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**TITLE**            **SYNTHESIS AND STRUCTURAL ANALYSIS OF -  
a - AMINOPHOSPHONIC ACIDS AND THEIR  
PHOSPHONATE ESTER DERIVATIVES .**

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**Synthesis and Structural Analysis of  $\alpha$ -Aminophosphonic  
Acids and their Phosphonate Ester Derivatives**

**Rosalind Jane Lee**

**A Thesis Submitted in Partial Fulfilment of the Requirements of the  
University of North London  
for the Degree of Doctor of Philosophy**

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## ABSTRACT

The aims of this project fall into two main categories. The primary objective was the preparation and characterisation of novel  $\alpha$ -aminophosphonic acids and their phosphonate ester derivatives. Compounds of these types are of interest because of their potential for biological activity, particularly in the area of agricultural chemistry. The second objective was to investigate the conformation of selected examples of these types of molecules in solution. This was achieved by considering the proton-proton and proton-phosphorus coupling constants. These coupling constants were obtained by the full analysis of the  $^1\text{H}$  NMR spectra.

The strategy adopted for the preparation of the phosphonic acids started from the synthesis of imine precursors. The imines were prepared by condensing aminodiphenylmethane or  $\alpha$ -methylbenzylamine with a wide variety of aldehydes and ketones, using very mild reaction conditions. The imine precursors were then reacted with diethyl (or dimethyl) phosphite to give diethyl (or dimethyl) 1-substituted-1-(diphenylmethylamino)methanephosphonates, which were isolated and characterised. The phosphonate esters prepared from the reactions of imines derived from  $\alpha$ -methylbenzylamine were not isolated.

A series of the phosphonate esters [diethyl 1-phenyl-1-(diphenylmethylamino)methanephosphonate, diethyl 1-(1'-naphthyl)-1-(diphenylmethylamino)methanephosphonate and diethyl 1-(1'-pyrenyl)-1-(diphenylmethylamino)methanephosphonate] were selected for full  $^1\text{H}$  NMR spectral analysis. The effects of the aromatic ring currents exerted by the extended aromatic substituents were investigated. The complex aromatic regions of the  $^1\text{H}$  NMR spectra were not analysed. The X-ray crystal structures of selected diethyl 1-substituted-1-(diphenylmethylamino)methanephosphonates, where the substituents are: phenyl, 1'-naphthyl, 9'-anthryl, 1'-pyrenyl, 2'-pyrrolyl and piperonyl, were determined and are discussed.

The phosphonate esters were subjected to acid-hydrolysis to yield the  $\alpha$ -aminophosphonic acids, including 1-N-phenylethylamino-1-(2'-thienyl)phosphonic acid which was prepared from the imine derived from  $\alpha$ -methylbenzylamine. Full  $^1\text{H}$  NMR spectral analysis was carried out on  $\alpha$ -aminopropanephosphonic acid at three different pH values. The results of these analyses are discussed and compared with the results of the  $^1\text{H}$  NMR spectral analysis of  $\alpha$ -aminopropanephosphonic acid.

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## CHAPTER FOUR

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## SYMBOLS AND ABBREVIATIONS

~	approximately equals
$\delta$	chemical shift
$\Delta$	heat
Ar	aromatic
br	broad
COSY	'COrelated SpectroscopY'
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEPT	'Distortionless Enhancement by Polarisation Transfer'
DOPA	dihydroxyphenylalanine
EI	electron impact
Et	ethyl
Esd	estimated standard deviation
eV	electron volt
FAB	fast atom bombardment
GC	gas chromatography
Hz	hertz
LSIMS	'liquid secondary ion mass spectrometry'
m	multiplet
Me	methyl
MHz	mega hertz
MS	mass spectrometry
NMR	nuclear magnetic resonance
PANIC	'Parameter Adjustment in NMR by Iteration Calculation'
Ph	phenyl
q	quartet
RMS	root mean square
s	singlet
spp.	species
t	triplet
THF	tetrahydrofuran

TLC	thin-layer chromatography
TMS	tetramethylsilane
TSP	trimethylsilylpropionate
VDU	visual display unit
w	weight
WIN-DAISY	'Windows-Düsseldorf Analysing and Iteration SYstem'





One aim of this project was to extend the range of compounds with the potential for biological activity by synthesising new  $\alpha$ -aminophosphonic acids and phosphonate ester derivatives.

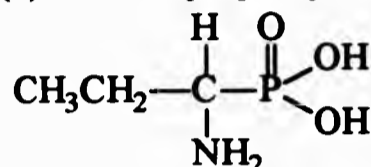
A further aim of this project was the structural analysis of selected compounds in solution using  $^1\text{H}$  NMR spectroscopy. Such studies are not trivial as compounds of these types frequently have complex  $^1\text{H}$  NMR spectra due to the presence of a chiral carbon atom and a prochiral phosphorus atom. A number of examples (Figure 1.2) were chosen in the present study for full  $^1\text{H}$  NMR spectral analysis. These include the known compounds 1-3 and several new compounds 4-6 prepared in the present work.

To complement the  $^1\text{H}$  NMR studies in solution, *X*-ray structural analyses were carried out on key compounds in order to establish conformational features which may be relevant to the biological and the chemical modes of action of these molecules.

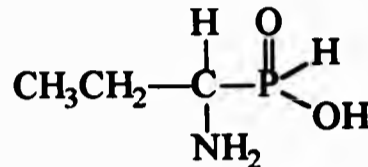
In the following sections, a survey is given of the main methods of preparation of aminophosphonic acids and phosphonate esters.

Figure 1.2 Selected compounds chosen for  $^1\text{H}$  NMR spectral analysis

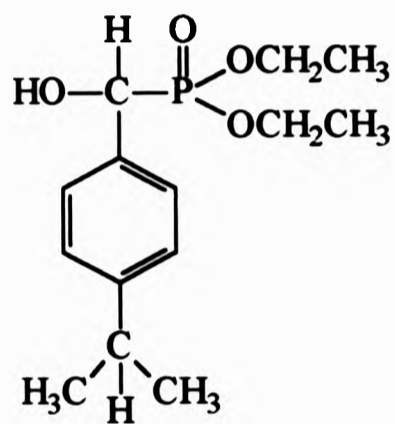
(1)  $\alpha$ -Aminopropanephosphonic Acid



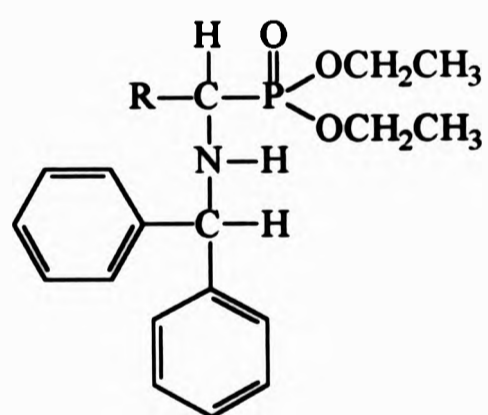
(2)  $\alpha$ -Aminopropanephosphinic Acid



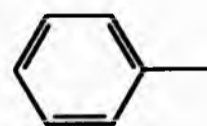
(3) Diethyl 1-Hydroxy-4'-isopropylbenzylphosphonate



Diethyl 1-substituted-1-(diphenylmethylamino)methanephosphonate



(4) R = Phenyl



(5) R = 1'-Naphthyl



(6) R = 1'-Pyrenyl



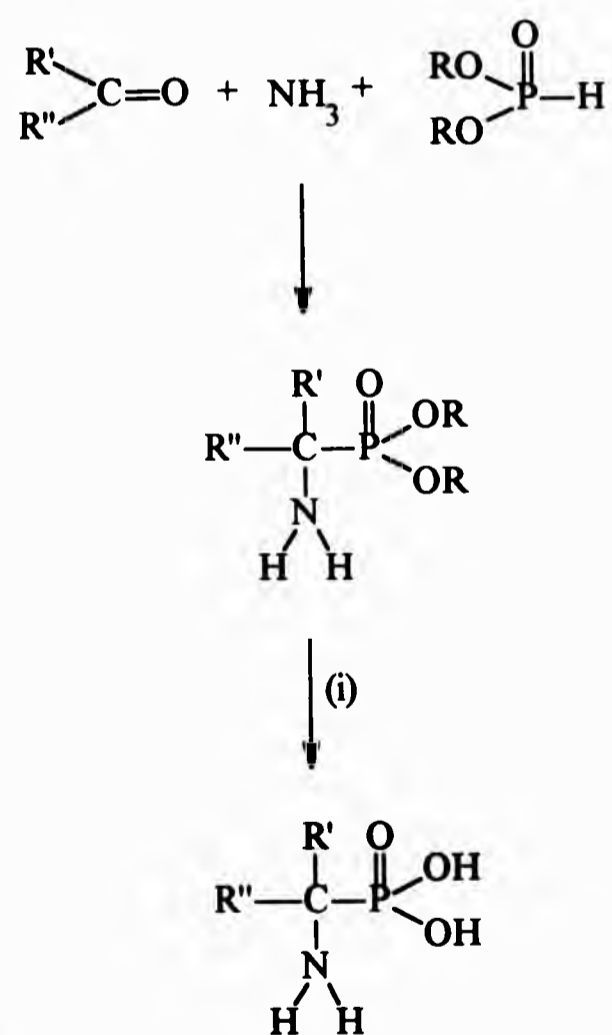
## 1.2 Synthetic Methods

A number of synthetic approaches were considered. The principal methods of preparation can be divided into four main categories and a brief outline of each of these is given below.

### 1.2.1 Kabachnik-Fields Reaction

Kabachnik and Medved<sup>[24-27]</sup> described a method for preparing  $\alpha$ -aminophosphonic acids in which ammonia is condensed with a dialkyl phosphite and a carbonyl compound (Scheme 1.1). The resulting dialkyl  $\alpha$ -aminophosphonate ester is hydrolysed to give the  $\alpha$ -aminophosphonic acid.

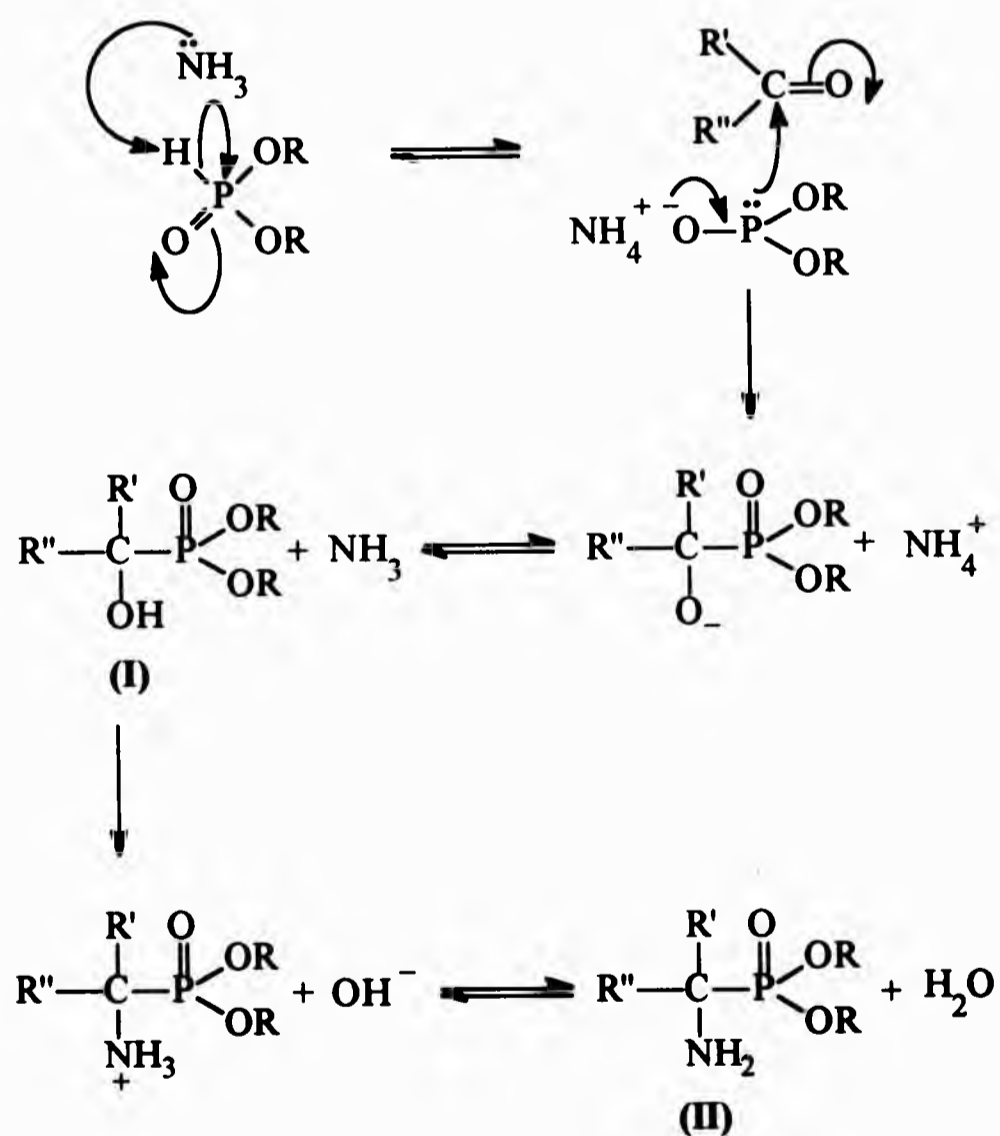
**Scheme 1.1** Kabachnik-Medved procedure for the preparation of  $\alpha$ -aminophosphonic acids



Reagent: (i) HCl/H<sub>2</sub>O

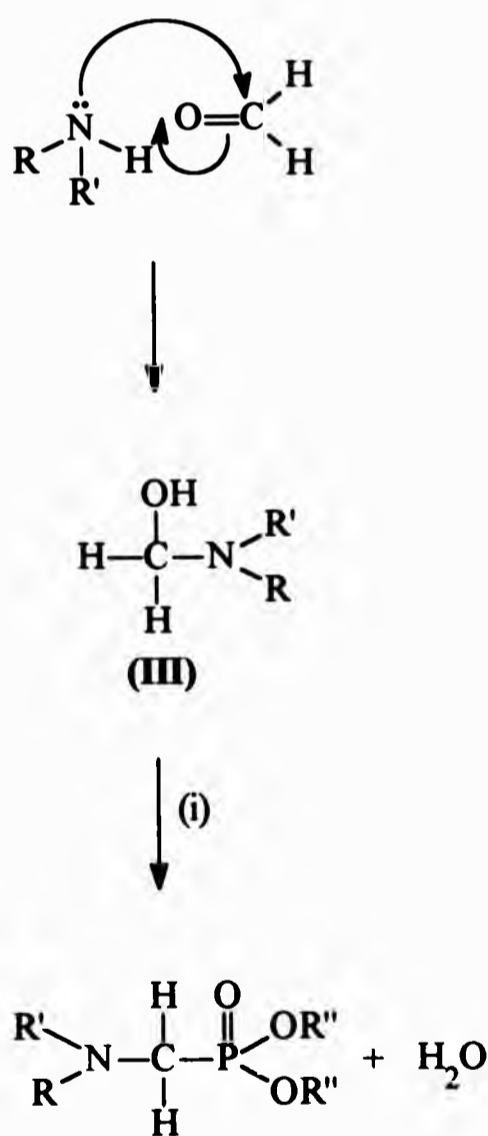
The mechanism for this reaction, according to Kabachnik and Medved, is given in Scheme 1.2.<sup>[22, 28]</sup> The hydroxyphosphonate (I) is formed by the ammonia catalysed addition of the dialkyl phosphite to the carbonyl compound. The aminophosphonate (II) is then formed by the nucleophilic substitution of the hydroxyl group by the amino group. The evidence for this reaction mechanism comes from the observation that the aminophosphonate (II) is only formed at elevated temperatures. The hydroxyphosphonate is observed after mixing of the reagents at room temperature and on heating the aminophosphonate is formed.<sup>[29, 30]</sup>

**Scheme 1.2** Mechanism according to Kabachnik and Medved for the preparation of  $\alpha$ -aminophosphonate esters



Fields<sup>[31]</sup> described a modification of this reaction using a primary or secondary amine instead of ammonia. The aminophosphonate that forms is hydrolysed to yield the N-substituted  $\alpha$ -aminophosphonic acid. However, Fields suggested a different mechanism from Kabachnik and Medved which involves the formation of an aminomethanol intermediate (III, Scheme 1.3).

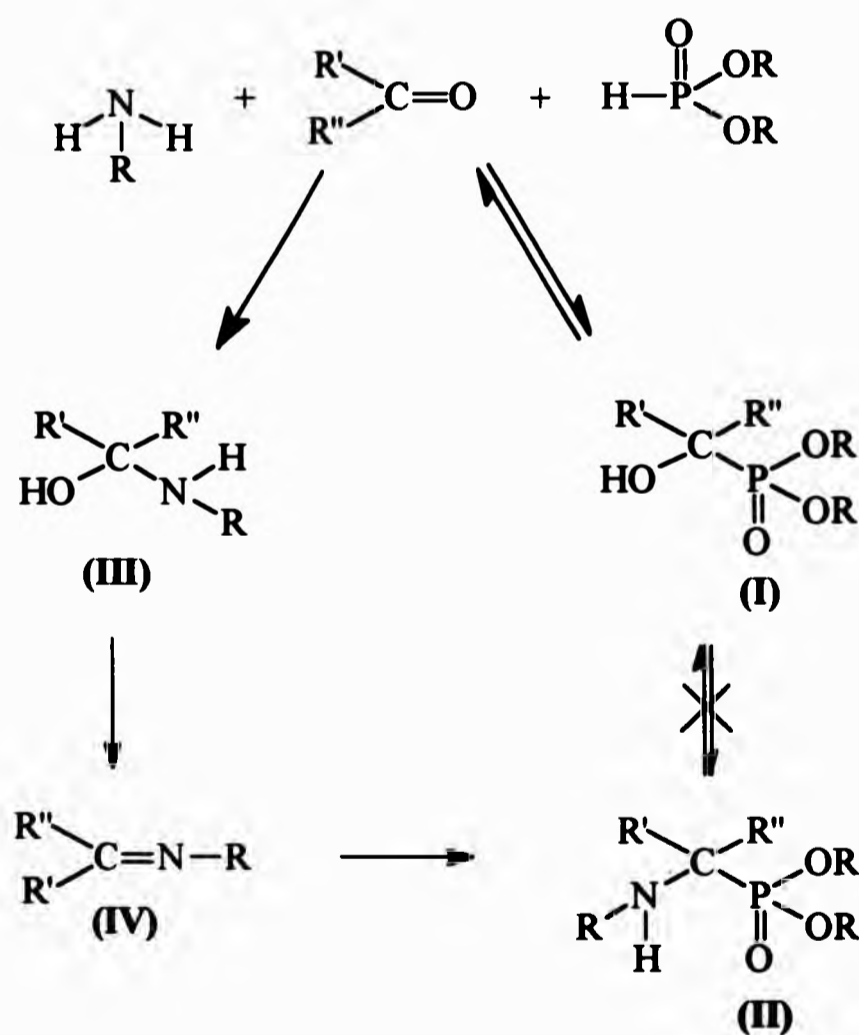
**Scheme 1.3** Mechanism according to Fields for the preparation of  $\alpha$ -aminophosphonate esters



Reagent: (i)  $\text{HPO}(\text{OR}'')_2$

Petrov<sup>[32]</sup> described another mechanism, based on that suggested by Fields. The Petrov mechanism (Scheme 1.4) involves the formation of an imine (IV) from the carbonyl compound and amine. The dialkyl phosphite then reacts with the imine to form the aminophosphonate (II). Gancarez<sup>[30, 33]</sup> and co-workers investigated the reaction and found that hydroxyphosphonate was formed. The hydroxyphosphonate does not, however, react with the amine to form the aminophosphonate, but decomposes to give the starting carbonyl and amine compounds (see Scheme 1.4). This supports the mechanism of the reaction suggested by Petrov. The hydroxyphosphonate is formed but the imine reacts with the dialkyl phosphite to give the desired aminophosphonate.

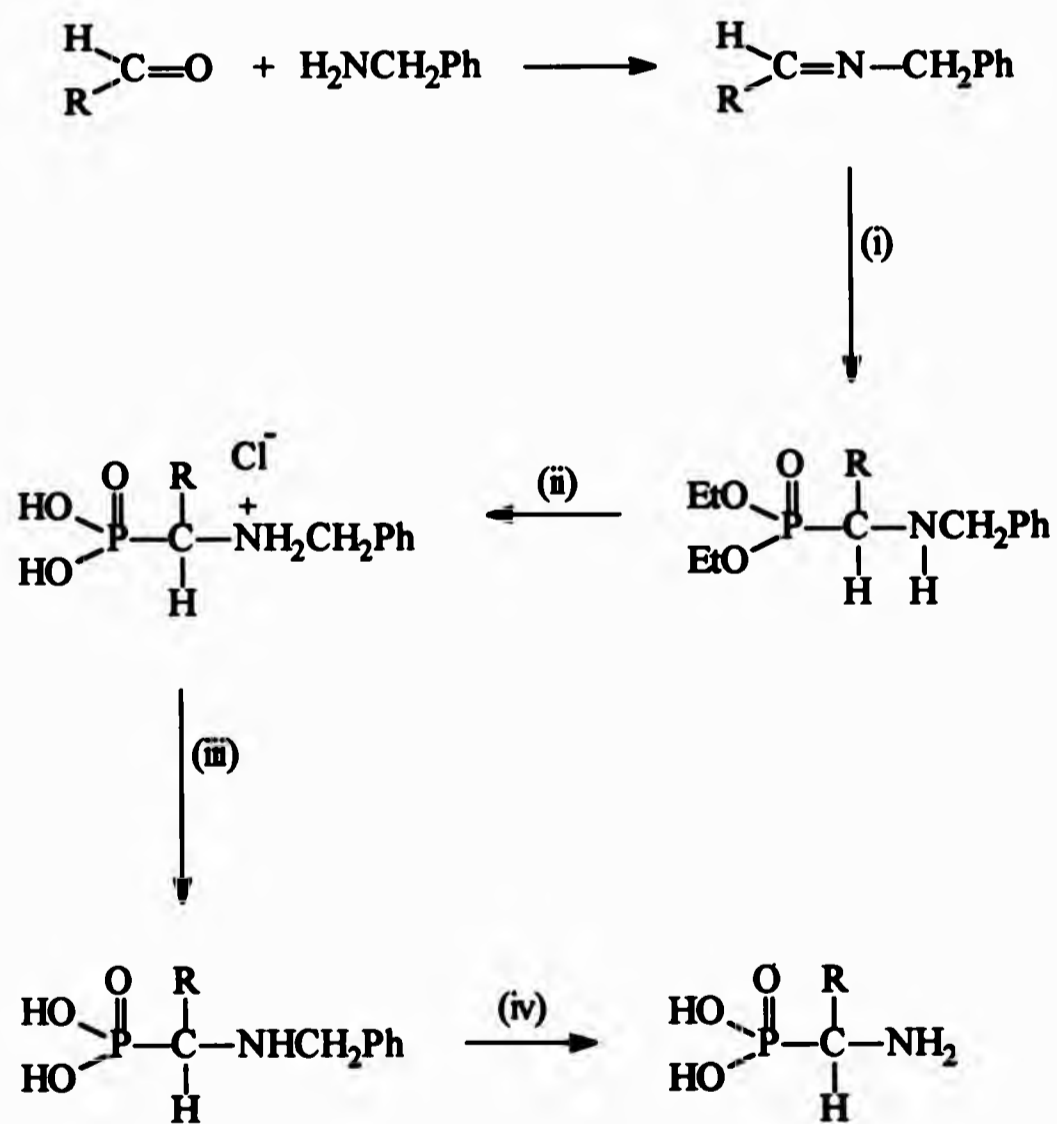
**Scheme 1.4** Mechanism according to Petrov for the preparation of  $\alpha$ -aminophosphonate esters



The Kabachnik-Fields reaction is an important general method for the synthesis of  $\alpha$ -aminophosphonic and  $\alpha$ -aminophosphinic acids.<sup>[12]</sup> Using this procedure the phosphonic analogues of alanine and phenylalanine have been prepared.<sup>[10]</sup>

Tyka<sup>[34]</sup> modified the Kabachnik-Fields reaction in an attempt to improve the yields obtained. In Tyka's method, imines are synthesised from a variety of aldehydes and benzylamine, and addition of a dialkyl phosphite to the imine then gives the N-benzyl- $\alpha$ -aminophosphonate ester which is hydrolysed to yield the N-benzyl- $\alpha$ -aminophosphonic acid. Deprotection of the amino group is then achieved by hydrogenolysis (Scheme 1.5). The esters of the N-benzyl- $\alpha$ -aminophosphonic acid are reported to be resistant to hydrogenolysis.<sup>[34]</sup>

**Scheme 1.5** Procedure for the preparation of  $\alpha$ -aminophosphonic acids using benzylamine



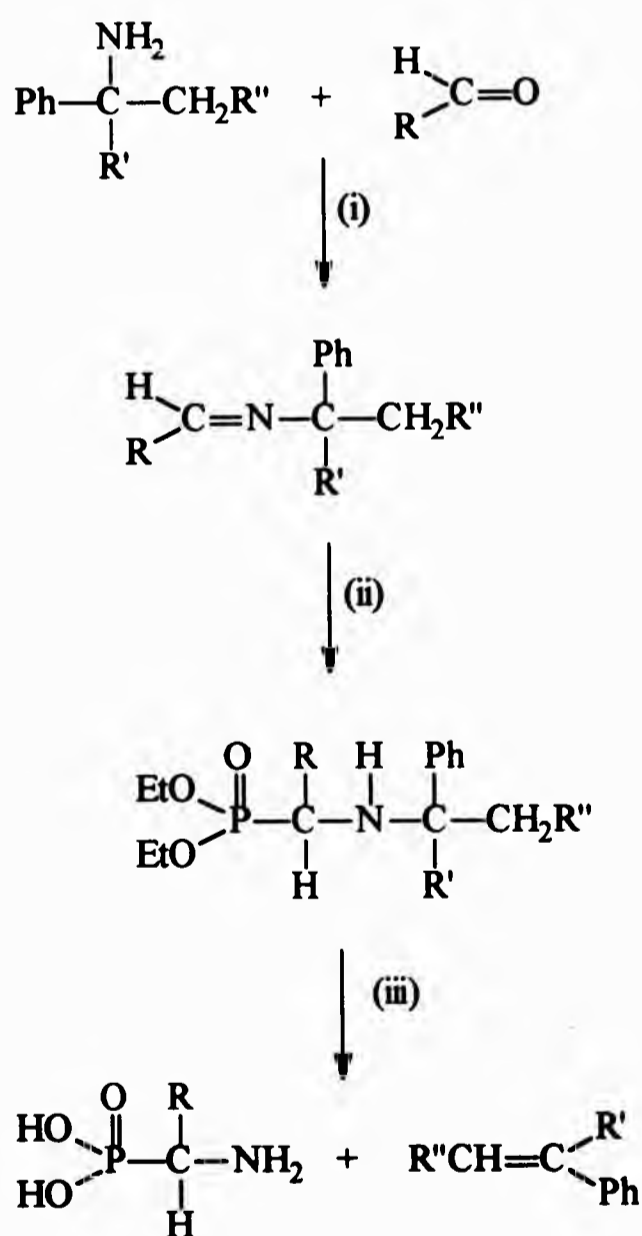
R = alkyl or aryl

Reagents: (i)  $\text{HPO}(\text{OEt})_2/\Delta$  (ii)  $\text{H}^+/\text{H}_2\text{O}/\Delta$  (iii)  $\text{Ag}_2\text{O}$  (iv)  $\text{H}_2/\text{Pd}/\text{C}$



Tyka<sup>[35]</sup> also described the use of a benzylic carbinamine instead of benzylamine (Scheme 1.6). This method requires hydrolysis rather than hydrogenolysis to deprotect the amino group and in the same step converts the phosphonate ester group to the phosphonic acid group. The facile deprotection of the amino group is due to the relative ease of formation and stability of the tertiary carbocation.

**Scheme 1.6** Procedure for the preparation of  $\alpha$ -aminophosphonic acids using a benzylic carbinamine

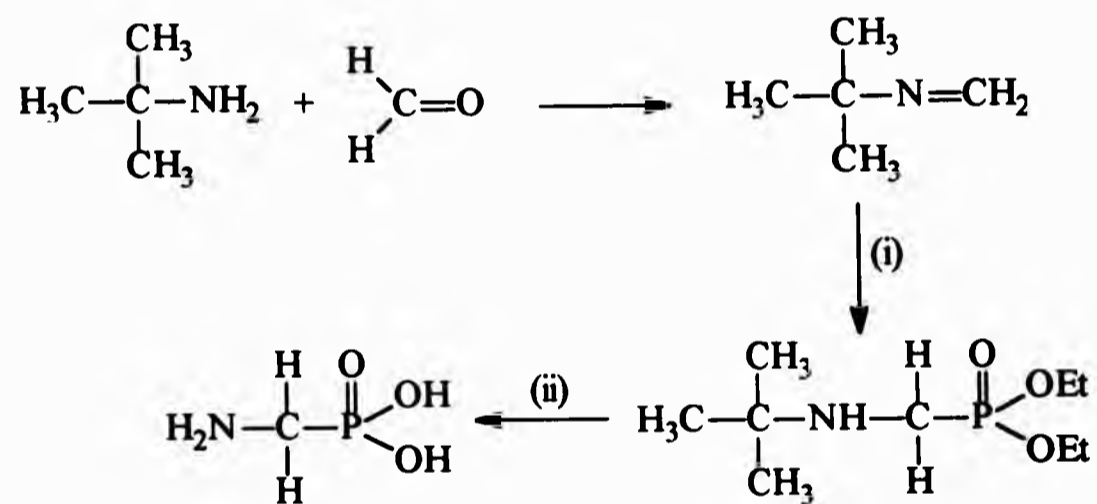


R = alkyl or aromatic, R' = H or alkyl and R'' = alkyl

Reagents: (i)  $\text{K}_2\text{CO}_3/\Delta$  (ii)  $\text{HPO}(\text{OEt})_2/\Delta$  (iii)  $\text{H}^+/\text{H}_2\text{O}/\Delta$

The reaction is reported to fail when the amino group is bound to a tertiary but not benzylic carbon atom;<sup>[35]</sup> however, Moedritzer<sup>[36]</sup> described the preparation of  $\alpha$ -aminomethanephosphonic acid using *tert*-butylamine and methanal (Scheme 1.7). Soroka<sup>[37]</sup> described using tritylamine (triphenylmethylamine) to prepare imines with a number of aldehydes. The imines obtained from these reactions are treated with dialkyl or diaryl phosphite, and the resulting phosphonate esters are acid-hydrolysed to give the corresponding  $\alpha$ -aminoalkanephosphonic acids.

**Scheme 1.7** Procedure for the preparation of  $\alpha$ -aminomethanephosphonic acid using *tert*-butylamine

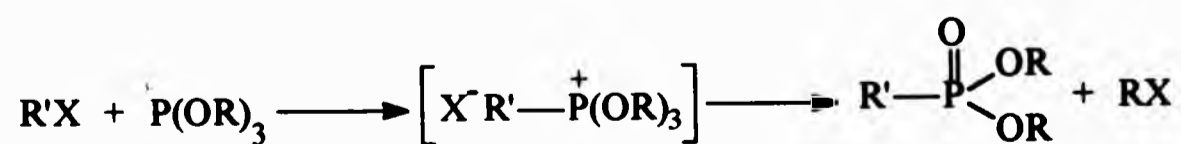


Reagents: (i)  $\text{HPO}(\text{OEt})_2/\Delta$  (ii)  $\text{HBr}/\text{H}_2\text{O}/\Delta$

### 1.2.2 The Arbuzov and Michaelis-Becker Reactions

The Arbuzov reaction and the Michaelis-Becker reaction<sup>[38, 39]</sup> are of great importance in organophosphorus chemistry. The Arbuzov reaction is essentially the conversion of a phosphite ester into a phosphonate ester by an alkyl halide (Scheme 1.8).

**Scheme 1.8** The Arbuzov reaction



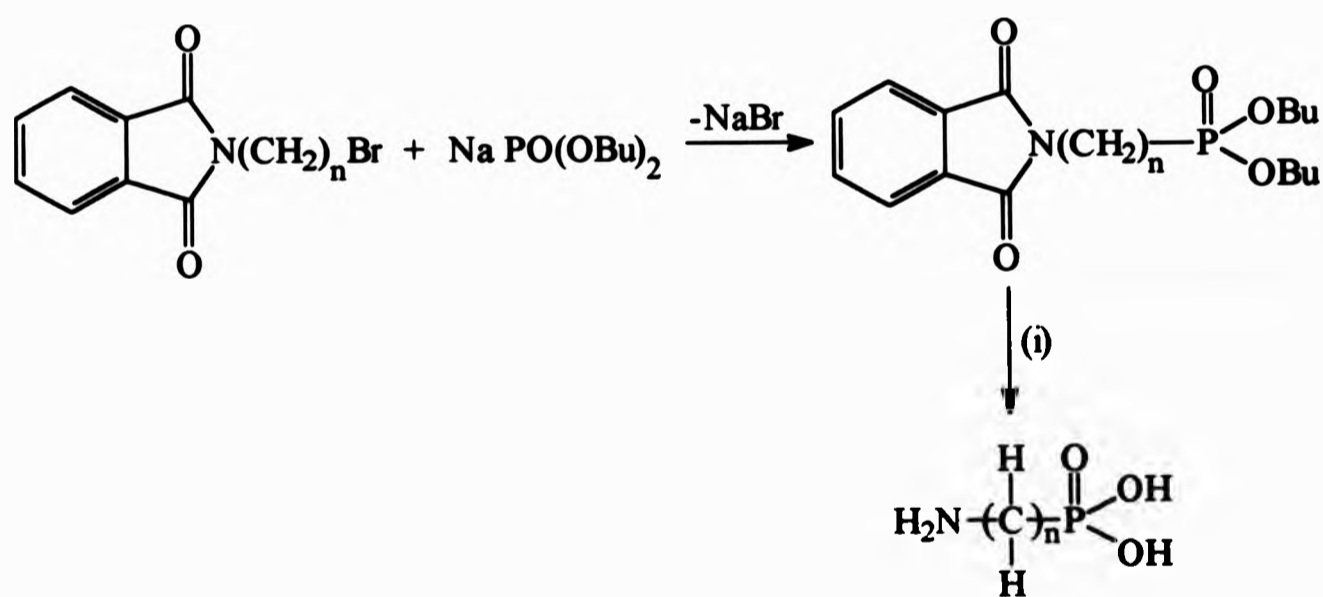
Michaelis and Becker<sup>[40]</sup> prepared the phosphonate ester by reacting an alkyl halide with sodium dialkyl phosphite (Scheme 1.9).

**Scheme 1.9** The Michaelis-Becker Reaction



Historically this was the first method used in the synthesis of  $\alpha$ -aminomethanephosphonic acid, the phosphorus analogue of glycine (Scheme 1.10).<sup>[41]</sup>

**Scheme 1.10** Michaelis-Becker reaction for the preparation of  $\alpha$ -aminoalkanephosphonic acids



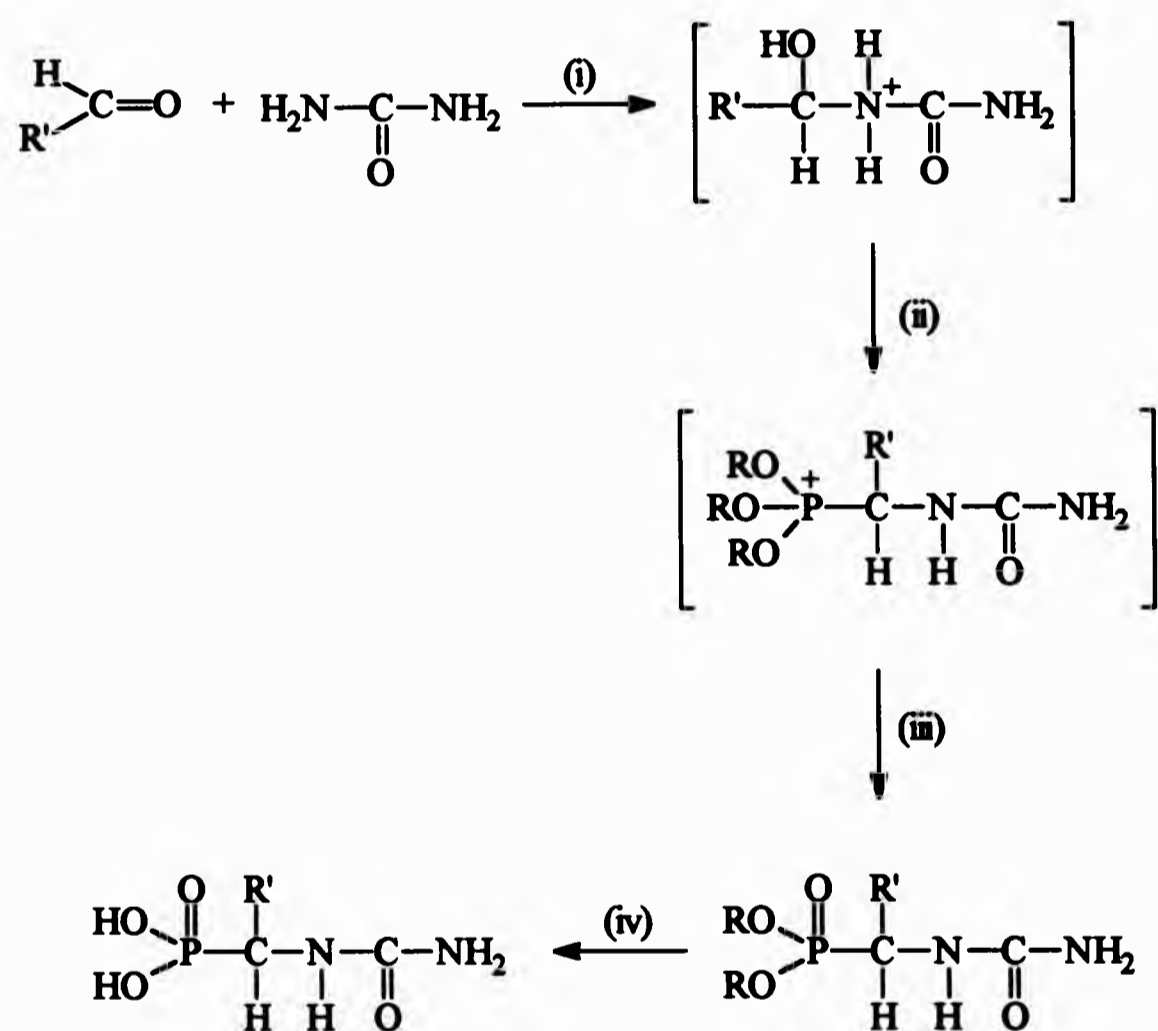
$\alpha$ -aminomethanephosphonic acid when  $n = 1$

Reagents: (i)  $\text{HCl}/\text{H}_2\text{O}/\Delta$

Trialkyl phosphites, sodium dialkyl phosphites, alkylphosphonous esters and phosphorus trichloride can all be used as phosphorylating agents. The amino group needs protecting to prevent side reactions. The use of dialkyl phosphonites makes it possible to obtain aminophosphonic acids.<sup>[42]</sup>

$\alpha$ -Ureidophosphonic acids are prepared by heating an aldehyde with a urea followed by addition of a phosphite (Scheme 1.11).<sup>[43]</sup> Mono- and di-substituted ureas give rise to monophosphonates while urea gives rise to a mixture of mono- and bis-phosphonates. The mono- and bis-phosphonates are easily separated from each other before the hydrolysis step. Again phosphonites can be substituted for the phosphite to give phosphinic acids.

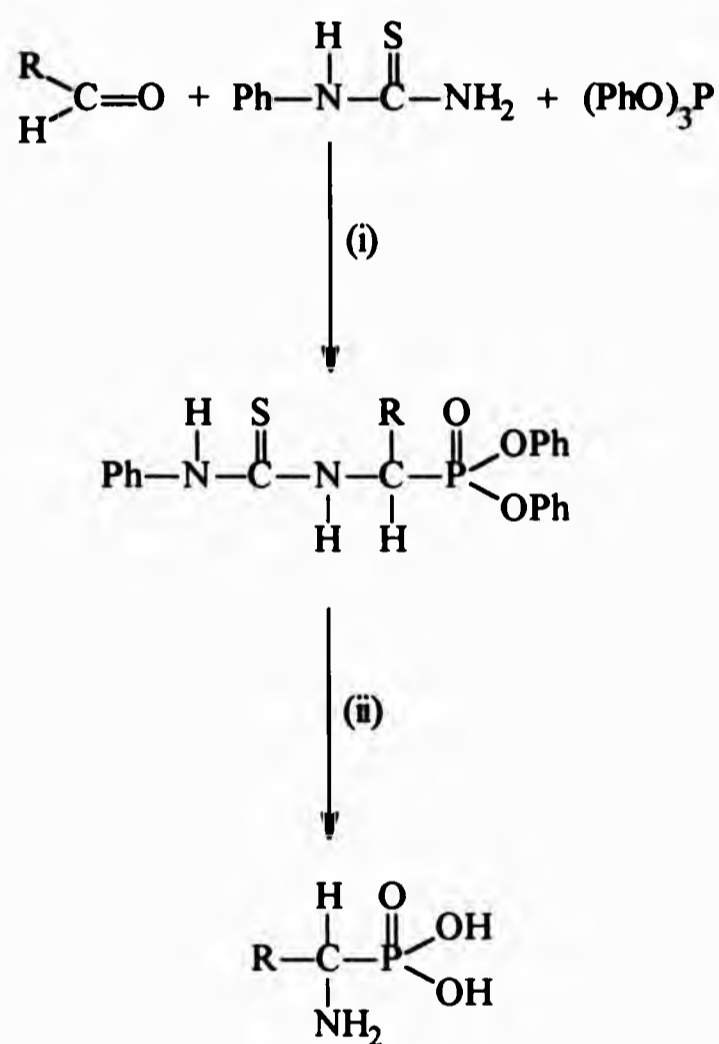
**Scheme 1.11** Procedure for the preparation of  $\alpha$ -ureidophosphonic acids using urea



*Reagents:* (i)  $\text{H}^+$  (ii)  $\text{P}(\text{OR})_3$  (iii)  $\text{H}_2\text{O}$  (iv)  $\text{H}_2\text{O}/\Delta$

Thiourea may be used in place of urea and, although it is less reactive, satisfactory results are obtained when triphenyl phosphite is used and the aldehydes are aliphatic aldehydes (Scheme 1.12).

