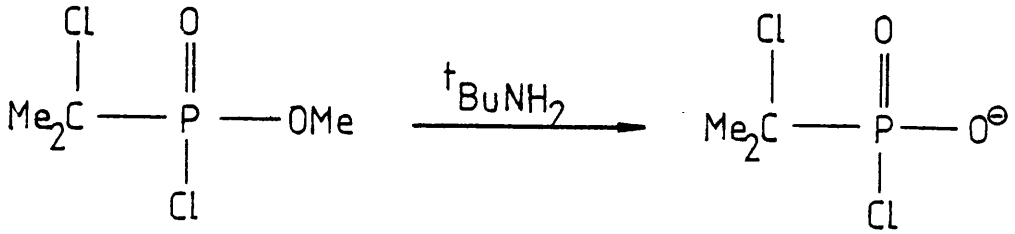
(27)

TABLE 3: THE ACTION OF ^{t}-BUTYLAMINE ON PHOSPHORUS ESTERS CONTAINING OTHER FUNCTIONAL GROUPS

	SUBSTRATE	PRODUCT*
79		
80		
81		
82		
82		3 Products
83		
85		

*As ^{t}-butylammonium salt, where appropriate.

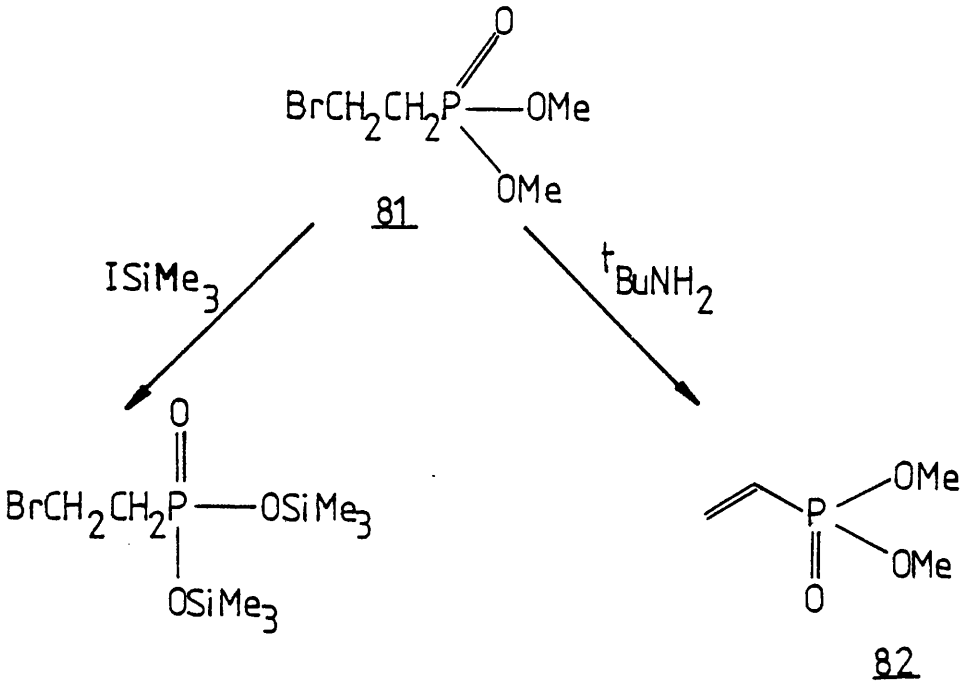
attack of hydroxide at phosphorus or ammonia at carbon is not clear. An even greater selectivity by *t*-butylamine itself has been noted in these laboratories[96], when phosphonic chloride (84) was smoothly demethylated under anhydrous conditions, with no formation of either a



84

phosphonamidate or aminophosphonates. Insertion of a further methylene group between the halogen and phosphorus was found to have a profound effect upon the course of the reaction with *t*-butylamine. Dimethyl 2-bromoethylphosphonate (81), readily produced by an Arbuzov reaction between 1,2-dibromoethane and trimethyl phosphite, underwent a very rapid, base-induced elimination of hydrogen bromide at room temperature. Filtration and removal of solvent at this stage allowed the isolation of dimethyl vinylphosphonate (82) in high yield, characterised by ^{1}H, ^{31}P and ^{13}C spectroscopy. This is again in contrast with similar reactions with iodotrimethylsilane[94], when exclusive dealkylation occurs (Scheme 42).

Yet another reaction pathway was obtained with the halogen three carbons distant from phosphorus, dimethyl



SCHEME 42

3-bromopropylphosphonate (83) undergoing substitution of bromide by *t*-butylamine to give the aminophosphonate (85) in 22h at room temperature. With more extended reaction times there was some evidence in the ^{31}P n.m.r. spectrum for subsequent dealkylation, either intra- or intermolecularly, with the appearance of a peak approximately 10 p.p.m. upfield of the chemical shifts of (83) and (85) (+31.9 and +34.1 p.p.m. respectively). The ^{1}H n.m.r. spectrum was, however, inconclusive.

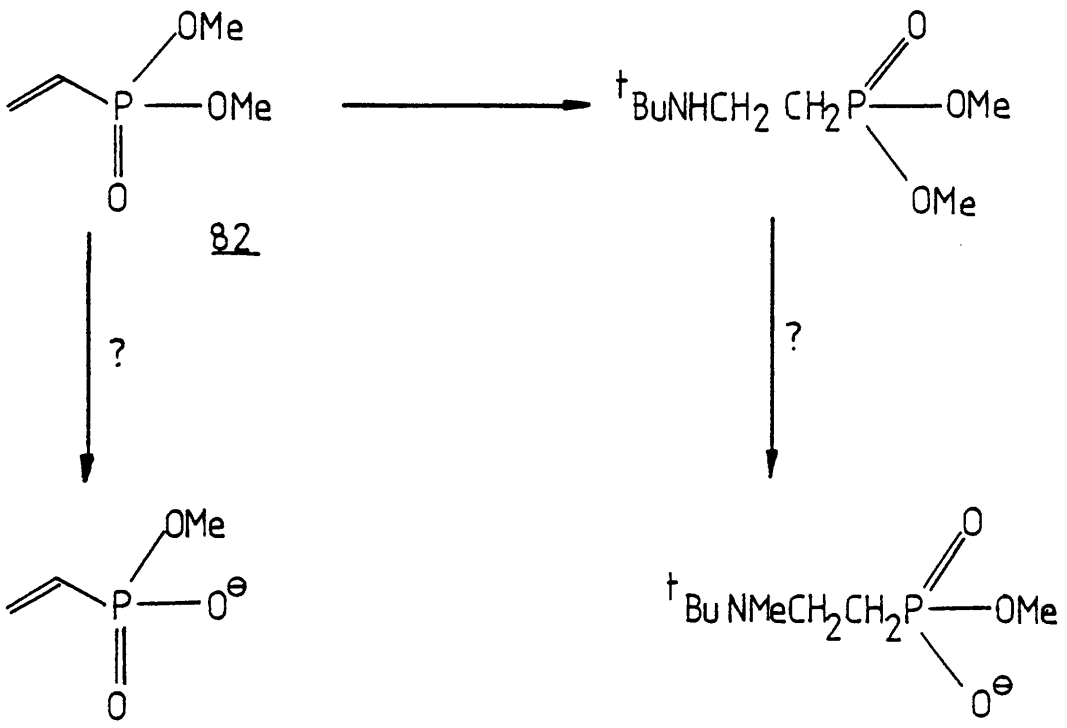
The differing products obtained from the action of *t*-butylamine on 2-bromoethyl- and 3-bromopropylphosphonates (81 and 83 respectively) reflect the difference in acidity of the methylene protons adjacent to the halogen-bearing

carbon. With stabilisation of the resultant anion by the adjacent phosphoryl group, removal of a proton from dimethyl 2-bromoethylphosphonate is very easy. Subsequent loss of a bromide ion leads to dimethyl vinylphosphonate (82). A similar pathway is not open to the 3-bromopropylphosphonate (83). With the most acidic protons again adjacent to phosphorus, formation of an unsaturated side-chain is unlikely. Nucleophilic substitution of bromide by the amine appears to be the preferred reaction, possibly accelerated by neighboring group participation by the phosphoryl function.

Dimethyl vinylphosphonate (82) reacted with *t*-butylamine as a Michael acceptor. Phosphoryl-stabilised addition of the amine to the double bond gave, initially dimethyl 2-*t*-butylaminoethylphosphonate, with an absorption at +32.9 p.p.m. in the ^{31}P spectrum, and two clear methylene multiplets in the ^{1}H n.m.r. Two unidentified secondary products, however, appeared concurrently, but more slowly, with peaks in the ^{31}P spectrum at chemical shifts of +9.5 and +21.6 p.p.m., possibly corresponding to the products of dealkylation of the two primary components of the mixture (Scheme 43).

Since it provides a method of monodealkylating phosphorus esters under very mild conditions, and in the presence of a number of functional groups, the reaction of *t*-butylamine appears complementary to that of halosilanes, whose use brings about complete removal of alkyl

ester groups.



SCHEME 43

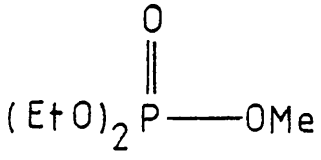
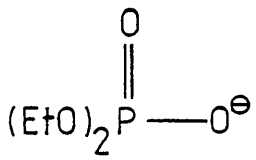
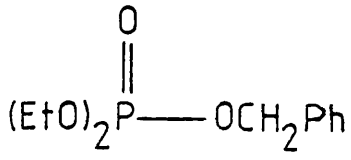
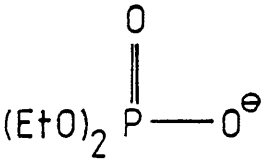
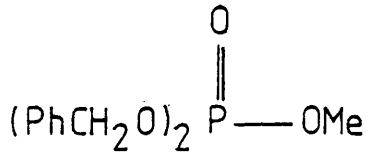
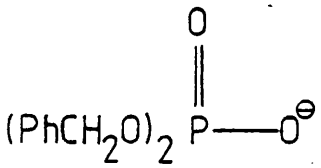
The Selective Monodemethylation of Phosphorus Esters

Having investigated the selectivity of *t*-butylamine for reaction with phosphorus esters in the presence of other functionalities within the molecule, it remained to discover any preference the reagent had for different alkoxy-substituents on phosphorus.

Whilst a variety of methyl esters of phosphorus acids were smoothly dealkylated by *t*-butylamine, as already described, no reaction at all was observed with equivalent ethyl esters. Even prolonged heating of triethyl phosphate, diethyl ethylphosphonate or diethyl phenylphosphonate in *t*-butylamine led only to a quantitative recovery of unchanged starting material.

Even more conclusive were the results obtained when using mixed esters of phosphoric acid (Table 4). The ^{1}H n.m.r. spectrum of the product obtained from reaction of diethyl methyl phosphate (86) with *t*-butylamine retained absorptions due to the ethyl groups, but lost the P-OMe doublet at a chemical shift of +3.7 p.p.m., indicating exclusive demethylation.

TABLE 4: THE DEMETHYLATION OF MIXED PHOSPHORUS ESTERS

	SUBSTRATE	PRODUCT*
86		
87		
88		

*As *t*- butylammonium salt.

Similar selectivity for the methyl group was found when using dibenzyl methyl phosphate (88), heating under reflux in *t*-butylamine for 4h leading only to the ammonium dibenzyl phosphate. In the absence of a methyl group, *t*-butylamine selectively removed a benzyl group, diethyl benzyl phosphate (87) undergoing dealkylation to the diethyl phosphate anion.

t-Butylamine was, thus, shown to possess a remarkable selectivity for the monodemethylation of phosphorus esters, in the presence of other functional groups both contained in a side-chain, and at phosphorus itself.

Although by no means the only amine shown to be capable of dealkylating phosphorus esters, *t*-butylamine is outstanding in terms of the selectivity exhibited. This preference for methyl over ethyl or even benzyl substituents may be explained in terms of the bulkiness of the $-C(Me)_3$ group, as the major difference between *t*-butyl- and other amines. Steric interaction of the *t*-butyl group on nitrogen and substituents in the ester as the nucleophile approaches (Figure 2) may prevent reaction in all cases except when R=H, without investing a large amount of energy.