**Scheme 1.12** Procedure for the preparation of  $\alpha$ -ureidophosphonic acids using thiourea

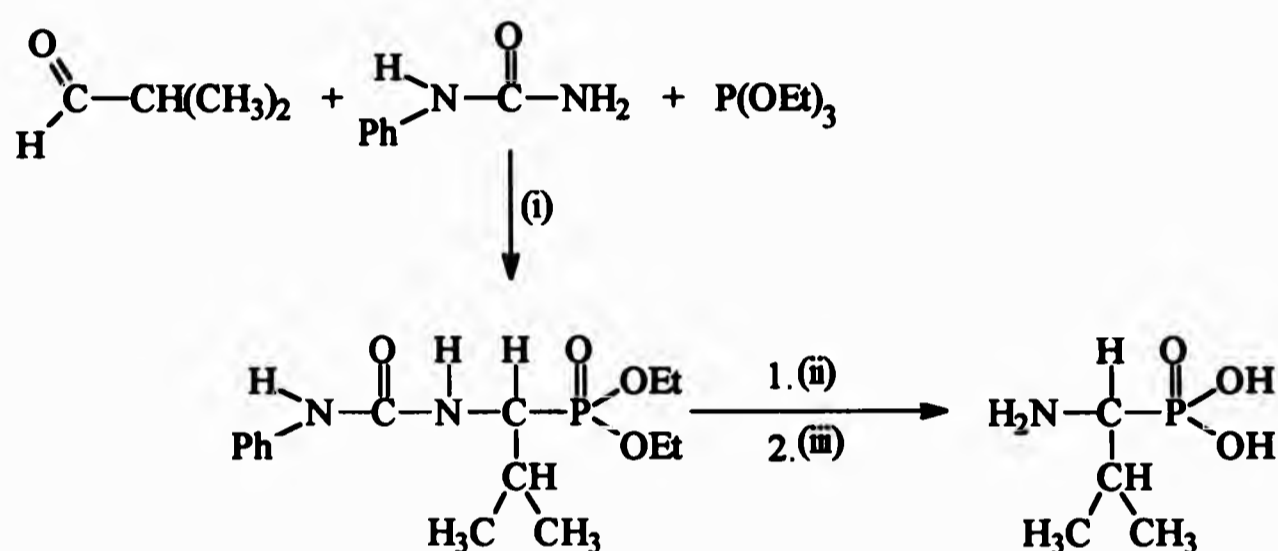


Reagents: (i) AcOH (ii)  $\text{H}^+/\text{H}_2\text{O}/\Delta$

The phosphonic analogues of alanine, valine, phenylalanine,<sup>[44]</sup> methionine<sup>[45]</sup> and cysteine<sup>[46]</sup> have all been prepared using this general procedure.

The phosphonic analogue of valine has also been prepared by heating N-phenylurea, triethyl phosphite and isobutyraldehyde in toluene using boron trifluoride etherate as a catalyst (Scheme 1.13).<sup>[47]</sup>

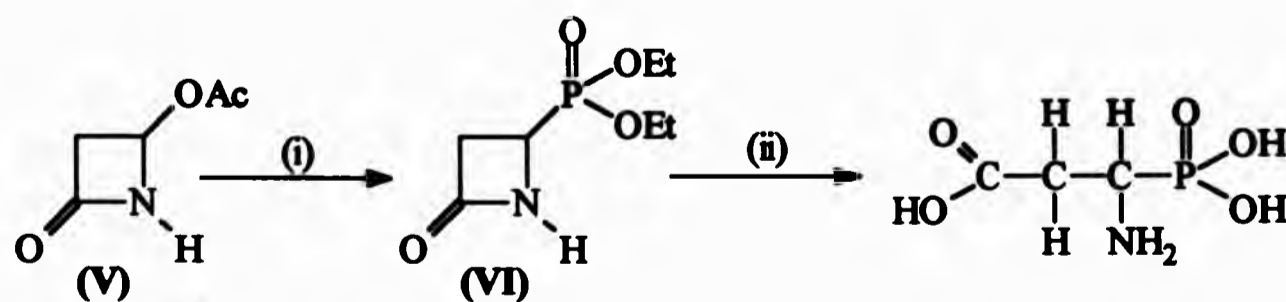
**Scheme 1.13** Preparation of the phosphonic analogue of valine



*Reagents:* (i)  $\text{BF}_3 \cdot \text{OEt}_2$  (ii)  $\text{HCl}/\text{H}_2\text{O}/\Delta$  (iii) Propylene oxide

The phosphonic analogue of aspartic acid was successfully synthesised (Scheme 1.14) starting from 4-acetoxyazetidin-2-one (V).<sup>[48]</sup> This readily reacts with diethyl phosphite to give diethyl 2-oxoazetidin-4-ylphosphonate (VI). Acid-hydrolysis gives the phosphonic acid.

**Scheme 1.14** Preparation of the phosphonic analogue of aspartic acid



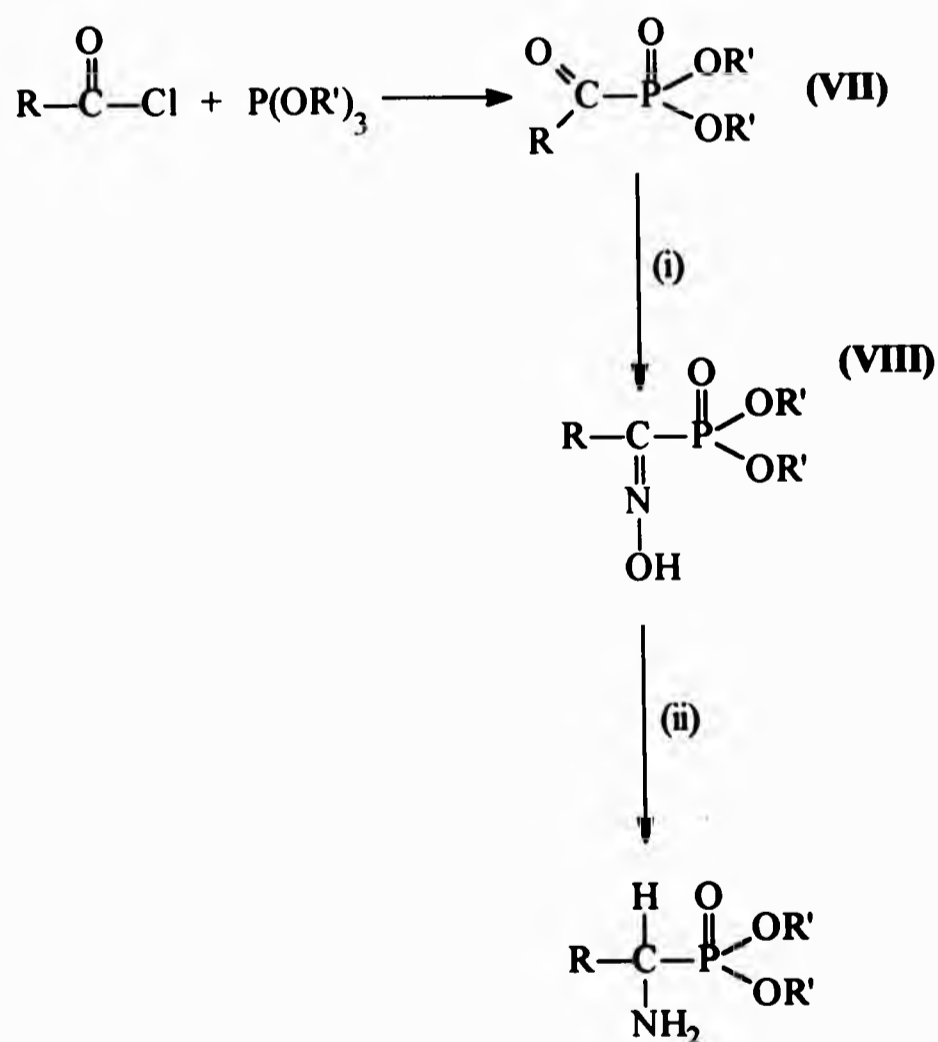
*Reagents:* (i)  $\text{HPO}(\text{OEt})_2$  (ii)  $\text{H}^+/\text{H}_2\text{O}/\Delta$

This group of reactions, based on introducing a phosphoryl group into a compound containing an organic amine, followed by either an Arbuzov reaction or a Michaelis-Becker reaction, gives rise to a wide variety of  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\omega$ -aminophosphonic acids<sup>[49-53]</sup> including many important phosphonic analogues of the aminocarboxylic acids.

### 1.2.3 The Oxime Method

This method for the synthesis of phosphonic acids (Scheme 1.15) involves the preparation of  $\alpha$ -oxoalkane phosphonates (VII) which are converted to oximes (VIII). The oximes are then reduced to  $\alpha$ -aminophosphonate esters.<sup>[12]</sup>

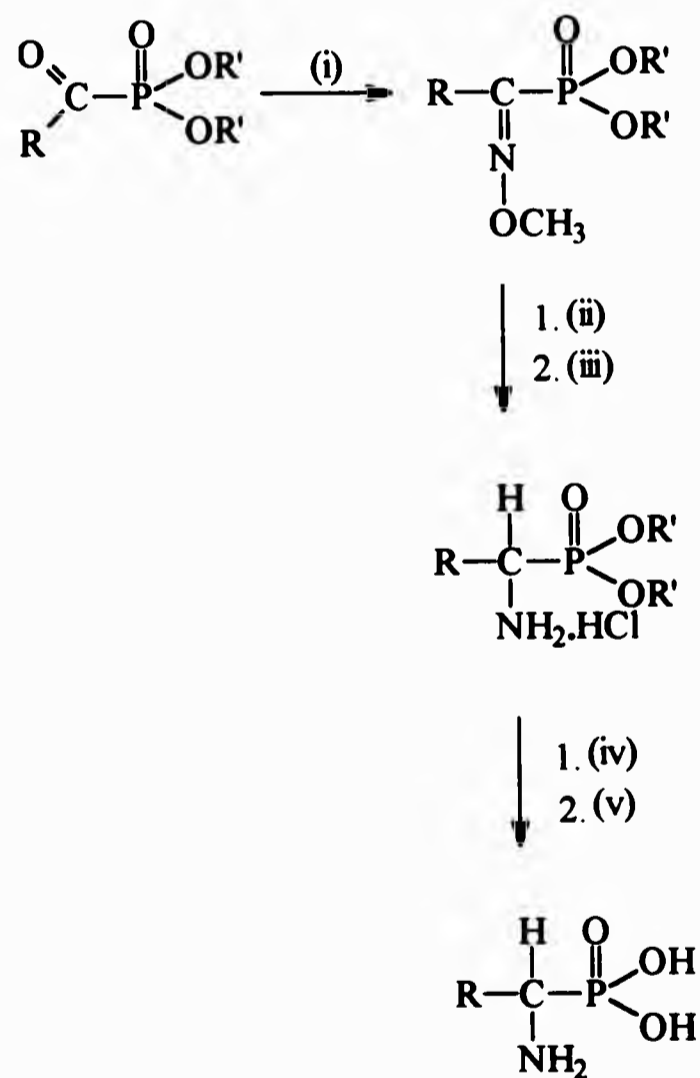
**Scheme 1.15** Preparation of  $\alpha$ -aminophosphonate esters by the reduction of an oxime group



Reagents: (i)  $\text{H}_2\text{NOH}$  (ii)  $[\text{H}]$

The oxime group can be reduced by a variety of reagents. The phosphonic analogue of dihydroxyphenylalanine (DOPA)<sup>[54]</sup> and a variety of other  $\alpha$ -aminophosphonic acids<sup>[55]</sup> have been prepared using aluminium amalgam as the reducing agent. O-Methylhydroxylamine hydrochloride can be used to give the O-methylated oximes instead of the more usual hydroxylamine hydrochloride.<sup>[55]</sup> Diborane has been used as the reducing agent in the preparation of the phosphonic analogues of alanine, valine, leucine and isoleucine (Scheme 1.16).<sup>[56]</sup>

**Scheme 1.16** Preparation of  $\alpha$ -aminophosphonate esters by the reduction of an oxime group with diborane

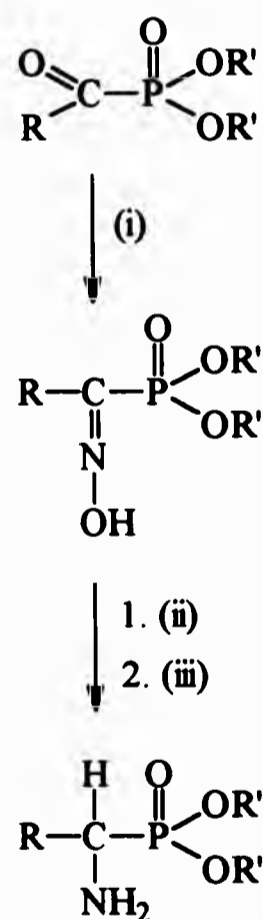


*Reagents:* (i)  $\text{CH}_3\text{ONH}_2 \cdot \text{HCl}$  in pyridine (ii)  $\text{B}_2\text{H}_6$  in THF  
 (iii)  $\text{HCl}$  -anhydrous (iv)  $\text{HCl}/\text{H}_2\text{O}$  (v) Propylene oxide



The phosphonic analogue of tryptophan was synthesised using this general method but using catalytic reduction with Raney nickel.<sup>[57]</sup> The oxime group can also be reduced using zinc in formic acid, although this reaction is complicated by the partial formylation of the amino group. The initial product needs treatment with hydrochloric acid in methanol in order to de-formylate the amino group and to yield the dialkyl aminophosphonate ester (Scheme 1.17). The phosphonate ester analogues of alanine, valine, leucine, phenylalanine, glutamic acid, methionine<sup>[58]</sup> and cysteine<sup>[59]</sup> have all been synthesised in this way.

**Scheme 1.17** Preparation of  $\alpha$ -aminophosphonate esters by the reduction of an oxime group by zinc in formic acid

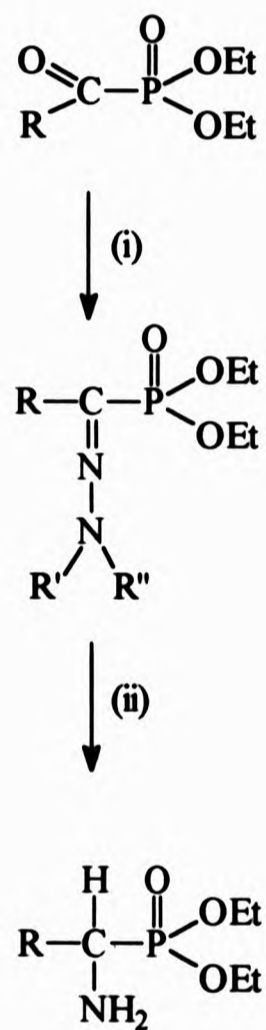


*Reagents:* (i)  $\text{HONH}_2 \cdot \text{HCl}$  (ii)  $\text{Zn}/\text{HCOOH} < 65^\circ\text{C}$

(iii)  $\text{HCl}/\text{MeOH}$  room temperature

An alternative procedure involves the conversion of  $\alpha$ -oxophosphonates into hydrazones which are subsequently reduced to give the  $\alpha$ -aminophosphonates with either aluminium amalgam<sup>[60]</sup> or zinc in acetic acid with trifluoroacetic acid (Scheme 1.18).<sup>[61]</sup>

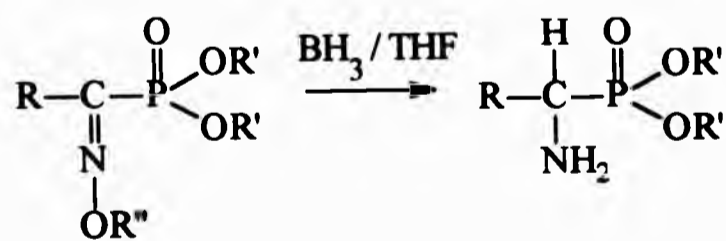
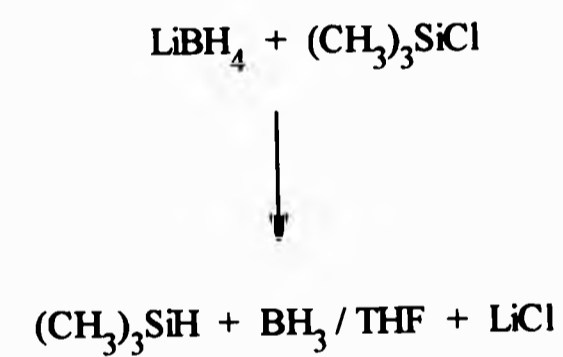
**Scheme 1.18** Preparation of  $\alpha$ -aminophosphonate esters by the reduction of a hydrazone group



*Reagents:* (i)  $\text{H}_2\text{NN}(\text{R}')\text{R}''$  (ii)  $\text{Zn}/\text{AcOH}$  and  $\text{CF}_3\text{COOH}/\text{H}_2\text{O}$

The direct conversion of  $\alpha$ -oxophosphonic acids to  $\alpha$ -aminophosphonic acids is achieved by treatment with ammonia and sodium tetrahydroborate.<sup>[62, 63]</sup> The phosphonic analogues of valine, alanine, leucine, phenylalanine and glutamic acid have all been obtained using this method.  $\alpha$ -Oxophosphonates can also be reduced to  $\alpha$ -aminophosphonates by a mixture of lithium borohydride and trimethylsilyl chloride in tetrahydrofuran (THF) (Scheme 1.19).<sup>[64, 65]</sup> The active reducing agent is thought to be a  $\text{BH}_3$  / THF complex.<sup>[66]</sup>

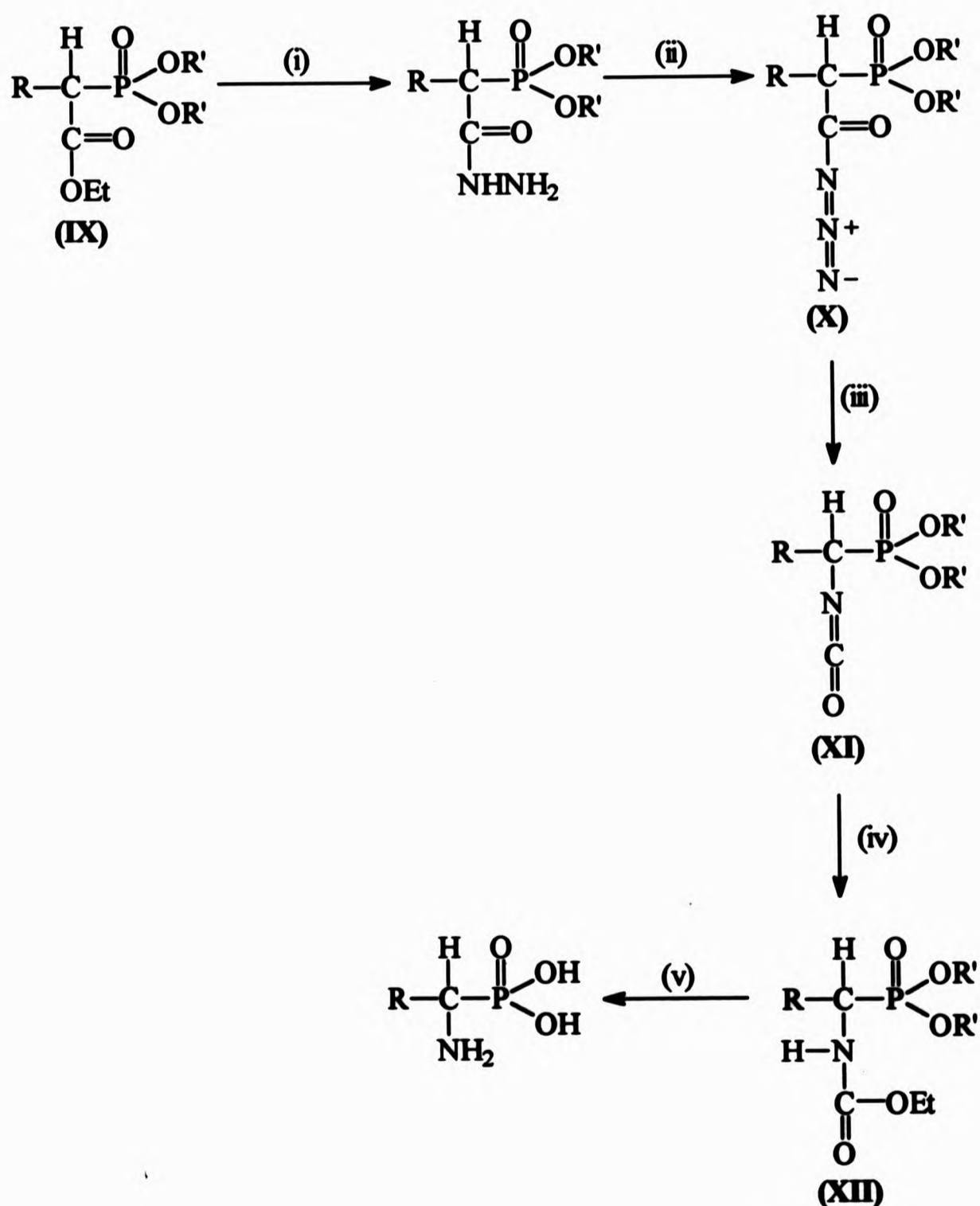
**Scheme 1.19** Preparation of  $\alpha$ -aminophosphonate esters by the reduction of an oxime group with a  $\text{BH}_3$  / THF complex



### 1.2.4 The Curtius and Hofmann Rearrangements

Amino-substituted phosphonic acids can be prepared by converting an existing carboxylate group into an amino group (Scheme 1.20). This can be done *via* a Curtius rearrangement (Scheme 1.21).<sup>[11]</sup>

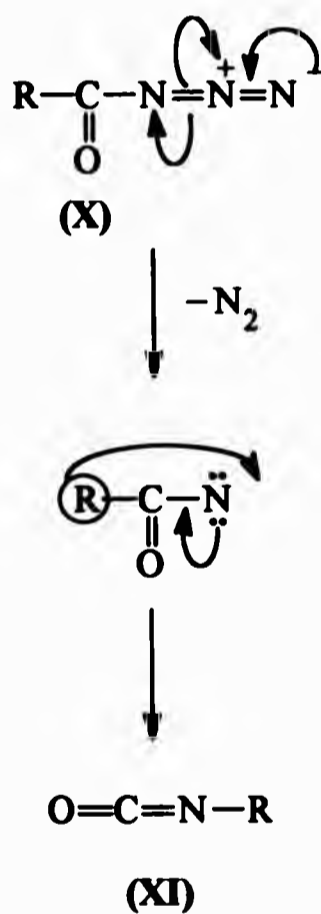
Scheme 1.20 Preparation of  $\alpha$ -aminophosphonic acids using a Curtius rearrangement



Reagents: (i)  $\text{H}_2\text{NNH}_2$  (ii)  $\text{HNO}_2$  (iii)  $\text{HCl}/\text{H}_2\text{O}$  (iv)  $\text{EtOH}$  (v)  $\text{HCl}/\text{H}_2\text{O}$

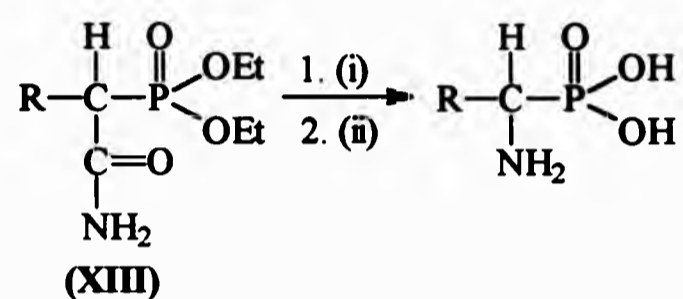
The phosphonocarboxylic acid ester (IX) is treated with hydrazine followed by nitrous acid to give the phosphonocarboxylic acid azide (X). This then undergoes a Curtius rearrangement (see Scheme 1.21) to give the isocyanate (XI, Scheme 1.20 and 1.21) which is treated with alcohol and the resulting ester is then hydrolysed with acid to give the aminophosphonic acid. The phosphonic analogues of alanine, glycine and phenylalanine<sup>[67]</sup> have been synthesised using this method and the phosphonic analogues of aspartic acid and glutamic acid by slightly modified methods.<sup>[11]</sup>

Scheme 1.21 Mechanism of the Curtius rearrangement



Phosphono-amides (XIII, Scheme 1.22) can undergo a Hofmann rearrangement (Scheme 1.23) to give aminophosphonic acids.<sup>[68]</sup>

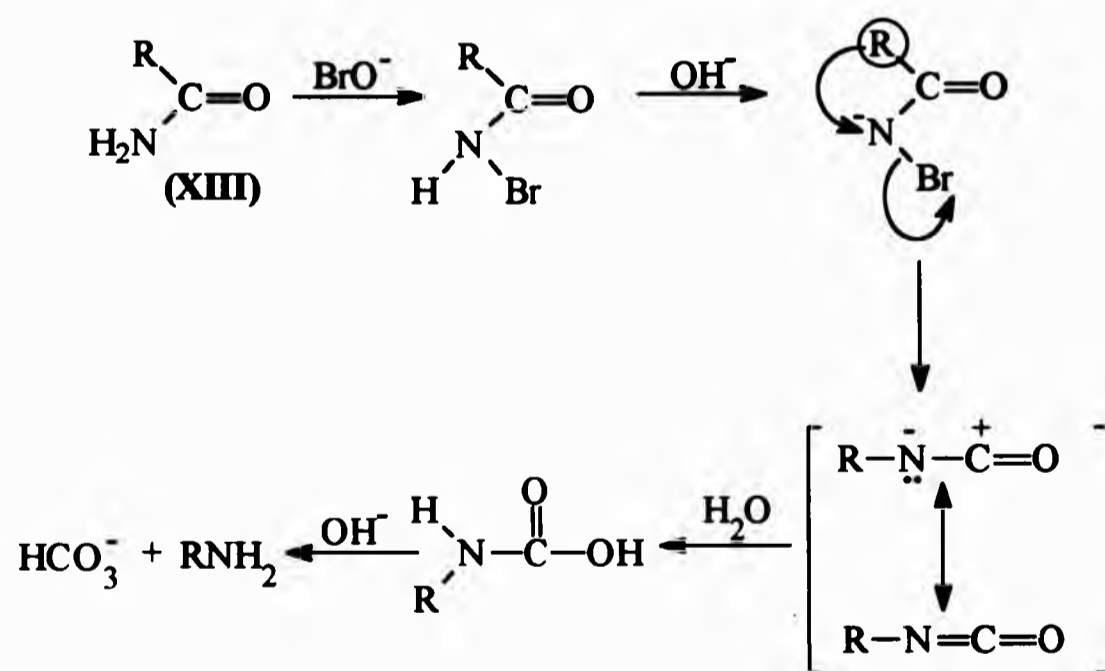
**Scheme 1.22** Preparation of  $\alpha$ -aminophosphonic acids using a Hofmann rearrangement



R = Et or Ph

Reagents: (i) NaOBr/NaOH (ii) HCl/H<sub>2</sub>O

**Scheme 1.23** Mechanism of the Hofmann rearrangement

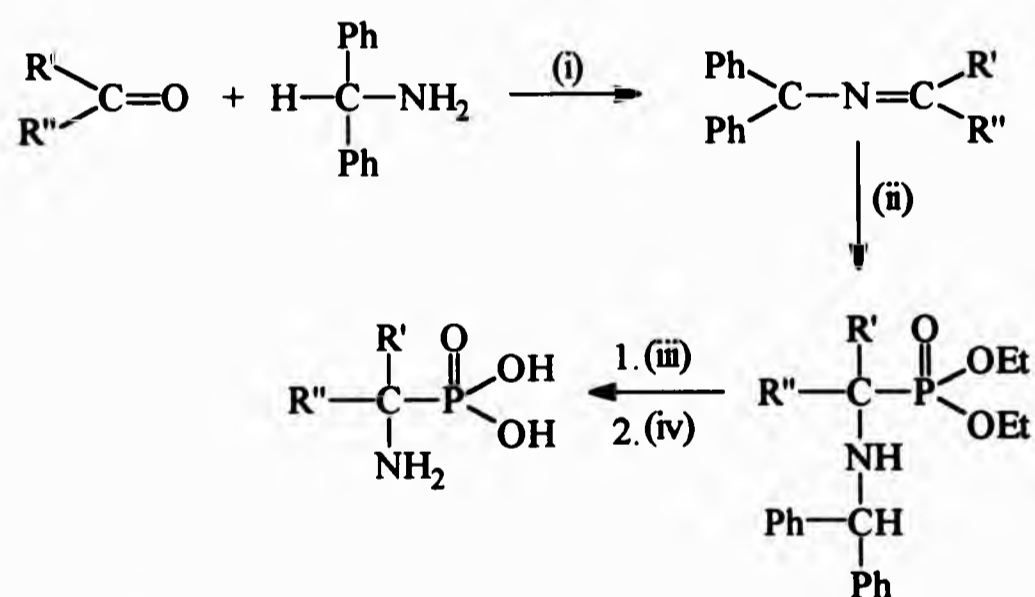


The first naturally occurring compound with a P-C bond to be discovered,  $\beta$ -aminoethanephosphonic acid, was first synthesised using a similar method.<sup>[69]</sup>

### 1.2.5 Synthetic Strategy

In this investigation, a modified Kabachnik-Fields reaction was adopted to prepare novel  $\alpha$ -aminophosphonic acids and their phosphonate ester derivatives. Imines were prepared from 1,1-diphenylmethanamine (otherwise known as aminodiphenylmethane,  $\text{NH}_2\text{CHPh}_2$ ) and a variety of carbonyl compounds, both aldehydes and ketones (Scheme 1.24), and were then isolated and characterised. The imines were heated with diethyl phosphite to give diethyl phosphonate esters which were again isolated and characterised. The diethyl phosphonate esters were hydrolysed with acid to give the  $\alpha$ -aminophosphonic acids.

**Scheme 1.24** Procedure for the preparation of  $\alpha$ -aminophosphonic acids and the phosphonate ester derivatives in this work

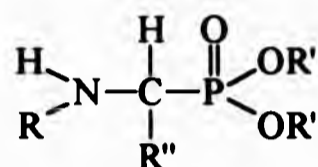


*Reagents:* (i)  $\text{K}_2\text{CO}_3$  (ii)  $\text{HPO}(\text{OEt})_2/\Delta$  (iii)  $\text{HCl}/\text{H}_2\text{O}/\Delta$   
(iv) Propylene oxide

The advantage of this procedure is that while the synthesis of  $\alpha$ -amino-substituted phosphonic acids from amines and carbonyl compounds can be carried out as a 'one-pot' procedure, the intermediates can be easily isolated. The method allows the substitution in the required  $\alpha$ -carbon position and the scope of the reaction is vast. With the systematic change of the  $\text{R}''$  group a change in polarity and solubility can be readily achieved (Figure 1.3) and the availability of the binding sites (the nitrogen and oxygen atoms of the

phosphoryl group) can also be modified. The other main advantage of this procedure is the easy deprotection of the nitrogen group by acid-hydrolysis.

**Figure 1.3** Phosphonic acids and phosphonate ester derivatives prepared in this work



R'' = various substituents

R = CHPh<sub>2</sub> and R' = alkyl

R = H and R' = H

This amine, aminodiphenylmethane, was first used by Issleib for the preparation of simple  $\alpha$ -aminophosphonic acids,<sup>[70]</sup> aminodiphosphonic acids,<sup>[71]</sup> and later by Baylis<sup>[6]</sup> to prepare a variety of  $\alpha$ -aminophosphonic acids.

### 1.3 Structural Analysis

#### 1.3.1 Introduction

It is reasonable to expect that the conformation which a molecule adopts in solution may play a part in determining any biological activity it might have. In principle, the conformation of the molecules can be determined from the values observed for proton vicinal coupling constants by applying the Karplus relationship between  $^3J_{\text{HH}}$  and the dihedral angle.<sup>[72]</sup> The  $^1\text{H}$  NMR spectra of even fairly simple  $\alpha$ -aminoalkanephosphonic acids and their phosphonate ester derivatives are more complicated than might be expected due to the presence of the chiral  $\alpha$ -carbon atom. In these cases, the values of  $^3J_{\text{HH}}$  coupling constants are not available by direct inspection of the  $^1\text{H}$  NMR spectra, and a more detailed consideration of the  $^1\text{H}$  NMR spectra is required.



### 1.3.2 Parameter Adjustment in NMR by Iteration Calculation (PANIC)

The detailed analysis of the  $^1\text{H}$  NMR spectra of  $\alpha$ -aminophosphonic and phosphinic acids 1-3 (Figure 1.3) was carried out using the program PANIC.<sup>[73]</sup> In this procedure, a proposed set of parameters is introduced which include the coupling constants and chemical shifts, but which can also include direct dipole-dipole couplings for axially orientated spin systems and quadrupolar coupling constants for nuclei with spins of greater than  $\frac{1}{2}$ . An X-approximation can be used, where strongly coupled nuclei are assigned the same label and weakly coupled nuclei are assigned to a different label. For example in compound 1 Figure 1.2, the protons are all strongly coupled to each other, so assigned the same label, but weakly coupled to the phosphorus atom which is given a different label. A spectrum is calculated using these parameters. The experimental spectrum is then compared with the calculated spectrum, and the parameters are adjusted in order to minimise the root mean square (RMS) of the errors of the differences between the experimental and calculated lines. The nuclear spin system being analysed can consist of up to nine non-equivalent groups. In spite of this capacity, PANIC cannot deal with the complex spin systems of the N-protected diethyl phosphonate ester structures 4-6 (Figure 1.3).

### 1.3.3 Düsseldorf Analysing and Iteration System (DAISY)

The detailed  $^1\text{H}$  NMR spectra of the N-protected diethyl phosphonate esters 4-6 (Figure 1.3) was carried out using the program WIN-DAISY.<sup>[74]</sup> As with PANIC a proposed set of spectral parameters is introduced, including resonance frequencies, scalar couplings, dipolar couplings and quadrupolar couplings. Unlike PANIC the signal linewidth is also a variable parameter, because the program uses total line shape fitting. The spectrum simulation is based on the solution of the time-independent Schrödinger equation to calculate the energy levels. The frequencies and intensities are determined using the selection rules for single quantum transitions. The program uses the digital experimental spectrum as the experimental data with which to iterate against. The experimental data must be exported from WIN-NMR (the program used to process the experimental spectrum) and connected to the spectral simulation data. The program uses

an algorithm based on least squares and a further algorithm called SPIRAL to fit the simulated spectrum to the experimental data.

#### **1.3.4 X-Ray Crystallography**

The *X*-ray crystal structures of several compounds synthesised in the present study were determined by Thomas Woodroffe at The University of North London. The structures were determined to deduce solid state characteristics to compare with any conformational information obtained for the molecules in solution by <sup>1</sup>H NMR spectral analysis.

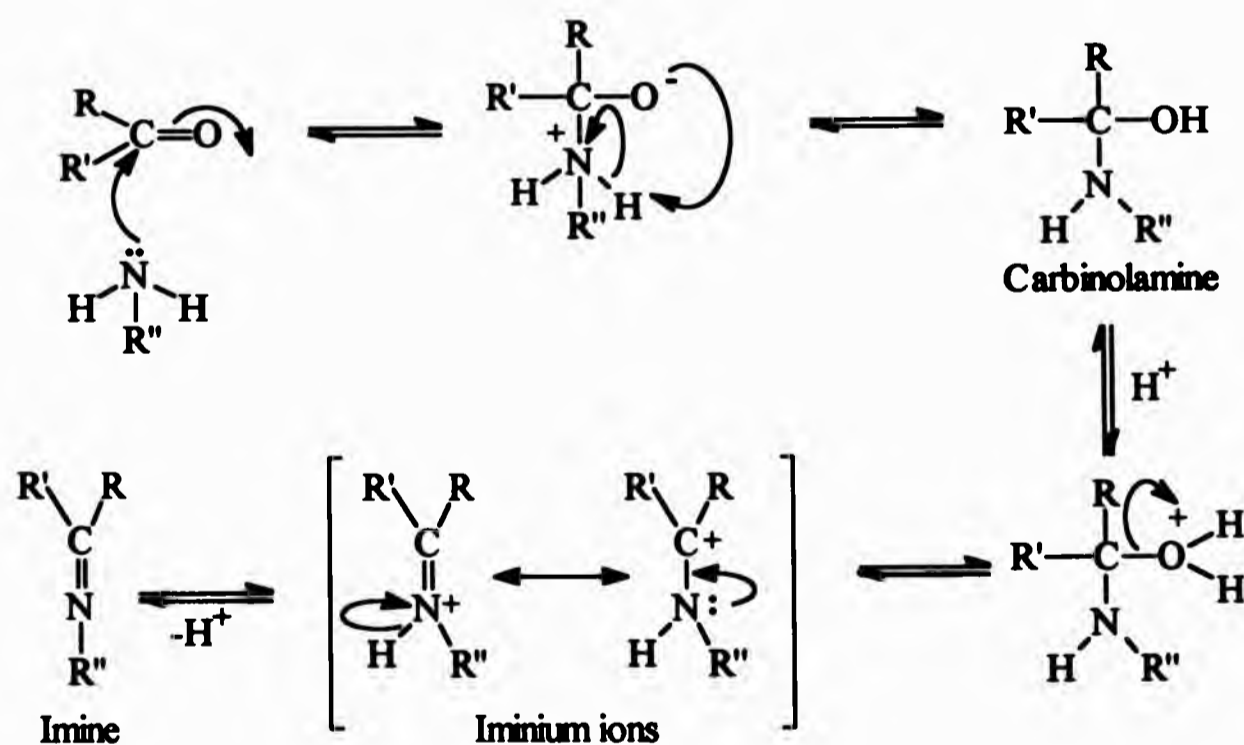
## CHAPTER TWO

### IMINE PRECURSORS

#### 2.1 Introduction

A general mechanism for the preparation of imines from the reaction of a carbonyl compound and an amine is shown in Scheme 2.1. This mechanism<sup>[75, 76]</sup> consists of two steps: nucleophilic addition of the amine to the carbonyl group to give a carbinolamine<sup>[77]</sup> is followed by the elimination of water *via* an iminium intermediate.

Scheme 2.1 Mechanism of imine formation from an amine and carbonyl compounds



The formation of imines can be laborious especially when the carbonyl compound is relatively inert.<sup>[78]</sup> The removal of the water formed as the condensation product is necessary to displace the equilibrium of the reaction in the desired direction. There are various methods of removing the water; the dehydrating agent anhydrous potassium carbonate is often sufficient, but other dehydrating agents such as molecular sieves,<sup>[79]</sup> alumina<sup>[80]</sup> or anhydrous salts that irreversibly trap the water<sup>[81]</sup> are often employed. The water can also be removed by azeotropic distillation of the reaction mixture in toluene or

benzene.<sup>[82]</sup> Surprisingly, potassium carbonate and other bases are reported to be inhibitors of imine formation,<sup>[38]</sup> presumably because the imine formation reaction is acid catalysed.<sup>[83]</sup> Potassium carbonate is nevertheless an effective dehydrating agent in imine formation reactions<sup>[84, 85]</sup> and was used in the present work.

The imine compounds were prepared as precursors to diethyl phosphonate esters but are worthy of attention in themselves; their synthesis and properties are discussed in the following sections.

## 2.2 Preparation of the Imine Precursors using Aminodiphenylmethane

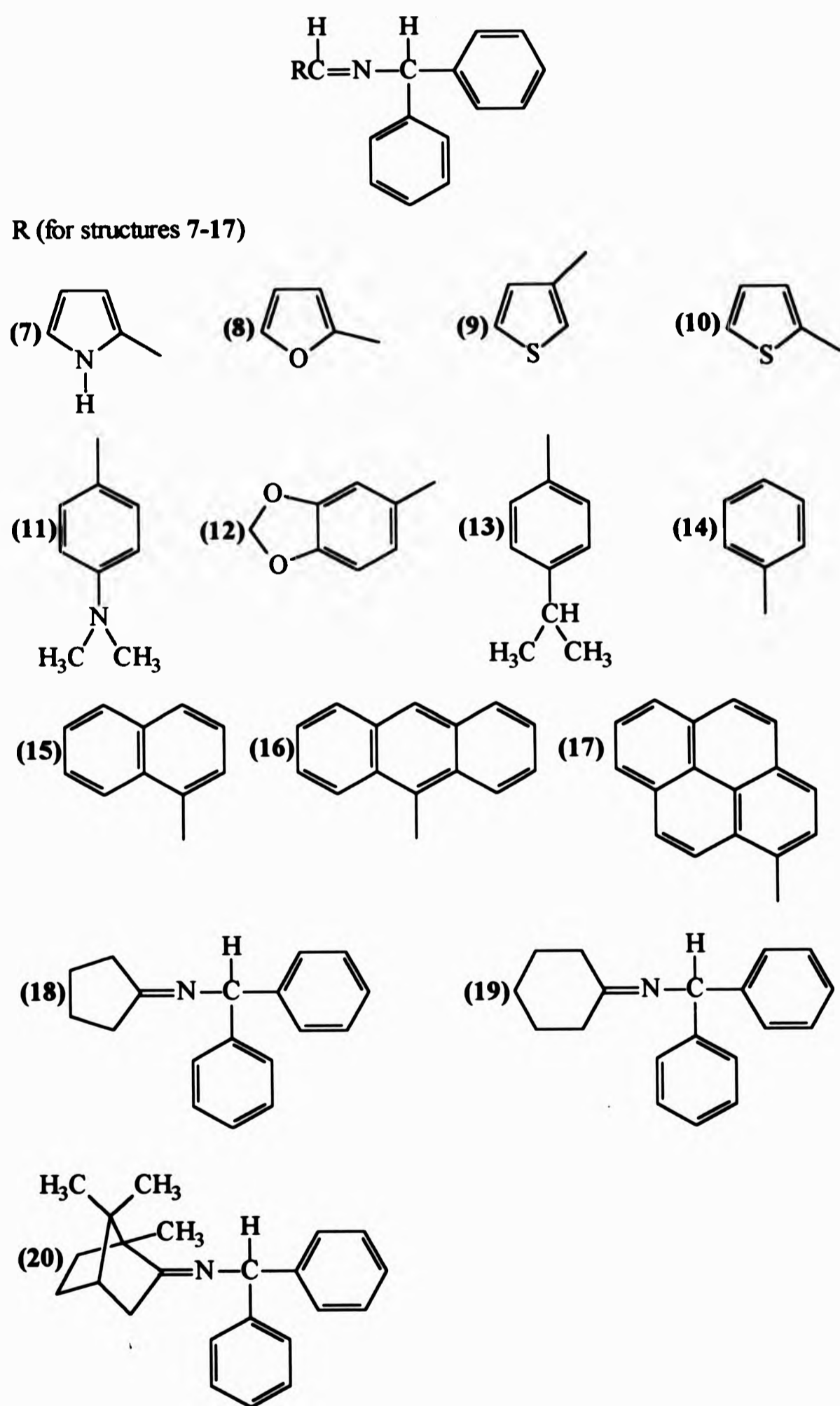
Imines 7-19 (Figure 2.1) were synthesised by stirring a 1:1 molar ratio of the appropriate carbonyl compound with aminodiphenylmethane (either as the hydrochloride salt or the free amine). The reactions were carried out at room temperature for about 6 hours using anhydrous potassium carbonate as the dehydrating agent, in either dichloromethane or diethyl ether (Scheme 2.2).

**Scheme 2.2** Preparation of imines from aminodiphenylmethane and carbonyl compounds



The imine precursors 7-19 were isolated in moderate to high yields as crystalline solids (Table 2.1). An excess of dehydrating agent,  $\text{K}_2\text{CO}_3$ , was used in all the reactions. When the hydrochloride salt of the amine is used, the hydrochloride salt is neutralised by potassium carbonate leaving the remaining potassium carbonate to act as a dehydrating agent.

Figure 2.1 The imine precursors prepared from aminodiphenylmethane in this work



**Table 2.1** Yields (%) of imines obtained using either aminodiphenylmethane or aminodiphenylmethane hydrochloride (after recrystallisation)

Imine	% yield using aminodiphenylmethane.HCl	% yield using aminodiphenylmethane
7	55.3	71.2
8	80.4	85.2 <sup>†</sup> and 94.9 <sup>‡</sup>
9	49.6	67.0
10	35.3	58.8
11	92.3	54.0
12	53.1	85.4
13	52.8	74.8
14	na <sup>§</sup>	66.7
15	na <sup>§</sup>	92.2
16	na <sup>§</sup>	87.0
17	na <sup>§</sup>	67.9
18	20.2	80.2
19	na <sup>§</sup>	42.4

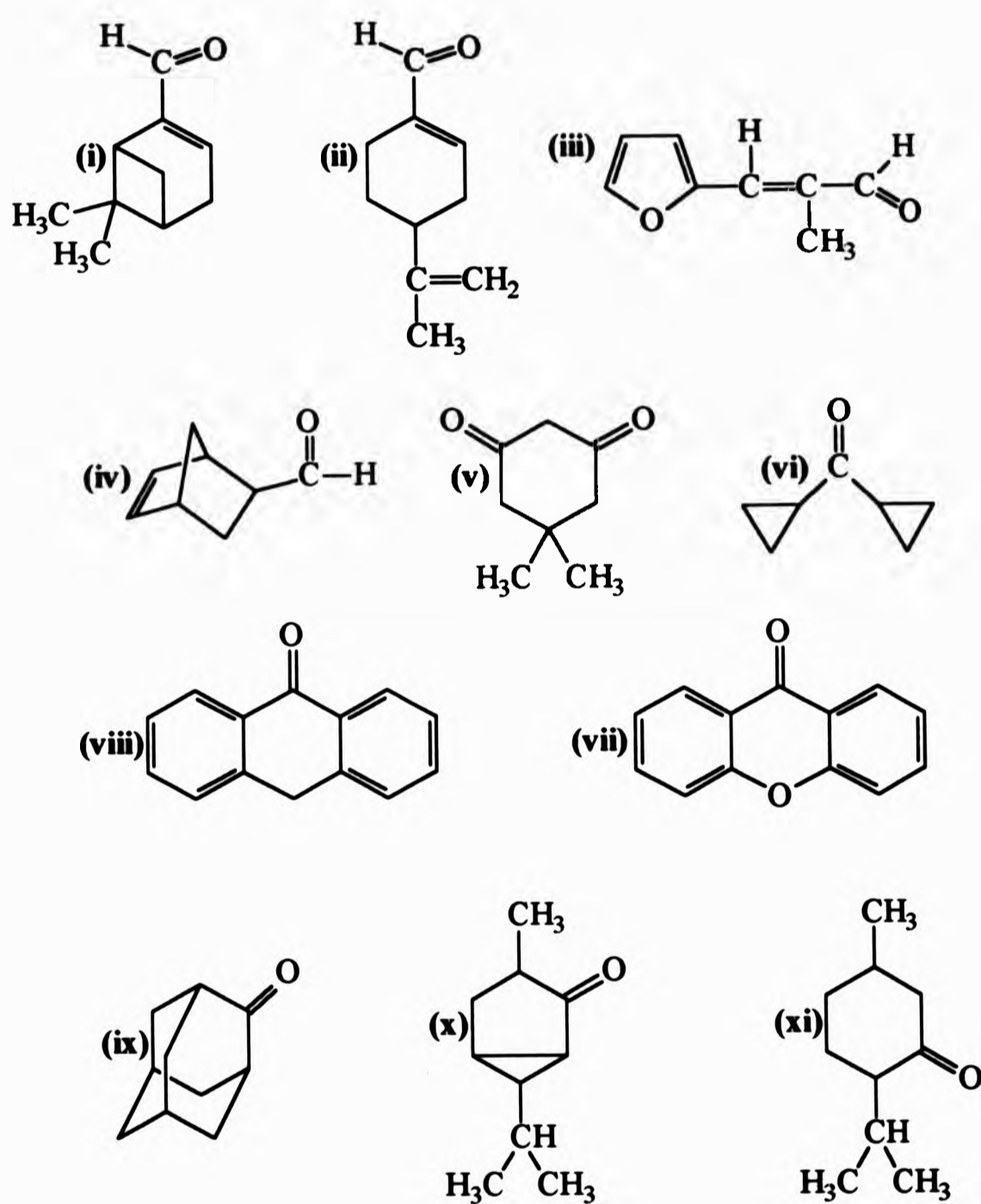
<sup>†</sup> The reaction was carried out by stirring at room temperature with K<sub>2</sub>CO<sub>3</sub>.

<sup>‡</sup> The reaction was carried out using the free amine with the azeotropic removal of water as formed using a Dean and Stark apparatus.

<sup>§</sup> These reactions were not attempted.

Imine precursors 7-19 (Figure 2.1) were isolated in moderate to high yields (Table 2.1) but other reactions attempted with both aldehydes and ketones (Figure 2.2) proved to be more problematic. The presence of the requisite molecular ion in the mass spectra of the crude reaction mixtures indicated that the desired imine had indeed formed. However, where the carbonyl compound was a ketone (v-xi, Figure 2.2) the <sup>1</sup>H NMR spectrum of a mixture of the two starting materials (the amine and carbonyl compound) would look very similar to the expected spectrum of the desired imine. Where the carbonyl compound was an aldehyde (i-iv, Figure 2.2) the <sup>1</sup>H NMR spectrum of the reaction mixture clearly indicated the presence of the aldehyde proton.

**Figure 2.2** Aldehydes and ketones which fail to give more than a trace of the desired imine



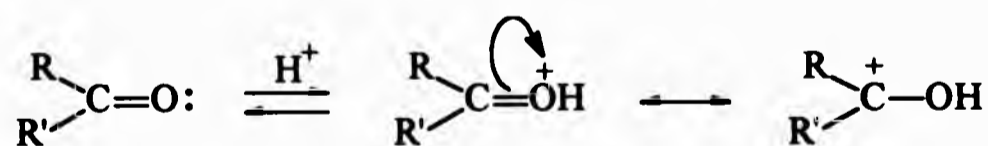
Analysis by thin-layer chromatography (TLC) was carried out in each case on the crude reaction mixtures which indicated the presence of the two starting materials and at least one other compound in each case. Any attempt to isolate this product by column chromatography failed.

Analysis by gas chromatography mass spectrometry (GC-MS) was carried out on the crude mixture from the reaction of aminodiphenylmethane and menthone. The GC separated three components from the reaction mixture in approximately equal amounts. The subsequent MS carried out on the individual components indicated, by the detection of the molecular ion, that the three components were the starting amine, the starting ketone menthone and the desired imine.

The imine precursors 18 and 19 were the only structures successfully synthesised from a ketone and the amine using the very mild reaction conditions.

The structure and reactivity of the carbonyl compounds explain why some of these reactions failed to give reasonable yields of the desired imines. Aldehydes are more reactive than ketones towards nucleophilic addition.<sup>[86]</sup> The rate of addition is reduced by electron donating groups, while electron withdrawing groups increase the polarisation of the carbonyl bond making the carbon atom more reactive towards the nucleophile. The positive character of the carbonyl carbon can also be increased by acid catalysis (Scheme 2.3).

**Scheme 2.3** Mechanism for the acid catalysis of the carbon atom of a carbonyl bond

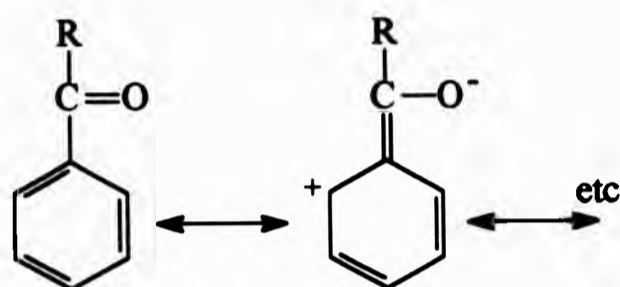


Aliphatic carbonyl compounds are more reactive than aromatic carbonyl compounds towards nucleophilic addition because aromatic carbonyl compounds have extra resonance stability due to delocalisation (Figure 2.3). The extra stability of the aromatic carbonyl compounds is lost as soon as it takes part in the reaction and reaches the transition state (see mechanism Scheme 2.1). It is notable that the ketones that did react successfully with the amine to give imines 18-20 (Figure 2.1) were aliphatic ketones.



Another factor to be considered in these failed reactions is steric hindrance; ketones are generally more sterically hindered than aldehydes.

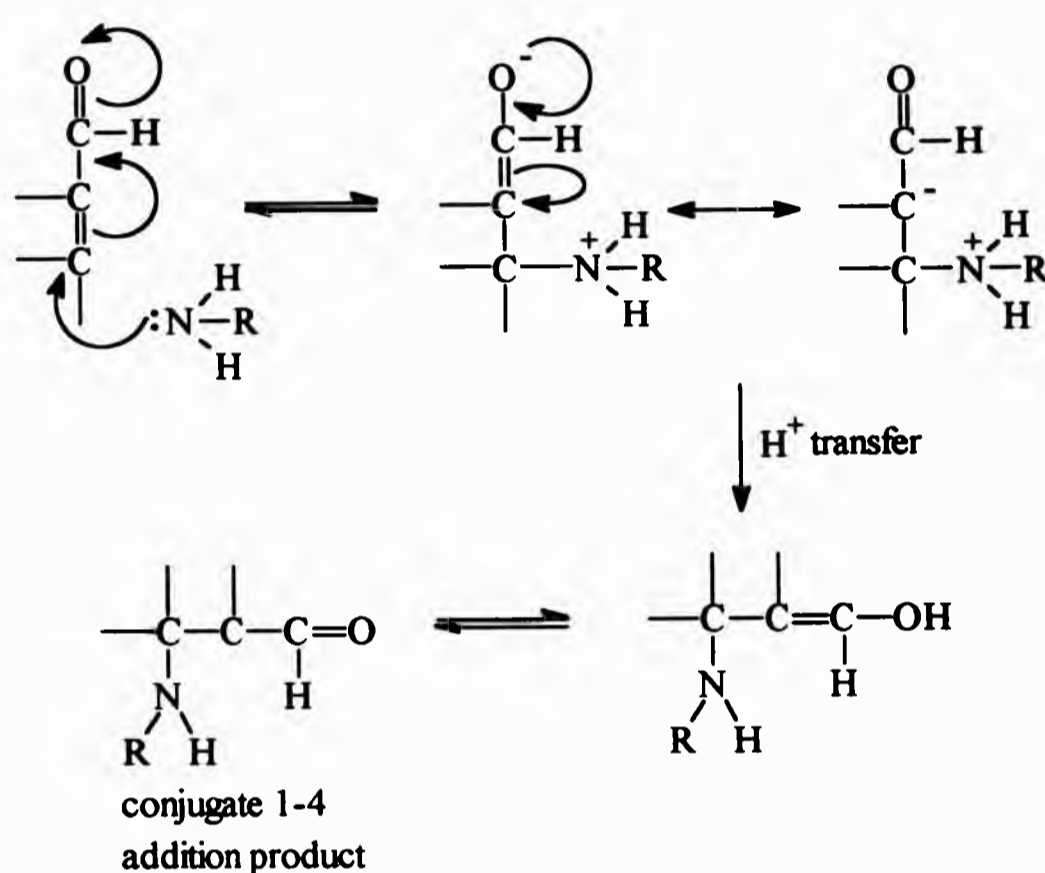
**Figure 2.3** Resonance structures of aromatic aldehydes



Imines 7-10 (Figure 2.1) containing pyrrole, furan and thiophene substituents were synthesised from aromatic aldehydes. The order of aromaticity of these compounds, as calculated by an aromaticity index based on bond distance measurements, is thiophene > pyrrole > furan (with furan being the least aromatic).<sup>[87-89]</sup> The trend seen for the yield (see Table 2.2) of the reactions shows the furan derivative 7 was obtained with the highest yield, followed by the pyrrole derivative 8 and finally the most aromatic aldehyde thiophene derivatives 9 and 10 were obtained in the lowest yield.

The aldehydes (i, ii and iii; Figure 2.2) all have a carbon-carbon double bond in conjugation with the carbonyl carbon-oxygen double bond. The resonance stabilisation discussed above for aromatic compounds (Figure 2.3) occurs in these structures also, but the initial carbonyl compound may be susceptible to nucleophilic attack at the carbon-carbon double bond in a conjugate 1-4 addition reaction (Scheme 2.4).

**Scheme 2.4** Mechanism for the formation of 1-4 conjugate addition product from an amine and a carbonyl compound with a carbon-carbon double bond in conjugation with the carbonyl carbon-oxygen double bond

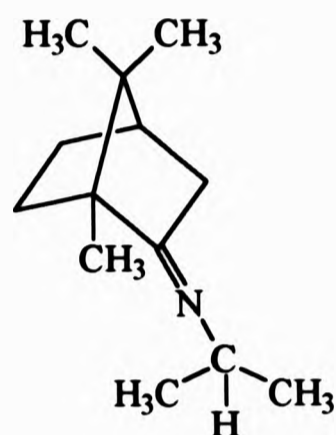


The <sup>1</sup>H NMR spectra and the mass spectra of the crude reaction mixtures showed no evidence for the production of these 1-4 addition products.

The preparation of the imine **20** (Figure 2.1) was not successful when using anhydrous potassium carbonate as a dehydrating agent or by refluxing the reaction mixture in toluene with the azeotropic removal of any water.

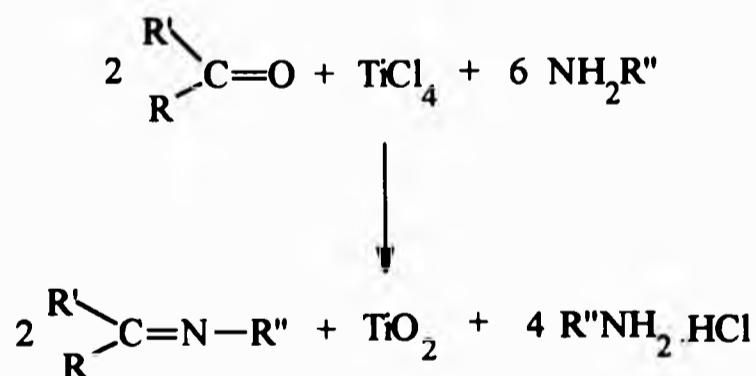
The imine derived from camphor and N-isopropylamine (Figure 2.4) was successfully prepared by Weingarten.<sup>[90]</sup> On account of the success of this reaction, the ketone camphor was chosen to investigate the reaction conditions required to achieve the synthesis of the imine derived from camphor and aminodiphenylmethane.

**Figure 2.4** The imine derived from camphor and N-isopropylamine



White and Weingarten<sup>[91]</sup> described the preparation of imines from carbonyl compounds, a primary or secondary amine and titanium tetrachloride. The titanium tetrachloride acts as a very efficient water scavenger but also acts as a Lewis acid catalyst. However, it cannot be considered a true catalyst as the reagent is consumed within the reaction (Scheme 2.5).

**Scheme 2.5** The titanium tetrachloride catalysed reaction of carbonyl compounds and an amine



The mechanism of the reaction is not fully understood but involves the titanium atom co-ordinating with the carbonyl oxygen to polarise the bond to make it more reactive towards the amine nucleophile. This is followed by the transfer of the oxygen atom to the titanium atom. The reaction is reported to work better if the titanium is allowed to form a complex with the amine prior to the addition of the carbonyl compound.<sup>[92-94]</sup> This procedure did allow the isolation and characterisation of the imine precursor **20**

(Figure 2.1), but the reaction was only carried out on small scale so the next step of the reaction scheme, to prepare the phosphonate ester and phosphonic acid, was not attempted.

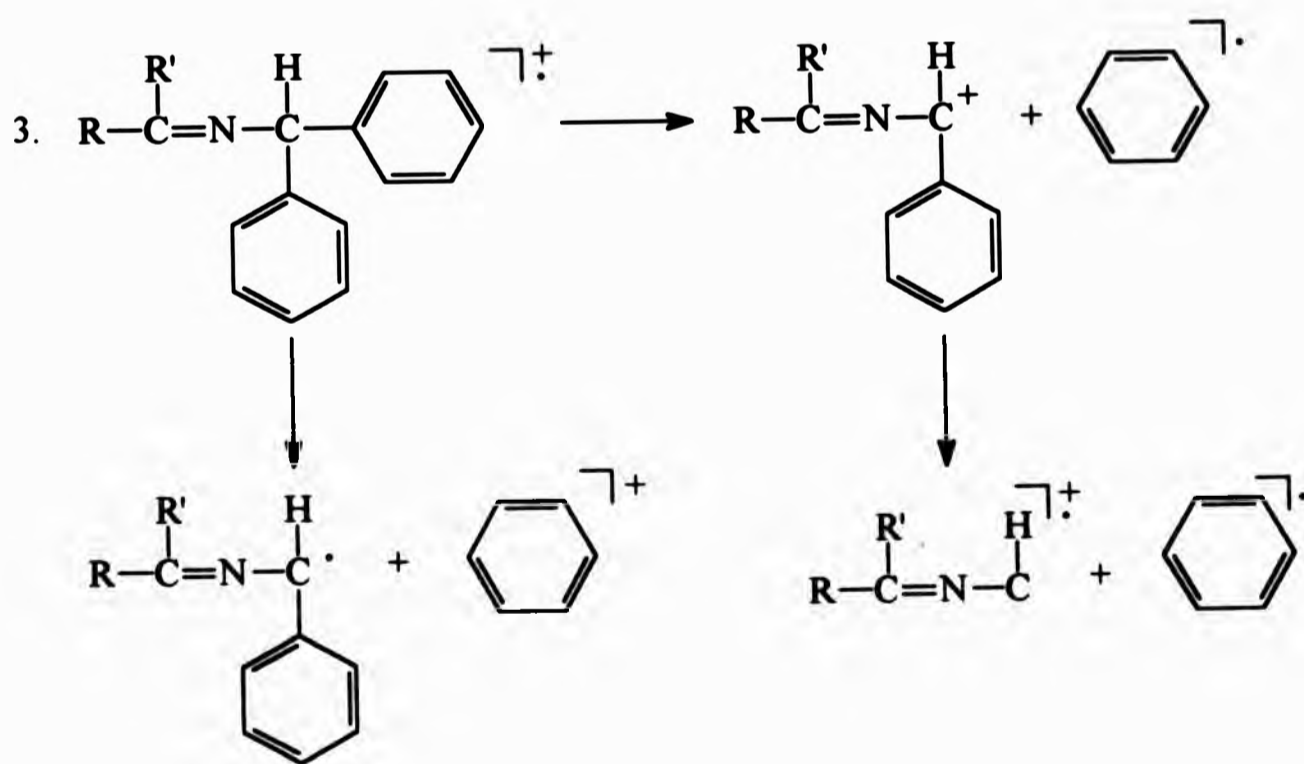
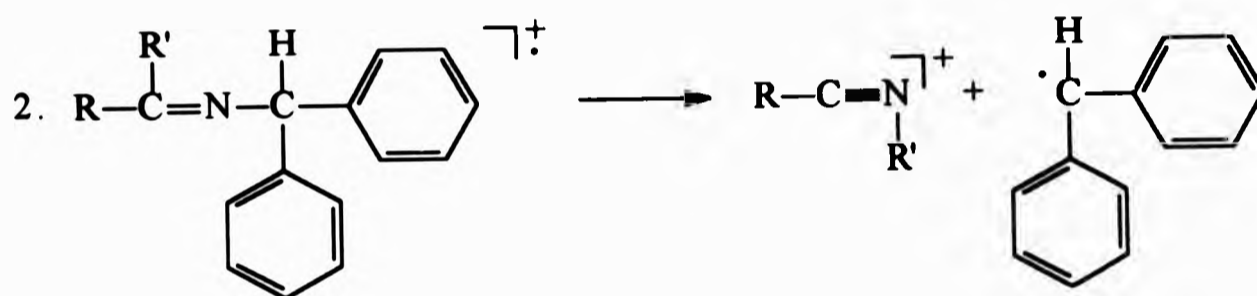
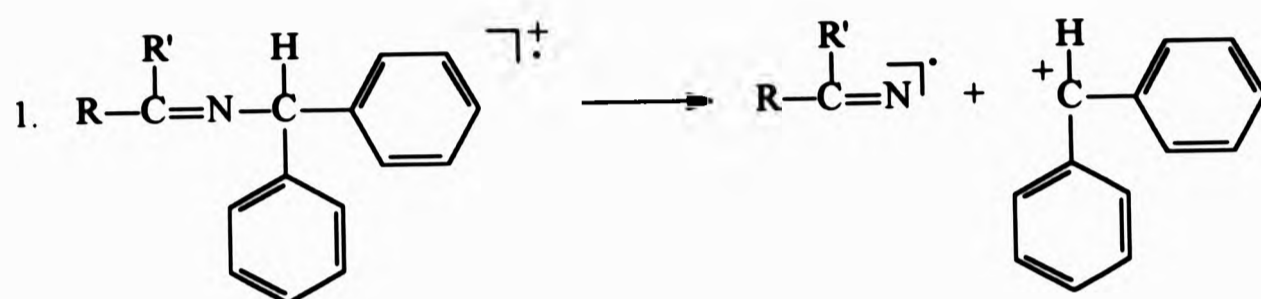
### **2.3 Characterisation of Imine Precursors Synthesised using Aminodiphenylmethane**

#### **2.3.1 Mass Spectrometry of Imine Precursors Synthesised using Aminodiphenylmethane**

Mass spectrometry of the imine precursors 7-20 (Figure 2.1) using low resolution electron impact (EI) gave rise to very similar fragmentation patterns (Scheme 2.6). The values of  $m/z$  and relative abundance (%) of the important fragments are given in Table 2.2.

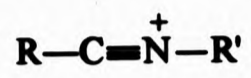
The molecular ion ( $M^+$ ) was seen for all the compounds 7-20 with relative abundances as high as 81% for N-(2'-thienylmethylidene)-1,1-diphenylmethanamine 10 and as low as 2% for N-(1'-pyrenylmethylidene)-1,1-diphenylmethanamine 17. Other identifiable ions were the molecular ion with the loss of one phenyl ring as a radical ( $C_6H_5^{\cdot}$ ), or both phenyl rings as radicals ( $C_6H_5^{\cdot}$ ), but most compounds showed a low relative abundance for these ions. N-(2'-Pyrrolylmethylidene)-1,1-diphenylmethanamine 7 was an exception having higher relative abundances for these ions than the other compounds. The  $R'RC=NCH^+$  ion is identified with a low relative abundance for all the compounds except for compound 7 which has this ion as the base peak. The structure of the ion that corresponds to  $(RCNR)^+$  is likely to be different for the imines 7-17 than the imines 18-20 (Figure 2.5). N-(1'-Pyrenyl-methylidene)-1,1-diphenylmethanamine 17 shows very few ions of large mass, the benzhydryl ion  $CHPh_2^+$  and the phenyl ion  $C_6H_5^+$  being the only ions with a high abundance. The  $C_6H_5^+$  phenyl ion was identified in the fragmentation pattern of all the compounds.

Scheme 2.6<sup>†</sup> Mass spectrometry fragmentation scheme for imine precursors 7-20

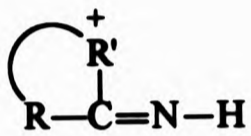


<sup>†</sup> For the imines 7-17 R' = H in Scheme 2.6, but for imines 18-20 R' is part of the appropriate ring system.

**Figure 2.5** Structures of the mass spectrometry fragment  $(RCNR)^+$



7-17



18-20

$R' = H$  in 7-17 and part of a ring system in structures 18-20

**Table 2.2** Values of m/z and relative abundance (%) for important fragments in the mass spectra of the imine precursors synthesised using aminodiphenylmethane

Imine	M <sup>+</sup>	[RRC=NCH(Ph)] <sup>+</sup>	[RRC=NCH] <sup>+</sup>	[RCNR] <sup>+</sup>	CHPh <sub>2</sub> <sup>+</sup> (m/z 167)	C <sub>6</sub> H <sub>5</sub> <sup>+</sup> (m/z 77)
7	260 (22)	183 (87)	106 (100)	93 (2)	(64)	(75)
8	261 (62)	184 (29)	107 (4)	94 (11)	(100)	(57)
8	277 (23)	200 (3)	123 (0)	110 (5)	(100)	(23)
10	277 (81)	200 (15)	123 (1)	110 (4)	(100)	(12)
11	314 (21)	237 (6)	160 (0)	147 (0)	(94)	(100)
12	315 (30)	238 (3)	161 (0)	148 (3)	(100)	(36)
13	313 (49)	236 (4)	159 (0)	146 (4)	(100)	(41)
14	271 (68)	194 (33)	117 (15)	104 (39)	(100)	(83)
15	321 (21)	244 (6)	167 <sup>†</sup>	154 (11)	(100) <sup>†</sup>	(37)
16	371 (23)	294 (19)	217 (7)	204 (49)	(100)	(41)
17	395 (2)	318 (0)	241 (0)	228 (8)	(64)	(100)
18	249 (19)	172 (3)	95 (1)	82 (6)	(100)	(40)
19	263 (33)	186 (5)	109 (3)	96 (2)	(81)	(82)
20 <sup>‡</sup>	317 (10)	240 (0)	163 (6)	150 (10)	(87)	(86)

<sup>†</sup> It should be noted that the two fragments have the same mass so the fragment RRC=NCH cannot be identified.

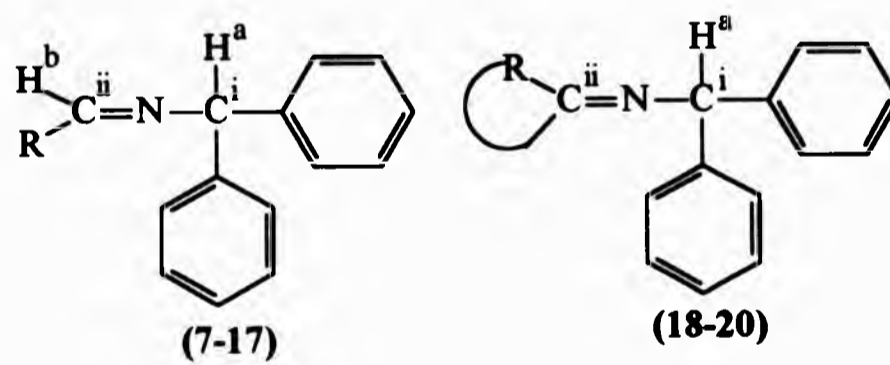
<sup>‡</sup> The base peak corresponds to m/z 95.

### 2.3.2 $^1\text{H}$ and $^{13}\text{C}$ NMR Spectroscopy of Imine Precursors Synthesised using Aminodiphenylmethane

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the imines (7-20, Figure 2.1) were obtained in  $\text{CDCl}_3$  solution (ca. 5% w/w), except for compound 17 whose NMR spectra were obtained for a saturated solution in  $\text{CDCl}_3$ . First order analyses of the spectra were carried out by inspection and the results of these analyses (chemical shifts and coupling constants) are given in Appendix II.

The chemical shift positions of  $\text{H}^a$ ,  $\text{H}^b$ ,  $\text{C}^i$  and  $\text{C}^{ii}$  (see Figure 2.6 for labels) are compared within the series of imine precursors studied (Table 2.3). Chemical shifts are determined mainly by the shielding and deshielding effects of the neighbouring substituents; aromatic ring current effects<sup>[95]</sup> are expected to be particularly important because of the extent of aromatic ring systems involved in these structures.

Figure 2.6 Labelling scheme of selected protons and carbons atoms in imines 7-20

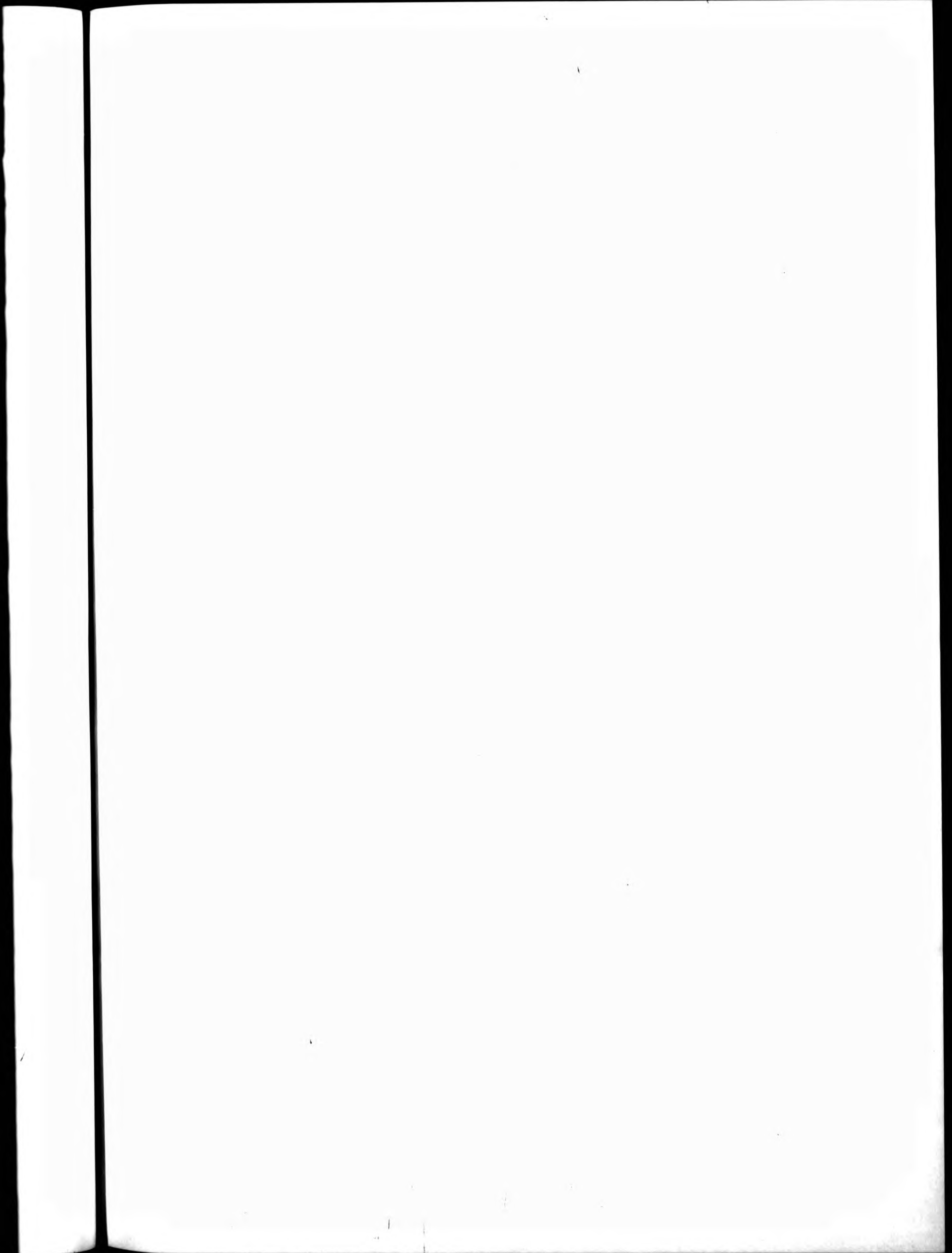


$\text{C}^{ii}$  and R are part of a ring system  
in compounds 18-20

The chemical shift of the singlet assigned to  $\text{H}^a$  varies very little within the series of compounds 7-15, but is shifted downfield in compounds 16, 17 and 19. The larger aromatic substituents in compounds 16-17 have a deshielding effect. The proton  $\text{H}^b$  is situated closer to the point of substitution and so, as expected, its chemical shift varies



more within the series (compared to the variation seen for the chemical shift position of H<sup>a</sup>), depending on the nature of the substituent R. The carbon C<sup>ii</sup> is the point of substitution so the variation in the series would again be expected to be largest here. In compounds 7-10 the signals assigned to this carbon are upfield compared to this signal in the other compounds. The positions of the signal for C<sup>ii</sup> follow an order which is the same as that of the aromaticity of the R substituents  $\delta_{C^{ii}}$  : 8 < 7 < 9 ~ 10; aromaticity<sup>[87-89]</sup> 8 < 7 < 9 and 10. The chemical shift of the signal assigned to C<sup>ii</sup> varies very little between the compounds 11-17. In the spectra of compounds 18-20 the carbon signal is shifted significantly further downfield because in these compounds the carbon is quaternary. Quaternary carbons resonate downfield compared to protonated carbons as there is no shielding effect from protons.<sup>[96]</sup>



**Table 2.3**  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts (ppm) for imines 7-20

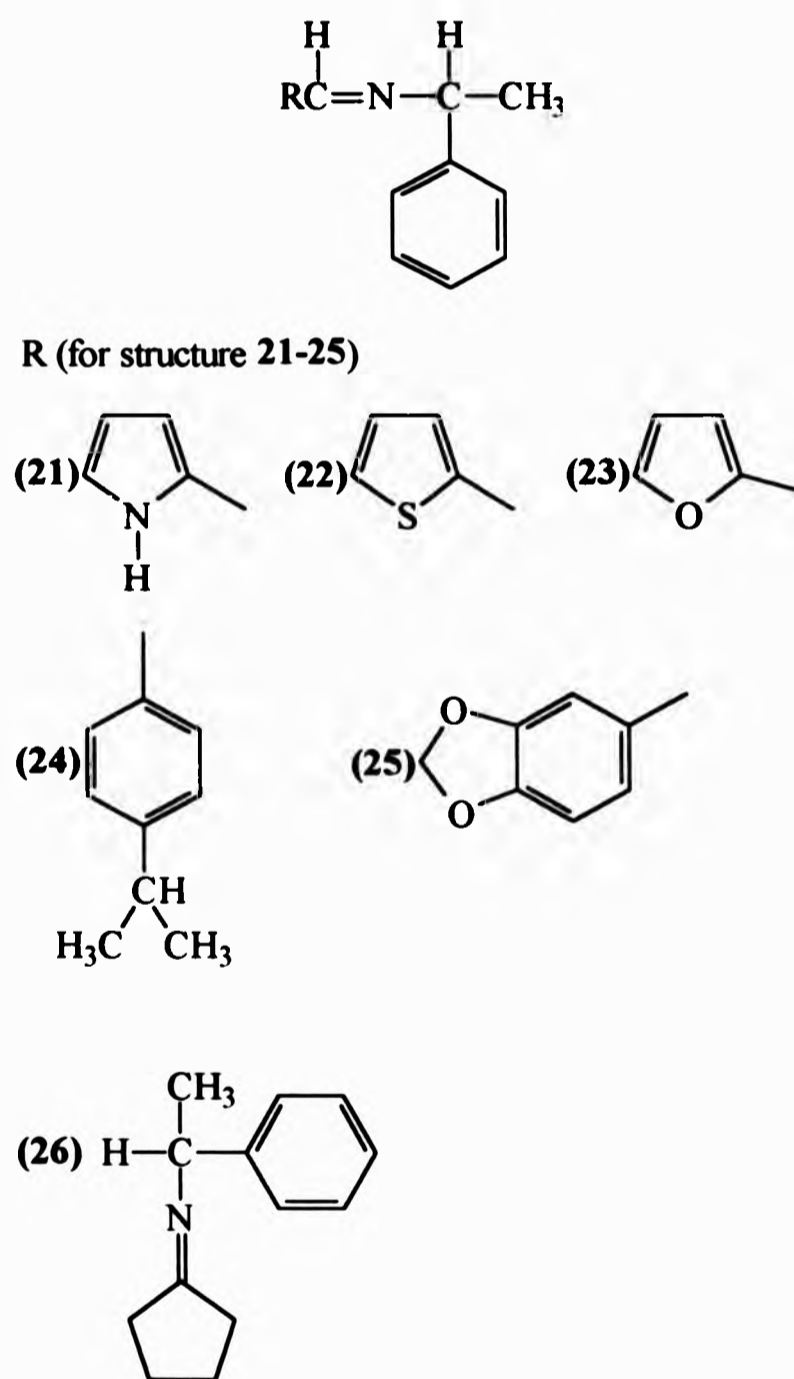
Imine	$\delta_{\text{H}^a}$	$\delta_{\text{C}^i}$	$\delta_{\text{H}^b}$	$\delta_{\text{C}^{ii}}$
7	5.56	77.7	8.13	151.3
8	5.53	77.9	8.13	149.6
9	5.52	77.6	8.35	155.0
10	5.57	77.2	8.43	154.1
11	5.51	77.7	8.28	160.6
12	5.55	77.6	8.29	159.8
13	5.55	77.8	8.34	160.6
14	5.59	77.8	8.40	160.7
15	5.59	79.2	8.92	160.8
16	5.83	80.3	9.49	160.7
17	5.80	79.3	9.42	159.8
18	5.46	70.6	-	180.6
19	5.91	66.5	-	173.2
20	5.43	68.2	-	181.4

#### 2.4 Preparation of Imines Precursors using $\alpha$ -Methylbenzylamine

The chiral amine  $\alpha$ -methylbenzylamine (either the *R* or *S* enantiomer) has been used to prepare optically active  $\alpha$ -aminophosphonic acids *via* the optically active imine.<sup>[97]</sup> Although the racemic amine has not been used previously in the preparation of  $\alpha$ -aminophosphonic acids, it is less expensive than aminodiphenylmethane. It might also be expected to react more readily with carbonyl compounds as less steric hindrance would be incurred. A number of imines were prepared 21-26 (Figure 2.7) using the same general method (Section 2.2) of mixing a 1:1 ratio of amine and carbonyl compound in ether with anhydrous potassium carbonate as dehydrating agent. One disadvantage in using this amine instead of the aminodiphenylmethane is that the desired imines were (without exception) obtained as oils containing traces of unreacted starting materials which were

difficult to purify. A further disadvantage is that to prepare the  $\alpha$ -aminophosphonic acids requires an extra hydrogenation step to achieve the amino de-protected product.

**Figure 2.7** The imine precursors prepared from  $\alpha$ -methylbenzylamine in this work



#### 2.4.1 Mass Spectrometry of the Imine Precursors using $\alpha$ -Methylbenzylamine

The fragmentation patterns of the imine precursors 21-26 were, as expected, very similar to those of the imine precursors 7-20 (see Scheme 2.6).