Firestone has suggested[120] that consideration of the Linnett structures for the SN2 transition state, formed on attack of the amine at carbon, may provide an

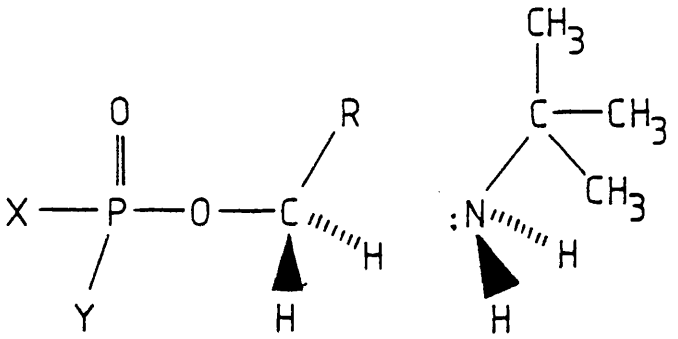
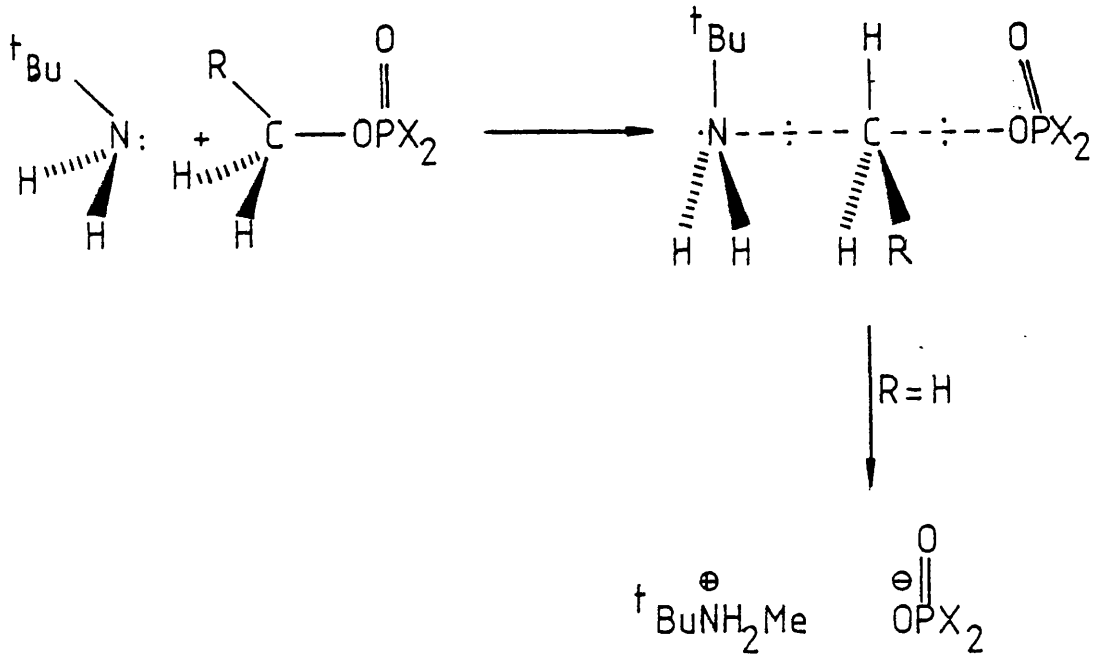


FIGURE 2

even more comprehensive explanation. As the amine interacts with the electrophilic carbon, both centres of reaction tend to become planar[121] (Scheme 44). With increasing size of substituent on the amine, increase of



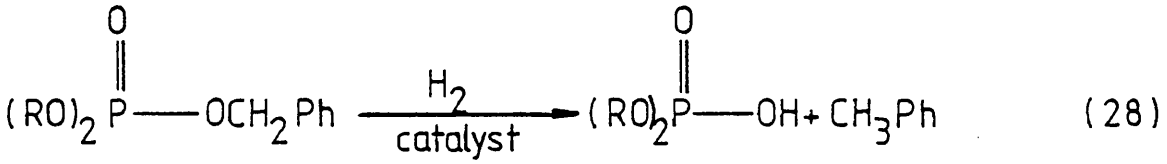
SCHEME 44

the bond-angle in going to the transition-state relieves strain in the tetrahedral conformation, and the process becomes easier. With the two adjacent reacting centres being planar, however, substituents on carbon and nitrogen are brought into closer proximity, and steric interactions increased. Thus if R is hydrogen (methyl esters), very little interaction with the *t*-butyl group may be anticipated, the extra energy gained in going from an SP^3 to an SP^2 hybridised nitrogen effectively lowering the energy barrier to dimethylation, relative to other, less bulky amines. If R is larger, however steric interaction greatly increases the energy barrier relative to other amines, allowing a high degree of selectivity for the methoxy group on phosphorus.

The Linnett Electronic Theory applied to the dealkylation of phosphorus esters by *t*-butylamine thus supplies an attractive explanation of the observed selectivity for methyl over benzyl or higher alkyl substituents.

A great deal of interest has been expressed in the temporary protection of phosphorus esters, particulary in some molecules of biological interest such as phospholipids or nucleotides. The necessity of sequential removal of a single ester group from phosphorus has led to the development of a number of systems specifically designed to allow this[97]. Of the more successful phosphate protecting groups, 2,2,2-trichloroethyl[98,99], 2-cyanoethyl[100],

and substituted phenyls[101-103] in particular have found widespread application. All, however, suffer from considerable disadvantages, either in the difficulty of their preparation, or in the formation of side-products during their removal from the phosphate ester[101,104]. Several methods have been reported for the selective debenzylation of phosphorus esters, leading to their frequent use as protecting groups. Of these, catalytic hydrogenation is probably the best known[76,105], giving the phosphorus acid and toluene (equation (28)).

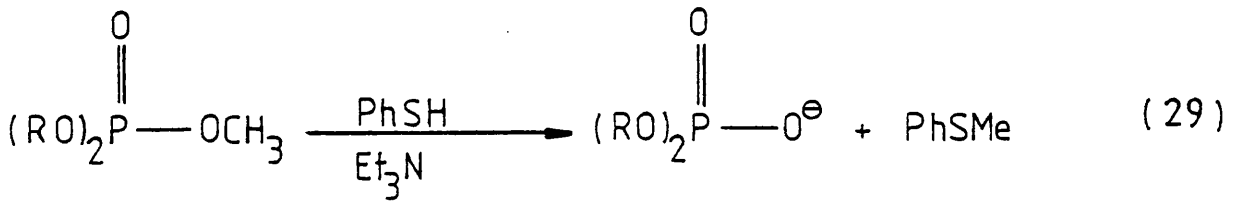


(28)

Benzyl esters are capable of undergoing hydrolysis under conditions mild enough not to affect other subtituents[106], although this is not usually the case in nucleotide chemistry, where silyl-ether blocking groups are commonplace[107]. Selective debenzylation of phosphate esters has been achieved by treatment with halide, or pseudo-halide ions, calcium, sodium or alkylammonium iodides proving the most effective[108-110], followed by lithium chloride[111], or a thiocyanate anion[112]. In all these cases, however, in the presence of a methyl ester, a mixture of products is obtained[108,109]. A similar lack of differentiation between methyl and benzyl groups is observed when dealkylation is carried out with tertiary

amines, such as *N*-methylmorpholine[113].

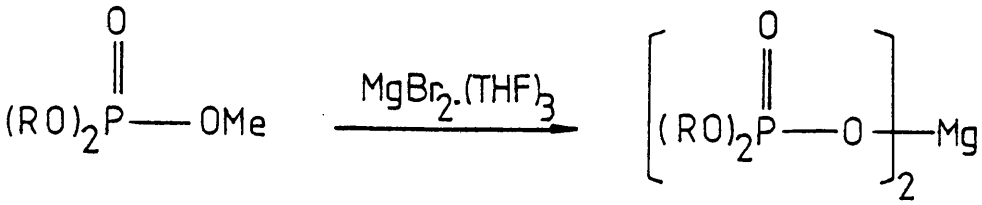
For the protection of phosphorus acids, the methyl group has several advantages. The starting materials to produce methyl esters are cheaply, and readily available, and under normal reaction conditions, the methoxy function is considerably more inert than other esters commonly employed as protecting groups. Procedures, therefore, for the selective removal of the methyl group assume considerable importance in the synthesis of phosphorus esters of biological interest. Van Tamelen[114] has reported that the thiophenolate anion may be used to cleanly demethylate phosphorus esters in nucleotide synthesis (equation (29)).



$$(RO)_2P(=O)-OCH_3 \xrightarrow[Et_3N]{PhSH} (RO)_2P(=O)-O^{\ominus} + PhSMe \qquad (29)$$

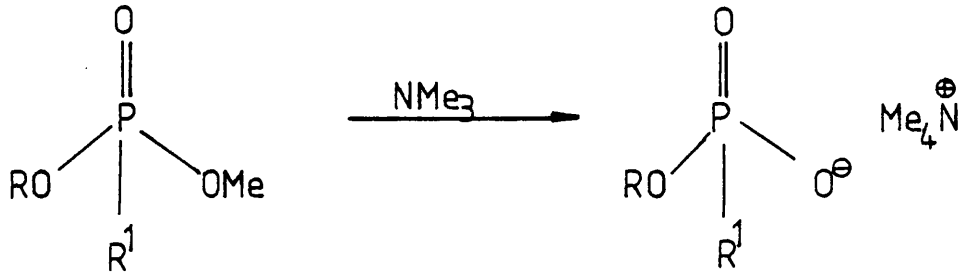
While providing an extremely efficient procedure, thiophenol is rather unpleasant to work with.

Demethylation in the presence of a number of other substituents, but not including benzyl esters, has been achieved by Ramirez with tetrahydrofuran complexes of anhydrous magnesium bromide[115] (equation (30)).



(30)

Rather closer to the method described in this thesis is the demethylation of phosphate and phosphonate esters by an acetone solution of trimethylamine[116], in a sealed reaction vessel (equation (31)).

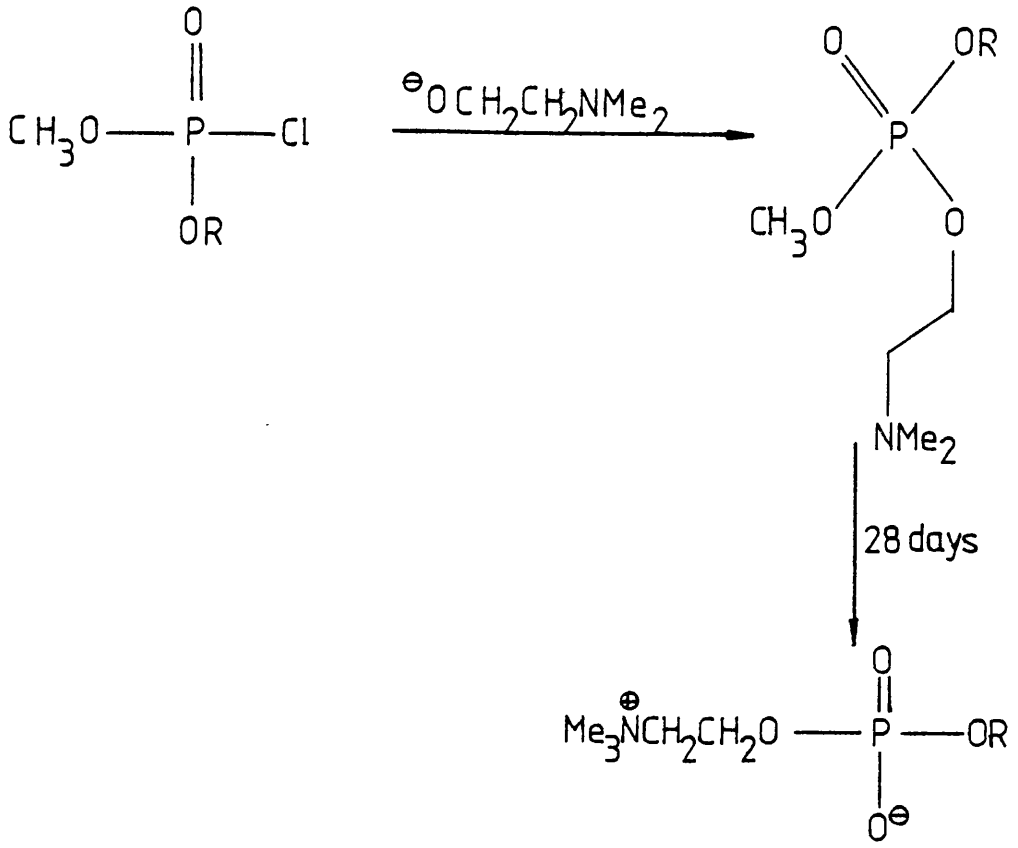


(31)

Selectivity for the methyl group is found in the presence of ethoxy, propyloxy and phenoxy substituents.

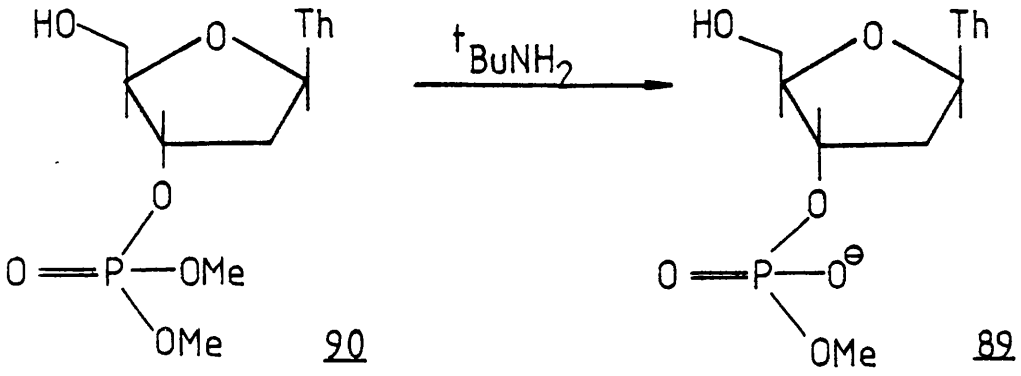
Specifically applicable to phospholipid synthesis, Loew has described[117] an intramolecular demethylation by a tertiary amine (Scheme 45).

t-Butylamine, with its extremely high selectivity for methyl esters of phosphorus acids, combined with mildness of conditions and convenience of procedure, should prove a valuable addition to this short list of reagents permitting the use of a methyl protecting group.