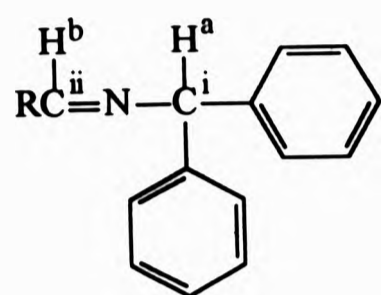
The molecular ion ( $M^+$ ) was identified for all the compounds 21-26 (see Table 2.4) with relative abundances ranging from 15-86%. The ion corresponding to the molecular ion with the loss of the  $CH_3$  group as a radical was seen in all the compounds with relative abundances ranging from 15-76%. The ion that corresponds to the molecular ion with the loss of the  $C_6H_5$  as a radical was also seen for all the compounds but with much lower relative abundances. This can be attributed to the ion  $(R'RC=NCHPh)^+$  being more stable, due to resonance stabilisation, than the ion  $(R'RC=NCHCH_3)^+$  which does not have the ability to spread the positive charge. The base peak for all the structures was the  $[CH(CH_3)Ph]^+$  ion.

**Table 2.4** Values of  $m/z$  and relative abundance (%)<sup>†</sup> for important fragments in the mass spectra of the imine precursors synthesised using  $\alpha$ -methylbenzylamine

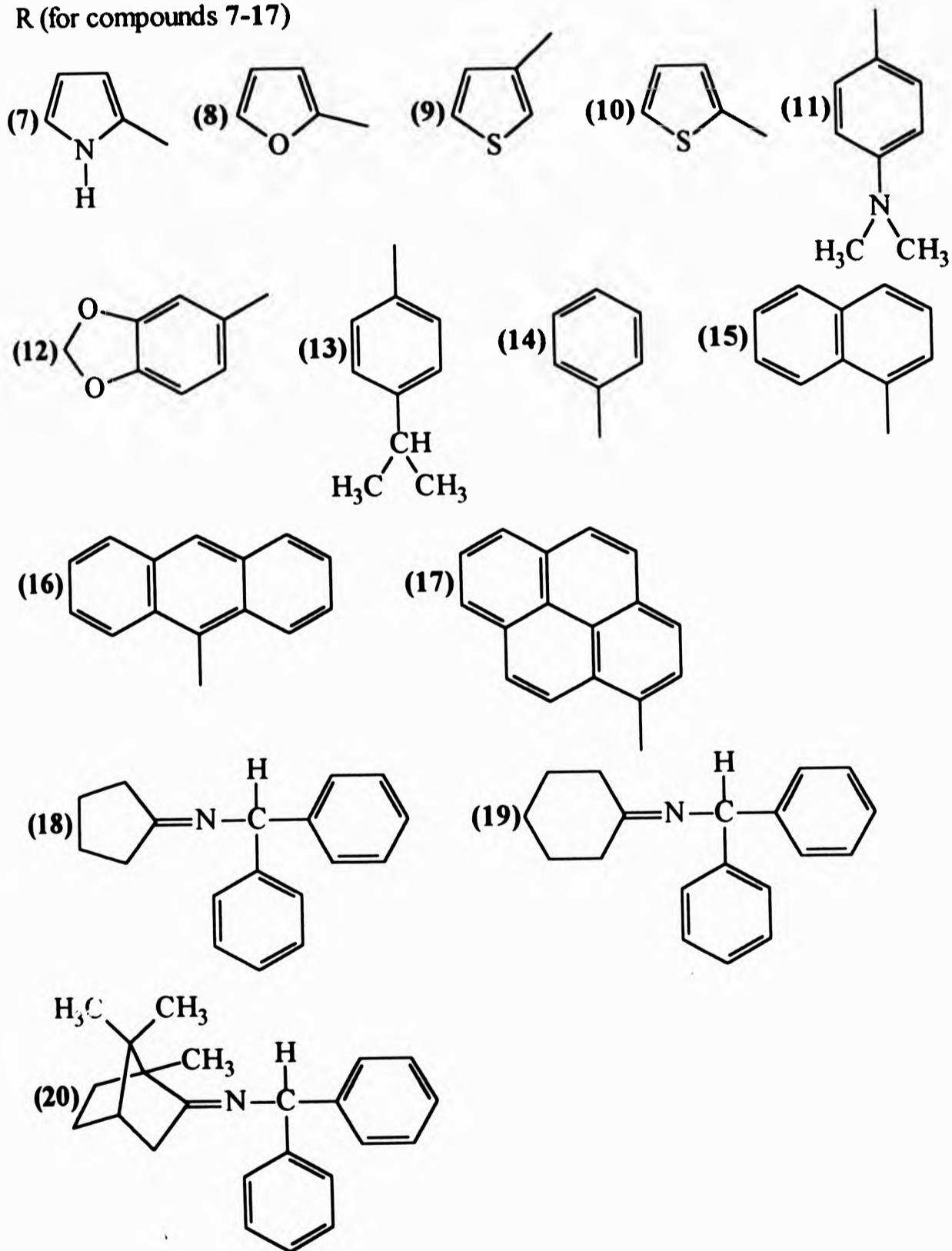
Imine	$M^+$	$[RRC=NCH(Ph)]^+$	$[RRC=NCH(CH_3)]^+$	$[RRC=NCH]^+$	$[RC=NR]^+$
<b>21</b>	198 (86)	183 (76)	121 (6)	106 (18)	93 (10)
<b>22</b>	215 (63)	200 (40)	138 (4)	123 (1)	110 (12)
<b>23</b>	199 (40)	184 (24)	122 (8)	107 (3)	94 (13)
<b>24</b>	251 (62)	236 (63)	174 (10)	159 (1)	146 (22)
<b>25</b>	253 (15)	238 (15)	178 (2)	161 (0)	148 (5)
<b>26</b>	187 (58)	172 (33)	110 (4)	95 (0)	82 (4)

<sup>†</sup> The base peak for all the imine precursors is  $m/z$  105 corresponding to  $CH(CH_3)Ph^+$ .

Table 2.3 Imines referred to in Table 2.3



R (for compounds 7-17)



**Table 2.3**  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts (ppm) for imines 7-20

Imine	$\delta_{\text{H}^a}$	$\delta_{\text{C}^i}$	$\delta_{\text{H}^b}$	$\delta_{\text{C}^{ii}}$
7	5.56	77.7	8.13	151.3
8	5.53	77.9	8.13	149.6
9	5.52	77.6	8.35	155.0
10	5.57	77.2	8.43	154.1
11	5.51	77.7	8.28	160.6
12	5.55	77.6	8.29	159.8
13	5.55	77.8	8.34	160.6
14	5.59	77.8	8.40	160.7
15	5.59	79.2	8.92	160.8
16	5.83	80.3	9.49	160.7
17	5.80	79.3	9.42	159.8
18	5.46	70.6	-	180.6
19	5.91	66.5	-	173.2
20	5.43	68.2	-	181.4

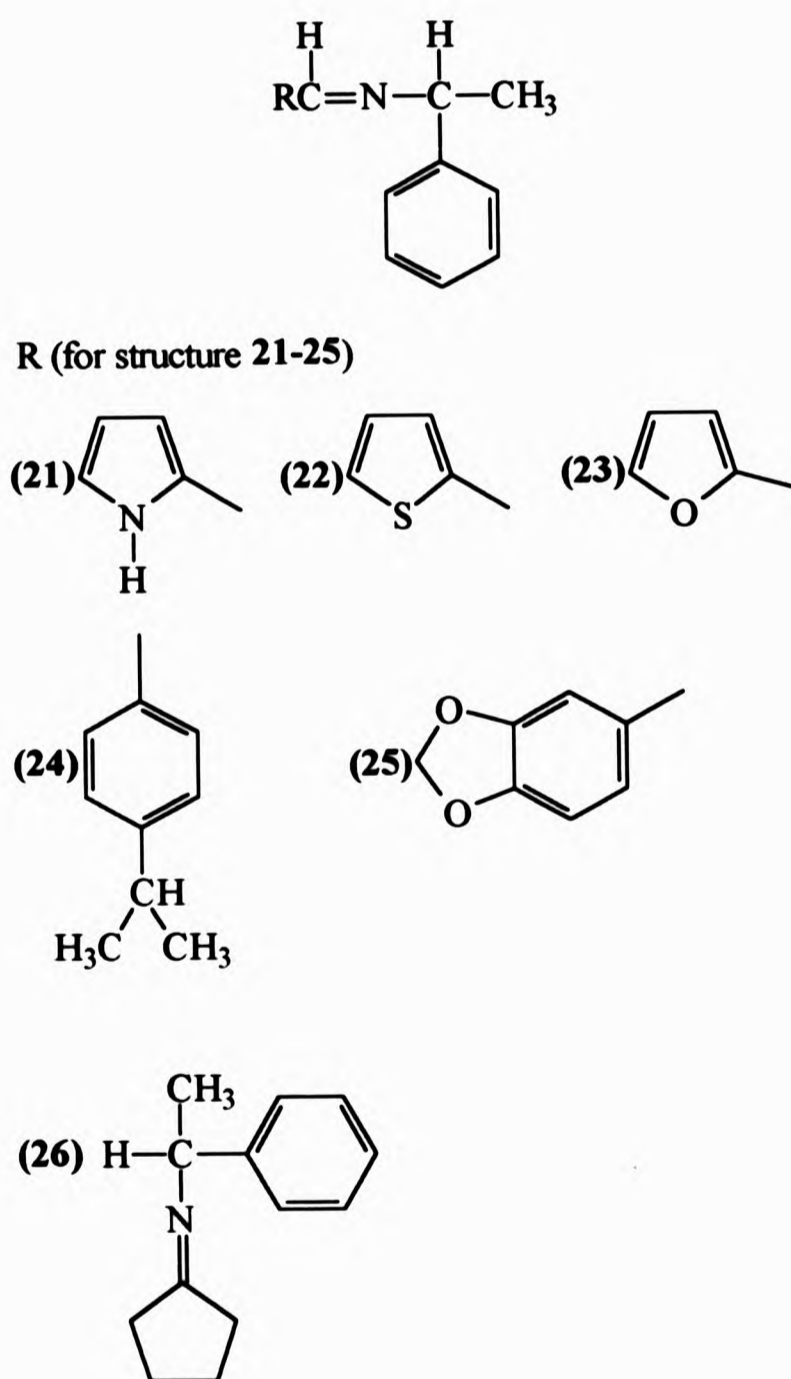
#### 2.4 Preparation of Imines Precursors using $\alpha$ -Methylbenzylamine

The chiral amine  $\alpha$ -methylbenzylamine (either the *R* or *S* enantiomer) has been used to prepare optically active  $\alpha$ -aminophosphonic acids *via* the optically active imine.<sup>[97]</sup> Although the racemic amine has not been used previously in the preparation of  $\alpha$ -aminophosphonic acids, it is less expensive than aminodiphenylmethane. It might also be expected to react more readily with carbonyl compounds as less steric hindrance would be incurred. A number of imines were prepared 21-26 (Figure 2.7) using the same general method (Section 2.2) of mixing a 1:1 ratio of amine and carbonyl compound in ether with anhydrous potassium carbonate as dehydrating agent. One disadvantage in using this amine instead of the aminodiphenylmethane is that the desired imines were (without exception) obtained as oils containing traces of unreacted starting materials which were



difficult to purify. A further disadvantage is that to prepare the  $\alpha$ -aminophosphonic acids requires an extra hydrogenation step to achieve the amino de-protected product.

**Figure 2.7** The imine precursors prepared from  $\alpha$ -methylbenzylamine in this work



#### 2.4.1 Mass Spectrometry of the Imine Precursors using $\alpha$ -Methylbenzylamine

The fragmentation patterns of the imine precursors **21-26** were, as expected, very similar to those of the imine precursors **7-20** (see Scheme 2.6).

The molecular ion ( $M^+$ ) was identified for all the compounds **21-26** (see Table 2.4) with relative abundances ranging from 15-86%. The ion corresponding to the molecular ion with the loss of the  $CH_3$  group as a radical was seen in all the compounds with relative abundances ranging from 15-76%. The ion that corresponds to the molecular ion with the loss of the  $C_6H_5$  as a radical was also seen for all the compounds but with much lower relative abundances. This can be attributed to the ion  $(R'RC=NCHPh)^+$  being more stable, due to resonance stabilisation, than the ion  $(R'RC=NCHCH_3)^+$  which does not have the ability to spread the positive charge. The base peak for all the structures was the  $[CH(CH_3)Ph]^+$  ion.

**Table 2.4** Values of  $m/z$  and relative abundance (%)<sup>†</sup> for important fragments in the mass spectra of the imine precursors synthesised using  $\alpha$ -methylbenzylamine

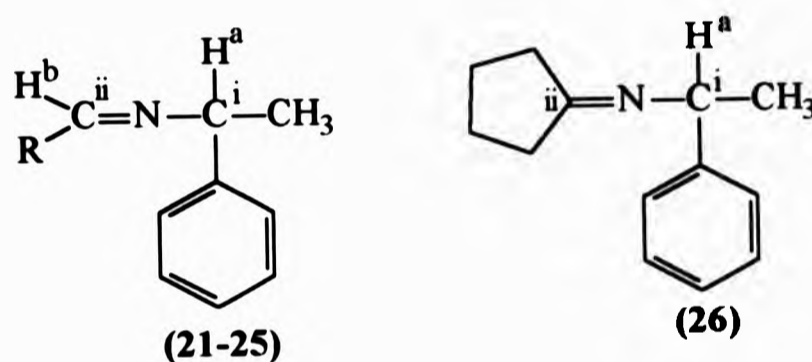
Imine	$M^+$	$[\text{RRC}=\text{NCH}(\text{Ph})]^+$	$[\text{RRC}=\text{NCH}(\text{CH}_3)]^+$	$[\text{RRC}=\text{NCH}]^+$	$[\text{RC}=\text{NR}]^+$
<b>21</b>	198 (86)	183 (76)	121 (6)	106 (18)	93 (10)
<b>22</b>	215 (63)	200 (40)	138 (4)	123 (1)	110 (12)
<b>23</b>	199 (40)	184 (24)	122 (8)	107 (3)	94 (13)
<b>24</b>	251 (62)	236 (63)	174 (10)	159 (1)	146 (22)
<b>25</b>	253 (15)	238 (15)	178 (2)	161 (0)	148 (5)
<b>26</b>	187 (58)	172 (33)	110 (4)	95 (0)	82 (4)

<sup>†</sup> The base peak for all the imine precursors is  $m/z$  105 corresponding to  $\text{CH}(\text{CH}_3)\text{Ph}^+$ .

### 2.4.2 $^1\text{H}$ and $^{13}\text{C}$ NMR Spectroscopy of the Imine Precursors Synthesised using $\alpha$ -Methylbenzylamine

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the imines **21-26** (Figure 2.7) were obtained in  $\text{CDCl}_3$  solution (ca. 5% w/w). First order analyses of the spectra gave the chemical shifts and coupling constants listed in Appendix II.

Figure 2.8 Labelling scheme of selected protons and carbon atoms in imines **21-26**

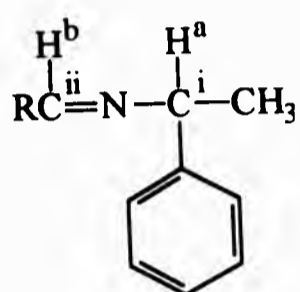


The chemical shift positions of  $\text{H}^a$ ,  $\text{H}^b$ ,  $\text{C}^i$  and  $\text{C}^{ii}$  (Figure 2.8) can be compared within the series of imine precursors **21-26** (Table 2.5). The chemical shift of the quartet assigned to  $\text{H}^a$  varies very little within the series except for *N*-(2'-thienylmethylidene)-1-phenylethylamine **22**, the thiophene derivative, where the quartet is shifted upfield by over 1 ppm. It has been reported<sup>[98]</sup> that 2-substituted-thienyl imines have the potential to delocalise the double bond (see Figure 2.9). The  $\text{C}=\text{N}$  bond has less double bond character so the proton adjacent to the thienyl ring is subjected to less 'deshielding effect' due to the double bond, compared with the other compounds. This effect is also seen with the chemical shift of the signal assigned to  $\text{H}^a$  in the *N*-(2'-thienylmethylidene)-1-diphenylamine **10** (section 2.3.2).

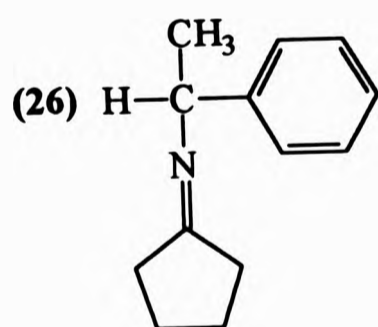
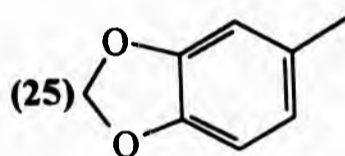
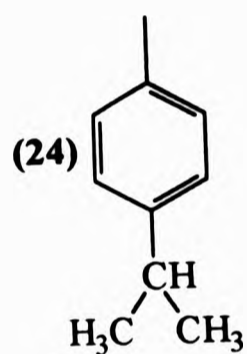
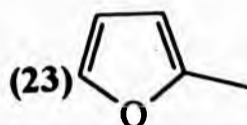
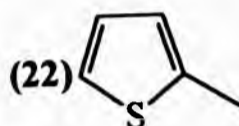
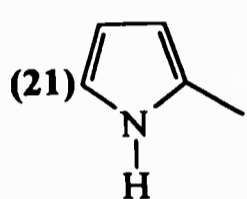
Figure 2.9 Resonance structures of 2-substituted imines



Table 2.5 Imines referred to in Table 2.5



R (for structures 21-25)



**Table 2.5**  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts (ppm) and coupling constants (Hz) for imines 21-26.

Imine	$\delta_{\text{Ha}}$	$^3J_{\text{HaMc}}$	$\delta_{\text{Ci}}$	$\delta_{\text{Hb}}$	$\delta_{\text{Cii}}$
21	4.46	6.68	68.9	8.14	150.8
22	3.00	6.69	69.6	8.10	148.4
23	4.48	6.65	69.6	8.29	159.2
24	4.43	6.64	69.3	8.16	158.4
25	4.38	6.70	68.9	8.24	152.5
26	4.40	6.60	62.0	-	179.1

The proton  $\text{H}^a$  couples to the adjacent methyl protons and the  $^3J_{\text{HH}}$  coupling constants are all very similar for these compounds. The signal assigned to the  $\text{C}^i$  carbon are all very similar within the series except for compound 26 where this signal is upfield compared to the other compounds which have aromatic substituents. The signals assigned to carbon  $\text{C}^{ii}$  are all similar, with the signal in compound 23 and 24 shifted downfield. In compound 26 the  $\text{C}^{ii}$  carbon is a quaternary carbon and therefore resonates downfield.<sup>[94]</sup>

## 2.5 Attempted Preparations of Imines

### 2.5.1 Attempted Imine Preparations using *tert*-Butylamine

The amine *tert*-butylamine and formaldehyde were used by Moedritzer<sup>[36]</sup> in the preparation of aminomethanephosphonic acid (see section 1.2.1 Scheme 1.7). Following this work, reactions were attempted to prepare and isolate imines using this amine with fairly reactive carbonyl compounds (*e.g.* propionaldehyde and 2-furaldehyde). In all cases the  $^1\text{H}$  NMR of the crude reaction mixture showed a mixture of the two starting materials and no trace of any imine.

### 2.5.2 Attempted Imine Preparations using Benzylamine

In an attempt to overcome the possible steric hindrance problem encountered in the reactions of aminodiphenylmethane the use of benzylamine as an alternative was investigated. This amine readily forms imines with carbonyl compounds and has been successfully used to prepare many  $\alpha$ -aminophosphonic acids (see section 1.2.1 Scheme 1.5).<sup>[35]</sup> However, the reactions performed in this study failed to give more than a trace of the desired imines with the ketones menthone and camphor, when refluxed in toluene. The ketones are all of low reactivity and the reactions are too sterically hindered to work to any extent. The steric problem encountered in these reactions seems to lie with the ketones and not the amine.

## CHAPTER THREE

### PHOSPHONATE ESTERS

#### 3.1 Introduction

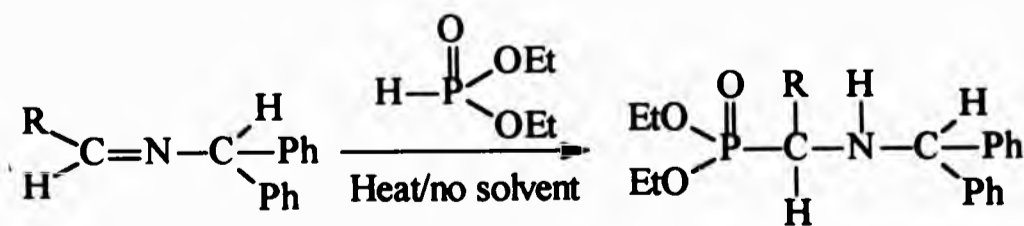
Phosphate esters are widespread in biological systems and have a wide variety of functions. As analogues of phosphate esters, phosphonate esters potentially have very interesting chemical behaviour and biological activity<sup>[99]</sup> e.g. interaction with metallo-enzymes<sup>[100, 101]</sup> and agricultural applications.<sup>[100]</sup>

The present studies were undertaken in order to prepare a range of novel diethyl phosphonate ester and  $\alpha$ -aminophosphonic acids which might have potential as biologically active molecules.

#### 3.2 Preparation of Diethyl Phosphonate Esters

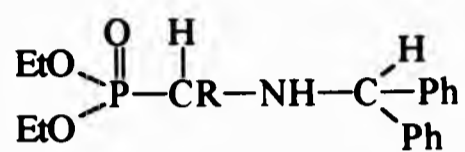
The diethyl phosphonate esters 4-6, 27-34 and 36 (Figure 3.1) were prepared by heating a 1:1 molar ratio of the imine with diethyl phosphite in the absence of solvent (Scheme 3.1). The nucleophilic addition of the diethyl phosphite to the imine bond is slowed greatly when solvent is present.<sup>[98]</sup> The temperature of the reaction was maintained between 90°C and 140°C for the duration of the reaction, which was monitored by <sup>31</sup>P NMR, the desired products giving rise to signals in the range of 21-32 ppm (see Table 3.5).

**Scheme 3.1** Procedure used for the preparation of diethyl phosphonate esters from imine precursors and diethyl phosphite

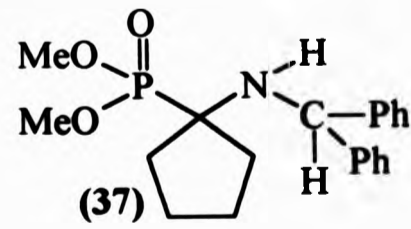
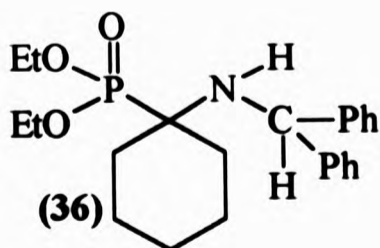
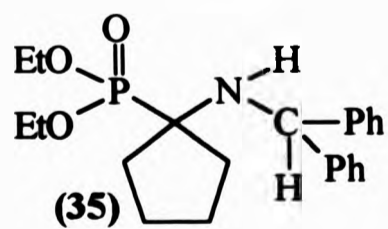
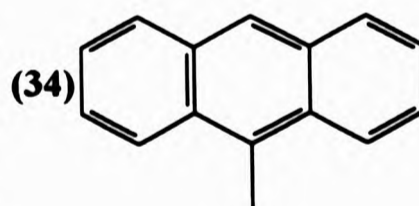
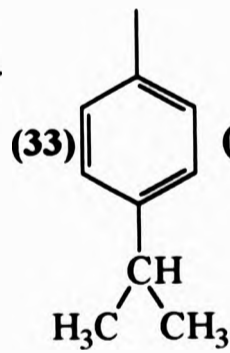
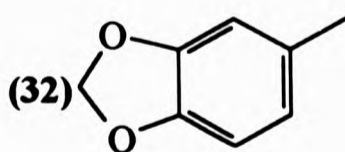
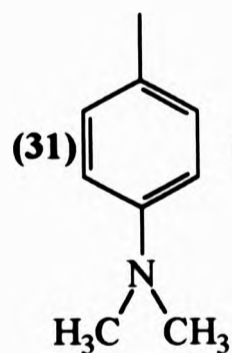
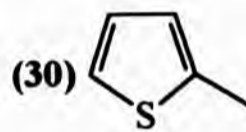
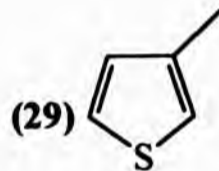
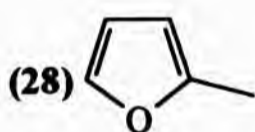
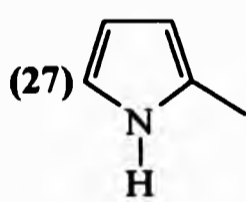
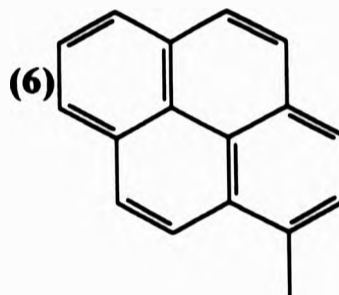
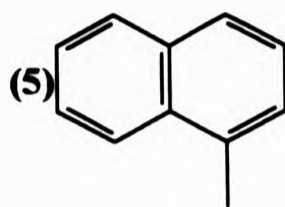
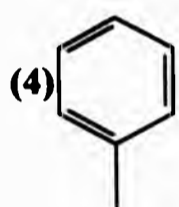




**Figure 3.1** The diethyl phosphonate esters prepared from imine precursors and diethyl phosphite in this work (compound 37 is a dimethyl phosphonate ester prepared from the imine precursor and dimethyl phosphite)



R (for compounds 4-6 and 27-34)



This method of using aminodiphenylmethane with various carbonyl compounds to form imines, followed by the addition of diethyl phosphite, was first used by Issleib who prepared a series of  $\alpha$ -aminoalkanephosphonic acids,<sup>[70]</sup> aminoalkanediphosphonic acids and diaminoalkanediphosphonic acids.<sup>[71]</sup> The method has subsequently been reported by Bawa<sup>[102]</sup> for the preparation of  $\alpha$ -aminopropanephosphonic acid (compound 1) and by Green<sup>[64, 103]</sup> for the preparation of a series of  $\alpha$ -amino-arylmethanephosphonic acids, with various fluoro-, fluoroalkyl-, and fluoroalkoxy-substituents in the aromatic ring. The diethyl phosphonate esters of these reactions were never isolated, but the reactions were carried straight through to the phosphonic acid by acid-hydrolysis.

The reaction conditions (times and temperatures) and yields obtained for the diethyl phosphonate esters are given in Table 3.1.

**Table 3.1** Reaction times and % yields for the preparation of diethyl phosphonate esters for compounds 4-6, 27-34 and 36

Diethyl phosphonate esters	Reaction time <sup>†</sup> (hours)	% Yield (after recrystallisation)
4	5 <sup>‡</sup>	74
5	10	53
6	4 <sup>§</sup>	70
27	3	23
27	6	59
28	6	87
29	6	50
30	8	88
31	6	88
32	6	93
32	24	81
33	4	72
34	8	52
36	3	8

<sup>†</sup> Reaction temperature was maintained between 90-100°C.

<sup>‡</sup> Reaction temperature was maintained between 85-90°C.

<sup>§</sup> Reaction temperature was maintained between 125-140°C.

The temperature required for the synthesis of diethyl 1-(1'-pyrenyl)-1-(diphenylmethyl-amino)methanephosphonate **6** was higher than that of the other reactions because the imine, **17**, involved has a high melting point. When the reaction was carried out at a lower temperature the imine did not melt and thus failed to react with the diethyl phosphite.

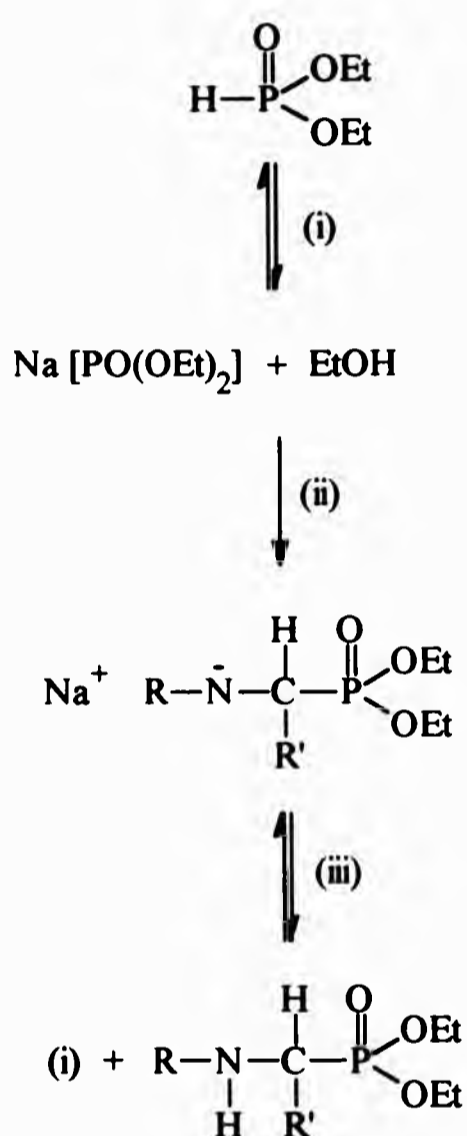
In general, the highest yields were achieved when the imine and diethyl phosphite were reacted without solvent at 100°C for 6 hours. The reactions were monitored by <sup>31</sup>P NMR by the disappearance of the signal due to diethyl phosphite (*ca.* 7.2 ppm) and the appearance of the signal due to phosphonate ester (*ca.* 20-30 ppm). Extended reaction times resulted in the decline of the phosphonate ester signal and increased intensity of another unidentified signal at *ca.* 4 ppm. In view of this, the reactions were never allowed to go to completion. There was usually a residual signal at *ca.* 7 ppm indicating unreacted diethyl phosphite. The product that gave rise to a signal at *ca.* 4 ppm in the <sup>31</sup>P NMR was not identified but was thought to be EtO(O)P(OH)H or a similar structure.<sup>[104, 105]</sup>

A catalyst was not required in these reactions, although there are many examples in the literature of similar reactions using both acid and basic catalysts. For example, sodium alkoxide<sup>[106]</sup> is often used as catalyst in these types of reaction. The proposed mechanism for this base-catalysed reaction is shown in Scheme 3.2.

The use of HCl<sup>[107]</sup> as a catalyst has also been reported. The required reaction time is shown to be reduced by two thirds.<sup>[107]</sup> The Lewis acid AlCl<sub>3</sub>, often used in Friedel-Crafts alkylation reactions, is reported to be a better catalyst<sup>[85, 108]</sup> for this type of reaction than sodium alkoxide.

The acid catalyst presumably works by making the carbon atom of the C=N bond more positive by bonding or co-ordinating to the nitrogen. The carbon atom is then more susceptible to nucleophilic attack from the phosphite.

**Scheme 3.2** Mechanism for the sodium ethoxide catalysed addition of diethyl phosphite to imines



*Reagents:* (i) NaOEt (ii) R'-CH=N-R (iii) EtOH

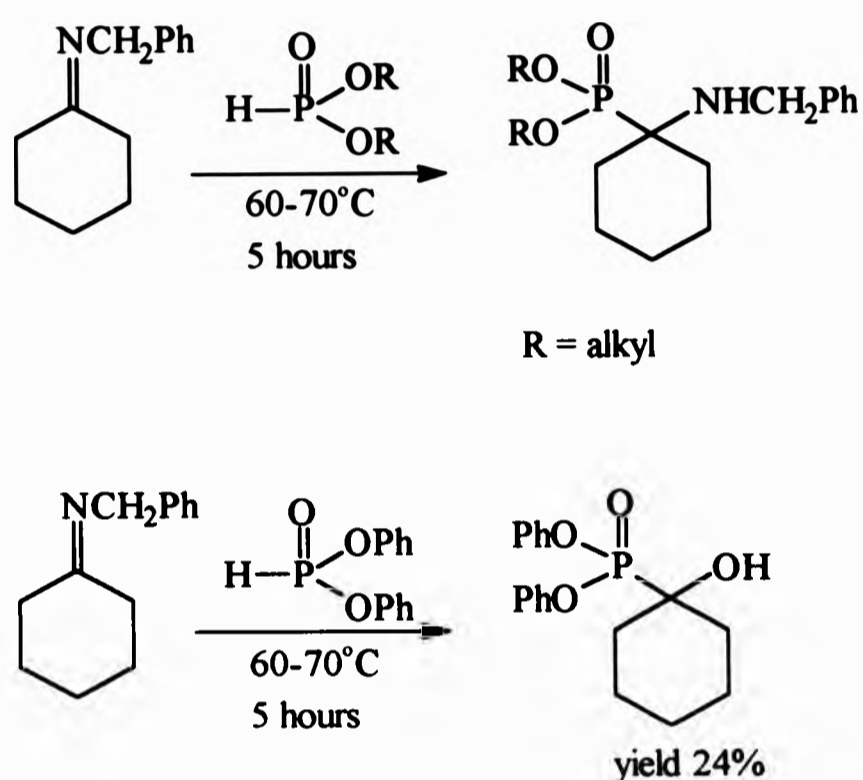
Ultra sound radiation has been reported to promote the reaction, thus reducing the length of time heating is required and therefore giving less by-product.<sup>[98]</sup> In general, it is reported that prolonged heating of the reaction mixture leads to the increased formation of by-products. The use of a catalyst was unnecessary in the reactions of imines 7-17 with diethyl phosphite, but the reactions were carefully monitored by <sup>31</sup>P NMR. It has been reported that the reaction between dialkyl phosphite and an imine with a pyrrole derivative gives rise to a black tar-like material containing many by-products.<sup>[98]</sup> This problem did not occur in the reaction between diethyl phosphite and N-(2'-pyrrolylidene)-1,1-diphenylmethylamine 7. Diethyl 1-(2'-pyrrolyl)-1-(diphenylmethylamino)methanephosphonate 27 was successfully prepared as a crystalline solid in reasonable yield.

Problems were encountered in the reactions of diethyl phosphite with imines **18** and **19**, the cyclopentyl and cyclohexyl derivatives. The appearance of a signal at *ca.* 4 ppm, due to an unidentified product, occurred more rapidly in these reactions. Shorter reaction times were employed to enable the maximum yield of diethyl phosphonate ester to be obtained. The diethyl phosphonate ester **35**, prepared from the imine N-cyclopentylidene-1,1-diphenylmethanamine **18** was not isolated. The <sup>31</sup>P NMR spectrum of this reaction mixture showed 3 signals, at 3.92 ppm, 7.22 ppm (the diethyl phosphite starting material) and a signal at 31.37 ppm which is most likely due to the desired phosphonate ester product **35**, although, without isolating the compound its identity could not be confirmed. The diethyl [1-(diphenylmethanamino)cyclohexyl]phosphonate **36** product was isolated, but only in very low yield.

Alkyl substitution on the nitrogen (compared to hydrogen) reduces the electrophilicity of the C=N bond, reducing the reactivity toward the diethyl phosphite nucleophile.<sup>[109]</sup> The substituent attached to the carbon of the C=N will also affect the reaction, thus an electron withdrawing group will also reduce the reactivity of the C=N bond.<sup>[107]</sup>

The size of the alkyl group on the dialkyl phosphite affects the rate and yield of the reaction, the larger the group the slower the reaction.<sup>[110]</sup> Dimethyl phosphite is more reactive than diethyl phosphite in these reactions. The diethyl phosphonate ester **35** could never be isolated, but the dimethyl phosphonate ester **37** of the analogous reaction was isolated in moderate yield. It is reported that the choice of phosphite can determine the product that is formed (see Scheme 3.3).<sup>[110]</sup> When dialkyl phosphite (alkyl = *n*-C<sub>3</sub>H<sub>7</sub>, *n*-C<sub>4</sub>H<sub>9</sub>, *iso*-C<sub>5</sub>H<sub>11</sub>) is reacted with N-cyclohexylidenebenzylamine the expected dialkyl [1-(benzyl-amino)cyclohexyl]phosphonate product is isolated. Under exactly the same reaction conditions, but reacting diphenyl phosphite instead of a dialkyl phosphite, with N-cyclohexylidenebenzylamine the expected diphenyl dialkyl [1-(benzylamino)cyclohexyl]-phosphonate product is not observed; instead diphenyl 1-hydroxy-1-cyclohexyl phosphonate is the only product obtained.

**Scheme 3.3** Reaction demonstrating the different products resulting from the reaction of N-cyclohexylidenebenzylamine with different di-substituted phosphites

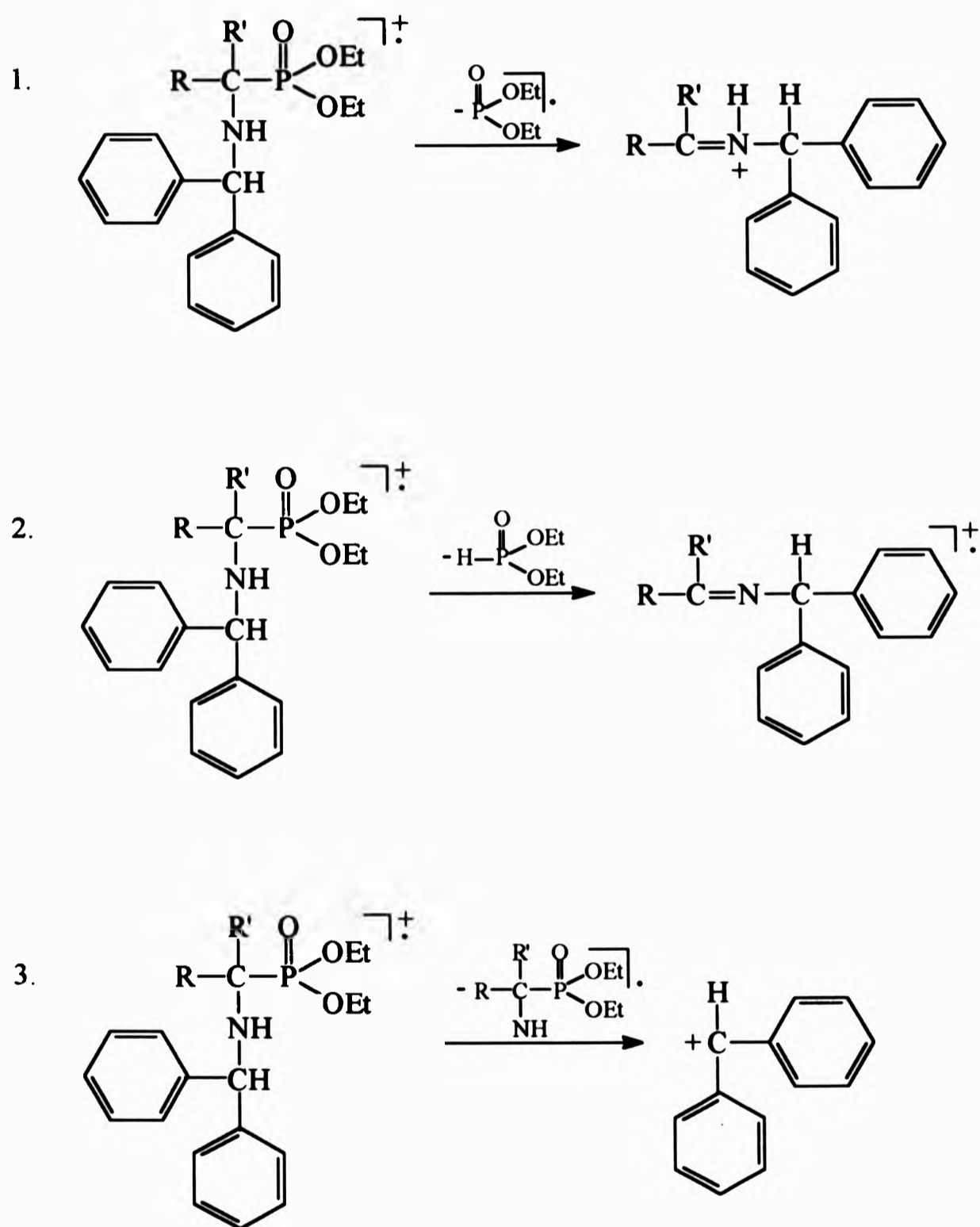


### 3.2.1 Mass Spectrometry of the Diethyl Phosphonate Esters

Mass spectrometry using low resolution EI gave very similar fragmentation patterns within the series of esters 4-6, 27-34 and 36 (Scheme 3.4). The important fragments are shown in Table 3.2.

The molecular ion was identified in all the compounds with a low relative abundance except in compounds 27 and 34 where the abundance was higher. The molecular ion with the loss of  $\text{PO}(\text{OEt})_2$  as a radical is the next identifiable ion in all the compounds except 28 and 32. In its most stable form this ion corresponds to the imine structure protonated at the nitrogen. The molecular ion with the loss of the neutral molecule  $\text{HPO}(\text{OEt})_2$  gave rise to the imine structure as a charged radical and was detected in all the compounds. In all the compounds, except compound 31, the base peak is the benzhydryl ion  $\text{CHPh}_2^+$ .

**Scheme 3.4<sup>†</sup>** Mass spectrometry fragmentation scheme of diethyl phosphonate esters **4-6**, **27-34** and **36**



<sup>†</sup> For compounds **4-6** and **27-34** R' = H; for compound **36** R' = part of the ring system.