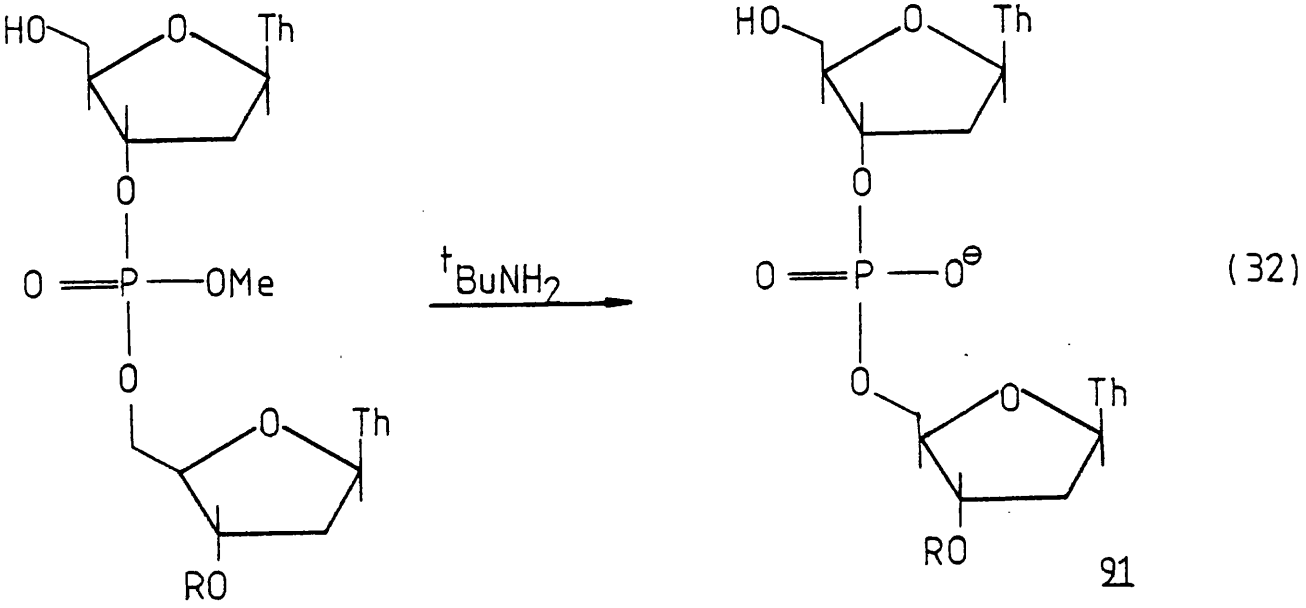


SCHEME 45

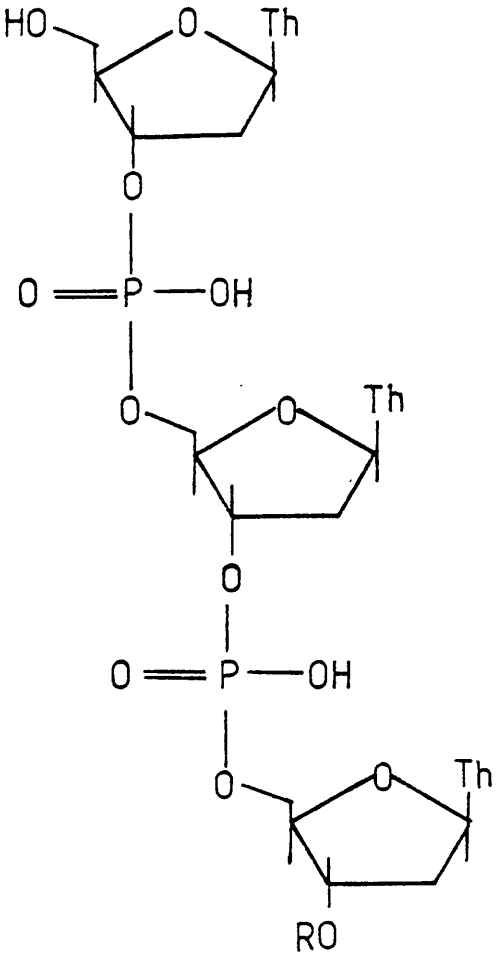
Indeed, at our suggestion, Ogilvie has since completed a successful nucleotide synthesis[118], based upon the Letsinger dichloridite procedure[119], using *t*-butylamine to remove methyl protecting groups from phosphate triester intermediates. In this way the monomethyl ester of thymidine 3^1-phosphate (89) is obtained quantitatively from the dimethylester (90), on refluxing in *t*-butylamine for 15h.



Similarly dinucleotide (91) is obtained from its methyl ester (equation (32)), and the system may be extended by a further phosphorylation to give trinucleotide (92) in 54% yield[118].



(32)



92

In his communication, Ogilvie expressed optimism for the future use of a reagent as selective as *t*-butylamine has proved to be.

APPENDIX

APPENDIX

Of the compounds described in this thesis, the following underwent biological evaluation as plant growth regulators (G), herbicides (H), fungicides (F), or insecticides (I) as indicated. Screening was carried out at I.C.I. Plant Protection Division, Jealotts Hill Research Station.

(i)	Dimethyl 2-bromoethylphosphonate	G,I
(ii)	Dimethyl (2-methylphenyl)phosphonate	G,H,I,F
(iii)	3-(Hydroxyphenylphosphinyl)propanoic acid	G,H,F
(iv)	6-Chloro-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-sulphide	G,I,F
(v)	6-Methoxy-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-sulphide [122]	H,I,F
(vi)	2-Biphenylylmethylphosphonic acid	H,I,F
(vii)	2-Biphenylylchloromethane	G,H,I,F
(viii)	1,2-Dihydro-1-hydroxyphosphinoline 1-oxide	G,F

Of these only (i) and (viii) showed any activity both exhibiting marginal, but inconsistent growth effects.

EXPERIMENTAL

EXPERIMENTAL

Instrumentation

Infra-red spectra were recorded on Perkin-Elmer 237, 257 or 580 spectrometers, as solutions, nujol mulls or potassium bromide discs.

Mass spectra were determined with a V.G. Micromass 16B instrument, with integral gas chromatographic facility. High resolution work was carried out by the P.C.M.U., Harwell.

Gas chromatography was carried out in a Pye-Unicam 104 chromatograph, with flame-ionisation detection, using 1.5 m glass columns with nitrogen as the carrier gas.

Ultra-violet spectra were recorded on a Pye-Unicam SP800 spectrophotometer, using 10mm silica cells.

^{1}H n.m.r. spectra were recorded at either 60MHz on a Varian T60, 90MHz on a Varian EM390, or 100MHz on a Jeol PS 100 spectrometer. Samples were dissolved in the solvent indicated, and positive chemical shifts are quoted downfield from an internal standard of tetramethylsilane (TMS). ^{31}P decoupling was achieved on the Varian T60 by using an HD-60 heteronuclear decoupler tuned to the appropriate frequency.

^{13}C and ^{31}P n.m.r. spectra were recorded on a Jeol JNM FX60 Fourier Transform spectrometer, in the solvent indicated. Positive chemical shifts are quoted downfield

of an internal standard of TMS for ^{13}C, and downfield relative to external 85% phosphoric acid for ^{31}P spectra.

Melting points were determined on a Kofler heating stage, and are uncorrected.

General Details

All operations involving air-or moisture-sensitive compounds were carried out under an atmosphere of dry, oxygen-free nitrogen.

Small scale distillations were carried out using Kugelrohr apparatus, and boiling points quoted are oven temperatures at which distillation occurred.

Diethyl ether and hydrocarbon solvents were dried over sodium wire, and distilled before use. Alcohols were refluxed over, and distilled from their magnesium alkoxides. Dichloromethane, chloroform, carbon tetrachloride, tetrachloroethane and dichlorobenzene were refluxed over, and distilled from calcium hydride. All amines were purified by distillation from potassium hydroxide pellets. All dried solvents were stored over molecular sieve, and if used with air-sensitive compounds, degassed immediately prior to use. All liquid reagents were distilled, and stored over molecular sieve.

N-Bromosuccinimide was recrystallised from water and dried in a vacuum over P_2O_5. Zinc chloride was fused and

cooled in a dessicator, then powdered before use.

Column chromatography was usually performed on either U.G.1 alumina, or M.F.C. silica, although difficult separations were occasionally achieved with low pressure column chromatography on kieselgel 80 PF254, supplied by E. Merck. Thin layer chromatography was carried out on commercially prepared, aluminium backed plates, supplied by Merck. Preparative plates were made from 80 PF254 silica or 60 PF254 alumina, again supplied by Merck.

Organic solutions were dried over anhydrous sodium sulphate, or magnesium sulphate, and solvents removed on a rotary evaporator, unless otherwise stated.

CHAPTER 1

3-Phenylpropylphosphonous dichloride (14)

This compound was prepared from 3-bromophenylpropane as described by Rowley and Swan[11], in 60% yield after distillation $b_{1.5}$ 116 - 120°C.

^1H $\delta(CDCl_3)$ 7.25(m,5H), 2.75(m,2H) and 2.1(m,4H) p.p.m.

^{31}P $(CHCl_3)$ + 194.8 p.p.m.

1-Hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide (15)

The phosphinoline (15) was prepared in the manner of Rowley and Swan[11], by cyclisation of 3-phenylpropylphosphonous dichloride with zinc chloride, followed by hydrolysis and oxidation. 1-Hydroxy-1,2,3,4-tetrahydrophosphinoline 1-oxide was recrystallised from ethanol (m.p. 138 - 140°C; 52% yield).

^1H $\delta(CDCl_3)$ 11.6 (s,1H:D_2O exchangeable), 7.3 (m,4H), 2.7 (m,2H), and 1.95 (m,4H) p.p.m.

^{31}P $(CHCl_3)$ + 38.9 p.p.m.

1-Chloro-1,2,3,4-tetrahydrophosphinoline 1-oxide (18)

Heating phosphinic acid (15) under reflux in excess thionyl chloride for ½h gave a quantitative yield of crude 1-chloro-1,2,3,4-tetrahydrophosphinoline 1-oxide as a brown oil. The acid chloride, exhibiting an

absorption at +48.6 p.p.m. in the ^{31}P ($CHCl_3$) spectrum was used crude in the following preparations.

1-Methyl-1,2,3,4-tetrahydrophosphinoline 1-oxide (19b)

1-Chloro-1,2,3,4-tetrahydrophosphinoline 1-oxide (2g, 10mmol) was dissolved in ether, and cooled to 0°C. An ethereal solution of methylmagnesium iodide, formed from methyl iodide (2.7g, 19mmol) and excess magnesium, was gradually added over ½h. The reaction was then heated under reflux for a further 1h. After cooling a saturated aqueous solution of ammonium chloride was added, and the organic layer separated. The aqueous layer was extracted with ether (50ml), and the combined organic layers washed with aqueous sodium hydroxide, and water, then dried and the solvent removed to give 1-methyl-1,2,3,4-tetrahydrophosphinoline 1-oxide as a light brown oil (1.1g, 62%). Further purification was carried out by column chromatography on alumina, eluted with chloroform, to give pale yellow crystals, m.p. 103 - 106°C.

^1H	$\delta(CDCl_3)$	8.2 - 7.1(m,4H), 2.9(m,2H), 2.7 - 1.9 (m,4H), and 1.8(d,3H, J = 15Hz)p.p.m.
^{31}P	($CHCl_3$)	+28.0 p.p.m.
ν max	(Nujol)	3060,1950,1850,1650,1600,1450,1290 1050,1035, and 930 cm^{-1}.

1-Benzyl-1,2,3,4-tetrahydrophosphinoline 1-oxide (19c)

The above procedure was repeated, using benzylmagnesium bromide instead of the methyl Grignard reagent

Crude 1-benzyl-1,2,3,4-tetrahydrophosphinoline 1-oxide was purified by column chromatography on alumina, eluted with chloroform, to give (19c) as a colourless oil in 50% yield.

^{1}H $\delta(CDCl_3)$ 7.75(m,1H), 7.3(m,3H), 3.3(2 x d) 2H J = 13 and 16Hz), 2.8 (m,2H) and 2.1(m,4H)p.p.m.

^{31}P $(CHCl_3)$ +29.5 p.p.m.

General preparation of 1,2-dihydrophosphinoline 1-oxides (20)

The tetrahydrophosphinoline (19) was dissolved in chloroform, and *N*-bromosuccinimide (1 equivalent) added. The mixture was heated under reflux, whilst being irradiated with a tungsten lamp. After dissipation of the bromine colour, the solution was filtered, and washed three times with dil. hydrochloric acid, dried and the solvent removed to give the 4-bromo-1,2,3,4-tetrahydrophosphinoline 1-oxide as a brown oil. This crude material was redissolved in dry dimethyl formamide (DMF), and heated under reflux for 1h. Removal of the solvent gave the crude dihydrophosphinoline as a black oil. Purification was by column chromatography on alumina, eluted with 1% methanol in chloroform, followed by distillation under high vacuum.

In this way the following 1,2-dihydrophosphinoline 1-oxides were prepared:

(i) 1,2-Dihydro-1-hydroxyphosphinoline 1-oxide (20a)

in 50% yield, m.p. 151°C - 155°C (ethyl/acetate/petrol), $b_{o.2}$ 180°C.

^1H $\delta(CDCl_3)$ 12.0(s,1H:D_2O exchangeable), 7.85 (ddd,1H, J=13,7 and 2Hz), 7.3(m,3H), 6.55(m,1H), 6.3-5.7(m,1H) and 2.7 (ddd, 2H, J=18, 6 and 2Hz)p.p.m.

^{31}P $(CHCl_3)$ + 34.3 p.p.m.

ν_{max} (Nujol) 2550,2240,1650,1600,1440,1280,1260,1215, 1175,1160,1130,1085,975,950,865,825,780 and 750 cm^{-1}.

$\lambda(\varepsilon)$ (MeOH) 220(25 500), 258(10 700) and 294(3000)nm.

m/e 180 (M^+).

(ii) 1,2-Dihydro-1-methylphosphinoline 1-oxide(20b)

in 30% yield $b_{o.o5}$ 180°C, as a colourless hygroscopic oil.

^1H $\delta(CDCl_3)$ 8.0(m,1H), 7.4(m,3H), 6.8 - 5.7(m,2H) 3.1 - 2.4(m,2H) and 1.7(d,3H, J = 17Hz)p.p.m.

^{31}P $(CHCl_3)$ +29.0 p.p.m.

ν_{max} (neat) 3400(water), 2940, 2890,1720,1670,1600 1450,1420,1310,1180,1140,1090,940 and 890 cm^{-1}.

m/e 179(M + 1), 178(M^+).

(iii) 1-Benzyl-1,2-dihydrophosphinoline 1-oxide (20c)

in 30% yield $b_{0.002}$ 180°C as a colourless, hygroscopic oil:

^1H $\delta(CDCl_3)$ 7.7(ddd, 1H, J = 198 and 2 Hz)
7.5 - 6.9(m,3H), 6.45(m,1H)
6.2 - 5.6(m,1H), 3.2(d,2H, J = 14Hz)
2.75 (m,1H) and 2.5(m,1H) p.p.m.

^{31}P $(CHCl_3)$ +29.7 p.p.m.

$C_{16}H_{15}OP$ Requires C 75.58, H 5.95, P 12.18
Found 72.40, 6.29, 11.92.

The analysis is correct if 4% water is present.

m/e 254.0865 (M^+ - corresponding to $C_{16}H_{15}OP$).

3-(Chlorophenylphosphinyl)propanoyl chloride (22)

(a) Phenylphosphonous dichloride (45g, 0.25mol) and acrylic acid (18.5g, 0.26mol) were mixed and heated to 100°C in a sealed tube for 24h. Removal of the volatile materials from the reaction mixture in a vacuum (0.1mmHg) gave crude 3-(chlorophenylphosphinyl)propanoyl chloride (59g, 94%) as a brown oil. Attempted distillation at 0.01mmHg led to decomposition (lit.[14] $b_{0.0001} = 234°$).

(b) 3-(Hydroxyphenylphosphinyl)propanoic acid (23) was gradually added, with stirring, to a five-fold excess of thionyl chloride at 0°C. Upon cessation of the initial vigorous effervescence, the reaction was heated under reflux for ½h, after which time surplus

thionyl chloride was distilled off to yield 3-(chlorophenylphosphinyl)propanoyl chloride quantitatively:

^{1}H $\delta(CDCl_3)$ 8.0(m,1H), 7.7(m,4H), 3.35(m,2H) and 2.75(m,2H) p.p.m.

^{31}P $(CHCl_3)$ +52.5 p.p.m.

νmax (neat) 3080, 2940, 1805, 1600, 1450, 1410, 1235, 1110, 750 and 700 cm^{-1}.

3-(Hydroxyphenylphosphinyl)propanoic acid (23)

Crude 3-(chlorophenylphosphinyl)propanoyl chloride (59g, 0.23moles) was poured into iced water (500ml), and vigorously stirred for 2h. The resulting brown solid was filtered and recrystallised from hot water to give off-white crystals of 3-(hydroxyphenylphosphinyl)propanoic acid (26g, 42%) m. 155 - 156°C

^{1}H $\delta(DMSO\text{-}d^6)$ 7.9(m,2H), 7.6(m,3H), 7.1(b.s., 2H:D_2O exchangeable), 2.6(m,2H) and 2.3(m,2H) p.p.m.

^{31}P (DMSO) +36.2 p.p.m.

νmax (Nujol) 3000,1740,1600,1460,1445,1230,1150, 1125,1070,1050,1000,970,940,810,740,and 700 cm^{-1}.

Attempted Cyclisations of 3-(Chlorophenylphosphinyl)propanoyl Chloride

Friedel-Crafts cyclisation of 3-(chlorophenylphosphinyl) propanoyl chloride using an aluminium chloride catalyst was

attempted under a range of conditions, summarised in Table 5. Work-up consisted of addition of aqueous hydrochloric acid, followed by continuous extraction with either dichloromethane or ether. In all cases investigation of both aqueous

TABLE 5: FRIEDEL-CRAFTS REACTIONS OF 22

MOLAR RATIO OF REACTANTS		REACTION CONDITIONS		
Acid Chloride	Aluminium Chloride	Solvent	Temperature	Reaction Time
1.0	1.0	DCB	110°	6h
1.0	1.25	DCB	140°	14h
1.0	1.0	CH_2Cl_2	40°	24h
1.0	2.0	CH_2Cl_2	20°	3h
1.0	3.0	CH_2Cl_2	40°	24h

solutions and organic extracts led to recovery of varying yields of 3-(hydroxyphenylphosphinyl)propanoic acid, with no indication that cyclisation to 1-hydroxy-1,2,3,4-tetrahydrophosphinoline 1,4-dioxide had occurred.

The Reaction Between Aluminium Chloride and 3-(Chlorophenylphosphinyl)propanoyl Chloride

3-(Chlorophenylphosphinyl)propanoyl chloride (0.30g, 1.2 mmol) was dissolved in dry dichloromethane, and an

initial ^{31}P spectrum obtained, giving an absorption at +52.5 p.p.m. Addition of aluminium chloride (0.35g, 2.4 mmol) led to a rapid evolution of gas, and an immediate change in the ^{31}P spectrum, to a chemical shift of +70.0 p.p.m. No further change was observed after standing at room temperature for 16h. The reaction was poured into dilute hydrochloric acid, and extracted twice with dichloromethane. The organic layer was dried, and the solvent removed to give 0.12g of brown oil, solidifying on standing.

Comparison of the ^{31}P absorption a solution of this material in aqueous sodium hydroxide, with a similar solution of 3-(hydroxyphenylphosphinyl)propanoic acid gave coincident peaks at +33.5 p.p.m.

Attempted Cyclisations of 3-(Hydroxyphenylphosphinyl)propanoic Acid

Acid-catalysed intramolecular ring closure of 3-(hydroxyphenylphosphinyl)propanoic acid was attempted using polyphosphoric acid (PPA) under the conditions summarised in Table 6. The phosphinic acid was gradually added to vigorously stirred PPA preheated to the reaction

TABLE 6:

W/w Ratio of Reactants		Reaction Conditions		
Phosphinic Acid (23)	PPA	Solvent	Temperature	Time
1	50	-	150 - 180°	3h
1	80	-	160°	¾h
1	100	-	180°	1h
1	100	-	80°	3h
1	10	DCB	175°	4h
1	15	DCB	175°	3h
1	10	Toluene	110°	1h*

* See text

temperature. After the required duration, the reaction mixture was cooled to 80°C and, whilst still mobile, poured into iced water and stirred until dissolution was complete. Continuous extraction of the resultant aqueous solution with dichloromethane or ether gave only starting material

in each case, as shown by melting point and ^{31}P spectroscopy.

Ethyl (diethoxyphosphino)acetate (24)

An ethereal solution of lithium diisopropylamide, prepared from diisopropylamine (1.85g, 18.3mmol) and butyl lithium (1 equivalent), was cooled to -78°C and vigorously stirred, while ethyl acetate (1.6g, 18.2mmol) in ether (10ml) was slowly added. After a further 15 min, maintaining the temperature at -78°C, a solution of diethyl phosphorochloridite (2.65g, 17mmol) in ether was added over ½h. The reaction was allowed to warm to room temperature and, after 2h, filtered and the solvent removed. Distillation of the residue gave ethyl (diethoxyphosphino)acetate (2.7g, 71%) as a colourless liquid, b_{20} 115°.

^{1}H $\delta(CDCl_3)$ 4.1(q,2H, J = 7Hz), 4.0(m,4H)
2.7(d,2H, J = 5Hz) and 1.25(t,9H,J = 7Hz)p.p.m

^{31}P (CH_2Cl_2)+167.4 p.p.m.

Ethyl Benzylcarbethoxymethylphosphinate (25)

Ethyl (diethoxyphosphino)acetate (1.0g, 4.8mmol) wax mixed with benzyl bromide (0.82g, 4.8mmol) and heated with vigorous stirring, at a bath temperature of 160°C for ½h. The reaction was cooled and the crude product distilled to give ethyl benzylcarbethoxymethyl phosphinate $b_{0.005}$ 120°C (1.1g; 85%).

^{1}H $\delta(CDCl_3)$ 7.3(bs, 5H), 4.2(q,2H, J = 7Hz), 4.1(dq,2H, J = 7Hz),3.3(d, 2H, J = 18Hz), 2.85(d, 2H, J = 17Hz), 1.3(t, 3H, J = 7Hz), and 1.27(t, 3H, J = 7Hz)p.p.m.

(^{31}P decoupling simplified the spectrum, causing the collapse of absorptions at 3.3 and 2.85 p.p.m. to singlets, and 4.1 p.p.m. to a quartet.)

^{31}P (CH_2Cl_2) +43.6 p.p.m.

νmax (Neat) 3030, 3015,2980,2930,1720,1600, 1495,1450,1400,1360,1250,1100, 1025,950,880,and 830cm^{-1}.

Ethyl 2-(bromomethyl)benzoate

2-Methylbenzoic acid (5g, 37mmol) was dissolved in benzene, and stirred at 0°C while excess thionyl chloride was added dropwise. The mixture was then warmed to reflux for 40min, after which the solvent and excess thionyl chloride were removed to give crude 2-methylbenzoyl chloride quantitatively. Without further purification, the acid chloride was redissolved in benzene, and a solution of sodium ethoxide (1 equivalent) in ethanol gradually added. After stirring at room temperature overnight, the reaction mixture was washed with water, sodium hydroxide solution, then again with water. The organic phase was dried, and the solvent removed to give crude ethyl 2-methylbenzoate (5.5g, 91%), used directly

in the next stage.

Ethyl 2-methylbenzoate (5.5g, 35mmol) in carbon tetrachloride was irradiated with a tungsten lamp in the presence of *N*-bromosuccinimide (6.6g, 37mmol), and heated under reflux, until the bromine colour dissipated. The solution was filtered and washed with dil. hydrochloric acid, then water, dried and the solvent removed to give a light brown oil. Distillation gave ethyl 2-(bromomethyl) benzoate $b_{0.1}$ 110° (6.8g, 75.5% overall).

^1H	$\delta(CCl_4)$	8.2 - 7.7(m, 1H), 7.3(m, 3H), 4.95(s, 2H), 4.35(q, 2H, J = 7Hz) and 1.4(t, 3H, J = 7Hz)p.p.m.
ν_{max}	(Neat)	3060, 2980, 1720, 1600, 1450, 1370, 1300, 1265, 1110, 1075, 1040, 760, and 705 cm^{-1}.

Ethyl [(2-carbethoxytolyl)ethoxyphosphinyl] acetate (27)

Ethyl 2-(bromomethyl)benzoate (0.64g, 2.6mmol) was mixed under an inert atmosphere with ethyl (diethoxyphosphino) acetate (0.55g, 2.6mmol) and heated to a bath temperature of 160°C for 2h. Removal of any remaining bromoethane under vacuum, followed by distillation gave triester (27) $b_{0.002}$ 140 - 150° (0.73g; 81%) as a colourless, hygroscopic oil.

^1H	δ $(CDCl_3)$	7.9(m, 1H), 7.5 - 7.2(m, 3H), 4.5 - 3.7(m, 8H), 2.85(d, 2H, J = 16Hz) and 1.25(m, 9H)p.p.m.
^{31}P	$(CHCl_3)$	+43.0 p.p.m.

ν_{max} (Neat)	2960, 1760, 1720, 1360, 1250, 1100, 1060, 1020, and 950 cm^{-1}.
m/e	342 (M^+), 243, 241, 179, 144, 143, 123, 109, 93 and 88.

2-Hydroxy-1,2,3,4-tetrahydroisophosphinoline 2,4-dioxide (26)

Ethyl [(2-carbethoxytolyl)ethoxyphosphinyl] acetate (27) (0.9g, 2.6 mmol) was dissolved in ethanol (10ml) and cooled to 0°C. Sodium metal (0.2g, 8.7mmol) was added, and the mixture stirred until dissolution was complete, when the reaction was warmed to room temperature. After 2h the bulk of the solvent was removed, and the brown residue heated under reflux with conc. hydrochloric acid (25ml) for 2h. After cooling and diluting with one volume of water, the aqueous solution was continuously extracted with ether for 24h. The organic extract was dried and the solvent removed to give a yellow oil.

Crystallisation from dichloromethane/petrol gave 2-hydroxy-1,2,3,4-tetrahydroisophosphinoline 2,4-dioxide (0.15g; 30%) m.p. 195 - 197°C.