**Table 3.2** Values of m/z and relative abundance (%) for the important fragments in the mass spectra of the diethyl phosphonate esters **4-6**, **27-34** and **36**

Compound	M <sup>+</sup>	[M-(EtO) <sub>2</sub> PO] <sup>+</sup>	[M-(EtO) <sub>2</sub> PHO] <sup>+</sup>	<sup>†</sup> CHPh <sub>2</sub> m/z167
<b>4</b>	409, (10)	272, (62)	271, (47)	(100)
<b>5</b>	459, (1)	322, (22)	321, (8)	(100)
<b>6</b>	534, (3)	397, (13)	396, (55)	(100)
<b>27</b>	398, (20)	261, (81)	260, (21)	(100)
<b>28</b>	399, (8)	263, (0)	262, (44)	(100)
<b>29</b>	415, (3)	278, (10)	277, (57)	(100)
<b>30</b>	415, (4)	278, (65)	277, (48)	(100)
<b>31</b>	452, (3)	314, (33)	313, (13)	(67) <sup>†</sup>
<b>32</b>	453, (4)	316, (0)	315, (74)	(100)
<b>33</b>	451, (7)	314, (56)	313, (74)	(100)
<b>34</b>	509, (38)	372, (67)	371, (55)	(100)
<b>36</b>	401, (5)	264, (74)	263, (58)	(100)

<sup>†</sup> Compound **31** has a base peak with m/z 65.



### 3.2.2 NMR Spectroscopy

The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of the diethyl phosphonate esters are complicated by the presence of a chiral  $\alpha$ -carbon atom (except **35** and **36**) a prochiral phosphorus atom. The complications can be explained in terms of the symmetry of the molecules.

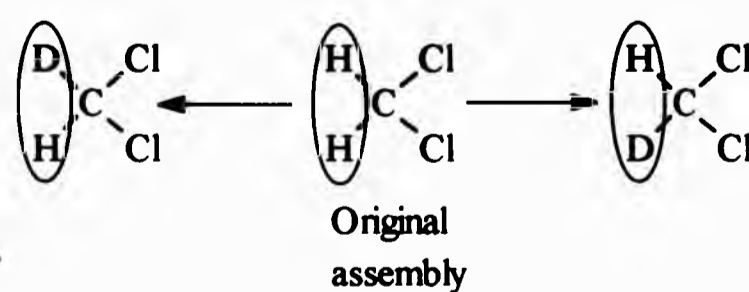
#### 3.2.2.1 Stereoisomeric Relationships of Groups within Molecules

Mislow and Raban<sup>[111]</sup> have shown that the relationship between intramolecular groups can be determined using a substitution test. The test involves the replacement of each of the groups in question with an achiral test group that is not already present in the molecule. The relationship between the resultant structures is examined and the groups can then be classified as homotopic, enantiotopic, or diastereotopic; these classifications are defined in the following sections.

##### Homotopic groups

If the resulting two structures are superimposable, the two groups (the groups in these examples are protons) in question in the original assembly are homotopic. Examples of homotopic groups are the methylene protons in dichloromethane (with the test group deuterium, Figure 3.2). In terms of symmetry in the original assembly, the groups in question can be interchanged by rotation about an axis of rotation possessed by the molecule  $C_n$  ( $n \geq 1$ ) to give a structure identical to the original. There is a  $C_2$  axis of rotation in this example.

**Figure 3.2** Example of the substitution test for homotopic groups



The original assembly is a C-2 centre<sup>[112]</sup> (see Figure 3.3). Homotopic nuclei in NMR spectra are always isochronous. For dichloromethane the methylene protons in the original assembly give rise to a single signal (a singlet) because the protons are isochronous and indistinguishable in the <sup>1</sup>H NMR spectrum.

**Figure 3.3** Examples of stereocentres of the carbon atom

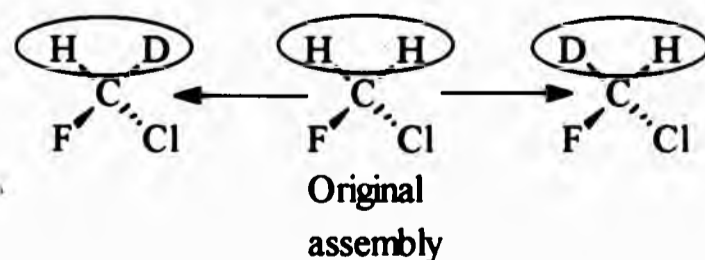


where **1 Chiral Assembly**  
**2 Prochiral Assembly**  
**3 C-2 Assembly**

### Enantiotopic groups

If the resultant structures after the substitution test are enantiomeric then the two groups in question in the original assembly are enantiotopic (enantiomers are stereoisomers which differ only in their ability to rotate plane polarised light in an equal but opposite direction; stereoisomers are compounds whose structure differs only in the three dimensional arrangement of their constituent atoms). An example is provided by the protons in chloro-fluoromethane (Figure 3.4) for which the test group is again deuterium. In the original assembly the groups can be interchanged only by a rotation-reflection operation ( $S_n$ ) and not a rotation alone. There is a mirror plane  $S_1$  (or  $\sigma$ ) in this example.

**Figure 3.4** Example of the substitution test for enantiotopic groups

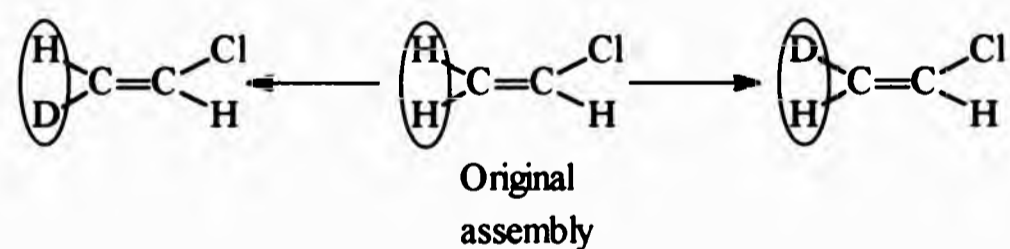


The original assembly with two enantiotopic groups is prochiral (see Figure 3.4). The definition of prochirality, according to Hanson,<sup>[113]</sup> is as follows: 'if a chiral assembly is obtained when a point ligand in a finite nonchiral assembly is replaced by a new point ligand, the original assembly is prochiral' with the term chiral assembly referring to the centre in question and not the whole molecule. Enantiotopic nuclei are isochronous in the NMR spectrum unless a chiral solvent or chiral shift reagent is used; *i.e.* they are indistinguishable in the <sup>1</sup>H NMR spectrum in an achiral environment.

#### Diastereotopic groups

If the resulting structures after the substitution test are diastereomers the two groups in question in the original assembly are diastereotopic (diastereomers are stereoisomers which are not enantiomers). An example is given by the methylene protons in chloroethene (Figure 3.5); the test group is again deuterium. In the original assembly the groups can not be interchanged by any rotation or reflection operation.

Figure 3.5 Example of the substitution test for diastereotopic groups

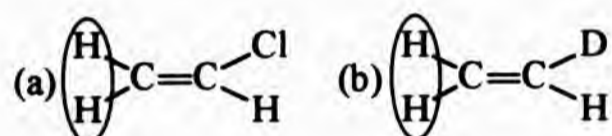


Diastereotopic groups are in principle anisochronous with distinct chemical shifts, but they can coincidentally resonate at the same frequency.

The symmetry rules described above determine whether groups are diastereotopic with respect to each other and therefore give rise to different chemical shifts, but the magnitude of the difference in chemical shift may not be large enough to observe. There are many factors that affect the extent of the non-equivalence. The observed difference in chemical shift can depend on the relative populations of the conformers which the molecules adopt.<sup>[112]</sup> The temperature can affect the magnitude either by changing the actual chemical shifts of the nuclei or by changing the populations of the conformers. The solvent

can also affect the magnitude of the non-equivalence,<sup>[114]</sup> this is especially the case for aromatic solvents which can exert an aromatic solvent induced shift.<sup>[115]</sup> Another factor affecting the magnitude of the chemical shift difference is the nature of the other substituents in the molecule. The greater the difference in size and magnetic anisotropy of the substituents in the molecule the greater the observed non-equivalence is likely to be, *e.g.* in Figure 3.6, the observed non-equivalence of the diastereotopic methylene protons is likely to be greater when the other ligand is chloride, (Figure 3.6 a), rather than if the ligand was deuterium (Figure 3.6 b).

**Figure 3.6** Diastereotopic methylene protons

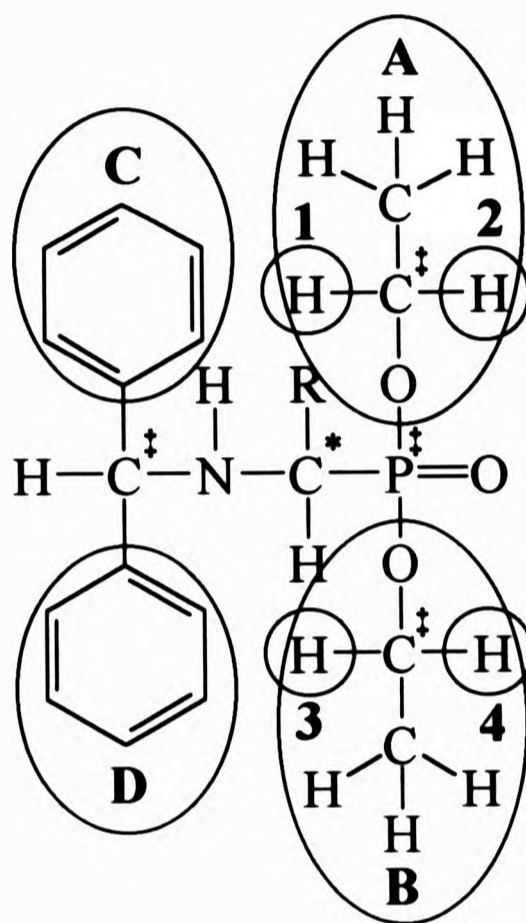


### 3.2.2.2 <sup>1</sup>H and <sup>13</sup>C NMR Spectroscopy of the Diethyl Phosphonate Esters

The two ethoxy groups, A and B, (Figure 3.7) in the diethyl phosphonate esters are anisochronous as a result of the adjacent chiral carbon atom (C\* Figure 3.7). The two phenyl groups labelled C and D are also anisochronous as a result of the chiral carbon atom C\*. The phosphorus atom, P<sup>+</sup>, is prochiral rendering the methylene protons within each ethoxy group anisochronous. The four methylene protons 1, 2, 3 and 4 are all therefore anisochronous due to the effect of the chiral carbon and the prochiral phosphorus.

The <sup>1</sup>H NMR spectra of esters 4-6 and 27-34 (Figure 3.1) show that, although anisochronous, the four methylene protons do not appear as four separate signals; one of the methylene groups appears as two distinct multiplets while the other gives rise to just one multiplet (actually, two overlapping multiplets). The <sup>13</sup>C NMR spectra show a signal for each methylene carbon and a signal for each of the methyl carbons. In each case the signals are doublets due to coupling to phosphorus. The <sup>13</sup>C NMR spectra also show the two phenyl rings to be anisochronous, although this effect is not observed in the <sup>1</sup>H NMR spectrum as the phenyl protons appear as overlapping multiplets (at 250 MHz).

**Figure 3.7** General structure of diethyl phosphonate esters with the stereocentres labelled



- \* denotes chiral atoms
- † denotes prochiral atoms (although only the prochiral P atom is important in the NMR spectra)

The diethyl phosphonate esters **35** and **36** (Figure 3.1) do not possess this chiral carbon atom and therefore give rise to simpler  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. The ethoxy group gives rise to one multiplet assigned to the four methylene protons and one triplet assigned to the two methyl groups in the  $^1\text{H}$  NMR spectrum. The  $^{13}\text{C}$  NMR spectra show one signal for the methylene signals and one signal for the methyl groups and the two phenyl rings are isochronous.

The  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{31}\text{P}$  NMR spectra of the diethyl phosphonate esters **4-6**, **27-34** and **36** were obtained in  $\text{CDCl}_3$  solution (*ca.* 7% w/w). First order analyses of the spectra were carried out, and the results (chemical shifts and coupling constants) are given in Appendix III. Chemical shifts and coupling constants<sup>†</sup> in compounds **4-6**, **27-34** and **36** are given in Tables 3.3 to 3.9.

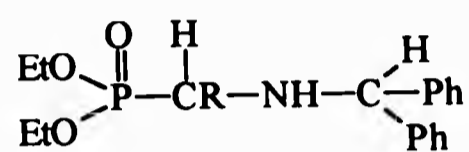
<sup>†</sup> Signs for the coupling constants were not determined.

In the  $^1\text{H}$  NMR spectra of compounds 4-6 and 27-34, one of the methylene groups gives rise to two separate multiplets and the other gives rise to one multiplet. There are two separate triplets assigned to the methyl protons. The methyl and methylene spectral data are given in Tables 3.3 and 3.4. From the evidence gained in the *X*-ray crystallographic analysis of compounds 4-6, 27, 32 and 34, (performed by Thomas Woodroffe section 3.2.3), it can be seen that, in the solid state, one ethoxy group lies over the R substituent and the other lies nearer to the diphenylmethane group. The aromatic substituents, especially in the series of compounds 4-6 and 34, were introduced to investigate this effect on the magnitude of the 'non-equivalence' of the ethoxy groups in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. A more detailed analysis and discussion of the  $^1\text{H}$  NMR spectra of compounds 4-6 is given in section 3.3.

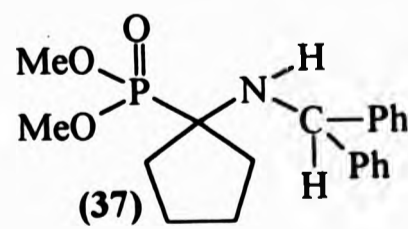
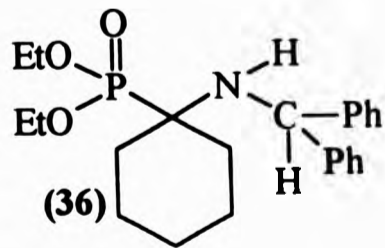
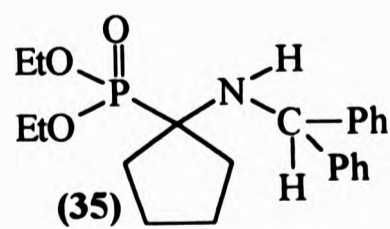
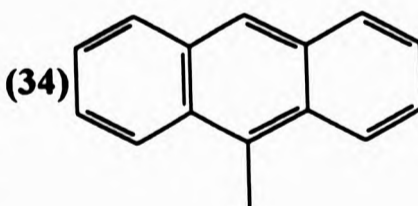
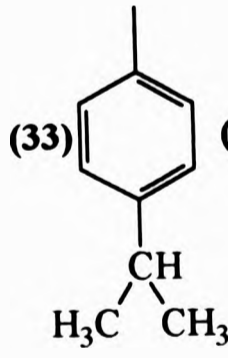
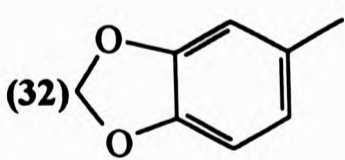
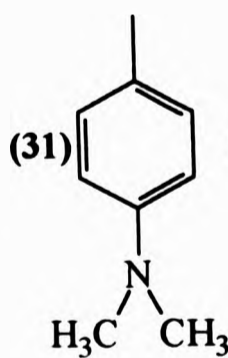
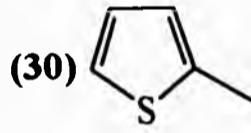
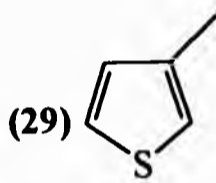
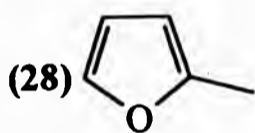
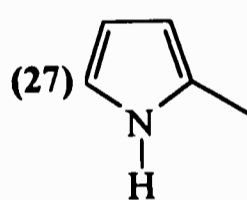
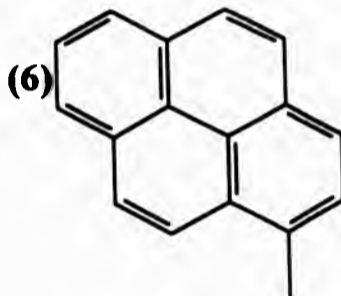
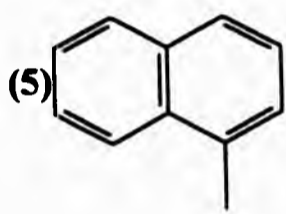
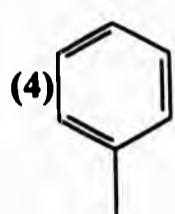
The chemical shift differences between the signals assigned to protons of the two methyl groups and differences between signals assigned to protons of the two methylene groups within a molecule are given in Table 3.3. The largest difference between the two signals for the methyl protons was seen in compound 34, the anthryl derivative, followed by compounds 6 and 5, the pyrene and naphthyl derivatives. The difference between the two methyl signals in compound 4, the phenyl derivative, is similar to the difference observed in the other compounds. The difference in the signal positions for the two methylene groups follows a similar trend with the largest difference seen in compounds 34, 6 and 5.

Considering the actual chemical shift values (see Table 3.4), it appears that protons of one of the methyl group protons are shifted upfield (by ring current effects). There is a wide variation in the chemical shift position of this group of protons. However, the downfield methyl group protons all give rise to signals that fall into a very narrow range 1.33-1.38 ppm, the only exception being compound 33 which is out of this range at 1.25 ppm.

Tables 3.3-3.9 Diethyl phosphonate esters referred to in Tables 3.3 to 3.9



R (for compounds 4-6 and 27-34)



**Table 3.3** Differences in  $^1\text{H}$  NMR chemical shift (ppm) of signals assigned to the two methyl group protons and the two methylene group protons for compounds 4-6 and 27-34

Compound	difference between methyl group signals	difference between methylene group signals <sup>†</sup>
4	0.28	0.40
5	0.60	0.68
6	0.63	0.72
27	0.32	0.51
28	0.21	0.27
29	0.25	0.34
30	0.20	0.27
31	0.28	0.43
32	0.23	0.27
33	0.24	0.37
34	0.73	0.73

<sup>†</sup> The difference between the methylene signals was measured by taking the mean between the centres of the two multiplets and then taking the mean of this value and the centre of the other methylene signal (just one multiplet for the two protons).

A four bond coupling between the methyl protons and the phosphorus atom is seen in compounds 4, 29 and 32; the magnitude of this coupling is 0.57, 0.47 and 0.43, respectively (see Table 3.4). The maximum magnitude for  $^4J_{\text{HH}}$  coupling is obtained when the protons in question adopt a 'W' configuration.<sup>[116]</sup> There is evidence that like the  $^4J_{\text{HH}}$  couplings  $^4J_{\text{PH}}$  couplings are also maximised when the proton and phosphorus atom adopt a 'W' arrangement.<sup>[117]</sup> It is possible that only in compounds 4, 29 and 32 do the methyl protons and phosphorus atoms can arrange themselves into a 'W' type arrangement. The three bond couplings between each of the methylene protons and the phosphorus atom cannot be determined from 'hand' analysis because the multiplets due to the methylene protons are too complex.



**Table 3.4** <sup>1</sup>H NMR chemical shifts (ppm) and coupling constants (Hz) of the methyl and methylene groups for compounds **4-6**, **27-34** and **36**

Compound	Methyl group	Methyl group	CH of CH <sub>2</sub>	CH of CH <sub>2</sub>	CH <sub>2</sub>
<b>4</b> <sup>†</sup>	1.07, <sup>3</sup> J <sub>HH</sub> 7.06, <sup>4</sup> J <sub>PH</sub> 0.57	1.36, <sup>3</sup> J <sub>HH</sub> 7.07, <sup>4</sup> J <sub>PH</sub> 0.56	3.62-3.78	3.83-3.99	4.12-4.29
<b>5</b> <sup>†</sup>	0.76, <sup>3</sup> J <sub>HH</sub> 7.06	1.36, <sup>3</sup> J <sub>HH</sub> 7.06	3.34-3.43	3.70-3.79	4.14-4.35
<b>6</b> <sup>†</sup>	0.75, <sup>3</sup> J <sub>HH</sub> 7.05	1.38, <sup>3</sup> J <sub>HH</sub> 7.04	3.35-3.45	3.67-3.80	4.18-4.39
<b>27</b>	1.01, <sup>3</sup> J <sub>HH</sub> 6.96	1.33, <sup>3</sup> J <sub>HH</sub> 7.06	3.41-3.51	3.67-3.76	4.00-4.21
<b>28</b>	1.15, <sup>3</sup> J <sub>HH</sub> 6.97	1.36, <sup>3</sup> J <sub>HH</sub> 7.19	3.80-4.00	4.01-4.09	4.17-4.33
<b>29</b>	1.11, <sup>3</sup> J <sub>HH</sub> 7.05, <sup>4</sup> J <sub>PH</sub> 0.47	1.36, <sup>3</sup> J <sub>HH</sub> 7.05, <sup>4</sup> J <sub>PH</sub> 0.46	3.69-3.84	3.88-4.03	4.10-4.33
<b>30</b>	1.15, <sup>3</sup> J <sub>HH</sub> 7.01	1.35, <sup>3</sup> J <sub>HH</sub> 7.12	3.80-3.93	3.97-4.09	4.13-4.30
<b>31</b>	1.07, <sup>3</sup> J <sub>HH</sub> 7.11	1.35, <sup>3</sup> J <sub>HH</sub> 7.05	3.62-3.75	3.85-3.95	4.14-4.29
<b>32</b>	1.12, <sup>3</sup> J <sub>HH</sub> 7.03, <sup>4</sup> J <sub>PH</sub> 0.43	1.35, <sup>3</sup> J <sub>HH</sub> 6.98, <sup>4</sup> J <sub>PH</sub> 0.43	3.76-3.90	3.93-4.14	4.19-4.23
<b>33</b>	1.01, <sup>3</sup> J <sub>HH</sub> 7.07	1.25, <sup>3</sup> J <sub>HH</sub> 7.01	3.61-3.77	3.82-3.97	4.07-4.27
<b>34</b>	0.62, <sup>3</sup> J <sub>HH</sub> 7.10	1.35, <sup>3</sup> J <sub>HH</sub> 7.12	3.27-3.37	3.61-3.71	4.12-4.31
<b>36</b>	1.17, <sup>3</sup> J <sub>HH</sub> 7.09	-	3.99	-	-

<sup>†</sup> The values given here are not exactly the same as the values given in the full analysis of these compounds (section 3.3) because the spectra were obtained at different concentrations and the parameters in this table were obtained by first order hand analysis.

The chemical shifts of the signals assigned to the methyl and methylene carbon atoms (see Table 3.5 and 3.6) show a similar pattern to that seen for the protons. The largest difference in the methyl signals is seen in the compounds **34**, **5** and **6** and the difference is smallest in the phenyl compound **4**. The difference in the methylene signals are all quite similar with an unexpectedly small difference in the signals of compound **34**, the anthryl derivative.

A three bond coupling (in the range 5.6-6.9 Hz) between phosphorus and the methyl carbon is observed in all the compounds (see Table 3.6). A two bond coupling (in the range 6.7-8.2 Hz) between the phosphorus atom and the methylene carbon is also seen in all the compounds.

**Table 3.5** Differences in  $^{13}\text{C}$  NMR chemical shift of signals assigned to the two methyl groups protons and the two methylene group protons (ppm) for compounds **4-6** and **27-34**

Compound	difference between methyl group signals	difference between methylene group signals
<b>4</b>	0.15	0.38
<b>5</b>	0.70	0.44
<b>6</b>	0.62	0.52
<b>27</b>	0.42	0.39
<b>28</b>	0.27	0.34
<b>29</b>	0.34	0.41
<b>30</b>	0.29	0.35
<b>31</b>	0.31	0.26
<b>32</b>	0.29	0.37
<b>33</b>	0.42	0.35
<b>34</b>	0.78	0.14

**Table 3.6**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) of the methyl and methylene groups for compounds **4-6**, **27-34** and **36**

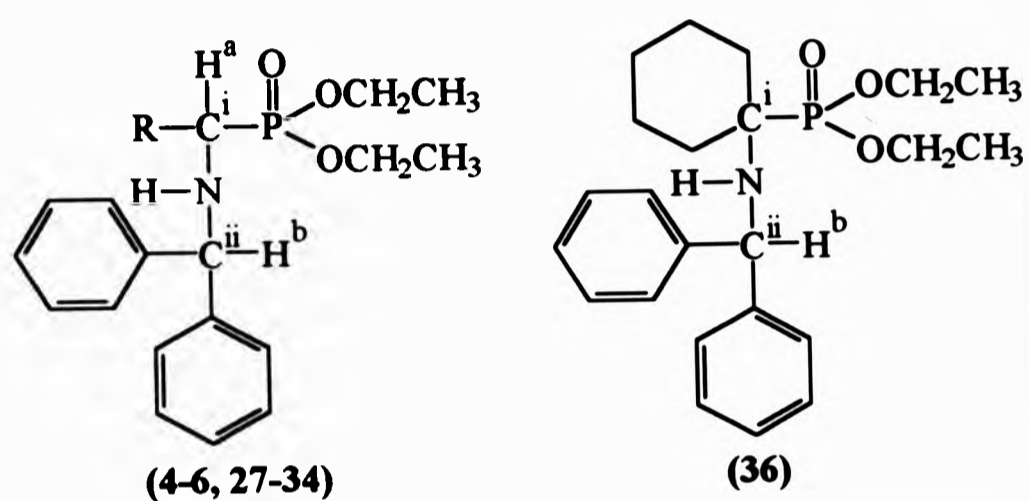
Compound	Methyl group	Methyl group	CH <sub>2</sub>	CH <sub>2</sub>
<b>4</b>	16.14, $^3J_{\text{PC}}$ 6.23	16.29, $^3J_{\text{PC}}$ 6.29	62.59, $^2J_{\text{PC}}$ 6.92	62.97, $^2J_{\text{PC}}$ 7.23
<b>5</b>	15.73, $^3J_{\text{PC}}$ 5.85	16.43, $^3J_{\text{PC}}$ 6.10	62.46, $^2J_{\text{PC}}$ 6.98	62.90, $^2J_{\text{PC}}$ 6.92
<b>6</b>	16.15, $^3J_{\text{PC}}$ 5.66	16.77, $^3J_{\text{PC}}$ 5.91	62.83, $^2J_{\text{PC}}$ 6.79	63.35, $^2J_{\text{PC}}$ 6.78
<b>27</b>	16.14, $^3J_{\text{PC}}$ 6.89	16.56, $^3J_{\text{PC}}$ 6.16	62.68, $^2J_{\text{PC}}$ 6.79	63.07, $^2J_{\text{PC}}$ 6.79
<b>28</b>	16.28, $^3J_{\text{PC}}$ 5.85	16.55, $^3J_{\text{PC}}$ 6.35	62.19, $^2J_{\text{PC}}$ 6.86	62.53, $^2J_{\text{PC}}$ 6.79
<b>29</b>	16.35, $^3J_{\text{PC}}$ 6.14	16.69, $^3J_{\text{PC}}$ 5.82	62.79, $^2J_{\text{PC}}$ 6.82	63.20, $^2J_{\text{PC}}$ 6.84
<b>30</b>	16.26, $^3J_{\text{PC}}$ 6.23	16.55, $^3J_{\text{PC}}$ 6.23	62.96, $^2J_{\text{PC}}$ 6.73	63.31, $^2J_{\text{PC}}$ 6.98
<b>31</b>	16.26, $^3J_{\text{PC}}$ 5.79	16.57, $^3J_{\text{PC}}$ 5.91	62.54, $^2J_{\text{PC}}$ 6.86	62.80, $^2J_{\text{PC}}$ 6.86
<b>32</b>	16.28, $^3J_{\text{PC}}$ 5.97	16.57, $^3J_{\text{PC}}$ 5.85	62.65, $^2J_{\text{PC}}$ 7.25	63.02, $^2J_{\text{PC}}$ 7.33
<b>33</b>	16.42, $^3J_{\text{PC}}$ 5.84	16.84, $^3J_{\text{PC}}$ 5.99	62.86, $^2J_{\text{PC}}$ 6.37	63.21, $^2J_{\text{PC}}$ 7.20
<b>34</b>	15.90, $^3J_{\text{PC}}$ 5.72	16.68, $^3J_{\text{PC}}$ 5.98	62.64, $^2J_{\text{PC}}$ 6.98	62.78, $^2J_{\text{PC}}$ 7.42
<b>36</b>	16.51, $^3J_{\text{PC}}$ 5.60		61.64, $^2J_{\text{PC}}$ 8.18	

The chemical shifts and coupling constants for H<sup>a</sup> and H<sup>b</sup> are given in Table 3.7 and the labels for the protons and carbon atoms are given in Figure 3.8. The chemical shift of the signal assigned to H<sup>a</sup> varies slightly more within the series of compounds than the chemical shift of the signal assigned to H<sup>b</sup>, as might be expected, since H<sup>a</sup> is closer to the point of substitution. The signals assigned to the H<sup>a</sup> are shifted downfield in some compounds; this can be attributed to a combination of the shielding effects of the R substituent and aromatic ring current effects of the R substituent and/or the phenyl rings in the diphenylmethane unit. The signals assigned to H<sup>a</sup> in compounds 6 and 34, which have the largest aromatic substituents, are shifted the most downfield. There was not the same degree of variation in the chemical shift positions for the signal assigned to H<sup>b</sup>, except in compound 36 where the signal is shifted downfield compared to the other compounds.

There is evidence of a dihedral angular relationship for  $^2J_{PH}$  coupling constants in four co-ordinate phosphorus compounds.<sup>[118]</sup> The coupling constant for  $^2J_{HbP}$  varies very little between the compounds except in compound 34 which has a significantly larger coupling and 32 which has a slightly smaller coupling, perhaps as a result of dihedral angular dependence.

A four bond coupling  $^4J_{PCNCH}$  of 1.13 Hz and 2.67 Hz is observed in compounds 4 and 36 respectively. This coupling is not observed in any of the other compounds in the series. It is possible that only in these compounds (4 and 36) are the phosphorus and H<sup>b</sup> atoms able to arrange themselves in a 'W' type arrangement.

**Figure 3.8** Labelling scheme for selected protons and carbon in compounds 4-6, 27-34 and 36



**Table 3.7** Selected  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for compounds 4-6, 27-34 and 36

Compound	$\delta_{\text{Ha}}$	$^2J_{\text{PHa}}$	$\delta_{\text{Hb}}$
4	3.93	22.47	4.68 <sup>†</sup>
5	4.86	23.01	4.65
6	5.41	22.80 <sup>‡</sup>	4.61
27	3.94	22.52	4.81
28	4.04	23.73	4.74
29	4.05	22.01	4.74
30	4.21	22.40	4.86
31	3.83	22.05	4.72
32	3.84	20.07	4.70
33	3.91	22.01	4.71
34	5.62	26.78	4.41
36	-	-	5.53 <sup>§</sup>

<sup>†</sup> Doublet  $^4J_{\text{PHb}}$  1.13.

<sup>‡</sup> Doublet of doublets; the coupling of this proton to the NH proton ( $^3J_{\text{HH}}$ ) is insufficiently well resolved to allow measurement.

<sup>§</sup> Doublet  $^4J_{\text{PHb}}$  2.67.

Aromatic ring current effects produced by the aromatic R substituents and the two phenyl rings can also play a part in shifting the signals up and down field depending on their position. Although aromatic ring current effects occur in both  $^1\text{H}$  and  $^{13}\text{C}$  NMR<sup>[119-123]</sup> spectra, the effects are more noticeable in the  $^1\text{H}$  NMR spectrum because it has a smaller chemical shift range (*ca.* 10 ppm) compared to that in the  $^{13}\text{C}$  NMR spectrum (*ca.* 200 ppm). The chemical shifts and coupling constants for the signals assigned to  $\text{C}^{\text{i}}$  and  $\text{C}^{\text{ii}}$  are given in Table 3.8. The signal assigned to  $\text{C}^{\text{i}}$  is a doublet with a large one bond coupling to the phosphorus atom. The carbon  $\text{C}^{\text{i}}$  is the point of substitution for the R group so the largest variation in chemical shift position due to the effects of the R substituent are expected to be seen here. The signal assigned to  $\text{C}^{\text{ii}}$  is a doublet in all the compounds with a three bond coupling to the phosphorus atom, except compound 36 where the signal is a singlet. The variation in the chemical shift position in the signal assigned to  $\text{C}^{\text{ii}}$  is small.

**Table 3.8** Selected  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for compounds 4-6, 27-34 and 36

Compound	$\delta_{\text{Ci}}$	$^1J_{\text{PC}}$	$\delta_{\text{Cii}}$	$^3J_{\text{PC}}$
4	57.99 <sup>†</sup>	155.3	63.56	17.04
5	52.05 <sup>†</sup>	155.0	63.76	16.67
6	52.95	158.4	64.09	16.98
27	51.53	161.8	63.87	17.17
28	52.02	163.0	64.47	16.29
29	53.74	157.9	64.05	16.35
30	53.45	130.5	63.79	15.79
31	57.22	157.4	63.35	17.23
32	57.69	156.7	63.56	16.86
33	57.75	155.6	63.89	17.05
34	53.84	157.3	64.53	15.41
36	58.60	138.1	61.20 <sup>‡</sup>	-

<sup>†</sup> These signals are broad doublets.

<sup>‡</sup> This signal is a singlet.

In tetra co-ordinate phosphorus compounds the  $^1J_{PC}$  coupling constant is dependent on the percentage of s character in the P-C bond. The Fermi contact mechanism is known to be important because coupling is transmitted better through  $\sigma$  bonds rich in s character.<sup>[124]</sup> Phosphonic acids and their derivatives have large  $^1J_{PC}$  constants (in the range 130-220 Hz<sup>[125]</sup>), which are extremely sensitive to  $\alpha$ -substituent effects.<sup>[126, 127]</sup> The  $^1J_{PC}$  coupling constant for compounds 4-6, 27-34 and 36 are given in Table 3.8. The  $^1J_{PC}$  values are fairly similar for most of the compounds (in the range 155-163 Hz); compounds 30 and 36 have significantly smaller coupling constants of 130.5 and 138.1 Hz, respectively.

The  $^{31}P$  NMR spectra of the compounds 4-6 and 27-37 show one signal, a singlet, in the range 21-34 ppm (see Table 3.9). It is known that there is no simple correlation between  $\delta_P$  and electronegativity of the substituents. The chemical shift position is a function of a combination of effects including substituent electronegativity,  $p\pi-d\pi$ -bonding and the  $\sigma$ -bond angles about the phosphorus atom.<sup>[128]</sup> Structural correlations of  $\delta_P$  are known to be valid only for structurally very similar compounds. In phosphate diesters it has been observed that a decrease in the O-P-O bond angle results in the deshielding of the phosphorus atom and a downfield shift in  $\delta_P$ .<sup>[128]</sup> In a series of dialkyl 1-(N,N-dialkylamino)alkanephosphonates it was observed<sup>[129]</sup> that an increase in the alkane chain length resulted in a deshielding of the phosphorus atom. This increase in alkane chain length was viewed as an increase in the steric bulk at the  $\alpha$ -carbon position, leading in turn to a change in the hybridisation of the phosphorus and thence resulting in deshielding.<sup>[129]</sup> The same trend is apparent in this series of compounds in as much as the most bulky substituent at the  $\alpha$ -carbon position must be the cyclo-alkane substituents in compounds 35-37. The phosphorus chemical shift in these compounds is significantly downfield compared to the other compounds. However, no other obvious correlation is apparent between  $\delta_P$  and the structures of compounds 3-6 and 27-34.

**Table 3.9**  $^{31}\text{P}$  chemical shifts (ppm) for compounds 3-6 and 27-37 for  $\text{CDCl}_3$

Compound	$\delta_{\text{P}}$
3 <sup>†</sup>	22.45
4	23.70
5	23.90
6	23.74
27	23.96
28	21.00
29	23.18
30	23.93
31	25.12
32	23.67
33	24.63
34	25.60
35 <sup>‡</sup>	31.37
36	30.90
37 <sup>§</sup>	33.67

- <sup>†</sup> Diethyl  $\alpha$ -hydroxyphosphonate.  
<sup>‡</sup> This compound was not isolated.  
<sup>§</sup> Dimethyl phosphonate ester.



### 3.2.3 X-Ray Crystallography of Selected Diethyl Phosphonate Esters

Single-crystal X-ray analysis was carried out on selected diethyl phosphonate esters, prepared in this work, by Thomas Woodroffe at the University of North London. X-ray analysis was carried out on compounds **4-6**, **27**, **32** and **34** (see Figure 3.1) and diethyl 1-hydroxy-4'-isopropylbenzylphosphonate **3** (see Figure 1.2).

The X-ray analyses confirmed the proposed formulation for each compound. The crystal data for each compound are given in Table 3.10. In compounds **4-6**, **27**, **32** and **34** there is a common P-C-N backbone to the structures. The phosphorus atom is bonded to a phosphoryl oxygen atom and two ethoxy ester groups. The geometry about the phosphorus atom in the compounds **4-6**, **27**, **32** and **34** is discussed in section 3.2.3.1. The carbon atom, adjacent to the phosphorus atom, is a chiral centre and is bonded to a hydrogen, a nitrogen atom and a carbon bonded aromatic substituent. It is the aromatic substituent that varies throughout the series of compounds. The nitrogen atom is bonded to a hydrogen and a diphenylmethane unit. In the solid state the nitrogen can be considered chiral as it is bonded to three different substituents, with the lone pair of electrons in the fourth site. Compounds with two chiral centres give rise to four possible isomers, *RR*, *SS* (*meso* isomers) and *RS*, *SR* (*rac* isomers).<sup>[130]</sup>

There are two molecules in the asymmetric unit for compounds **4** and **27**, whereas in all the other compounds **5**, **6**, **32** and **34** there is just one. The structures are shown in Figures 3.9-3.24.

Table 3.10 Crystal data<sup>†</sup> for the X-ray analysis of compounds 3-6, 27, 32 and 34

Compound	3	4	5	6	27	32	34
formula	C <sub>14</sub> H <sub>23</sub> O <sub>4</sub> P	C <sub>24</sub> H <sub>28</sub> NO <sub>3</sub> P	C <sub>28</sub> H <sub>30</sub> NO <sub>3</sub> P	C <sub>34</sub> H <sub>32</sub> NO <sub>3</sub> P	C <sub>22</sub> H <sub>27</sub> N <sub>2</sub> O <sub>3</sub> P	C <sub>25</sub> H <sub>28</sub> NO <sub>3</sub> P	C <sub>32</sub> H <sub>32</sub> NO <sub>3</sub> P
<i>M</i> <sup>f</sup>	286.29	409.44	459.50	533.58	398.43	453.45	509.56
crystal system	monoclinic	trigonal	monoclinic	triclinic	triclinic	monoclinic	monoclinic
space group	<i>P</i> <sub>2<sub>1</sub>/n</sub>	<i>P</i> <sub>3<sub>1</sub></sub>	<i>P</i> <sub>2<sub>1</sub>/c</sub>	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> <sub>2<sub>1</sub>/n</sub>	<i>C</i> <sub>2</sub>
<i>a</i> <sup>§</sup>	14.542(2)	17.8895(7)	9.4206(12)	9.3089(4)	11.101(3)	9.354(2)	10.930(1)
<i>b</i>	5.5798(7)	17.8895(7)	18.022(2)	12.0248(5)	20.498(4)	15.642(3)	15.538(2)
<i>c</i>	20.241(4)	12.4553(5)	15.222(2)	13.1977(4)	10.298(3)	16.233(3)	16.196(2)
<i>a</i> <sup>#</sup>	90	90	90	98.689(3)	103.36(3)	90	90
<i>β</i>	101.342(6)	90	107.873(7)	105.422(4)	95.59(2)	97.99(2)	92.892(8)
<i>γ</i>	90	120	90	96.61(4)	102.35(3)	90	90
<i>U</i> <sup>††</sup>	1610.2(4)	3452.1(2)	2459.6(5)	1388.9(9)	2200.5(10)	2352.1(8)	2747.1(5)
<i>Z</i> <sup>‡‡</sup>	4	6	4	2	4	4	4
<i>D</i> <sup>§§</sup>	1.181	1.818	1.241	1.276	1.203	1.281	1.232
radiation, λ <sup>##</sup>	0.7107	1.5418	1.5418	1.5418	0.7107	0.7107	0.7107

<sup>†</sup> Esd's are given in parentheses.