^{1}H δ(DMSO-d^{6}) 8.0 - 7.7(m, 2H), 7.6 - 7.2(m, 2H), 3.35(d, 2H, J = 17Hz) and 3.25(d, 2H, J = 17Hz)p.p.m.

^{31}P (DMSO) +37.7 p.p.m.

ν max (KBr) 2960,2900,1660,1595,1450,1400,1300, 1250,1160,1100,1010,860, and 760cm^{-1}.

m/e 197(M^{+}+1), 196(M^{+}), 168,118,104,91 and 90.

Reaction of (24) with α,α^{1} -dibromo-*o*-xylene

Ethyl (diethoxyphosphino)acetate (0.275g, 1.3mmol) was dissolved in dimethyldigol (15ml), and slowly added to a dimethyldigol solution of dibromo-*o*-xylene (0.38g, 1.4mmol). The mixture was heated under reflux for 1h. Removal of the solvent gave a brown residue exhibiting ^{31}P absorption at +36.3 and +19.4 p.p.m.

Distillation gave three fractions:

(i) $b_{0.001}$ 60 - 70°C, showing a single ^{31}P absorption at +19.6 p.p.m., while the ^{1}H n.m.r. spectrum indicated it probably consisted largely of oxidised (24).

^{1}H $\delta(CDCl_3)$ 4.7 - 4.0 (m,4H), 2.9(d, 2H, J = 21Hz) and 1.3(t, 6H, J = 7Hz)p.p.m.

(ii) $b_{0.001}$ 150°C, ^{31}P containing 9 peaks.

(iii) Residue $b_{0.001}$ > 180°C

^{31}P (CH_2Cl_2) +43.2 p.p.m.

In both cases the ^{1}H spectrum was too complex to obtain an indication of the compounds present.

CHAPTER 2

General Procedure for the Photolysis of 1,2-dihydrophosphinoline 1-Oxides

The appropriate 1,2-dihydrophosphinoline 1-oxide (20) was dissolved in 35ml of thoroughly dried solvent, and the solution deoxygenated either ultrasonically, or by displacement with a continuous stream of nitrogen. 5ml of solution was retained in a masked sample tube as a dark-reaction for comparison, and the remainder placed in a quartz tube, suspended in a Rayonet Photochemical Reactor fitted with low-pressure mercury lamps radiating at 254nm (unfiltered). The extent of photolytic reaction was monitored by spectral or chromatographic methods, as indicated for each compound. Upon completion of the reaction, removal of solvent gave the crude product mixture, further investigation and purification being carried out as described.

Photolysis of 1,2-Di hydro-1-hydroxyphosphinoline 1-Oxide (20a) in Methanol

A solution of 1,2-dihydro-1-hydroxyphosphinoline 1-oxide (0.19g, 1.06mmol) in degassed methanol (35ml) was photolysed at 254nm. At timed periods during the reaction an aliquot (30 µl) of the solution was withdrawn and diluted to 5ml with methanol, and an U.V. spectrum obtained. After 9h, an absorption at 220nm had significantly decreased and similarly a peak at 258nm all but disappeared. No further change was observed with longer periods of photolysis.

The solvent was removed from the product mixture to give 0.22g of a yellow oil, exhibiting a single peak in the ^{31}P ($CHCl_3$) spectrum at +22.0 p.p.m. Gas chromatography gave a single broad peak R_t = 9.8 min under conditions (3% OV17, 190°, 50mlmin$^{-1}N_2$) that failed to remove the starting phosphinic acid (20a) from the column. The ^1H spectrum was consistent with a mixture containing predominantly (88%) methyl 2-(prop-2-enyl)phenyl-phosphonate (29a)

^1H $\delta(CDCl_3)$ 9.8(s, 1H: D_2O exchangeable), 7.8(m, 1H), 7.3(m, 3H), 6.2 - 5.7(m, 1H), 5.1(m, 2H), 3.6(d, 3H, J = 12Hz), and 3.6(m, 2H).

This was superimposed upon the spectra for the two isomers of methyl 2-(prop-1-enyl)phenylphosphonate (56a) and (57a). Further purification by chromatography proved impractical, no movement from the baseline being observed on silica T.L.C. plates eluted with 50% EtOH/EtOAc. Attempted distillation at 0.02mmHg led to considerable decomposition and isomerisation.

Methylation of a further sample of the photolysis mixture with excess diazomethane allowed the purification of dimethyl 2-(prop-2-enyl)phenylphosphonate (29, R = OMe) by distillation $b_{0.004}$ 120° followed by preparative T.L.C. on alumina eluted with chloroform (R_f = 0.6).

^1H $\delta(CCl_4)$ 7.8(ddd, 1H, J = 12,8 and 2Hz), 7.3(m, 3H), 6.2 - 5.6(m, 1H), 5.1(m, 1H), 4.9(m,1H), 3.7(m, 2H) and 3.65(d, 6H, J = 11Hz)p.p.m.

^{31}P ($CHCl_3$) +22.2 p.p.m.

Still superimposed upon these spectra were those of (56 and 57, R = OMe), contributing 7% total by integration of the ^1H n.mr. spectrum.

^1H $\delta(CCl_4)$ 7.8(m, 1H), 7.3(m, 3H), 6.8 - 5.8(m, 2H and 1.8(m, 3H)p.p.m.

^{31}P ($CHCl_3$)+21.6 p.p.m.

Photolysis of 1,2-Dihydro-1-methylphosphinoline 1-Oxide (20b)

(i) In Methanol

Monitoring the photolysis of 1,2-dihydro-1-methyl phosphinoline 1-oxide (0.145g, 0.8 mmol) by G.C. (10% E30, 200°, 50ml $min^{-1}N_2$) showed the complete consumption of starting material (R_t = 10 min) after 3h. The solvent was removed to give a brown residue distilled $b_{0.02}$ 100°C to give a colourless oil(0.105g).

G.C.(3% OV17, 165°C, 55ml $min^{-1}N_2$) showed this mixture to contain three compounds, R_t = 10.5, 13.4 and 14.8 min. Mass spectral analysis of each component showed them to be isomeric, with m/e 210 (M^+). High resolution mass spectrometry gave molecular ions of m/e 210.082, corresponding to a molecular formula of $C_{11}H_{15}O_2P$. In each case the base peak was m/e 196.06 ($C_{10}H_{12}O_2P$), from loss of a methyl group.

The ^1H and ^{31}P spectra of the mixture were consistent with methyl methyl-2-(prop-2-enyl)phenyl-phosphinate (29b , 50%) and the *cis* and *trans* isomers of

methyl methyl-2-(prop-1-enyl)phenylphosphinate (56b and 57b, 25% each) being the major constituents. Integration of ^1H spectra and G.C. traces were in close agreement as to relative proportions.

^1H $\delta(CDCl_3)$ (29b) 8.2 - 7.8(m, 1H), 7.8 - 7.2(m, 3H), 6.4 - 5.8(m,1H), 5.4 - 5.0 (m, 2H), 3.85(m, 2H), 3.7(d,3H, J = 11Hz), and 1.7(d, 3H, J = 14Hz)p.p.m.

(56b) and (57b) 8.2 - 7.8(m, 1H), 7.8 - 7.0(m, 4H) 6.4 - 5.8(m, 1H), 3.7(d, 3H, J = 11Hz) and 2.0 - 1.4(m, 6H)p.p.m.

^{31}P $(CHCl_3)$ +44.6, +44.2 and +43.0 p.p.m.

(ii) In *t*-Butylamine

The course of the photolysis of (20b)(0.237g, 1.3mmol) *t*-butylamine at 254nm was similarly followed by G.C. (3% OV17, 200°, 55mlmin$^{-1}N_2$), the starting material (R_t = 11 min) being completely replaced by a single major peak (R_t = 8.6 min) after 7h. High resolution mass spectral investigation gave a molecular ion of m/e 251.144 corresponding to $C_{14}H_{22}NOP$. Integration of the ^1H spectrum again indicated an even distribution between *t*-butyl methyl-2-(prop-2-enyl)phenyl-phosphinamidate and *t*-butyl methyl-2-(prop-1-enyl)phenyl-phosphinamidate.

^1H $\delta(CDCl_3)$ 8.2 - 7.8(m, 1H), 7.3(m, 3.5H), 6.2 - 5.8(m, 1H), 5.2 - 4.8(m, 1H), 3.9(bd, 1H, J = 6Hz), 1.9 - 1.2 (m, 4.5H)and

1.3(s, 9H) p.p.m.

(N-H proton was not visible).

^{31}P ($CHCl_3$)+26.2p.p.m. (2 minor peaks at +41.5 and +42.4p.p.m.).

Photolysis of 1-Benzyl-1,2-dihydrophosphinoline 1-Oxide (20c) in Methanol

Photolysis of 1-benzyl-1,2-dihydrophosphinoline 1-oxide (20c) was complete after 15h by G.C.(3% OV17, 200°C, 55.mlmin^{-1} N_2).

Separation of the product mixture from polymeric material was achieved by preparative T.L.C. on silica, eluted with 5% methanol in dichloromethane (Rf = 0.6). Integration of the ^1H n.m.r. spectrum gave proportions of 60% (29c), 20% (56c) and 20% (57c).

^1H δ($CDCl_3$) (29c) 7.8 - 7.4 (m, 1H), 7.3 - 6.9 (m, 3H), 6.2 - 5.7(m,1H), 5.1(m, 1H), 4.9(m, 1H) 3.65(m, 2H) 3.6(d, 3H, J = 11Hz) and 3.25(d, 2H, J = 17Hz)p.p.m.

(56c)and(57c) 7.8 - 7.4(m, 1H), 7.3 - 6.9(m, 4H) 6.2 - 5.7(m, 1H), 3.6(d, 3H, J = 11Hz), 3.25(d, 2H, J = 17Hz) and 1.85(m, 3H)p.p.m.

^{31}P (CH_2Cl_2) +42.8 p.p.m.

ν max (CH_2Cl_2) 3010, 2940, 1640, 1600, 1500, 1220, 1130, 1040, 910, and 830 cm^{-1}.

m/e 286(M^+), 271, 195, 163, 117, 116, 115, 86, 84 and 83.

CHAPTER 3

2-Biphenylylphosphorodichloridothioate (60)

A solution of 2-phenylphenol (25g, 0.16mol), thiophosphoryl chloride (27.2g, 0.16mol) and pyridine (12.6g, 0.16mol) in benzene (400ml) was heated under reflux for 15h. After cooling, the solution was filtered, and the solvent removed to give 2-biphenylylphosphorodichloridothioate (60) as a pink syrup (48g, 98%).

^{1}H $\delta(CDCl_3)$ 7.6 - 7.2(m)p.p.m.

^{31}P $(CHCl_3)$+53.1p.p.m.

νmax (Neat) 1960, 1590, 1505, 1480, 1455, 1435, 1250, 1175, 1110, 1077, 1050, 1040, 1012, 935, 790, 770, 755, 730 and 695 cm^{-1}.

Purification by distillation proved impossible, with the product decomposing.

6-Chloro-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-Sulphide (59)

Friedel-Crafts cyclisation of 2-biphenylylphosphorodichloridothioate (60) with aluminium chloride was attempted under a variety of conditions, already summarised in Table 1. The procedure found to give the best and most reproducible results is described below.

2-Biphenylylphosphorodichloridothioate (60) (20g, 66mmol) was mixed with aluminium chloride (1g, 7.5mmol) and heated to 200°C with vigorous stirring. After 1h, the

reaction mixture was cooled, dissolved in dichloromethane, and washed with water. The organic layer was separated, dried and the solvent removed to give a brown oil, crystallising on standing. Recrystallisation from dichloromethane/petrol gave (59) (15.9g, 90%), as white crystals m.p. 137 - 139°C.

^1H	$\delta(CDCl_3)$	8.2 - 7.9 (m, 2H) and 7.6 - 7.2 (m, 7H)p.p.m.
^{31}P	$(CHCl_3)$	+73.4p.p.m.
ν_{max}	(Nujol)	1510, 1480, 1270, 1200, 1190, 1120, 1055, 940, 810, 800, 770, 760, 725 and 710 cm^{-1}.

6-Methoxy-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-Sulphide (65)

A solution of chloro-oxaphosphorin (59) (20g, 7.5mmol) in dichloromethane was cooled to 0°C, and stirred while a methanolic solution of sodium methoxide (0.405g, 7.5mmol) was added dropwise. The reaction was then heated under reflux for 5h. After cooling, the mixture was poured into water and the product extracted with dichloromethane. Removal of the solvent from the organic extract gave a light brown oil, crystallising from methanol to give (65) as a white solid m.p. 80 - 81°C (15g, 76%).

^1H	$\delta(CDCl_3)$	8.2 - 7.8(m, 3H), 7.8 - 7.0(m, 6H) and 3.65 (d, 3H, J = 14Hz)p.p.m.
^{31}P	(CH_2Cl_2)	+77.5 p.p.m.
ν_{max}	(Nujol)	1600, 1585, 1570, 1422, 1180, 1140,

1109, 1020, 890, 810, 783, 770, 750, 740, 710, 700, and, 645 cm^{-1}.

λ_{max} 245nm.

^{13}C ($CDCl_3$) 149.60(d, 1C, J = 11.7Hz), 134.5 - 119.6 (m, 11C) and 52.66 (d, 1C, J = 5.8Hz)p.p.m.

Attempted Photolysis of (65)

(i) In Methanol

6-Methoxy-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-sulphide (4g, 15.3mmol) was dissolved in methanol (500ml) and photolysed at 254nm in a falling-curtain apparatus (p. 61) for 72h. During this period, the spot produced by the starting ester (65) (Rf = 0.67) on silica T.L.C. plates (eluted with chloroform) was gradually replaced by three others of Rf = 0.00, 0.13 and 0.37. Removal of solvent from the photolysis mixture gave a brown oil (4.6g).

^{1}H $\delta(CDCl_3)$ 8.6(bs, 1H: D_2O exchangeable), 8.2 - 7.0(m, 9H), and 3.5 - 4.0(m, 5H).

^{31}P ($CHCl_3$)+87.7, +20.1 and +11.9p.p.m.

Repeated use of column chromatography and preparative T.L.C. led only to recovery of starting ester (65), by ^{31}P and ^{1}H n.m.r. spectroscopy. Attempts to prevent reversion of products during purification by treatment with excess diazomethane gave no discernable change in any of the physical characteristics of the product mixture.

(ii) In *t*-Butylamine

Dissolving (65) in *t*-butylamine led to a rapid and quantitative precipitation of the *t*-butylammonium salt of 6-mercapto-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-oxide. The pure salt was filtered, washed with ether and dried m.p. 185 - 188°C.

^1H	δ ($CDCl_3$)	8.2 - 7.0(m, 8H), 5.3(bs, 4H) and 1.2(s, 10H)p.p.m. (containing amine of crystallisation).
^{31}P	($CHCl_3$)	+59.1p.p.m.
ν_{max}	(KBr)	3200 - 2700(broad), 1472, 1430, 1380, 1210, 1150, 1110, 1070, 870, 770, 760, 715, and 700 cm^{-1}.

6-Mercapto-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-oxide(75)

(i) The *t*-butylammonium salt obtained above was dissolved in water and acidified with dil. hydrochloric acid. Extraction of the product with dichloromethane, followed by removal of the solvent gave the free acid in 80% yield as a white crystalline solid.

(ii) 6-Methoxy-6*H* -dibenz(c,e)(1,2)oxaphosphorin 6-sulphide (1g, 3.8mmol) was heated for 10h under reflux in methanol, in the presence of 1 equivalent of sodium methoxide. The solution was poured into water, and extracted with chloroform. Removal of the solvent gave unreacted (65). Acidification of the aqueous layer, followed by extraction with chloroform gave, after removal of the solvent, a colourless oil, crystallising

on standing. Recrystallisation from dichloromethane gave the pure acid m.p. 145 - 145.5°.

^1H	$\delta(CDCl_3)$	8.3 - 7.7(m, 3H), 7.7 - 7.1(m, 5H) and 5.4(s, 1H: D_2O exchangeable)p.p.m.
^{31}P	$(CHCl_3)$	+71.2 p.p.m.
ν_{max}	(KBr)	3200 - 2700(broad), 1590, 1580, 1557 1471, 1445, 1428, 1240, 1195, 1145, 1120, 950, 934, 920, 910, 790, 769, 751, 710, and 655 cm^{-1}.

$C_{12}H_9O_2PS$: Requires C 58.07, H 3.60, P 12.48%
Found C 58.11, H 3.63, P 12.38%.

2-Biphenylylmethylphosphonic acid (68)

This compound was synthesised from 2-phenylbenzoic acid as described by Lynch[61], in 58% overall yield, m.p. 166 - 169°C. Spectral details of the phosphonic acid and all intermediates were comparable to those reported by Lynch. In addition, the ^{31}P spectrum was obtained:

^{31}P	(DMSO)	+22.2 p.p.m.

9,10-Dihydro-9-hydroxyphosphaphenanthrene 9-Oxide

Polyphosphoric acid (200g) was heated to 60°C, and vigorously stirred while 2-biphenylylmethylphosphonic acid (2g, 8.0mmol) was gradually added. The suspension was heated to a bath temperature of 220°C for 3h, cooled to 100°C and poured into iced water (150ml). After sitrring for 15h, the resultant suspension was filtered. The solid was dissolved in dilute aqueous sodium hydroxide,

washed with ether, and the aqueous solution acidified. The crude product was filtered and recrystallised from ethanol to give pure 9,10-dihydro-9-hydroxyphosphaphenanthrene 9-oxide (0.95g, 56%) as a white, crystalline solid m.p. 234 - 235°C.

^{1}H δ(DMSO-d^{6}) 10.2(bs, 1H: D_2O exchangeable), 8.2 - 7.2(m, 8H) and 3.2(d, 2H, J = 18Hz)p.p.m.

^{31}P (DMSO) +24.6 p.p.m.

9,10-Dihydro-9-methoxyphosphaphenanthrene 9-Oxide (67)

9,10-Dihydro-9-hydroxyphosphaphenanthrene 9-oxide (0.2g, 0.9mmol) was dissolved in excess thionyl chloride, and heated under reflux for 22h. The remaining thionyl chloride was distilled off, the last traces being removed by codistillation with toluene. The solid residue was redissolved in toluene (25ml), and heated under reflux in the presence of pyridine (1g, 12mmol) and methanol (3g, 93.7mmol) for 4h. After cooling the reaction mixture was washed with water, dil. hydrochloric acid and again with water. The organic solution was dried and the solvent evaporated to give a cream-coloured solid. Recrystallisation from dichloromethane/petrol gave pure (67)(0.20g, 86%) m.p. 168 - 169°C.

^{1}H $\delta(CDCl_3)$ 8.4 - 7.2(m, 8H), 3.65(d, 3H, J = 11Hz) and 3.4(dm, 2H, J = 19Hz)p.p.m

^{31}P	($CHCl_3$)	+34.1 p.p.m.
λmax		220 and 265 nm.

Attempted Photolysis of (67)

9,10-Dihydro-9-methoxyphosphaphenanthrene (0.075g, 0.31mmol) was dissolved in methanol (35ml), and the solution degassed. Subsequent photolysis at 254nm in a Rayonet Photochemical Reactor for 72h showed no change in the T.L.C.(silica plates eluted with 10% methanol in ether), and removal of the solvent gave a quantitative recovery of (67).

CHAPTER 4

The Dealkylation of 6-Methoxy-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-Sulphide (65) by Amines

A solution of oxaphosphorin (65) in excess of the appropriate amine was maintained at room temperature. If no precipitation of the ammonium salt of 6-mercapto-6*H*-dibenz(c,e)(1,2)oxaphosphorin 6-oxide(75) occurred, the solution was heated under reflux until the ^{31}P spectrum of an aliquot indicated reaction had occurred. If the product did not precipitate on cooling, the excess amine was removed and the residue investigated. The following amines gave the salts of thiophosphonate (75), which were washed in ether, and dried:

(i) *t*-Butylamine

Gave quantitative precipitation after 30min. at room temperature. The spectral details for this compound have been quoted in the experimental part of Chapter 3.

(ii) *cyclo*-Hexylamine

Precipitation occurred on cooling after heating under reflux for 1h. The salt was obtained in 75% yield, m.p. 110 - 112°C.

^{1}H $\delta(CDCl_3)$ 8.2 - 7.7(m, 3H), 7.6 - 7.0(m, 5H), 5.2(bs, 3H), 2.55(m, 1H) and 2.0 - 0.9(m, 10H)p.p.m.

(sample contained 20% amine of crystallisation)

^{31}P $(CHCl_3)$ +59.0 p.p.m.

(iii) Di-*iso* propylamine

Heating under reflux for 3h gave a 35% yield of salt on cooling, m.p. 210 - 217 °C (decomposes).

^{1}H $\delta(CDCl_3)$ 8.2 - 7.6(m, 5H), 7.5 - 7.0(m, 5H), 2.9(9 lines, 1H, J = 6Hz) and 1.0(d, 6H, J = 6Hz)p.p.m.

(sample contained 20% amine of crystallisation)

^{31}P $(CHCl_3)$+58.7 p.p.m.

(iv) Triethylamine

The product separated as an oil after heating under reflux for 6h. The reaction did not occur cleanly, at least two products being formed, the major one being the anticipated methyltriethylammonium salt (comprising 66% by ^{1}H n.m.r.).

^{1}H $\delta(CDCl_3)$ 8.2 - 7.6(m, 3H), 7.6 - 6.9(m, 5H), 3.1(q, 4H, J = 7Hz), 2.7(s, 2.5H), 2.2(s, 1H), 1.2(s, 2H) and 1.0(t, 6H, J = 7Hz)p.p.m.

^{31}P $(CHCl_3)$+54.8 and +53.8 p.p.m. (with minor absorptions at +55.9, +39.0 and +2.2 p.p.m.).

t-Butylmethylamine

t-Butylamine (0.5g, 6.9mmol) was dissolved in benzene (5ml), and stirred while a benzene solution of iodomethane (0.97g, 6.9mmol) was added. After 1h, the precipitate was filtered, washed with benzene and dried to

give a quantitative yield of t-butylmethylammonium iodide. This salt was dissolved in water, and aqueous sodium hydroxide added (5ml, 2M). The liberated amine was extracted into chloroform-d. G.C. on a Pennwalt 223 column (initial temperature 40°C, with 3°C min^{-1} increase 42ml min^{-1} N_2) gave R_t = 7.2 min.

^1H $\delta(CDCl_3)$ 1.55(s, 1H: D_2O exchangeable), 1.15(s, 9H) and 2.3(s, 3H)p.p.m.

Dimethyl 2-methylphenylphosphonate

A mixture of trimethyl phosphite (3.6g, 28.8mmol), 2-bromotoluene (4.9g, 28.8mmol) and anhydrous nickel chloride (2.7g, 28.8mmol) was heated under an inert atmosphere with stirring, to 140° for 4h. The cooled mixture was added to water, and extracted with dichloromethane. The organic phase was dried and the solvent removed. The residue was distilled to give dimethyl 2-methylphenylphosphonate (2.6g, 44%) $b_{0.5}$ 112 - 115°C.

^1H $\delta(CDCl_3)$ 8.1 - 7.7(m, 1H), 7.6 - 7.0(m, 3H), 3.7(d, 6H, J = 11Hz), and 2.6(s, 3H)p.p.m.

^{31}P (CH_2Cl_2) +22.0 p.p.m.

ν_{max} (Neat) 3060, 2950, 2850, 1600, 1450, 1245, 1180, 1143, 1090, 1030, 820, 760, 720, and 680 cm^{-1}.

λ_{max} (ε)(MeCN) 225(2300), 270(1070) and 277.5(980)nm.

Methyl 3-(methoxyphenylphosphinyl)propanoate (79)

3-(Hydroxyphenylphosphinyl)propanoic acid (23) (1g, 4.7mmol) was added to excess thionyl chloride, and the mixture stirred overnight. The thionyl chloride was distilled off, the last traces being removed by codistillation with toluene, and the residue dissolved in benzene and cooled to 0°C. A methanolic solution of sodium methoxide (0.6g, 9.5mmol) was added dropwise, the reaction allowed to warm to room temperature and stirred for 15h. After washing the solution with water, the solvent was removed, and the residue vacuum distilled to give methyl 3-(methoxyphenylphosphinyl)propanoate (0.7g, 62%) as a colourless oil $b_{0.1}$140°C.

^1H	$\delta(CCl_4)$	8.0 - 7.3(m, 5H), 3.6(s, 3H), 3.55(d, 3H, J = 17Hz) and 2.8 - 1.8(m, 4H)p.p.m.
^{31}P	(CH_2Cl_2)	+43.2 p.p.m.
ν_{max}	(Neat)	2950, 1740, 1590, 1440, 1360, 1230, 1175, 1120, 1030, 820, 790, 750 and 730 cm^{-1}.

Dimethyl 2-Bromoethylphosphonate (81)

A mixture of trimethyl phosphite (5.3g, 42.4mmol) and 1, 2-dibromoethane (50ml) was heated under reflux for 20h. Excess dibromoethane was removed by distillation, initially at atmospheric pressure, and finally on a water-pump. The residue was distilled give dimethyl 2-bromo-ethylphosphonate (6.3g, 73%) as a colourless liquid

$b_{0.04}$ 90°C.

^1H $\delta(CDCl_3)$ 3.8(d, 6H, J = 11Hz), 3.5(m, 2H) and 2.4(m, 2H)p.p.m.

^{31}P $(CHCl_3)$+28.0 p.p.m.

Dimethyl 3-bromopropylphosphonate (83)

1,3-Dibromopropane (20ml) was warmed to 120°C, and stirred while trimethyl phosphite (1.0g, 8.5mmol) was added dropwise. The temperature was maintained for a further 1½h, until examination of the ^{31}P spectrum indicated the reaction was complete. Excess dibromopropane was removed, and the residue distilled to give dimethyl 3-bromopropylphosphonate (0.35g, 19%) as a colourless oil

$b_{0.05}$ 70 - 80°C.

^1H $\delta(CDCl_3)$ 3.7(d, 6H, J = 11Hz), 3.45(m, 2H) and 2.3 - 1.2(m, 4H)p.p.m.

^{31}P $(CHCl_3)$+32.7 p.p.m.

ν_{max} (Neat) 2950, 2840, 1470, 1440, 1250, 1190, 1030, and 820 cm^{-1}.