<sup>‡</sup> Molecular weight (g)

<sup>§</sup> Unit cell dimensions (Å)

<sup>#</sup> Unit cell dimensions (°)

<sup>††</sup> Volume (Å<sup>3</sup>)

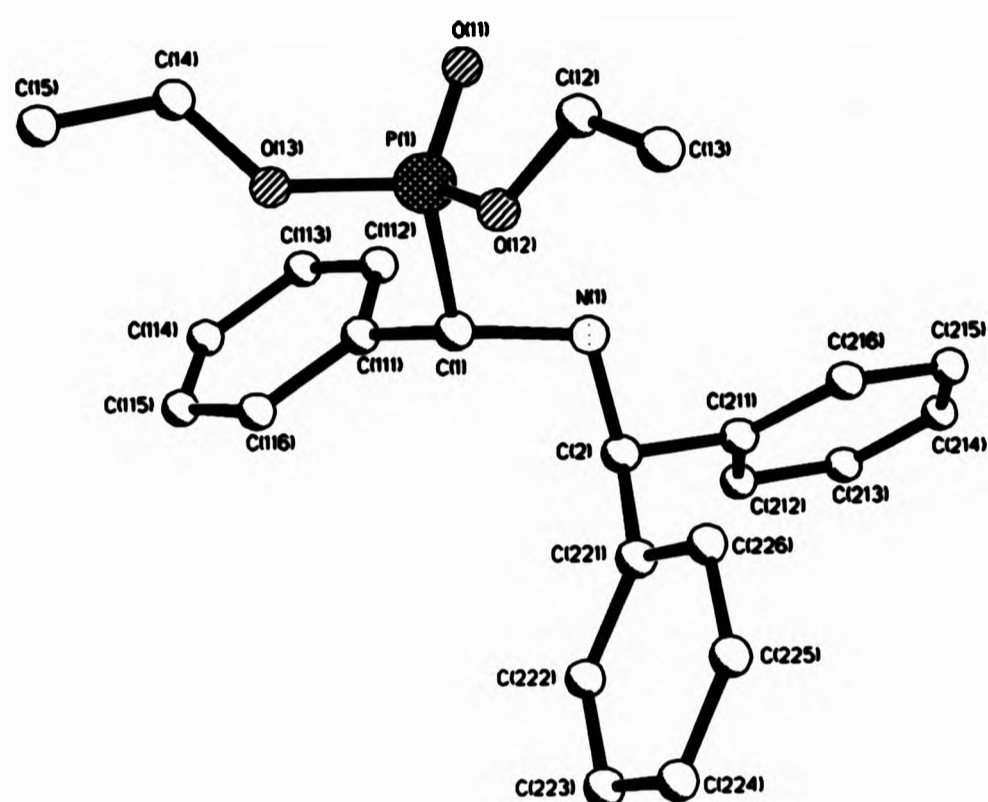
<sup>‡‡</sup> Molecules per unit cell

<sup>§§</sup> Calculated density (g/cm<sup>3</sup>)

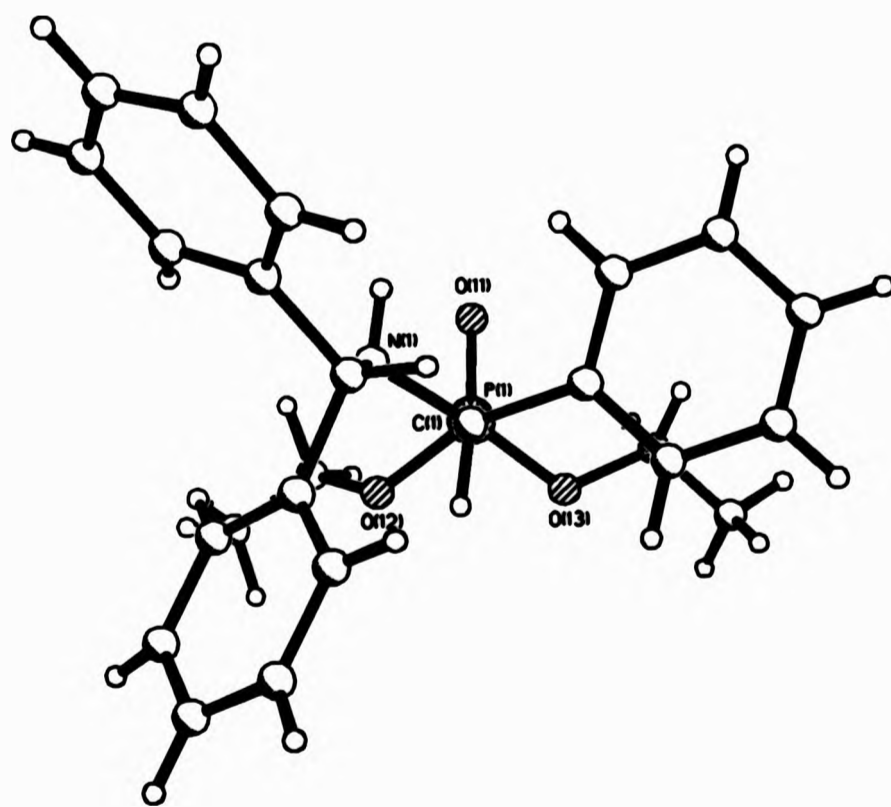
<sup>##</sup> Radiation wavelength Mo-Kα (λ = 0.7107 Å) and

Cu-Kα (λ = 1.5418 Å)

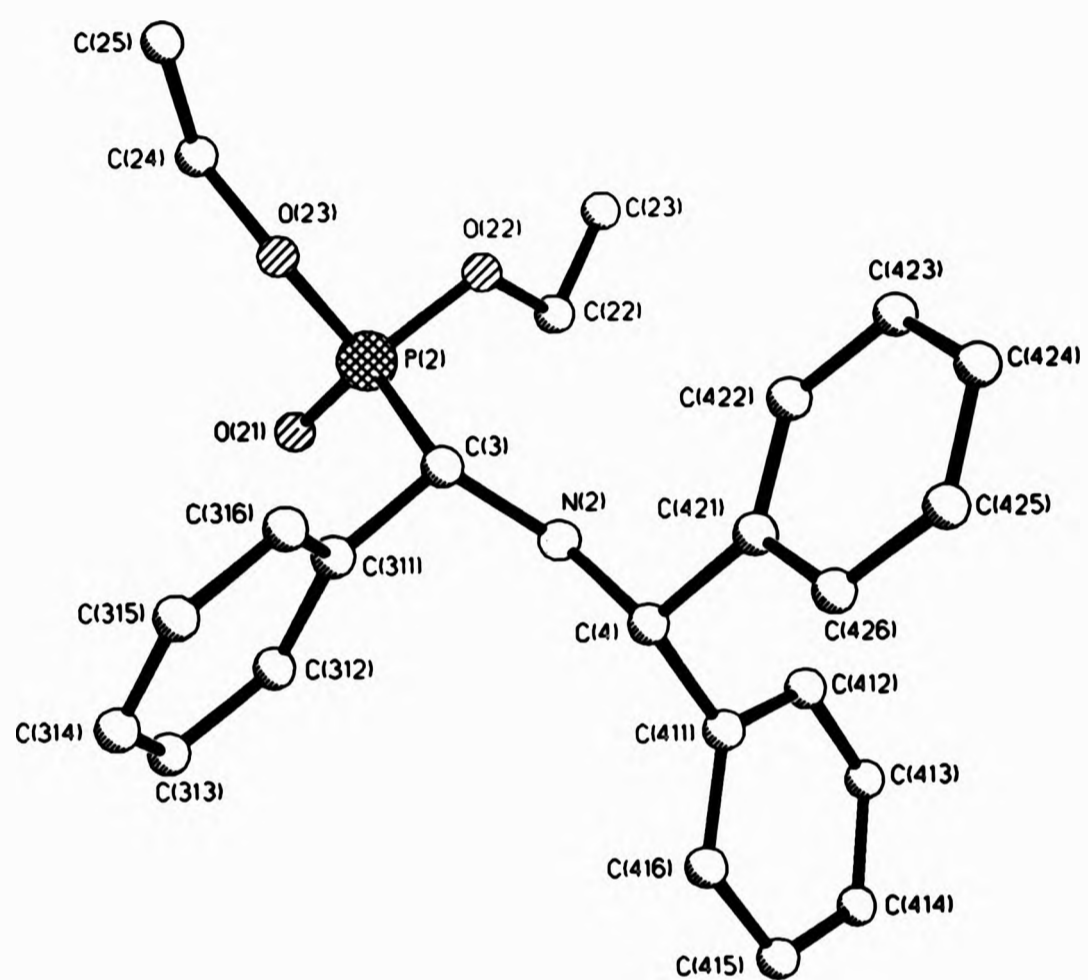
**Figure 3.9** X-ray structure of Compound 4, molecule I (the configurations at the chiral carbon atom and the nitrogen atom are *R*)



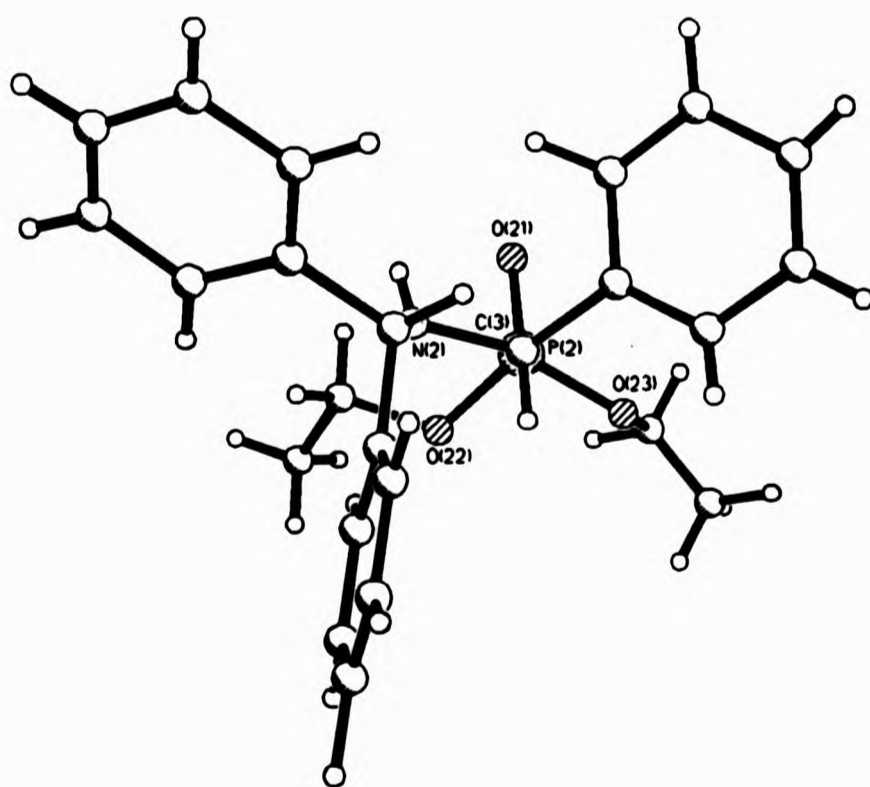
**Figure 3.10** X-ray structure of Compound 4, molecule I, view down the C-P bond



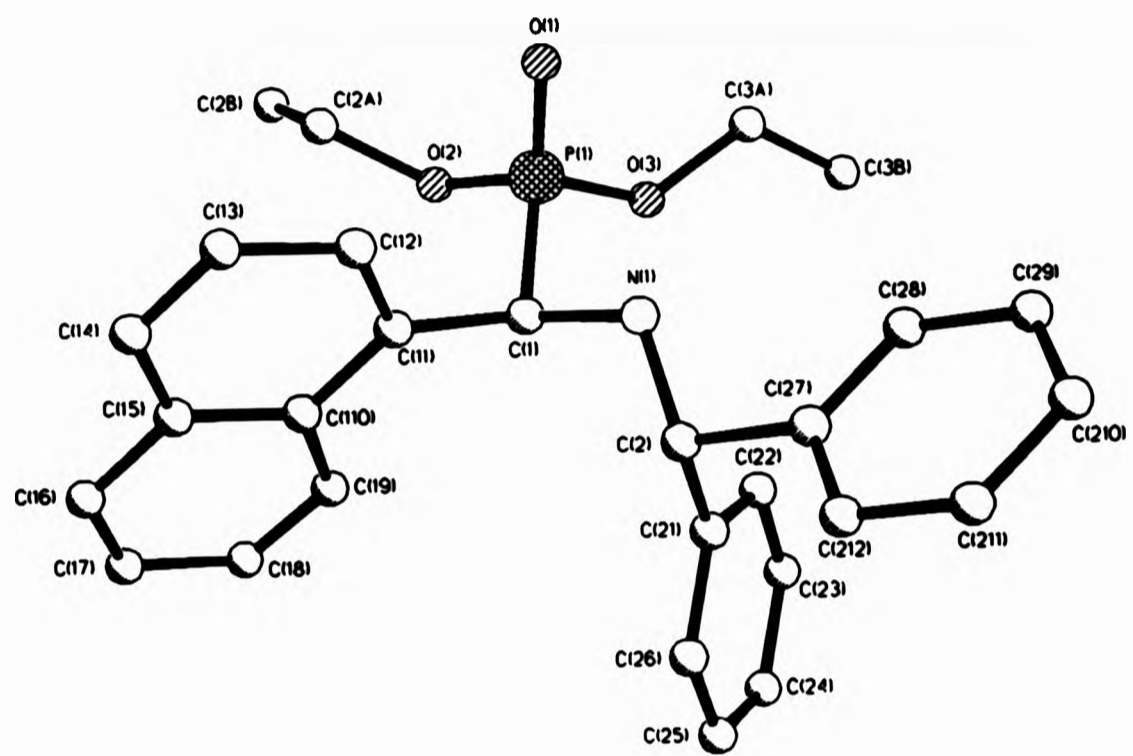
**Figure 3.11** X-ray structure of compound 4, molecule II (the configuration at the chiral carbon atom is *R* and the configuration at the nitrogen atom is *S*)



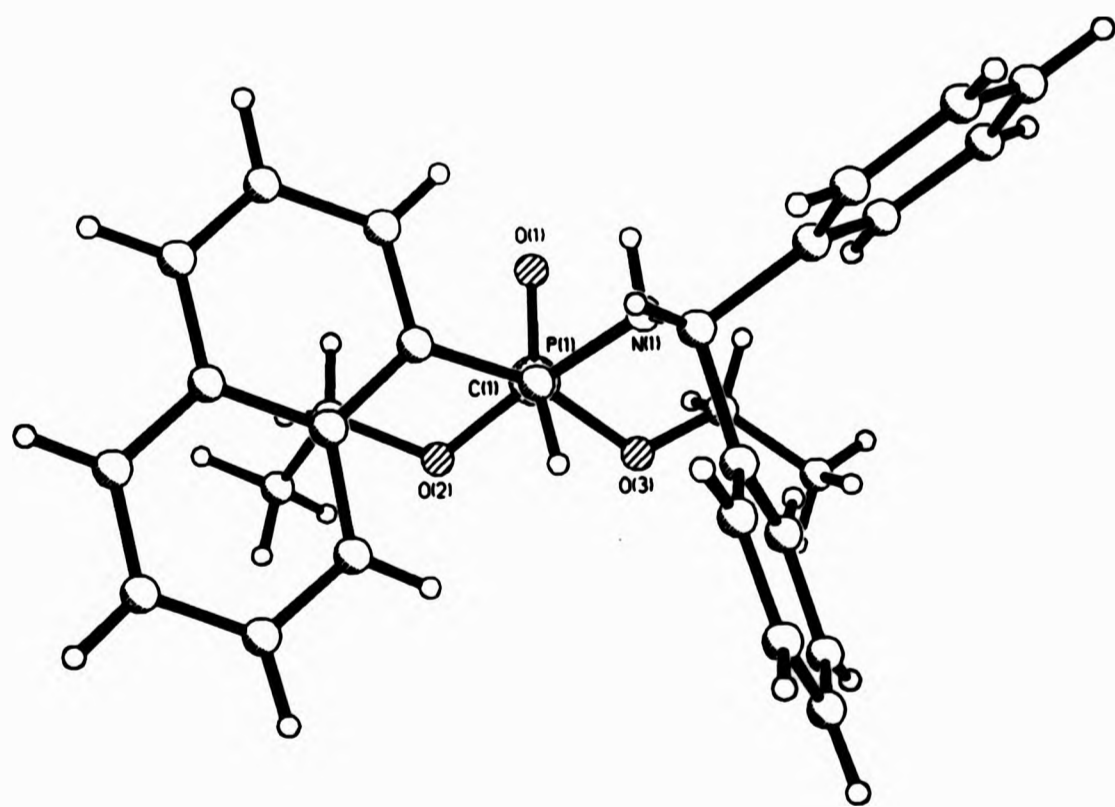
**Figure 3.12** X-ray structure of compound 4, molecule II, view down the C-P bond



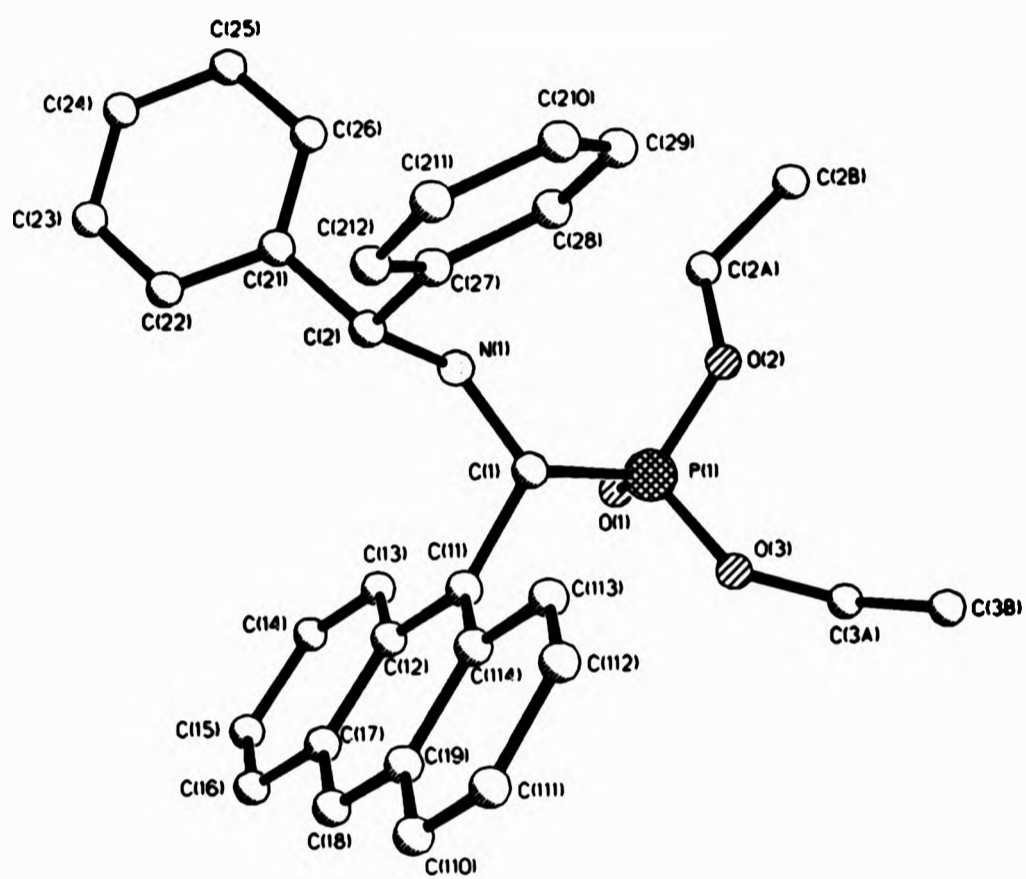
**Figure 3.13** X-ray structure of Compound 5 (the configuration at the chiral carbon atom is *R* and the configuration at the nitrogen atom is *S*)



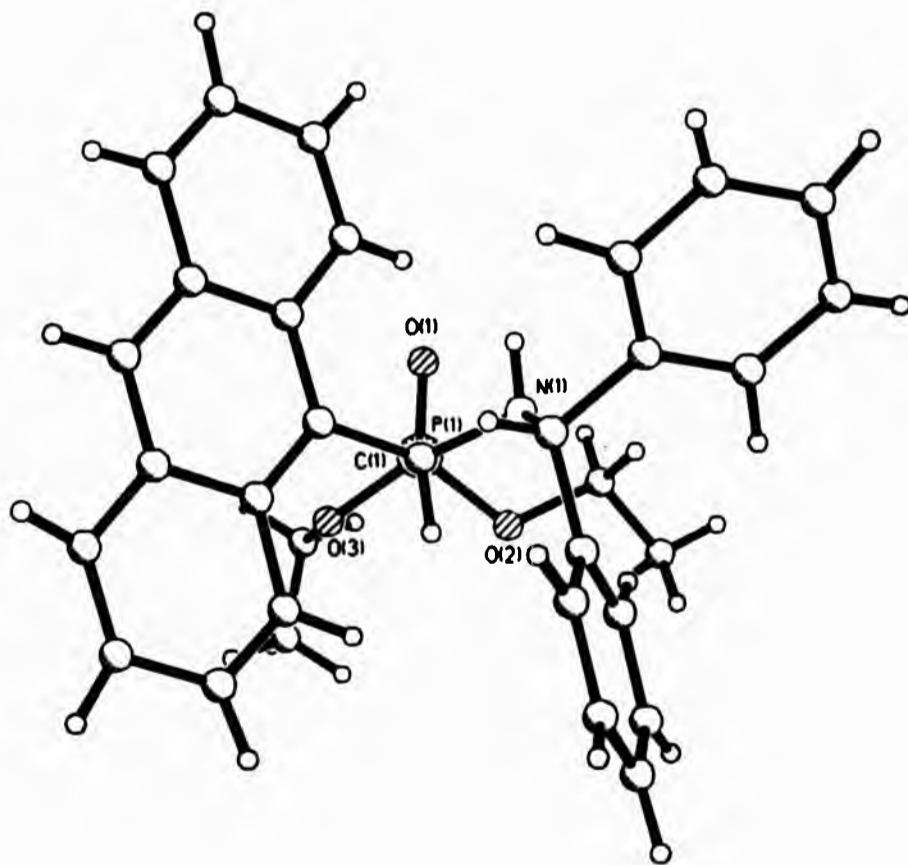
**Figure 3.14** X-ray structure of Compound 5, view down C-P bond



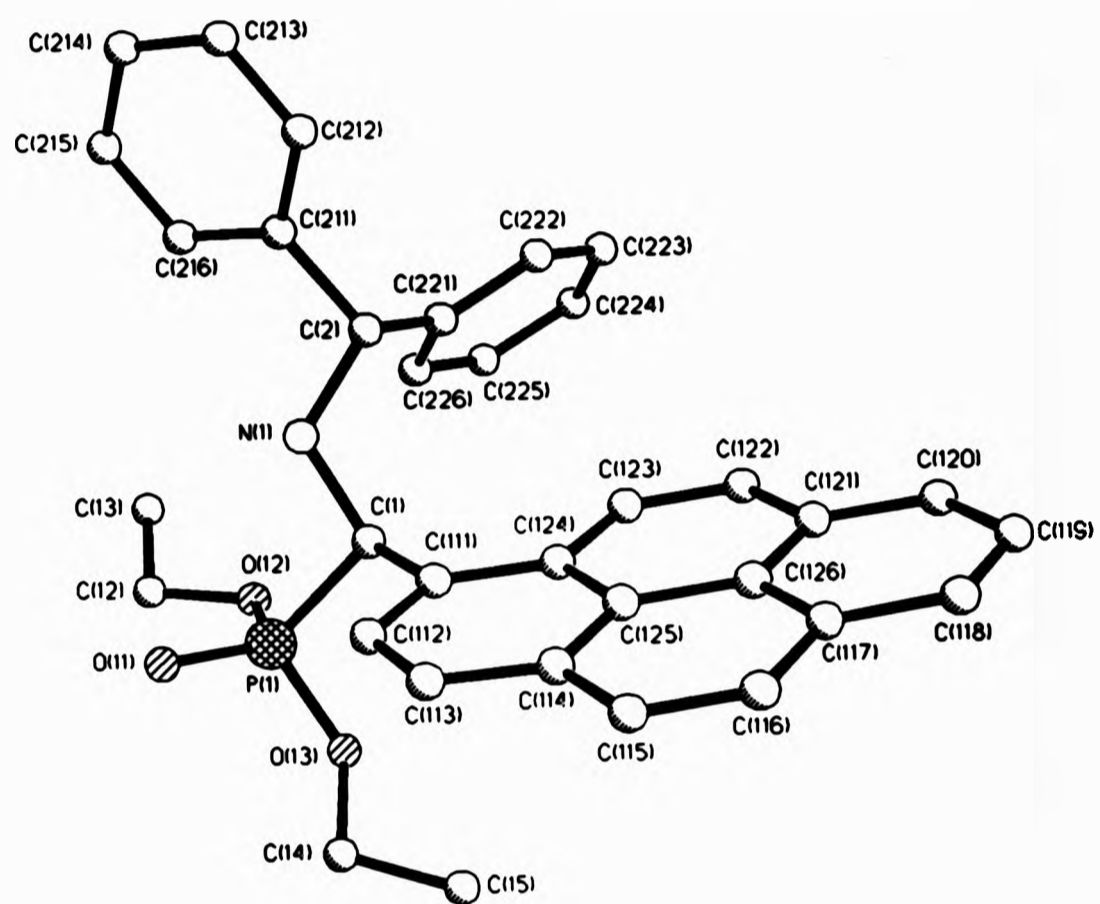
**Figure 3.15** X-ray structure of Compound 34 (the configuration at the chiral carbon atom is *R* and the configuration at the nitrogen atom is *S*)



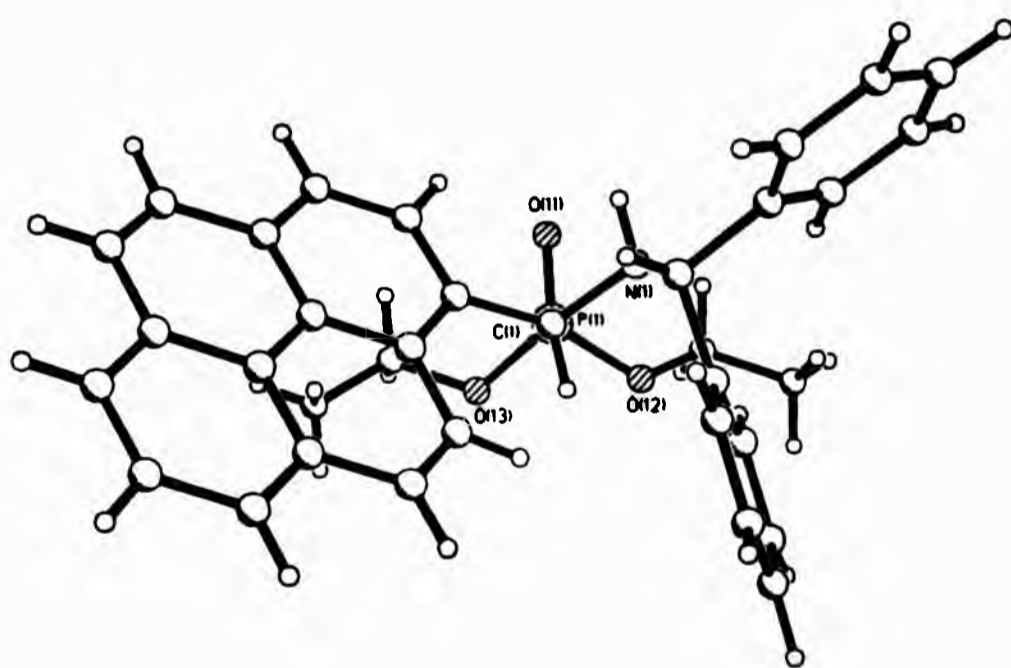
**Figure 3.16** X-ray structure of Compound 34, view down C-P bond



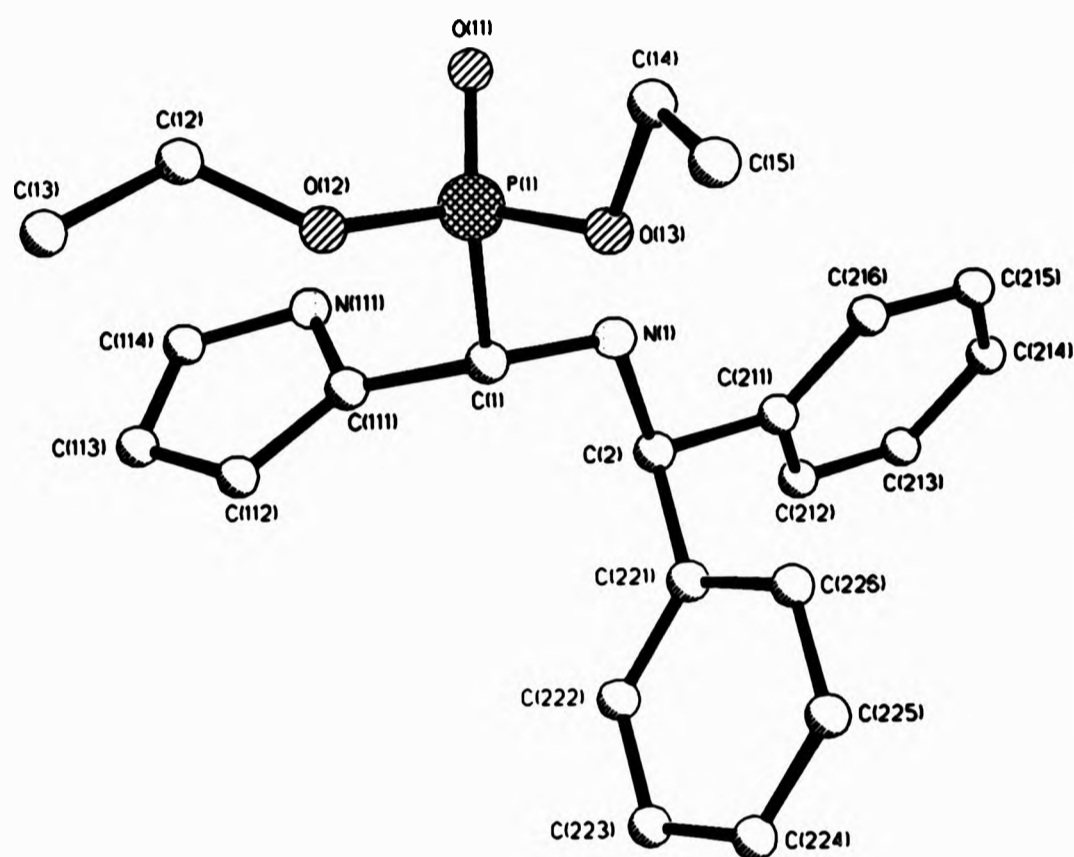
**Figure 3.17** X-ray structure of Compound 6 (the configuration at the chiral carbon atom is *R* and the configuration at the nitrogen atom is *S*)



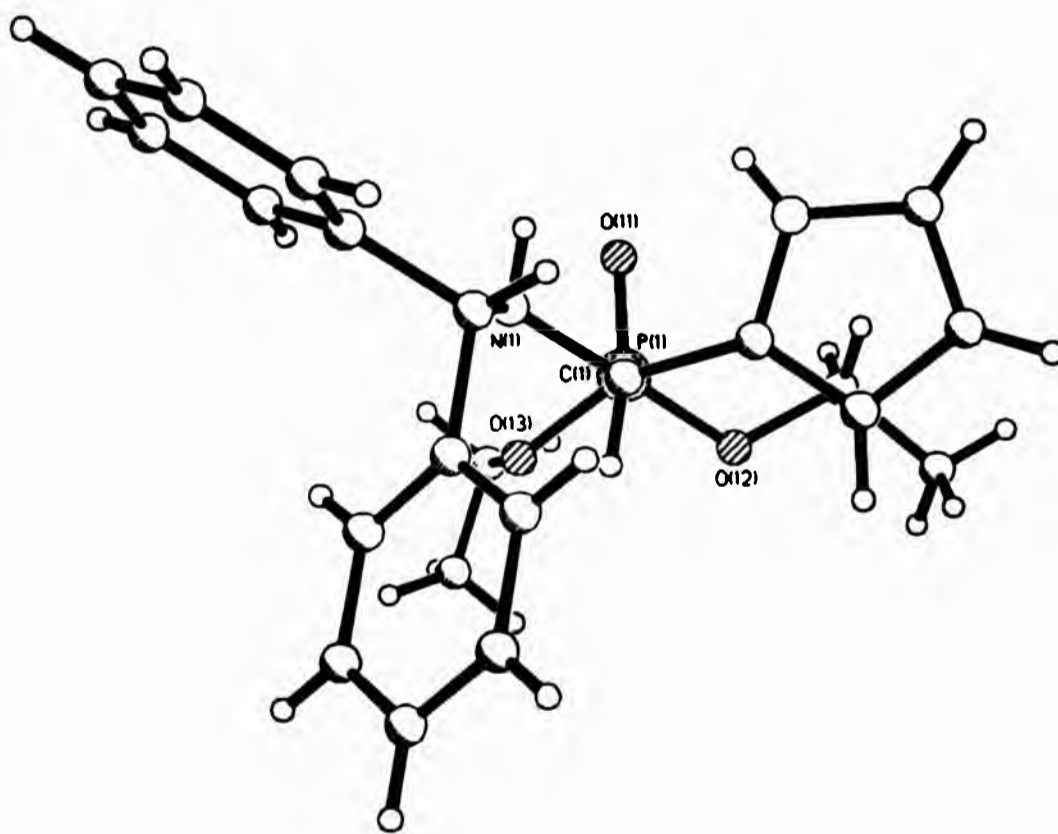
**Figure 3.18** X-ray structure of Compound 6, view down the C-P bond



**Figure 3.19** X-ray structure of Compound 27, molecule I (the configuration at the chiral carbon atom is *S* and the configuration at the nitrogen atom is *R*)

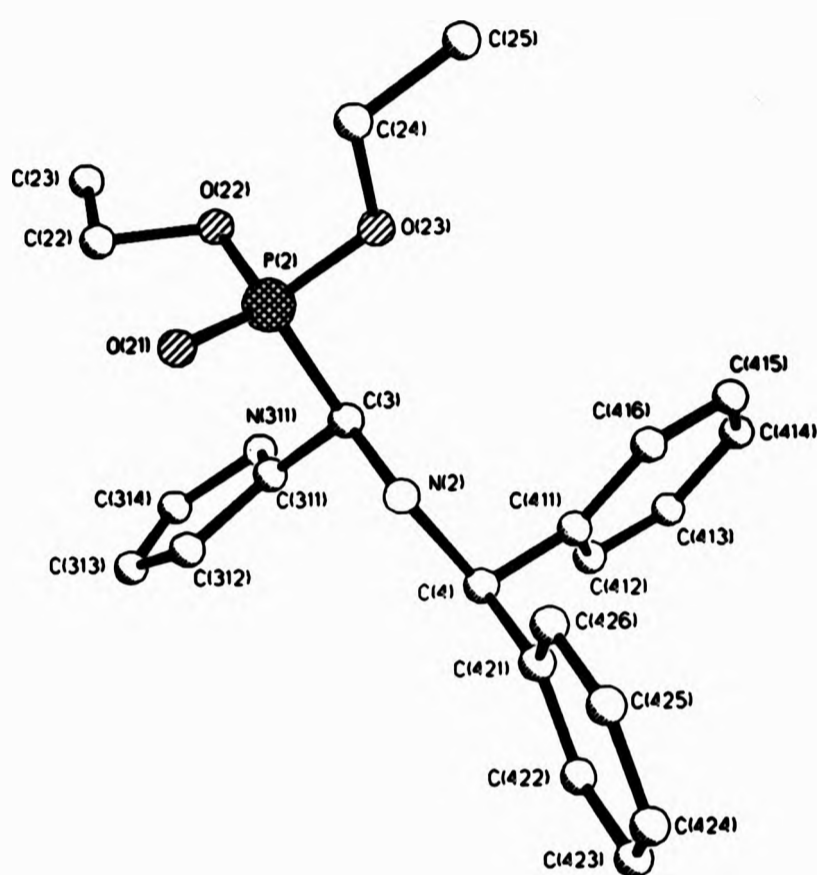


**Figure 3.20** X-ray structure of Compound 27, molecule I, view down the C-P bond

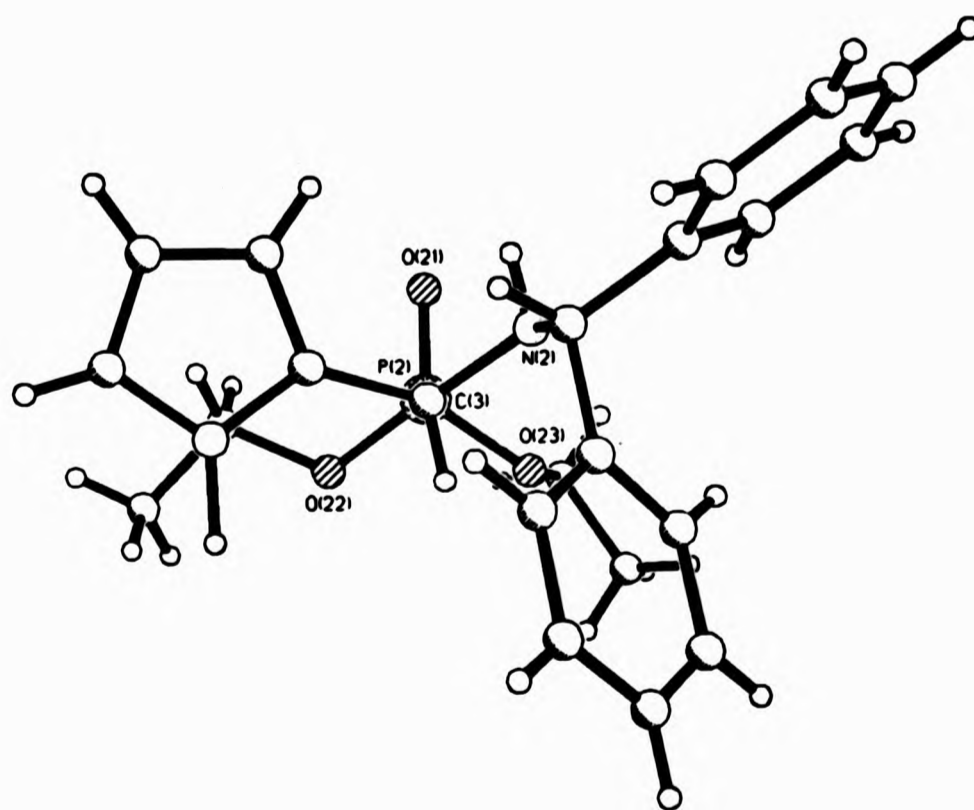




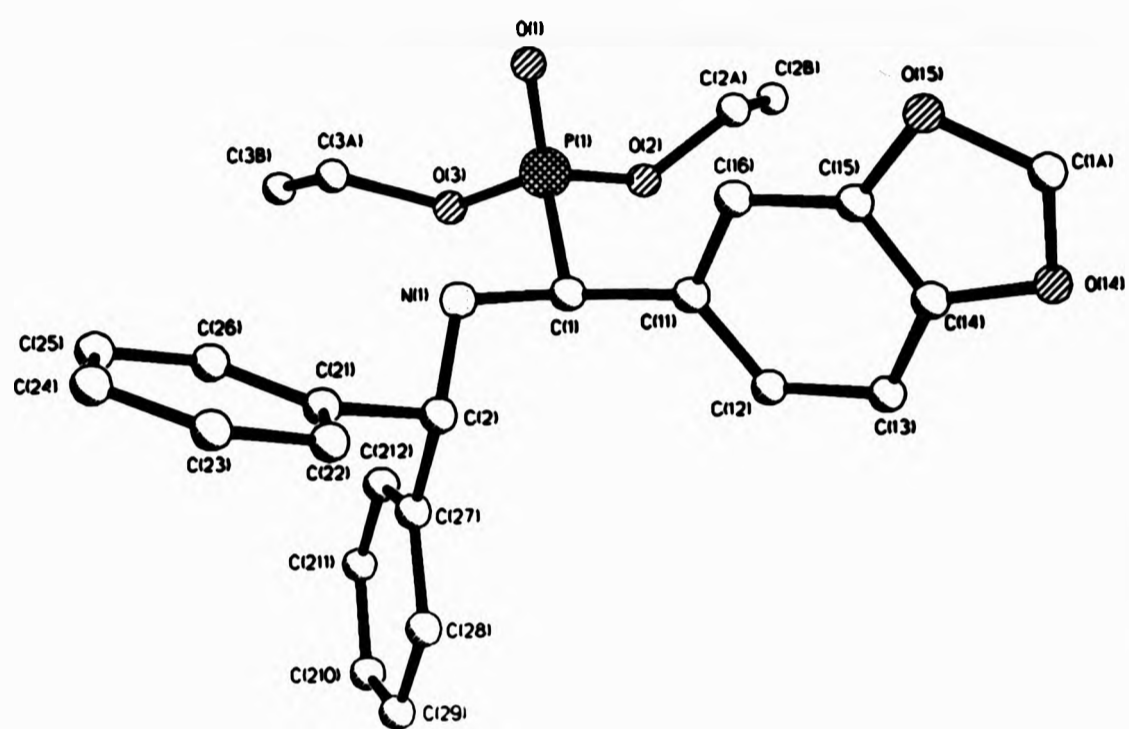
**Figure 3.21** X-ray structure of Compound 27, molecule II (the configuration at the chiral carbon atom is *R* and the configuration at the nitrogen atom is *S*)



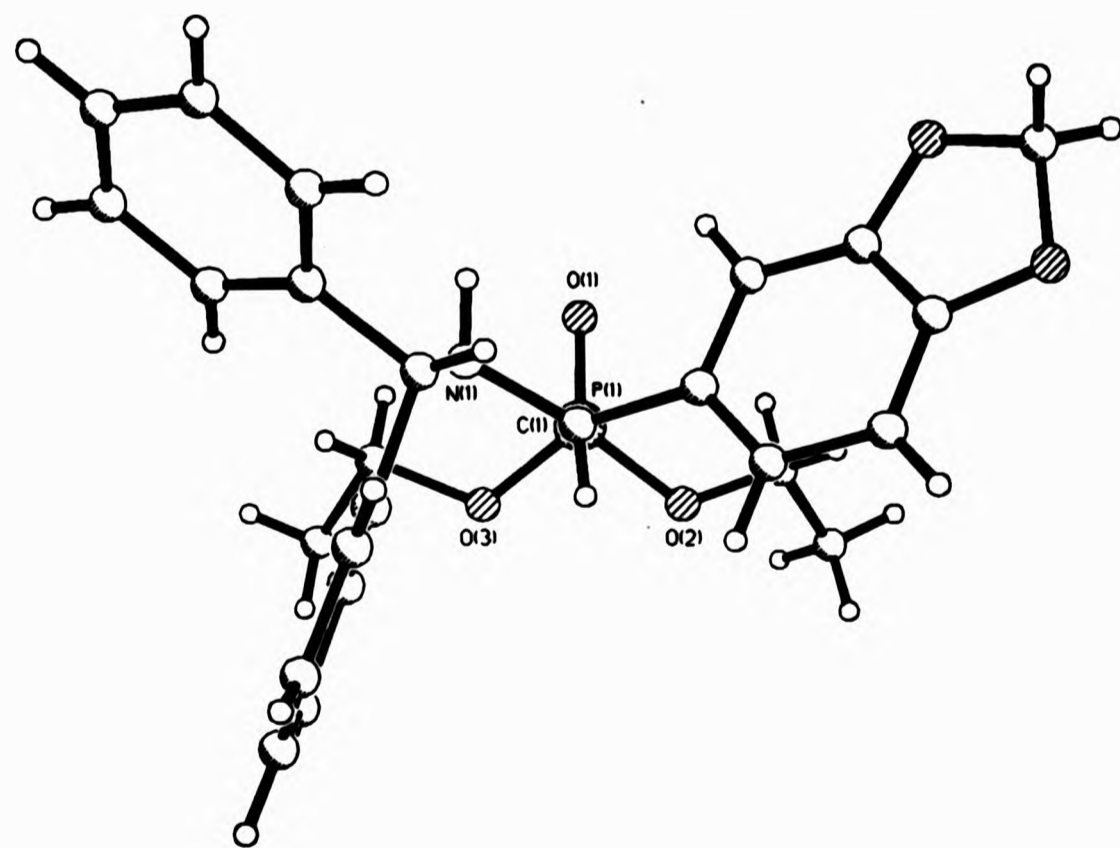
**Figure 3.22** X-ray structure of Compound 27, molecule II, view down the C-P bond



**Figure 3.23** X-ray structure of Compound **32** (the configurations at the chiral carbon atom and the nitrogen atom are *S*)



**Figure 3.24** X-ray structure of Compound **32**, view down the C-P bond



In most of the compounds the varying substituent (4 = phenyl, 5 = 1'-naphthyl, 34 = 9'-anthryl, 6 = 1'-pyrenyl, 27 = 2'-pyrrolyl and 32 = piperonyl) lies perpendicular to the PCN plane. The diphenylmethane unit also lies perpendicular to this plane. However, there are some exceptions namely the diphenylmethane unit of molecule II of compound 4; the pyrrolyl substituent of molecule I of compound 27 and the diphenylmethane unit of molecule II of compound 27. In these cases, the substituents lie in a more parallel arrangement to the PCN plane.