Dimethyl Vinylphosphonate (82)

Dimethyl 2-bromoethylphosphonate (81) (0.1g, 0.45mmol) was dissolved in *t*-butylamine (5ml) and left at room temperature for 10min. The precipitated amine hydrochloride was filtered and the solvent removed from the filtrate to give pure dimethyl vinylphosphonate (0.068g, 100%).

^{1}H $\delta(CDCl_3)$ 6.6 - 5.7(m, 3H) and 3.7(d, 6H, J = 11Hz)p.p.m.

^{31}P $(CHCl_3)$+19.8 p.p.m.

^{13}C $(CDCl_3)$ 136.2(s, 1C), 124.5(d, 1C, J = 183.6Hz) and 52.4(d, 2C, J = 5.9Hz)p.p.m.

Diethyl Methyl Phosphate

Diethyl phosphate (1.5g, 9.7mmol) was dissolved in thionyl chloride (10ml), and heated under reflux for 0.5h. The excess thionyl chloride was removed, and the residue taken up in benzene. The solution was stirred at 0°C while a mixture of methanol (0.4g, 12.9mmol) and triethylamine (1.2g, 12mmol) in benzene was added. The reaction was heated under reflux for 72h, then the solvent evaporated and the residue extracted with ether. The organic solution was washed with dil. hydrochloric acid, sodium hydroxide solution, and water. The organic layer was dried and the solvent removed to give a light brown oil. Distillation afforded diethyl methyl phosphate (0.17g, 12%) as a colourless liquid b_{15} 110°C.

^{1}H $\delta(CDCl_3)$ 4.1(dq, 4H, J = 7 and 7Hz), 3.7(d, 3H, J = 11Hz) and 1.3(t, 6H, J = 7Hz)p.p.m.

31P (CH_2Cl_2) 0 p.p.m.

Dibenzyl Methyl Phosphate

Dibenzyl phosphate (0.5g, 1.8mmol) was suspended in ether, and an excess of an ethereal solution of diazomethane added. The solution was filtered after 0.5h, and the solvent removed to give dibenzyl methyl phosphate (0.52g, 98%) as a colourless oil.

^{1}H $\delta(CDCl_3)$ 7.35(s, 10H), 5.05(d, 4H, J = 9Hz) and 3.65(d, 3H, J = 11Hz)p.p.m.

^{31}P $(CHCl_3)$ 0.0 p.p.m.

Dibenzyl Ethyl Phosphate

A mixture of dibenzyl phosphite (2g, 7.3mmol) and *N*-chlorosuccinimide (1.0g, 7.3mmol) was stirred at room temperature in benzene for 4h. After this period the succinimide was filtered off, and mixture of ethanol (0.35g, 7.3mmol) and triethylamine (0.76g, 7.3mmol) added to the filtrate. The solution was heated under reflux for 5h, then filtered and the solvent removed to give a brown oil. Preparative T.L.C. on alumina plates eluted with ether gave dibenzyl ethyl phosphate Rf = 0.65 (1.8g, 86%) as a colourless oil.

^{1}H $\delta(CCl_4)$ 7.2(m, 10H), 4.9(d, 4H, J = 8Hz), 4.0(dq, 2H, J = 7 and 7Hz) and 1.3(t, 3H, J = 7Hz)p.p.m.

^{31}P (CH_2Cl_2) -1.0 p.p.m.

General Procedure for the Reaction of Phosphorus Esters with *t*-Butylamine

A 0.1g sample of the phosphorus ester was dissolved in 10ml *t*-butylamine, and left at room temperature for a period. If no precipitation of product was observed, the solution was heated under reflux until the reaction was complete. Where the product precipitated, it was collected by filtration, but occasionally no solid was obtained, when removal of excess amine afforded the products. Unless otherwise stated the reactions gave almost quantitative yields of dealkylated products. Thus reaction of *t*-butylamine with:

(i) Trimethyl phosphate

for 72h at room temperature gave *t*-butylammonium dimethyl phosphate m.p. 165 - 167°C

^{1}H $\delta(CDCl_3)$ 8.2(bs, 3H), 3.6(d, 6H, J = 11Hz) and 1.3(s, 9H)p.p.m.

^{31}P $(CHCl_3)$ +1.8p.p.m.

(Experiments using molar equivalents of reactants in an inert solvent (benzene, dichloromethane and dioxan) in an n.m.r. tube all showed gradual depletion of starting materials as the product precipitated.)

(ii) Dimethyl methylphosphonate

for 22h, heated under reflux, gave *t*-butylammonium methyl methylphosphonate m.p. 173 - 176°C

^{1}H $\delta(CDCl_3)$ 8.1(bs, 3H), 3.5(d, 3H, J = 10Hz), 1.4(s, 9H) and 1.25(d, 3H, J = 16Hz)p.p.m.

^{31}P $(CHCl_3)$+23.6 p.p.m.

(iii) 9,10-Dihydro-9-methoxyphosphaphenanthrene 9-oxide

at room temperature for 7d. gave the *t*-butylammonium salt of 9,10-dihydro-9-hydroxyphosphaphenanthrene 9-oxide m.p. 193 - 199°C

^{1}H $\delta(CDCl_3)$ 8.1 - 7.5(m, 3H), 7.5 - 7.1(m, 5H), 3.9(bs, 3H), 3.1(d, 2H, J = 17Hz) and 1.2(s, 9H)p.p.m.

^{31}P $(CHCl_3)$+19.0 p.p.m.

(iv) Dimethyl 2-methylphenylphosphonate

at room temperature for 7d gave *t*-butylammonium methyl 2-methylphenylphosphonate m.p. 168 - 171°C

^{1}H $\delta(CDCl_3)$ 8.3(bs, 3H), 8.1 - 7.7(m, 1H), 7.6 - 7.1(m, 3H), 3.6(d, 3H, J = 11Hz), 2.5(s, 3H) and 1.2(s, 9H)p.p.m

(v) Methyl 3-(methoxyphenylphosphinyl)propanoate

heated under reflux for 48h to give the *t*-butylammonium salt of methyl 3-(hydroxyphenylphosphinyl)propanoate m.p. 130 - 135°C

^{1}H $\delta(CDCl_3)$ 7.8 - 7.5(m, 2H), 7.25(m, 3H), 8.0 - 6.6(bs, 3H), 3.5(s, 3H), 2.5 - 1.6(m, 4H) and 1.15(s, 9H)p.p.m.

^{31}P $(CHCl_3)$+27.6 p.p.m.

(vi) 1-Methoxy-2,2,3,4,4-pentamethylphosphetan 1-oxide

heated under reflux for 6h gave the *t*-butylammonium salt of 1-hydroxypentamethylphosphetan 1-oxide

^{1}H $\delta(D_2O)$ 1.4(s, 9H), 1.1(dd, 12H, J = 17 and 1Hz), and 0.75(dd, 3H, J = 8 and 2Hz)p.p.m.

(absorption of methyne proton was indistinguishable)

^{31}P (D_2O) +49.2 p.p.m.

Acidification generated 1-hydroxypentamethyl-phosphetan 1-oxide

^{1}H $\delta(CDCl_3)$ 8.1(bs, 1H), 1.8 - 1.4(m, 1H), 1.2(2 x d, 12H, J = 18Hz) and 0.9(m, 3H)p.p.m.

^{31}P $(CHCl_3)$+59.5 p.p.m.

(vii) Dimethyl 2-bromoethylphosphonate

at room temperature for 10 mins gave a precipitate of *t*-butylammonium bromide, the excess amine of the mother liquor being removed to give dimethyl vinylphosphonate (spectral details given previously).

(viii) Dimethyl vinylphosphonate

for 10d at room temperature gave three phosphorus containing products, with an ^{1}H spectrum difficult to interpret (see text).

^{31}P $(BuNH_2)$ +33.1, +22.0 and +9.9p.p.m.

(ix) Dimethyl 3-bromopropylphosphonate

for 23h at room temperature gave dimethyl 3-(t-butylamino)propylphosphonate

^{1}H $\delta(CDCl_3)$ 4.5(bs, 1H), 3.7(d, 6H, J = 11Hz), 2.7(t, 2H, J = 7Hz), 2.2 - 1.6(m, 4H) and 1.15(s, 9H)p.p.m.

^{31}P $(BuNH_2)$+34.1 p.p.m.

(x) Diethyl methyl phosphate

for 24h at room temperature gave t-butylammonium diethyl phosphate m.p. 125 - 127°C

^{1}H $\delta(CDCl_3)$ 8.2 - 6.5(bs, 3H), 3.9(dq, 4H, J = 7 and 7Hz), 1.4(s, 9H) and 1.2(t, 6H, J = 7Hz)p.p.m.

^{31}P $(CHCl_3)$ +0.6 p.p.m.

(xi) Dibenzyl methyl phosphate

heated under reflux for 4h, gave t-butylammonium dibenzyl phosphate

^{1}H $\delta(CDCl_3)$ 8.2(bs, 3H), 7.2(bs, 10H), 4.9 (d, 4H, J = 7Hz) and 1.3(s, 9H)p.p.m.

^{31}P $(CHCl_3)$ -0.6 p.p.m.

(xii) Dibenzyl ethyl phosphate

was heated under reflux for 5d, and the solvent removed to give the dealkylation product, contaminated with benzyl-t-butylamine. Washing with dil. hydrochloric acid gave benzyl ethyl phosphate as a colourless oil

^{1}H $\delta(CDCl_3)$ 7.6(bs, 1H), 7.3(bs, 5H), 5.0(d, 2H, J = 7Hz), 4.05(dq, 2H, J = 7 and 7Hz) and 1.3(t, 3H, J = 7Hz)p.p.m.

^{31}P $(CHCl_3)$ -0.4 p.p.m.

(xiii) Triethyl phosphate, diethyl ethylphosphonate and diethyl phenylphosphonate, all heated under reflux for 7d showed no sign of reaction, removal of solvent allowing a quantitative recovery of ester.

REFERENCES

1 F.G. Holliman, and F.G. Mann, J.Chem. Soc., 1634 (1947).

2 M.H. Beeby, and F.G. Mann, J.Chem.Soc., 411 (1951).

3 G. Märkl, Angew. Chem., Internat.Ed., 2, 153 (1963).

4 M.J. Gallagher, E.C. Kirby, and F.G. Mann, J.Chem.Soc., 4846 (1963).

5 C.E. Griffin, and W.L. Bryant, Phosphorus, 2, 49 (1972).

6 G.A. Dilbeck, D.L. Morris, and K.D. Berlin, J.Org.Chem., 40, 1150 (1975).

7 W.R. Purdum, G.A. Dilbeck, and K.D. Berlin, J.Org.Chem., 40, 3763 (1975).

8 M.El Deek, G.D. Macdonell, S.D. Venkataramu, and K.D.Berlin, J.Org.Chem., 41, 1403 (1976).

9 G.A. Dilbeck, Ph.D. Thesis, Oklahoma State University (1974

10 C.M.Brown, Ph.D. Thesis, University of Leicester (1979).

11 L.E. Rowley, and J.M. Swan, Aust. J.Chem., 27, 801 (1974).

12 D.J. Collins, L.E. Rowley, and J.M. Swan, Aust. J.Chem., 27, 815 (1974).

13 G. Märkl and K.H. Heier, Angew.Chem., Internat Ed., 11, 1016 (1972).

14 A.N. Pudovik, V.K. Khairullin, and V.N. Eliseenkov, J.Gen.Chem. (USSR), 37, 423 (1967).

15 P. Broughton, University of Leicester, unpublished results.

16 R.C. Hinton, F.G. Mann, and D. Todd, J.Chem. Soc., 5454 (1961)

17 H.G. Henning, Z.Chem., 5, 417 (1965).

18 H.G. de Graaf, J. Dubbeldam, H. Vermeer, and F. Bickelhaupt, Tetrahedron Letters, 2397 (1973).

19 H.G. de Graaf, and F. Bickelhaupt, Tetrahedron, 31, 1097 (1975).

20 Z.S. Novikova, M.A. Krasnovskaya, and I.F. Lutsenko, J. Gen. Chem. (U.S.S.R.), 39, 1032 (1969).

21 M.V. Proskurnina, Z.S. Novikova, and I.F. Lutsenko, Dokl. Akad. Nauk. SSSR, 159, 619 (1964), Chem. Abs., 62, 6508 (1965).

22 Z.S. Novikova, S.N. Zdorova, V.N. Kirzner, and I.F. Lutsenko, J. Gen. Chem. (U.S.S.R.), 46, 572 (1976).

23 P. Tavs, Chem. Ber., 103, 2428 (1970).

24 G.M. Kosolapoff, and L. Maier, 'Organic Phosphorus Compounds', 7, 23, Wiley-Interscience, New York (1972).

25 F.G. Mann, and A.J. Wilkinson, J.Chem. Soc., 3336 (1957).

26 The Aldrich Library of N.M.R. Spectra, Aldrich Chemical Co. (1974).

27 H. Heimgartner, L. Ulrich, H.-J. Hansen, and H. Schmid, Helv. Chim. Acta , 54, 2313 (1971).

28 U. Widmer, H. Heimgartner, and H. Schmid, Helv. Chim. Acta , 58, 2210 (1975).

29 (i) A. Padwa, and S. Clough, J. Amer. Chem. Soc., 92, 5803 (1970).

(ii) W.G. Dauben, R.C. Williams, and R.D. McKelvey, J. Amer. Chem. Soc., 95, 3932 (1973).

(iii) S.W. Spangler, and R.P. Hennis, J.Chem. Soc. Chem. Comm., 24 (1972).