In most of the structures the bond angles about the chiral carbon atoms are close to those of tetrahedral geometry (see Table 3.11). The greatest distortion of this geometry occurs in the anthryl substituted compound 34. The bond angles in this compound are midway between planar and tetrahedral geometry.

**Table 3.11** Mean bond angles<sup>†</sup> about chiral carbon atom for compounds 4-6, 27, 32 and 34

Compound	Mean bond angle
4 <sup>‡</sup>	111.4
4 <sup>§</sup>	112.1
5	111.3
34	114.2
6	111.6
27 <sup>#</sup>	110.7
27 <sup>††</sup>	111.3
32	112.6

<sup>†</sup> The mean bond angle is taken as the sum of the three angles P-C-R, R-C-N and N-C-P (where R is the varying substituent) divided by three.

<sup>‡</sup> These data refer to molecule I.

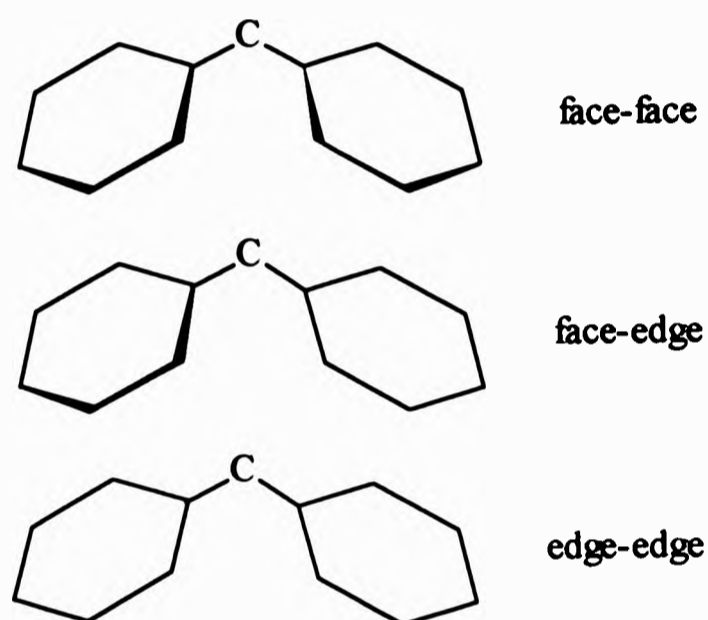
<sup>§</sup> These data refers to molecule II.

<sup>#</sup> These data refers to molecule I.

<sup>††</sup> These data refers to molecule II.

In compounds **4-6**, **27**, **32** and **34** the phenyl rings of the diphenylmethane unit lie face-face rather than face-edge or edge-edge (see Figure 3.25). This is due to the constraints imposed by the tetrahedral geometry of the methine carbon of this unit.

**Figure 3.25** Possible arrangements of the phenyl rings of the diphenylmethane unit



Viewing the molecules down the C-P bond (see Figures 3.10, 3.12, 3.14, 3.16, 3.18, 3.20, 3.22 and 3.24) it is apparent that, in all but one of the structures, one ethoxy ester group lies over the varying substituent. The other ethoxy ester group lies close to one of the phenyl rings of the diphenylmethane unit. The exception is molecule II of compound **4** where one of the ethoxy ester group lies close to one of the phenyl rings of the diphenylmethane unit, but the other ethoxy ester group lies parallel to the PCN plane and does not lie over the phenyl substituent.

There is no evidence of any intramolecular hydrogen bonding in any of the compounds but there are intermolecular hydrogen bonds in most of the compounds. Most of the compounds have hydrogen bonds between the phosphoryl oxygen and the amino group of an adjacent molecule which gives rise to the formation of hydrogen bonded dimers. Some compounds also have short (C)H...O contacts. Only compound **34** does not have hydrogen bonds between the phosphoryl oxygen atom and the amino group of an adjacent

molecule. The short contact interactions give rise to the formation of polymeric chains of molecules. The intermolecular interactions with the interatomic distances are given in Table 3.12.

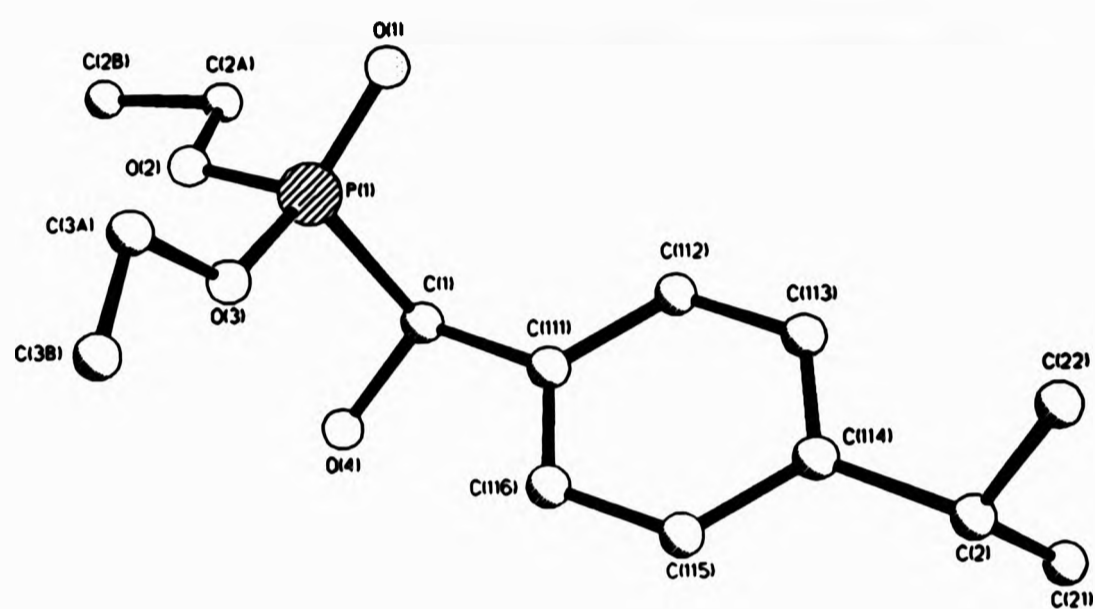
**Table 3.12** Intermolecular interactions for compounds 4-6, 27, 32 and 34

Compound	Labelling scheme	Interatomic distance (Å)
4	O(11) ··· N(2)	2.917
	O(11) ··· H(N2)	2.180
	O(21) ··· N(1)	3.154
	O(21) ··· H(N1)	2.304
5	O(1) ··· N(1)	3.283
	O(1) ··· H(N1)	2.444
	O(1) ··· H(C12)	2.561
34	O(1) ··· H(C210)	2.542
6	O(11) ··· N(1)	3.021
	O(11) ··· H(N1)	2.094
27 <sup>†</sup>	O(11) ··· H(N1)	2.372
	O(11) ··· N(111)	2.815
	O(11) ··· H(N111)	2.028
32	O(1) ··· H(N1)	2.222

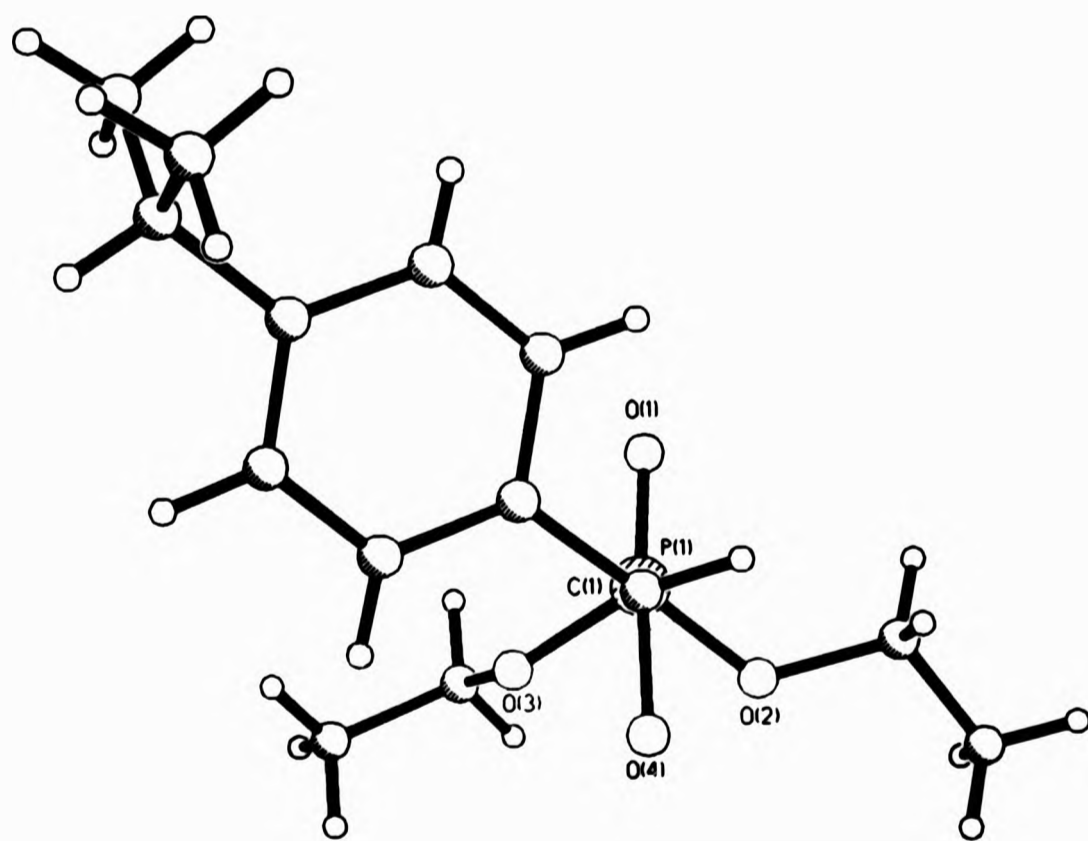
<sup>†</sup> There are no similar interactions for molecule II.

Compound 3 does not follow exactly the pattern of the series of compounds already discussed, although many features are similar. There is only the one chiral centre; Figures 3.26 and 3.27 show the structure of the *S* enantiomer. The centrosymmetric space group is consistent with there being an equal mixture of *R* and *S* enantiomers in the solid state. The geometry at the chiral carbon is close to tetrahedral geometry with average bond angles about the chiral carbon atom of 112.6°. There is no evidence of intramolecular hydrogen bonding, although there are intermolecular hydrogen bonds between the phosphoryl oxygen atoms and the hydroxy groups of adjacent molecules. This gives rise to the formation of hydrogen bonded chains, as opposed to hydrogen bonded dimers, as previously reported in a similar phosphonate ester.<sup>[131]</sup>

**Figure 3.26** X-ray structure of Compound 3



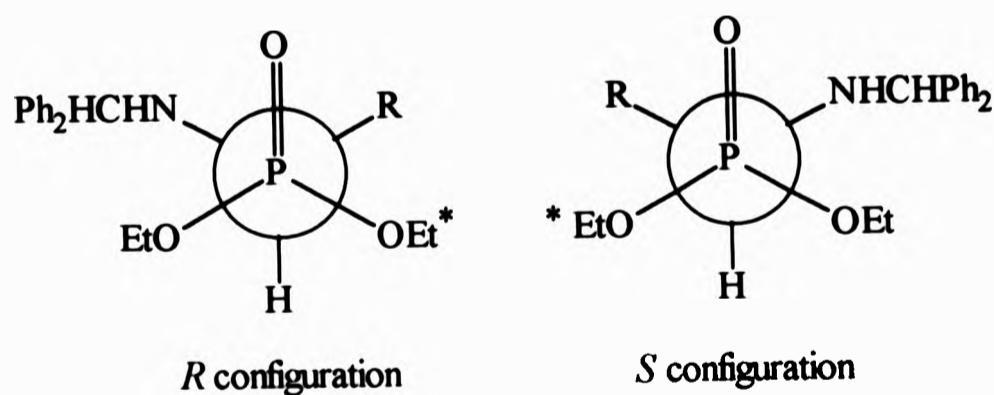
**Figure 3.27** X-ray structure of Compound 3, view down the C-P bond



### 3.2.3.1 Comparison of the Geometry Around the Phosphorus Atom Between Compounds 3-6, 27, 32 and 34

Selected bond lengths from the *X*-ray crystallography for compounds 3-6, 27, 32 and 34 are given in Table 3.13. The two P-O bond lengths corresponding to the P-OEt groups do not vary significantly between the different compounds (significant variation is considered to be more than 3 x esd). The two P-O bond lengths within each compound are equal within experimental error and are comparable with P-O bond lengths in similar phosphonic acids and phosphonate esters.<sup>[132-136]</sup> The third P-O bond in the compounds is significantly shorter than the other two P-O bonds and is consistent with a localised P=O double bond. These bond lengths do not vary significantly between the compounds and are comparable with P=O double bonds in related phosphonate ester systems.<sup>[132-136]</sup>

**Figure 3.28** Arrangement of the ethoxy ester groups around the phosphorus atom viewing down the P-C bond (the configuration refers to the chiral carbon atom)



**Table 3.13** Selected bond lengths (Å)<sup>†</sup> from the X-ray analysis of compounds 3-6, 27, 32 and 34

Compound	P=O	P-O <sup>‡</sup>	P-O	P-C
3	1.461 (3)	1.566 (3)	1.575 (3)	1.826 (4)
4 <sup>§</sup>	1.451 (4)	1.560 (4)	1.568 (5)	1.809 (6)
4 <sup>#</sup>	1.463 (4)	1.577 (4)	1.574 (4)	1.806 (5)
5	1.465 (2)	1.577 (2)	1.575 (2)	1.810 (3)
6	1.470 (2)	1.581 (2)	1.570 (2)	1.818 (2)
27 <sup>††</sup>	1.468 (4)	1.559 (5)	1.564 (5)	1.809 (6)
27 <sup>‡‡</sup>	1.470 (4)	1.563 (4)	1.566 (5)	1.805 (6)
32	1.451 (5)	1.561 (6)	1.562 (6)	1.822 (9)
34	1.459 (3)	1.576 (3)	1.560 (3)	1.831 (4)

<sup>†</sup> Esd's are shown in parentheses.

<sup>‡</sup> Where the ethoxy ester group labelled OEt\* resides nearer to the varying substituent R see Figure 3.28.

<sup>§</sup> These data refers to molecule I.

<sup>#</sup> These data refers to molecule II.

<sup>††</sup> These data refers to molecule I.

<sup>‡‡</sup> These data refers to molecule II.

The bond angles around the phosphorus atom are given in Table 3.14. The geometry of the atoms around the phosphorus atom are considerably distorted from the angles expected in an ideal tetrahedron. This distortion is a result of the repulsive effect of the localised P=O double bond towards the other atoms. This distortion reduces the O-P-O bond angle by as much as 11° and increases the O=P-O angles by as much as 8°. This geometry of the atoms around the phosphorus atom is very common in similar phosphonate ester compounds.<sup>[132-136]</sup>



Table 3.14 Selected bond angles (°)<sup>†</sup> from the X-ray analysis of compounds 3-6, 27, 32 and 34

Compound	O=P-O <sup>‡</sup>	O=P-O	O-P-O	O=P-C	<sup>‡</sup> O-P-C	O-P-C
3	116.2 (2)	114.2 (2)	102.0 (2)	113.9 (2)	102.4 (2)	106.7 (2)
4 <sup>§</sup>	114.4 (3)	117.4 (3)	100.5 (2)	114.2 (3)	105.6 (2)	103.1 (3)
4 <sup>#</sup>	116.1 (2)	114.2 (2)	101.8 (2)	115.5 (3)	100.9 (2)	106.6 (2)
5	115.7 (1)	115.5 (1)	100.2 (1)	113.6 (1)	105.9 (1)	104.3 (1)
6	115.2 (1)	115.1 (1)	101.6 (1)	115.2 (1)	105.5 (1)	102.6 (1)
27 <sup>††</sup>	114.0 (3)	116.3 (3)	102.7 (3)	113.0 (3)	107.8 (3)	101.9 (3)
27 <sup>‡‡</sup>	113.7 (7)	116.5 (3)	102.1 (3)	112.9 (3)	107.6 (3)	102.7 (3)
32	117.1 (4)	116.3 (4)	98.2 (4)	113.4 (4)	103.9 (4)	106.0 (4)
34	117.1 (2)	113.5 (2)	102.1 (2)	117.2 (2)	100.6 (2)	104.3 (2)

<sup>†</sup> Esd's are given in parentheses.

<sup>‡</sup> Refers to the ethoxy ester group that lies over the varying substituent R see Figure 3.28.

<sup>§</sup> These data refers to molecule I.

<sup>#</sup> These data refers to molecule II.

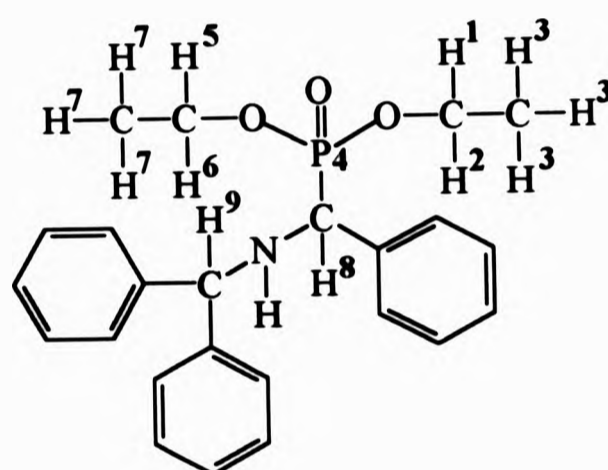
<sup>††</sup> These data refers to molecule I.

<sup>‡‡</sup> These data refers to molecule II.

### 3.3 Analysis of $^1\text{H}$ NMR Spectra by Simulation and Iteration using WIN-DAISY<sup>[74]</sup>

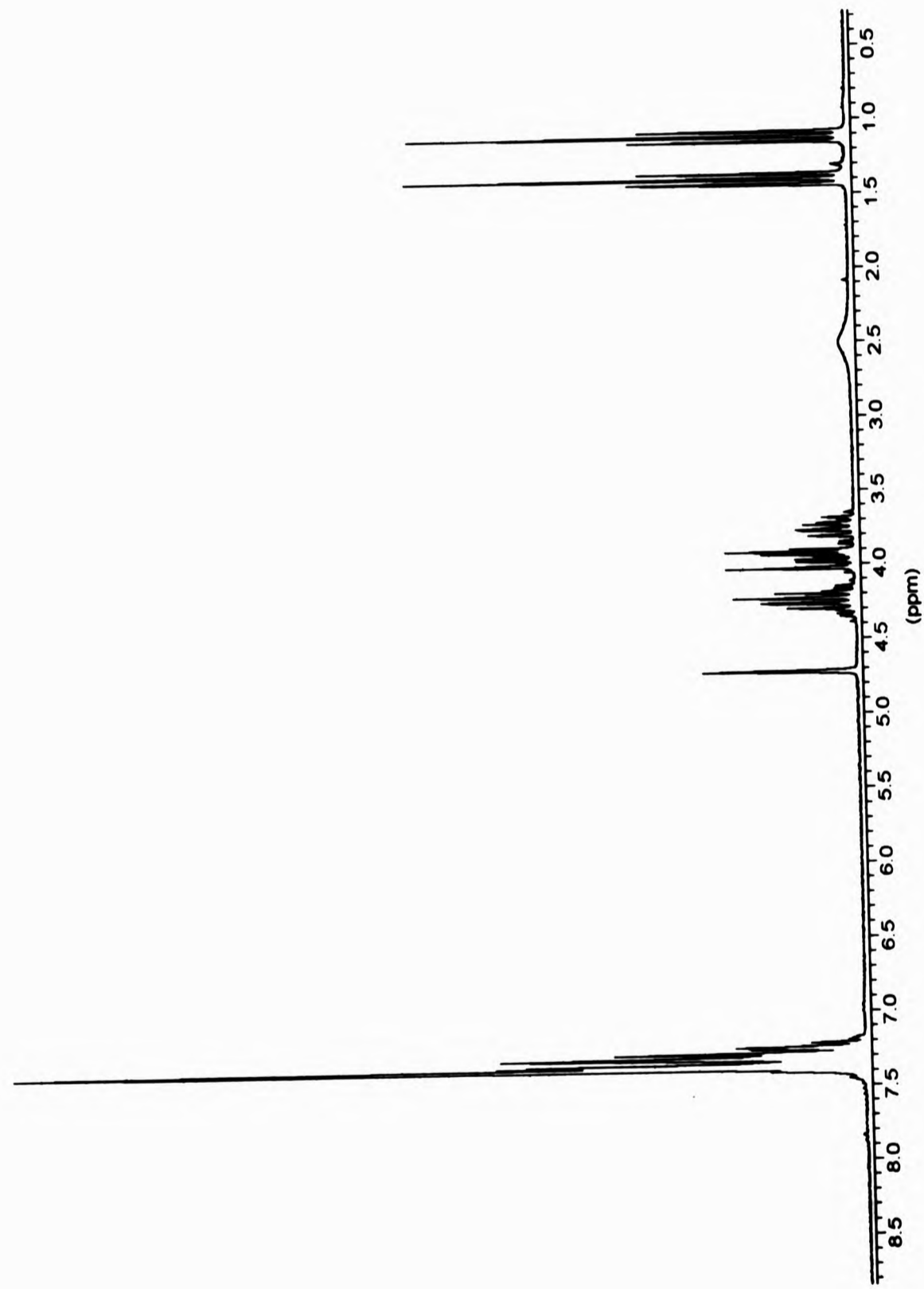
#### 3.3.1 $^1\text{H}$ NMR Spectrum of Diethyl Phenyl-1-(diphenylmethylamino)methane-phosphonate (4)

Figure 3.29 Numbering scheme used in assigning the  $^1\text{H}$  NMR spectrum of compound 4



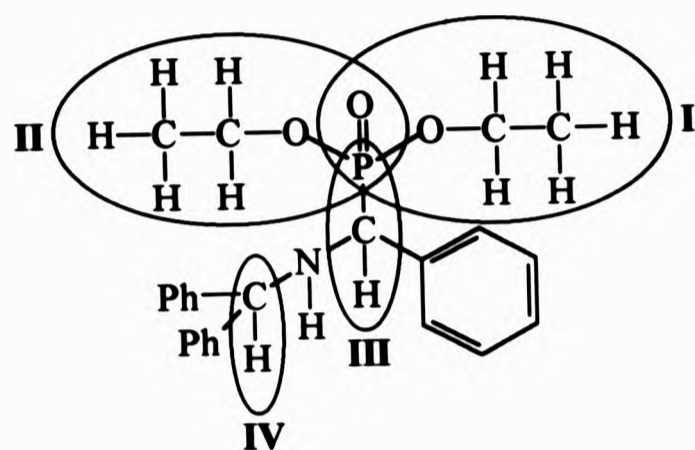
The experimental spectrum (2% w/w solution in  $\text{CDCl}_3$ ) of compound 4 (Figure 3.30) shows two triplets (1.12 and 1.40 ppm) which are assigned to the two methyl groups  $\text{H}^3$  and  $\text{H}^7$ . There are three distinct multiplets centred at 3.76, 3.98 and 4.20 ppm assigned to the four methylene protons ( $\text{H}^1$ ,  $\text{H}^2$ ,  $\text{H}^5$  and  $\text{H}^6$ ); the multiplet at 3.98 ppm overlaps with a doublet assigned to  $\text{H}^8$ . The singlet at 4.72 ppm is assigned to the methine proton  $\text{H}^9$ . The aromatic protons were not simulated in this analysis. An HH-COSY experiment was required to identify methylene-methyl couplings. Notably, the methylene proton signals that resonate furthest downfield are coupled to the methyl signals that also resonate downfield compared to the signal of the other methyl protons.

The strategy for analysis involved carrying out separate analyses for fragments of the molecule whose NMR parameters were independent of each other. The four fragments of the molecule are shown in Figure 3.31. The parameters obtained from preliminary first order analysis were used as input parameters and are shown in the following tables (Table 3.15-3.18).



**Figure 3.30** Experimental  $^1\text{H}$  NMR spectrum of compound 4 at 200.13 MHz.

**Figure 3.31** Fragment divisions used in the  $^1\text{H}$  NMR spectrum analysis



**Table 3.15** Starting parameters used in the analysis of  $^1\text{H}$  NMR spectrum for Fragment I

Nucleus	Group	Chemical shift (Hz)	Linewidth (Hz)	Coupling constants (Hz)			
				$\text{H}^2$	$\text{H}^3$	$\text{P}^4$	
$\text{H}^1$	$\text{CH}_2$	795.9	1.0	$\text{H}^2$	$\text{H}^3$	$\text{P}^4$	
$\text{H}^2$	$\text{CH}_2$	753.4	1.0	$\text{H}^1$	$10^\dagger$	$7^\ddagger$	7.2
$\text{H}^3$	$\text{CH}_3$	223.4	1.0	$\text{H}^2$	-	$7^\ddagger$	8.4
$\text{P}^4$	P	-	-	$\text{H}^3$	-	-	-

$^\dagger$  The range for similar coupling constants is -10 to  $-18^{[137]}$  but trial simulations showed -10 Hz to be the better approximation.

$^\ddagger$  The best approximation from trial simulations.

**Table 3.16** Starting parameters used in the analysis of  $^1\text{H}$  NMR spectrum for Fragment II

Nucleus	Group	Chemical shift (Hz)	Linewidth (Hz)	Coupling constants (Hz)			
				$\text{H}^2$	$\text{H}^3$	$\text{P}^4$	
$\text{H}^5$	$\text{CH}_2$	860.0	1.0	$\text{H}^2$	$\text{H}^3$	$\text{P}^4$	
$\text{H}^6$	$\text{CH}_2$	840.0	1.0	$\text{H}^1$	$10^\dagger$	$7^\ddagger$	7.5
$\text{H}^7$	$\text{CH}_3$	280.8	1.0	$\text{H}^2$	-	$7^\ddagger$	8.6
$\text{P}^4$	P	-	-	$\text{H}^3$	-	-	0.5

$^\dagger$  The range for similar coupling constants is -10 to  $-18^{[137]}$  but trial simulations showed -10 Hz to be the better approximation.

$^\ddagger$  The best approximation from trial simulations.

**Table 3.17** Starting parameters used in the analysis of  $^1\text{H}$  NMR spectrum for Fragment III

Nucleus	Group	Chemical shift (Hz)	Linewidth (Hz)	Coupling constants (Hz)
H <sup>8</sup>	CH	795.1	1.3	P <sup>4</sup>
P <sup>4</sup>	P	-	-	H <sup>3</sup> -22.6

**Table 3.18** Starting parameters used in the analysis of  $^1\text{H}$  NMR spectrum for Fragment IV

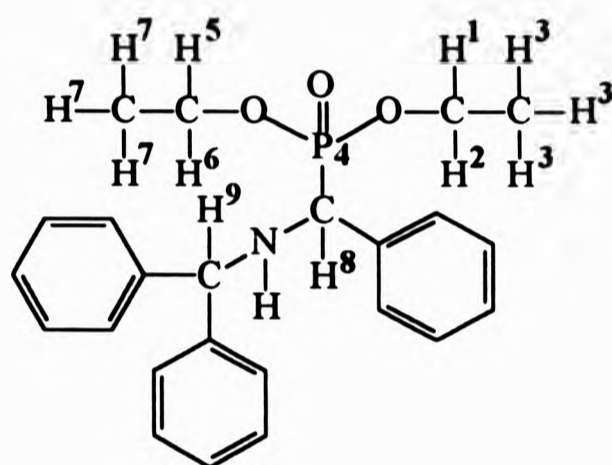
Nucleus	Group	Chemical shift (Hz)	Linewidth (Hz)
H <sup>9</sup>	CH	945.3	1.8

The program requires that each type of atom (*e.g.*  $^1\text{H}$ ,  $^{31}\text{P}$ ) in the spin system is identified and given a unique ISO-number; based on this, an X-approximation is carried out. The program takes into account various other properties of the nuclei such as natural abundance, magnetogyric ratio, relative sensitivity, and the magnetic moment. The number of magnetically equivalent nuclei is also required for each nucleus; this determines if a single spin or a composite particle calculation is required for the nuclei (*i.e.* the methyl protons of H<sup>3</sup> and H<sup>7</sup> are composite particles).

For the iteration calculation the regions of the experimental spectrum that have the signals of the nuclei being simulated must be exported from WIN-NMR<sup>[73]</sup> and connected to the simulation input data. The experimental spectral regions must contain at least 10 data points per signal in order to obtain a satisfactory result; too many data points, however, would result in extended iteration times. The iteration algorithm uses successive steepest descent and Gauss-Newton corrections.<sup>[138]</sup>

Refinement was considered complete when the final sum of squares was 100 times less than the number of experimental spectral points. Final parameters are shown in Tables 3.19 and 3.20 and the simulated spectrum is shown in Figures 3.32 and 3.33.

Tables 3.19 and 3.20 Numbering scheme used in assigning the  $^1\text{H}$  NMR spectrum of compound 4



**Table 3.19**  $^1\text{H}$  NMR Chemical shifts and linewidths for compound 4 determined by simulation and iteration

Nucleus	Group	Chemical shift <sup>†</sup> (Hz)	Chemical shift (ppm)	Linewidth (Hz)
H <sup>3</sup>	CH <sub>3</sub>	223.22 (1)	1.12	0.83
H <sup>7</sup>	CH <sub>3</sub>	280.62 (1)	1.40	0.84
H <sup>1</sup>	CH of CH <sub>2</sub>	750.67 (1)	3.75	0.83
H <sup>2</sup>	CH of CH <sub>2</sub>	791.86 (1)	3.96	0.83
H <sup>8</sup>	CHP	795.06 (1)	3.97	1.31
H <sup>5</sup>	CH of CH <sub>2</sub>	843.64 (1)	4.22	0.84
H <sup>6</sup>	CH of CH <sub>2</sub>	855.98 (1)	4.28	0.84
H <sup>9</sup>	CHN	945.05 (1)	4.72	2.11

<sup>†</sup> Esd's are given in parentheses.

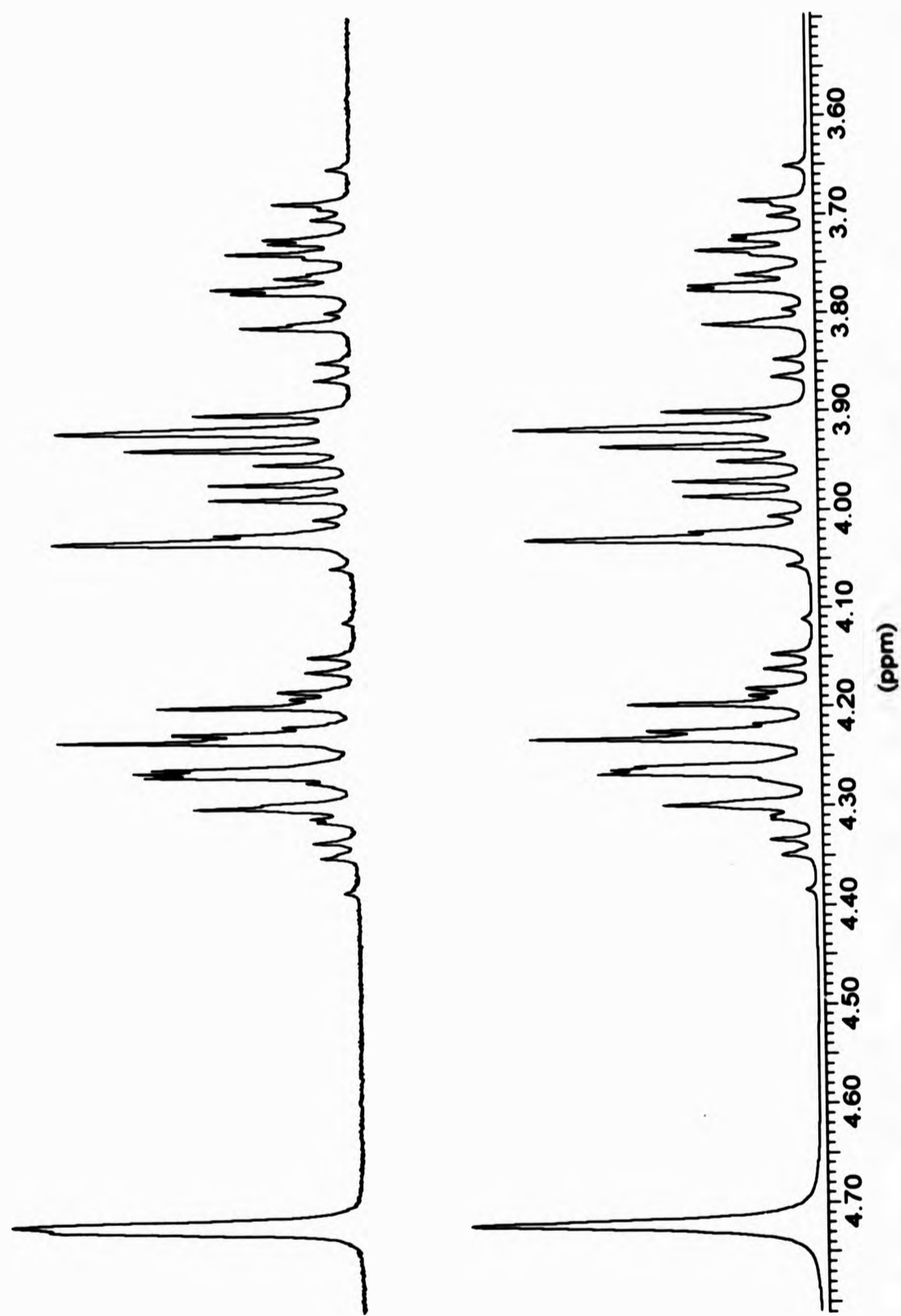
**Table 3.20**  $^1\text{H}$  NMR coupling constants for compound 4 determined by simulation and iteration

Coupling constant <sup>†</sup> (Hz)		Coupling constant (Hz)	
J <sub>H1-H2</sub>	-10.12 (1)	J <sub>P4-H6</sub>	6.88 (6)
J <sub>H1-H3</sub>	7.06 (2)	J <sub>P4-H7</sub>	0.57 (1)
J <sub>H1-P4</sub>	7.10 (6)	J <sub>P4-H8</sub>	22.45 (2)
J <sub>H2-H3</sub>	7.06 (2)	J <sub>H5-H6</sub>	-10.10 (3)
J <sub>H2-P4</sub>	8.02 (2)	J <sub>H5-H7</sub>	7.06 (2)
J <sub>H3-P4</sub>	0.59 (1)	J <sub>H6-H7</sub>	7.08 (2)
J <sub>P4-H5</sub>	7.99 (2)		

<sup>†</sup> Esd's are given in parentheses.

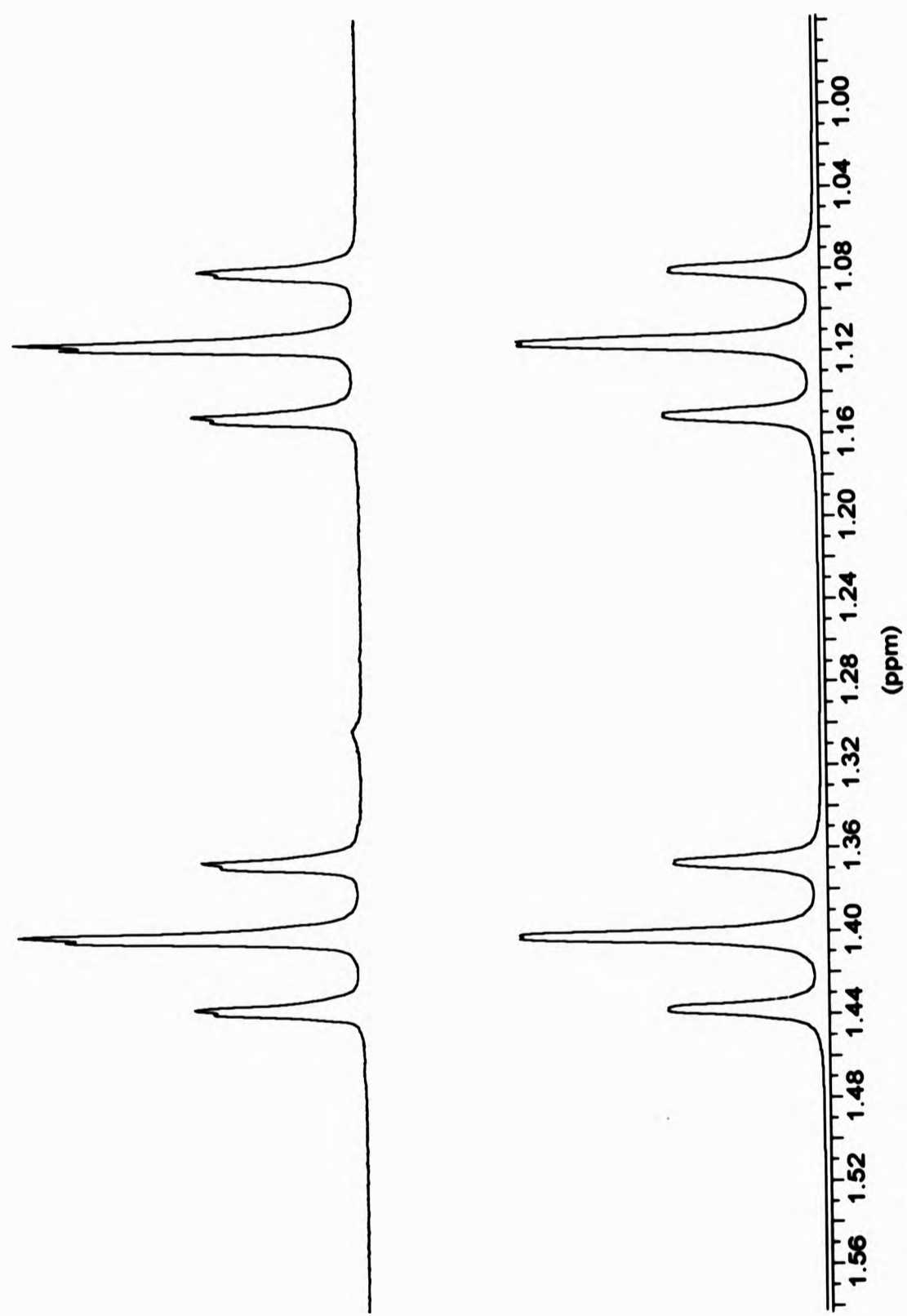
Statistics for iteration calculation

Final sum of squares 47.429  
(number of spectral points 4620)  
Standard deviation 0.101  
R-factor 1.44%



**Figure 3.32**  $^1\text{H}$  NMR spectra of the methylene and methine regions of compound 4. The upper trace is the experimental spectrum and the lower trace is the simulated spectrum.