30 M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi, and Y. Tamura, J. Chem. Soc. Chem. Comm., 575 (1975).

31 J. Kolc, and R.S. Becker, J. Chem. Soc. Perkin II, 17 (1972).

32 A. Padwa, A. Au, G.A. Lee, and W. Owens, J. Org. Chem.,

40, 1142 (1975).

33 J. Kolc, and R.S. Becker, J. Phys. Chem., 72, 997 (1968).

34 J. Kolc, and R.S. Becker, J.Phys. Chem., 71, 4045 (1967).

35 J. Kolc, and R.S. Becker, J. Amer. Chem. Soc., 91 6513 (1969).

36 C.R. Hall, and D.J.H. Smith, Tetrahedron Letters, 3633 (1974).

37 J.D. Finlay, University of Leicester, Ph.D. Thesis (1978).

38. J.F. King, Accounts Chem. Res., 8, 10 (1975).

39 B.S. Lukjanow, M.I. Knjazschanski, J.W. Rewinski, L.E. Niworozschkin, W.I. Minkin, Tetrahedron Letters, 2007 (1973).

40 K. Salisbury, Tetrahedron Letters, 737 (1971).

41 M. Fisher, and F. Wagner, Chem. Ber., 102, 3486 (1969).

42 T. Saito, Chem. Abs., 77, 15237 (1972).

43 H. Nedachi, Chem. Abs., 82, 141127 (1975).

44 T. Kuribeyaski, K. Nagayoshi, and H. Shinada, Chem. Abs., 81, 14304 (1974).

45 I. Susaki, A. Inoue, and S. Kohno, Chem. Abs., 80, 83962 (1974).

46 G.M. Kosolapoff,'Organophosphorus Compounds' John Wiley, New York (1950).

47 E.A. Cherneyshev, E.F. Bugerenko, and V.I. Aksenov, J. Gen. Chem.(U.S.S.R.), 40, 1409 (1970).

48 (i) M.S. Bhatia, U.S. Gill, and P.Jit, Indian J. Chem., 14B, 812 (1976).

(ii) M.S. Bhatia, and P.Jit, Chem. and Ind. (London), 1058 (1975).

49 G.M. Kosolapoff,'Friedel-Crafts and Related Reactions' (ed. G.A. Olah), Vol. IV, Chapter LI.

50 E.A. Cherneyshev, E.F. Bugerenko, and V.I. Aksenov, J.Gen. Chem.(U.S.S.R.), 42, 88 (1972).

51 T. Saito, Chem. Abs., 76, 99823 (1972); 78, 43708 (1973); 83, 19799 (1975).

52 B. Buchner, and L.B. Lockhane Jr., J. Amer. Chem. Soc., 73, 755 (1951).

53 A. Michaelis, Ber., 12, 1009 (1879).

54 A. Michaelis, Annalen, 293, 193 (1896).

55 A. Michaelis, Annalen, 294, 1 (1897).

56 L. Maier, Helv. Chim. Acta , 47, 120 (1964).

57 L. Maier, Z. Anorg. Allgem. Chem., 345, 29 (1966).

58 'The Merck Index', No 7166, Merck and Co. Inc., Rahway, N.J. (9th Edition, 1976); Moeller *et al* Inorg. Syn., 4, 71 (1953).

59 R.A. Baldwin, K.A. Smitheman, and R.M. Washburne, J. Org. Chem., 26, 3547 (1961).

60 L. Maier, Topics in Phosphorus Chemistry, 2, 96 (1965).

61 E.R. Lynch, J. Chem. Soc., 3729 (1962).

62 I.G.M. Campbell, and J.K. Way, J.Chem. Soc., 5034 (1960).

63 M.J.S. Dewar, and V.P. Kubba, J. Amer. Chem. Soc., 82 5685 (1960).

64 (a) B.J. Walker, 'Organophosphorus Chemistry', Penguin Books Ltd., Harmondsworth, England (1972).

(b) J. Emsley and D. Hall, 'The Chemistry of Phosphorus', Harper and Rowe, London (1976).

(c) S. Trippett (ed.), 'Organophosphorus Chemistry,

Specialist Periodical Reports, Royal Society of Chemistry, London.

65 A.D.F.Toy, J. Amer. Chem. Soc., 66, 499 (1944).

66 C.R. Noller, and G.R. Dutton, J. Amer. Chem. Soc., 55, 424 (1933).

67 J. H. Billman, A. Radike, and B.W. Mundy, J. Amer. Chem. Soc., 64, 2977, (1942).

68 A. Barker and C.C. Barker, J.Chem. Soc., 2034 (1953).

69 D.G. Thomas, J.H. Billman and C.E. Davis, J. Amer. Chem. Soc., 68, 895 (1946).

70 M. Harris, and P.K. Patel, Chem. and Ind.(London), 1002 (1973).

71 K. Yamauchi, M. Hayashi, and M. Kinoshita, J. Chem. Soc. Perkin I, 391 and 2506 (1973).

72 K. Yamauchi, M. Hayashi, and M. Kinoshita, J. Org. Chem., 41, 3691 (1976).

73 P. Sutter, and C.D. Weis, Phosphorus and Sulfur, 4, 335 (1978).

74 K. Yamauchi, M. Kinoshita, and M. Hayashi, Bull. Chem. Soc. Japan, 49, 238 (1976).

75 K. Yamauchi, M. Hayashi and M. Kinoshita, J. Org. Chem., 40, 385 (1975).

76 G.M. Kosolapoff, and L. Maier, 'Organic Phosphorus Compounds', Vol. 7, Wiley-Interscience, New York (1972).

77 J. Houben, and T. Weyl, 'Methoden der Organischer Chemie', Vol 12/1, 409, Georg Thieme, Stuttgart (4th edition, 1963).

78 C. Brown, J. A. Boudreau, B. Hewitson, and R.F. Hudson, J. Chem. Soc. Chem. Comm., 504 (1975).

79 V.S. Abramov, Zh. Obsch. Khim., 12, 270 (1942).

80 G. Hilgetag, and H. Teichmann, Angew. Chem., 77, 1001 (1965).

81 J. Houben, and T. Weyl, 'Methoden der Organischer Chemie', Vol 12/2, 262, Georg Thieme, Stuttgart (4th edition, 1963).

82 D.G. Hewitt, and G.L. Newland, Aust. J. Chem., 30, 579 (1977).

83 K. Zieloff, H. Paul, and G. Hilgetag, Z. Chem., 4, 148 (1964).

84 D.M. Graifer, B.F. Zarytova, E.M. Ivanova, and A.B. Levedev, Dokl. Akad. Nauk., 242, 616 (Chem. Abs., 90, 22763 (1979)).

85 J. Michalski, S. Musierowicz, and B. Zielinska, Zesz. Nauk. Politech. Lodz., Chem., 161 (1973) (Chem. Abs., 80, 108119 (1974)).

86 R. Kluger, and P. Wasserstein, J. Amer. Chem. Soc., 95, 1071 (1973).

87 R. Rabinowitz, J. Org. Chem., 28, 2975 (1963).

88 J. Zygmunt, P. Kafarski, and P. Mastalerz, Synthesis, 609 (1978).

89 T. Morita, Y. Okamoto, and H. Sakurai, Tetrahedron Lett., 2523 (1978).

90 T.L. Ho, and G.A. Olah, Proc. Nat. Acad. Sci., U.S.A., 75, 4 (1978).

91 C.E. McKenna, N.T. Higa, N.H. Cheung, and M.C. McKenna, Tetrahedron Lett., 155 (1977).

92 C.E. McKenna, and J. Schmidhauser, J. Chem. Soc. Chem. Comm., 739 (1979).

93 G.M. Blackburn, and D. Ingleson, J. Chem. Soc. Perkin I, 1150 (1980).

94 G.M. Blackburn, and D. Ingleson, J. Chem. Soc. Chem. Comm., 870 (1978).

95 M.I. Kabachnik, and T.J. Medved, Izv. Akad. U.S.S.R., 635 (1950) (Chem. Abs., 45, 8444 (1951)).

96 A. Williams, University of Leicester, Personal Communication.

97 H. Kössel, and H. Seleger, Prog. in the Chem. of Org. Nat. Prod., 32, 297 (1975).

98 F. Eckstein, Chem. Ber., 100, 2228 (1967).

99 T. Neilson, and E.S. Werstiuk, Can. J. Chem., 49, 3004 (1971).

100 R.L. Letsinger, and K.K. Ogilvie, J. Amer. Chem. Soc., 89, 4801 (1967).

101 J.H. van Boom, P.M.H. Burgers, P.H. van Deursen, R. Arentzen, and C.B. Reese, Tetrahedron Letts., 3785 (1974).

102 K. Itakura, N. Katagiri, and S.A. Narang, Can. J. Chem., 52, 3689 (1974).

103 T. Mukaiyama, N. Morito, and Y. Watanabe, Chem. Letts., 895 (1979).

104 J. C. Catlin, and F. Cramer, J. Org. Chem., 38, 245 (1973).

105 F.R. Atherton, H.T. Openshaw, and A.R. Todd, J. Chem. Soc., 382 (1945).

106 J. Baddiley, and A.R. Todd, J. Chem. Soc., 648 (1947).

107 K.K. Ogilvie, Can. J. Chem., 56, 2768 (1978).

108 R.J.W. Cremlyn, G.W. Kenner, J. Mather, and A.R. Todd, J. Chem. Soc., 528 (1958).

109 L. Zervas, and I. Dilaris, J. Amer. Chem. Soc., 77, 5354 (1955).

110 V.M. Clark, and A.R. Todd, J. Chem. Soc., 2023 (1950).

111 J. Lecocq, and A.R. Todd, J. Chem. Soc., 2381 (1954).

112 T.D. Smith, J. Chem. Soc., 5050 (1961).

113 J. Baddiley, V.M. Clark, J.J. Michalski, and A.R. Todd, J. Chem. Soc., 815 (1949).

114 G.W. Daub, and E.E. van Tamelen, J. Amer. Chem. Soc., 99, 3526 (1977).

115 F. Ramirez, R. Sarma, Y.F. Chaw, T.M. McCaffrey, J.F. Marecek, B. McKeever, and D. Nierman, J. Amer. Chem. Soc., 99, 5285 (1977).

116. A. Carayon-Gentil, T. Nguyen Thanh, G. Gonzy, and P. Chabrier, Bull. Soc. Chim. Fr., 1616 (1967).

117 C.J. Lacey, and L.M. Loew, Tetrahedron Letts., 21, 2017 (1980).

118 D.J.H. Smith, K.K. Ogilvie, and M.F. Gillen, Tetrahedron Letts., 21, 861 (1980).

119 R.L. Letsinger, and W.B. Lunsford, J. Amer. Chem. Soc., 99, 3526 (1977).

120 R.A. Firestone, Personal Communication.

121 R.A. Firestone, J. Org. Chem., 36, 702 (1971).

122 M.S. Bhatia, J. Pawan, S.K. Gandhi, and S.P. Ahuja, Ann. Chim. (Paris), 2, 145 (1977).

123 M.E. Jung, and M.A. Lyster, J. Amer. Chem. Soc., 99, 968 (1977).

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

SOME ASPECTS OF ORGANOPHOSPHORUS CHEMISTRY

By: M.D.M. GRAY

An evaluation is made of ethyl (diethoxyphosphino)-acetate as a common intermediate for the synthesis of various phosphinoline and isophosphinoline systems. Two syntheses of 2-hydroxy-1,2,3,4-tetrahydroisophosphinoline 2,4-dioxide from α-bromotoluene and 2-(bromomethyl)benzoic acid are described.

Attempts to induce cyclisation of 3-(hydroxyphenyl-phosphinyl)propanoic acid with polyphosphoric acid, and the corresponding bis-acid chloride with aluminium chloride, prove unsuccessful, due to deactivation of the ring towards electrophilic attack.

Three 1-substituted-1,2-dihydrophosphinoline 1-oxides are synthesised, which when photolysed in a nucleophilic solvent give the three double-bond isomers of 1-(2-phosphorylphenyl)propene derivatives. This is rationalised in terms of solvent trapping of a phospha-quinoidal intermediate, obtained by electrocyclic ring-opening of the phosphinoline.

The Lewis acid catalysed cyclisation of 2-biphenylylphosphorodichloridothioate to 6-chloro-6H-dibenz (c,e)(1,2)oxaphosphorin 6-sulphide is investigated under a variety of conditions, leading to the identification of the optimum procedure as a neat reaction at 200°C for 1h, in the presence of 0.1 equivalent of aluminium chloride. Esterification of the resultant heterocycle, followed by photolysis of a methanolic solution gives three unidentified products. The complete absence of any photolytic reaction of the analogous 9,10-dihydro-9-methoxyphosphaphenanthrene leads to the conclusion that reaction is not by a concerted, electrocyclic pathway.

t-Butylamine is found to selectively monodemethylate phosphorus esters in the presence of carboxylate esters in a side-chain. Marked preference for removal of a methyl over benzyl or higher alkyl groups is demonstrated by reactions with mixed esters. Treatment of dimethyl 2-bromoethylphosphonate with *t*-butylamine, however, gives dimethyl vinylphosphonate, while dimethyl 3-bromopropyl-phosphonate undergoes nucleophilic substitution. The mildness of conditions required to demethylate a phosphorus ester leads to the suggestion of using methyl as a phosphate protecting-group in nucleotide synthesis.