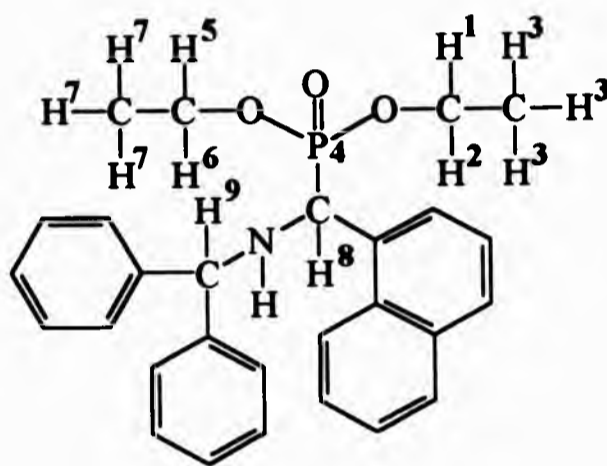




**Figure 3.33**  $^1\text{H}$  NMR spectra of the methyl region of compound 4.  
The upper trace is the experimental spectrum and the lower trace is the simulated spectrum.

### 3.3.2 $^1\text{H}$ NMR Spectrum of Diethyl 1-(1'-Naphthyl)-1-(diphenylmethylamino)-methanephosphonate (5)

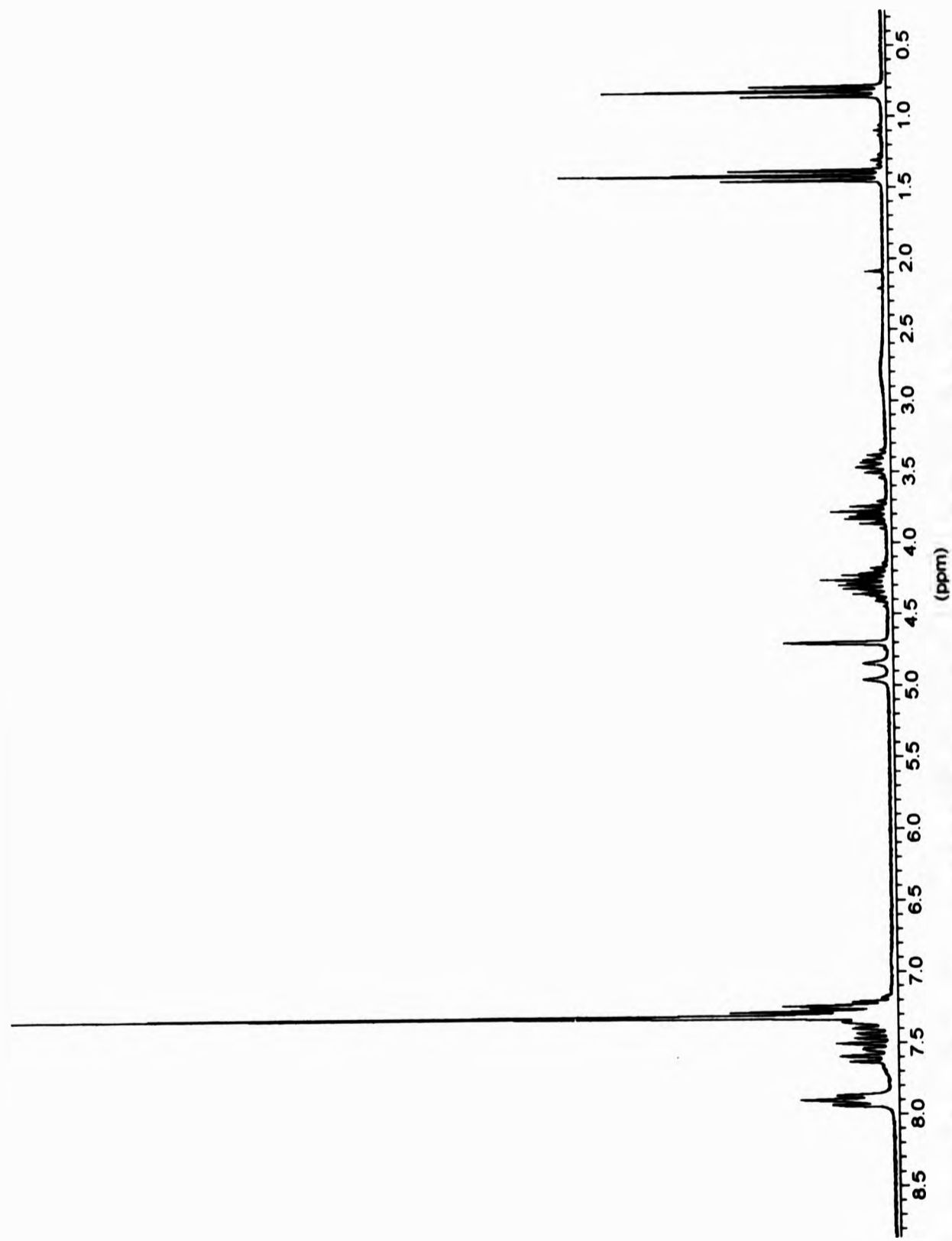
Figure 3.34 Numbering scheme used in assigning the  $^1\text{H}$  NMR spectrum of compound 5



The experimental spectrum (2% w/w solution in  $\text{CDCl}_3$ ) of compound 5 (Figure 3.35) shows two triplets (0.82 and 1.42 ppm) which are assigned to the two methyl groups  $\text{H}^3$  and  $\text{H}^7$ . There are again three distinct multiplets for the four methylene protons ( $\text{H}^1$ ,  $\text{H}^2$ ,  $\text{H}^5$  and  $\text{H}^6$ ) centred at 3.44, 3.80 and 4.30 ppm. The doublet assigned to the methine proton  $\text{H}^8$  is not overlapping a methylene multiplet but has shifted downfield to 4.90 ppm. The singlet at 4.70 ppm is assigned to the methine proton  $\text{H}^9$ .

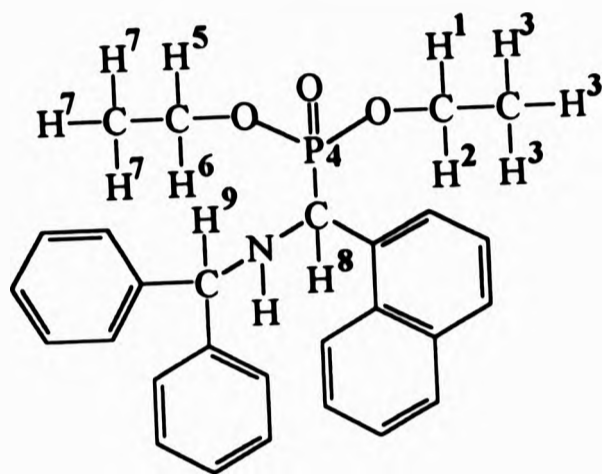
The fragmentation, simulation and iteration procedure is the same as in the previous section 3.3.1 for compound 4. The input parameters for the procedure were the chemical shifts measured by first order hand analysis of the experimental spectrum and the coupling constants were the coupling constants obtained for compound 4 (Table 3.20) in the previous section.

The final parameters are shown in Tables 3.21 and 3.22 and the simulated spectrum is shown in Figure 3.36 and 3.37.



**Figure 3.35** Experimental  $^1\text{H}$  NMR spectrum of compound **5** at 200.13 MHz.

Tables 3.21 and 3.22 Numbering scheme used assigning the  $^1\text{H}$  NMR spectrum of compound 5



**Table 3.21** <sup>1</sup>H NMR Chemical shifts and linewidths for compound 5 determined by simulation and iteration

Nucleus	Group	Chemical shift <sup>†</sup> (Hz)	Chemical shift (ppm)	Linewidth (Hz)
3	CH <sub>3</sub>	164.49 (1)	0.82	1.15
7	CH <sub>3</sub>	283.10 (1)	1.42	0.96
1	CH of CH <sub>2</sub>	690.01 (1)	3.45	1.15
2	CH of CH <sub>2</sub>	760.92 (1)	3.80	1.15
5	CH of CH <sub>2</sub>	848.93 (1)	4.24	0.96
6	CH of CH <sub>2</sub>	868.44 (1)	4.34	0.96
9	CHN	941.02 (1)	4.70	2.36
8	CHP	980.81 (4)	4.90	4.99

<sup>†</sup> Esd's are given in parentheses.

**Table 3.22** <sup>1</sup>H NMR coupling constants of compound 5 determined by simulation and iteration

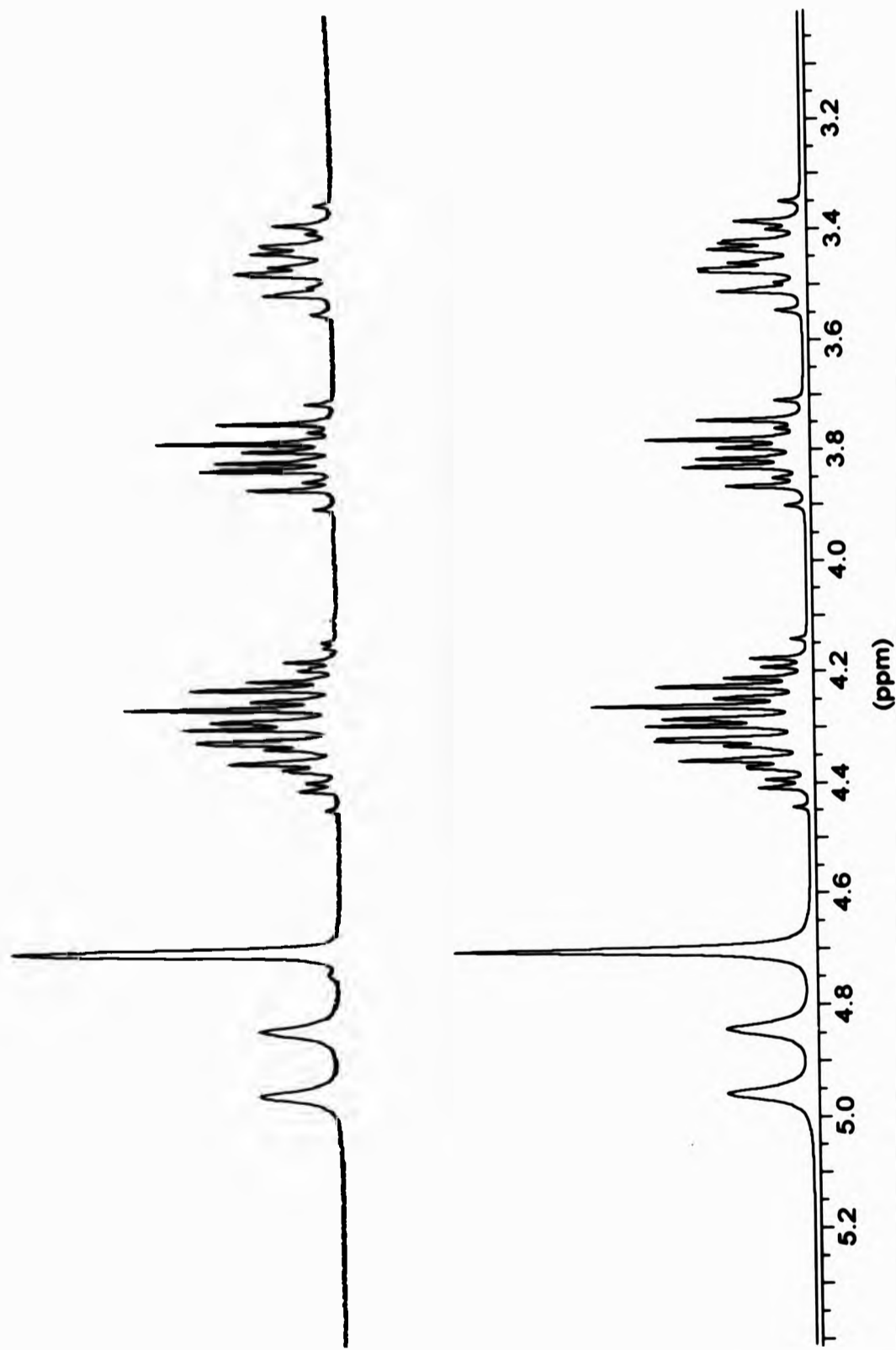
Coupling constant <sup>†</sup> (Hz)		Coupling constant (Hz)	
J <sub>H1-H2</sub>	-10.10 (1)	J <sub>P4-H6</sub>	6.64 (1)
J <sub>H1-H3</sub>	7.06 (2)	J <sub>P4-H7</sub>	0.54 (2)
J <sub>H1-P4</sub>	7.03 (7)	J <sub>P4-H8</sub>	-22.45 (81) <sup>‡</sup>
J <sub>H2-H3</sub>	7.05 (2)	J <sub>H5-H6</sub>	-10.05 (2)
J <sub>H2-P4</sub>	8.07 (2)	J <sub>H5-H7</sub>	7.04 (1)
J <sub>H3-P4</sub>	-0.57 (1)	J <sub>H6-H7</sub>	7.10 (2)
J <sub>P4-H5</sub>	8.05 (1)		

<sup>†</sup> Esd's are given in parentheses.

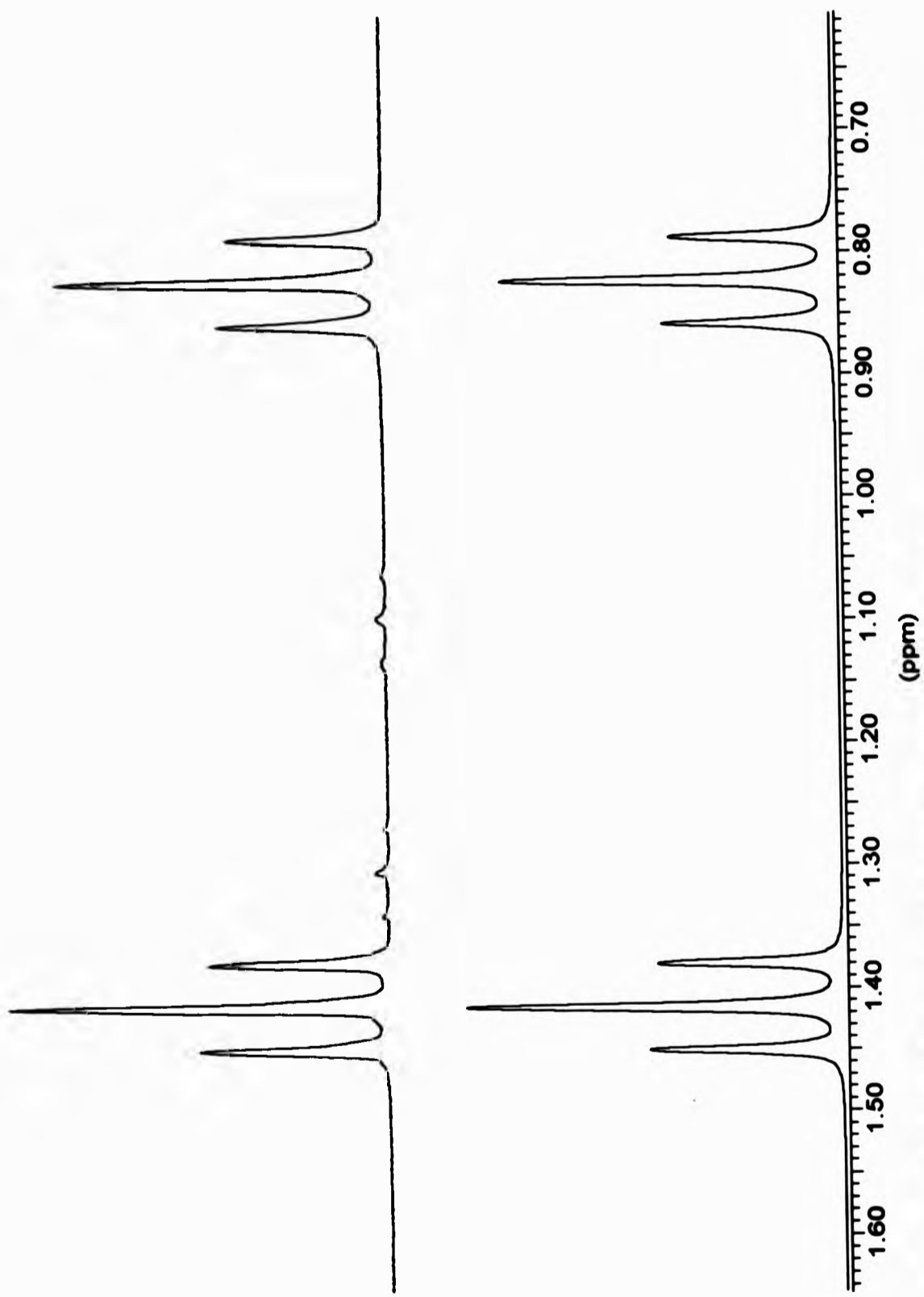
<sup>‡</sup> The large esd is due to the broad nature and fairly high noise level of this doublet and to a poor fit of the experimental spectrum to the simulated spectrum.

Statistics for iteration calculation

Final sum of squares 39.116  
(number of spectral points 6492)  
standard deviation 0.078  
R-factor 1.21%



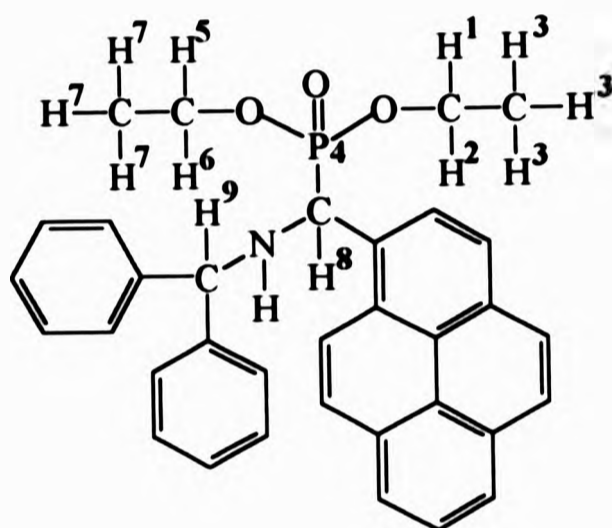
**Figure 3.36** <sup>1</sup>H NMR spectra of the methylene and methine regions of compound 5. The upper trace is the experimental spectrum and the lower trace is the simulated spectrum.



**Figure 3.37**  $^1\text{H}$  NMR spectra of the methyl region of compound 5.  
The upper trace is the experimental spectrum and the lower trace is the simulated spectrum.

### 3.3.3 $^1\text{H}$ NMR Spectrum of Diethyl 1-(1'-Pyrenyl)-1-(diphenylmethylamino)-methanephosphonate (6)

**Figure 3.38** Numbering scheme used in assigning the  $^1\text{H}$  NMR spectrum of compound 6

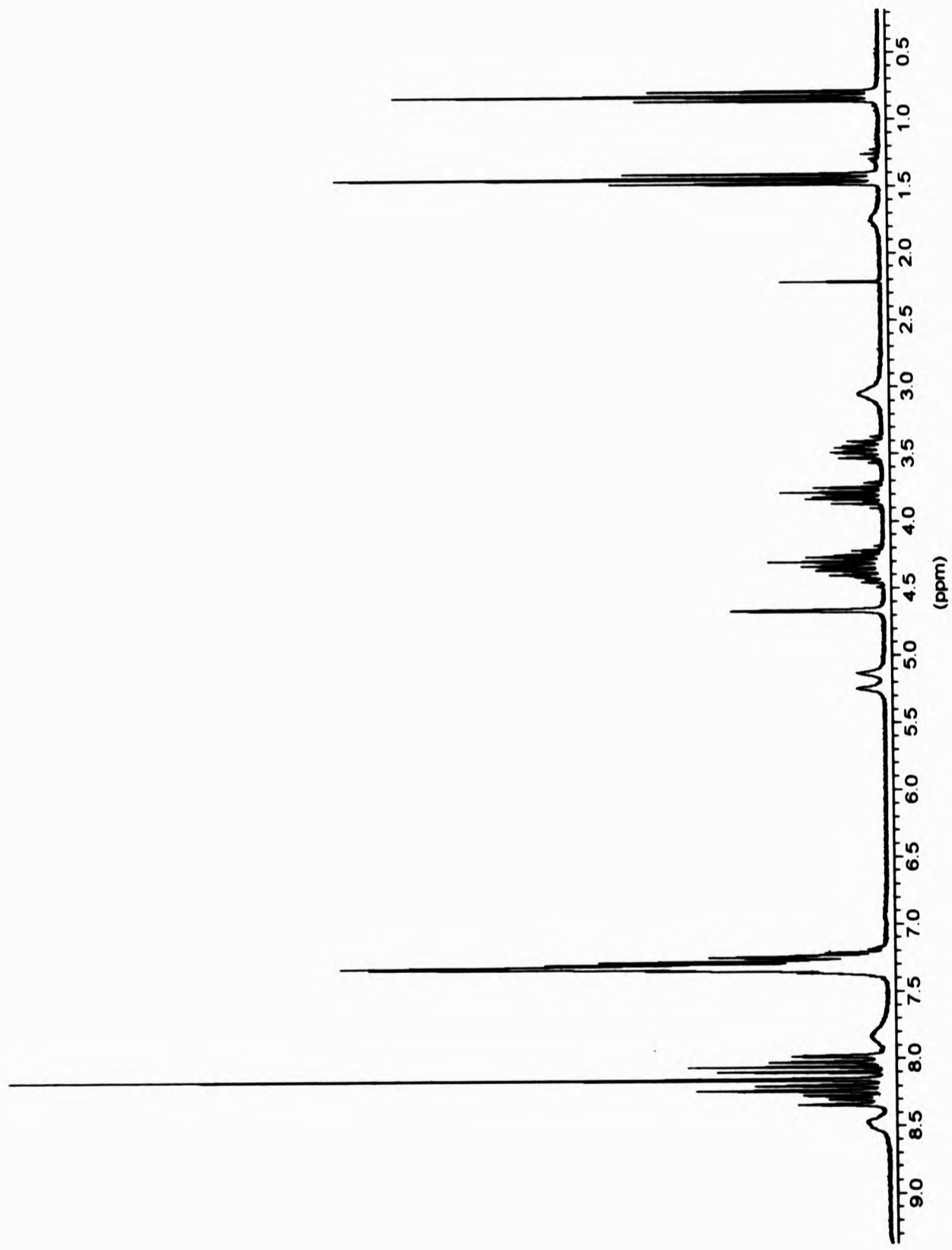


The experimental spectrum (2% w/w solution in  $\text{CDCl}_3$ ) of compound 6 (Figure 3.39) shows two triplets (0.83 and 1.44 ppm) which are assigned to the two methyl groups  $\text{H}^3$  and  $\text{H}^7$ . There are again three distinct multiplets for the four methylene protons ( $\text{H}^1$ ,  $\text{H}^2$ ,  $\text{H}^5$  and  $\text{H}^6$ ) centred at 3.47, 3.81 and 4.32 ppm. The doublet assigned to the methine proton  $\text{H}^8$  resonates as a very broad doublet at 5.19 ppm. The singlet at 4.67 ppm is assigned to the methine proton  $\text{H}^9$ .

The fragmentation, simulation and iteration procedure is exactly the same as in section 3.3.1 for compound 4. The starting parameters for the procedure were the chemical shifts from the first order hand analysis of the experimental spectrum and the coupling constants from the analysis of compound 4 section 3.3.1 (Table 3.20).

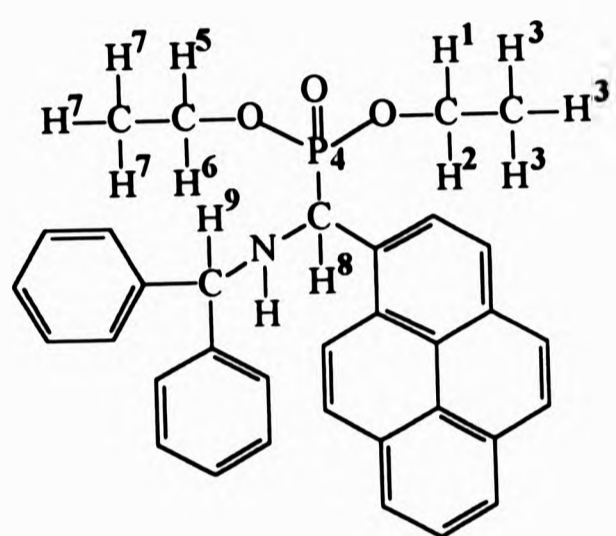
The final parameters are given in Tables 3.23 and 3.24 and the simulated spectrum is shown in Figures 3.40 and 3.41.





**Figure 3.39** Experimental <sup>1</sup>H NMR spectrum of compound 6 at 200.13 MHz.

Tables 3.23 and 3.24 Numbering scheme used in assigning the  $^1\text{H}$  NMR spectrum of compound 6



**Table 3.23**  $^1\text{H}$  NMR chemical shifts and linewidths for compound 6 determined by simulation and iteration

Number	Group	Chemical shift <sup>†</sup> (Hz)	Chemical shift (ppm)	Linewidth (Hz)
H <sup>3</sup>	CH <sub>3</sub>	165.36 (1)	0.83	0.70
H <sup>7</sup>	CH <sub>3</sub>	288.96 (1)	1.44	0.81
H <sup>1</sup>	CH of CH <sub>2</sub>	693.91 (1)	3.47	0.70
H <sup>2</sup>	CH of CH <sub>2</sub>	761.90 (1)	3.81	0.70
H <sup>5</sup>	CH of CH <sub>2</sub>	857.32 (1)	4.28	0.81
H <sup>6</sup>	CH of CH <sub>2</sub>	877.49 (1)	4.38	0.81
H <sup>9</sup>	CHN	933.79 (1)	4.67	2.42
H <sup>8</sup>	CHP	1038.37 (8)	5.19	7.50

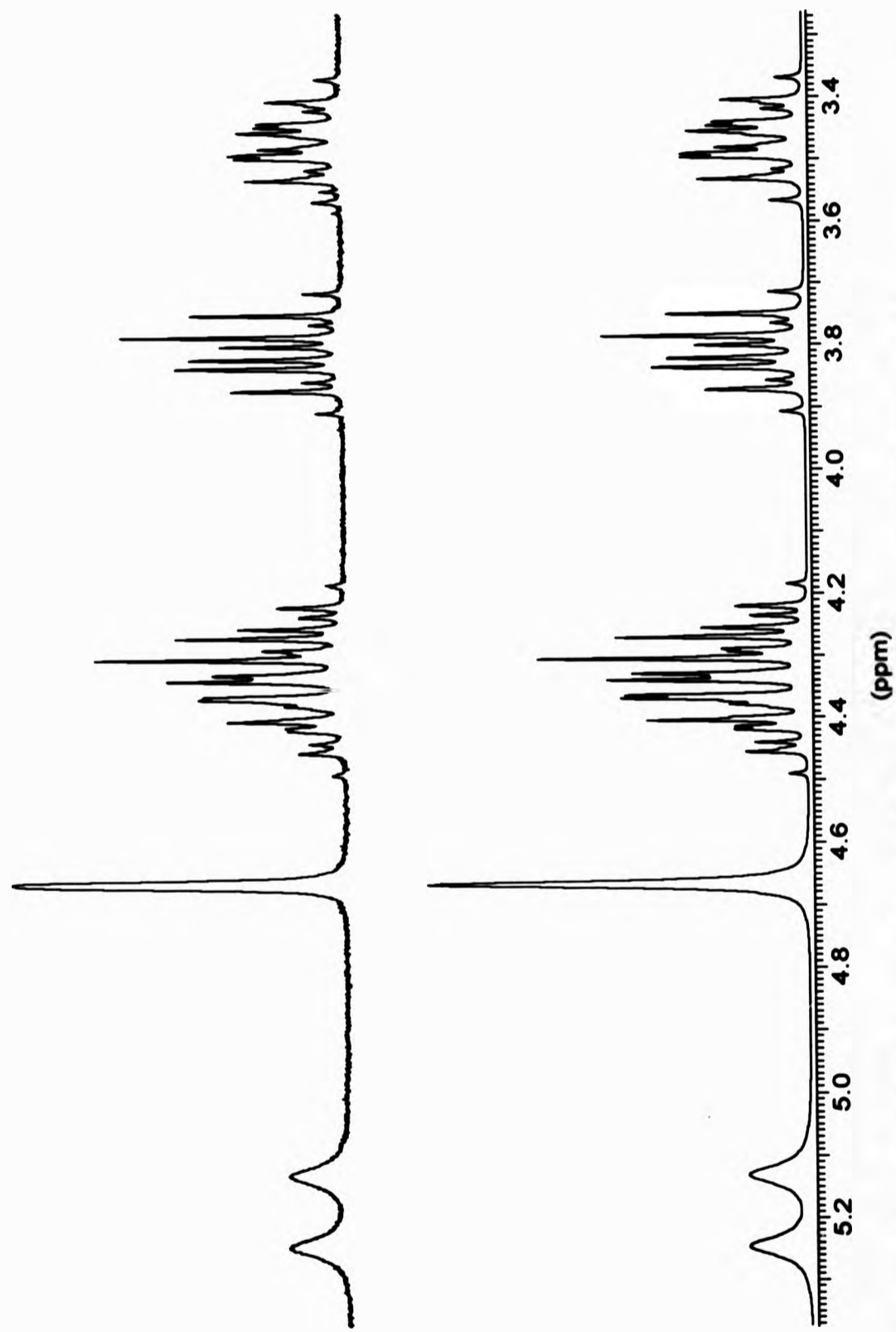
**Table 3.24**  $^1\text{H}$  NMR coupling constants for compound 6 determined by simulation and iteration

Coupling constant <sup>†</sup> (Hz)		Coupling constant(Hz)	
J <sub>H1-H2</sub>	-10.12 (1)	J <sub>P4-H6</sub>	6.67 (2)
J <sub>H1-H3</sub>	7.06 (1)	J <sub>P4-H7</sub>	-0.55 (1)
J <sub>H1-P4</sub>	7.17 (4)	J <sub>P4-H8</sub>	-23.05 (2)
J <sub>H2-H3</sub>	7.06 (1)	J <sub>H5-H6</sub>	-10.08 (1)
J <sub>H2-P4</sub>	8.20 (2)	J <sub>H5-H7</sub>	7.04 (1)
J <sub>H3-P4</sub>	0.53 (1)	J <sub>H6-H7</sub>	7.10 (1)
J <sub>P4-H5</sub>	8.10 (1)		

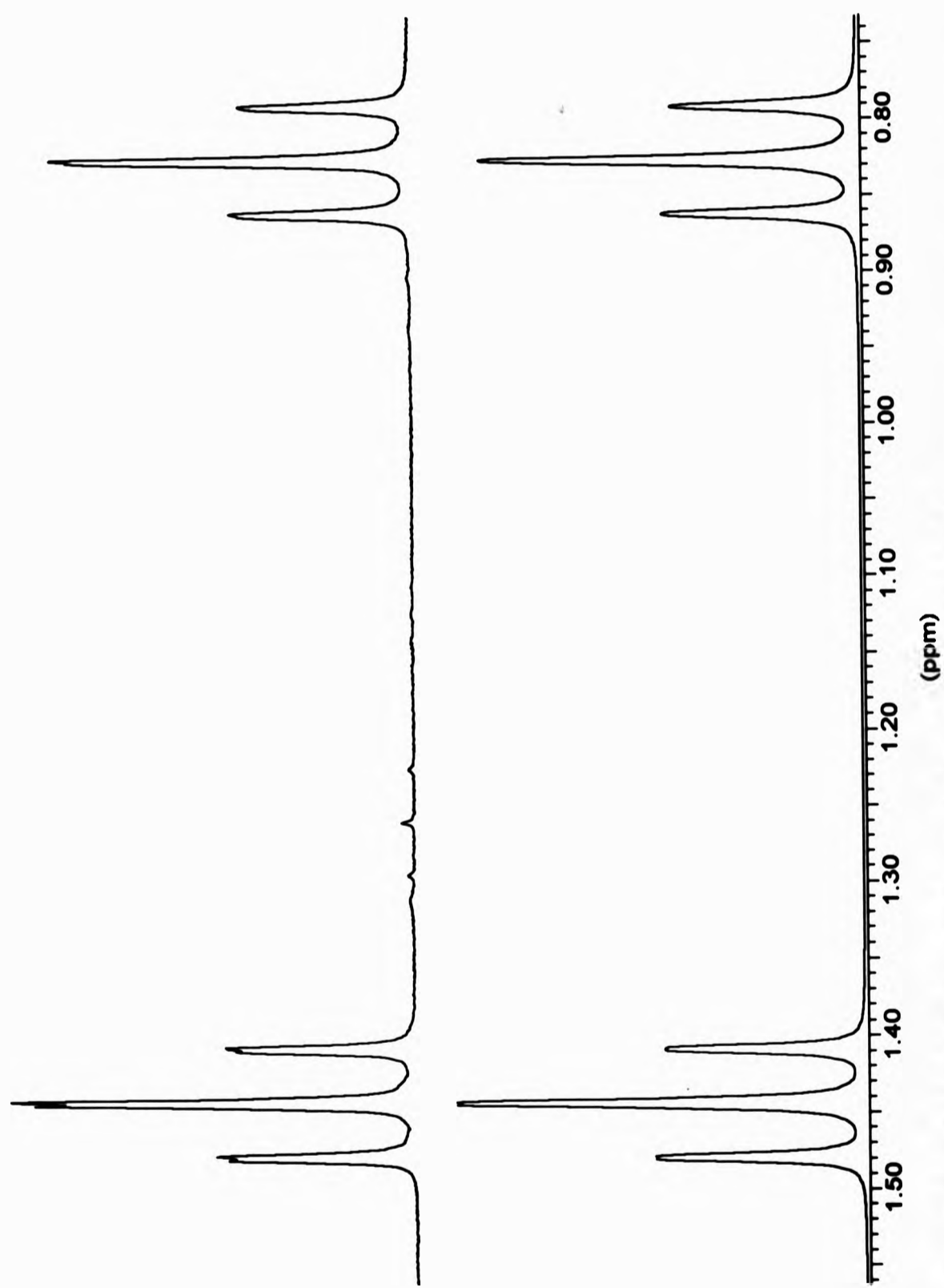
<sup>†</sup> Esd's are given in parentheses.

Statistics for iteration calculation:

Final sum of squares 29.83  
(number of spectral points 5789)  
standard deviation 0.072  
R-factor 1.02%

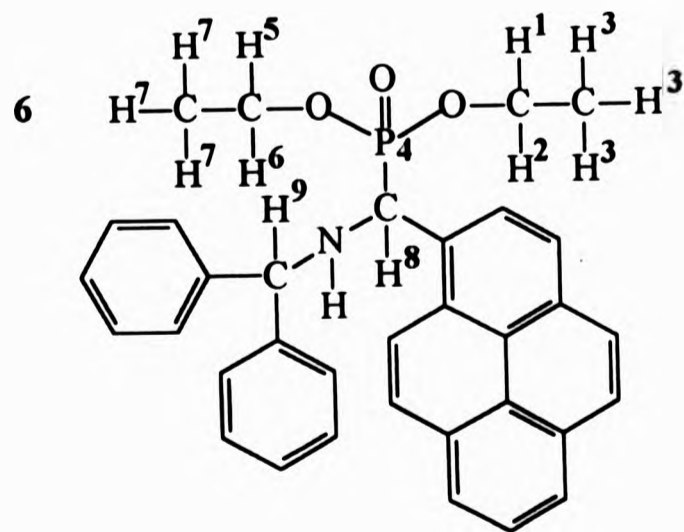
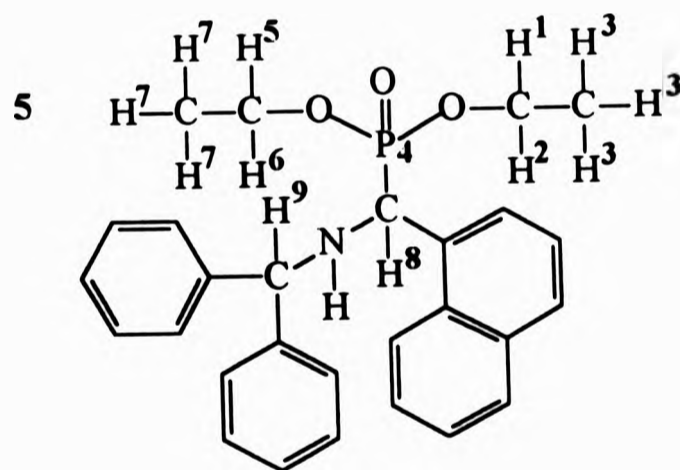
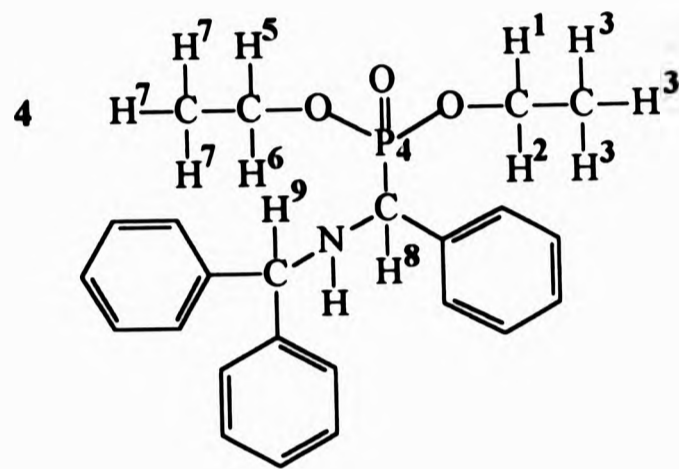


**Figure 3.40**  $^1\text{H}$  NMR spectra of the methylene and methine regions of compound 6. The upper trace is the experimental spectrum and the lower trace is the simulated spectrum.



**Figure 3.41** <sup>1</sup>H NMR spectra of the methyl region of compound **6**.  
The upper trace is the experimental spectrum and the lower trace is the simulated spectrum.

Tables 3.25 - 3.28 Numbering schemes used in assigning the  $^1\text{H}$  NMR spectra for compounds 4-6



### 3.3.4 Comparison of $^1\text{H}$ NMR Parameters of Diethyl Phosphonate Esters 4-6 from the Simulation Results

The coupling constants for compounds 4, 5 and 6 are given in Table 3.25. Analogous coupling constants do not vary very much between these compounds. This is expected if the differences between the three spectra are due to ring current effects arising from one ethyl group being closer in space to the R group.

Table 3.25  $^1\text{H}$  NMR coupling constants (Hz) for compounds 4, 5 and 6

	4	5	6
$^2J_{\text{H1-H2}}$	-10.12	-10.10	-10.12
$^3J_{\text{H1-H3}}$	7.06	7.06	7.06
$^3J_{\text{H1-P4}}$	7.10	7.03	7.17
$^3J_{\text{H2-H3}}$	7.06	7.05	7.06
$^3J_{\text{H2-P4}}$	8.02	8.07	8.20
$^4J_{\text{H3-P4}}$	0.59	-0.57	0.53
$^3J_{\text{P4-H5}}$	7.99	8.05	8.10
$^3J_{\text{P4-H6}}$	6.88	6.64	6.67
$^4J_{\text{P4-H7}}$	0.57	0.54	-0.55
$^2J_{\text{P4-H8}}$	-22.45	-22.45	-23.05
$^2J_{\text{H5-H6}}$	-10.10	-10.05	-10.08
$^3J_{\text{H5-H7}}$	7.06	7.04	7.04
$^3J_{\text{H6-H7}}$	7.08	7.10	7.10

The geminal couplings,  $^2J_{\text{HH}}$ , are very similar throughout the series of compounds 4-6. The values (*ca.* -10 Hz) are within the range expected for  $\text{sp}^3$  hybridised groups (-10 to -15 Hz).<sup>[139]</sup> The magnitude of geminal couplings is known to depend on H-C-H bond angle as well as hybridisation of the groups, and the nature and orientation of substituents on adjacent atoms is also known to affect the geminal couplings.<sup>[139]</sup>

The vicinal couplings,  $^3J_{\text{HH}}$ , (in the range 7.05 to 7.10 Hz) are again very similar within the series of compounds 4-6. The magnitude of vicinal couplings is known to have a dihedral angular dependence<sup>[140]</sup> and the substituents on adjacent atoms also affect the magnitude of the coupling. These factors do not vary much within the series.

The magnitude of the  $^2J_{\text{PH}}$  couplings do not vary greatly within the series of compounds. This  $^2J_{\text{PH}}$  coupling has been shown to be negative, both experimentally<sup>[141]</sup> and theoretically,<sup>[142]</sup> and has been shown to have a dihedral angular dependence.<sup>[118]</sup>

The  $^4J_{\text{PH}}$  couplings vary within the series of compounds; the magnitude of the couplings are similar but the signs vary. This has been noted in other simulations, where satisfactory results are only achieved when some negative  $^4J_{\text{PH}}$  couplings are included.<sup>[143-145]</sup>



**Table 3.26**  $^1\text{H}$  NMR chemical shifts (ppm) for compounds 4, 5 and 6

Nucleus	Group	4	5	6
H <sup>3</sup>	CH <sub>3</sub>	1.12	0.82	0.83
H <sup>7</sup>	CH <sub>3</sub>	1.40	1.42	1.44
H <sup>1</sup>	CH of CH <sub>2</sub>	3.75	3.45	3.47
H <sup>2</sup>	CH of CH <sub>2</sub>	3.96	3.80	3.81
H <sup>5</sup>	CH of CH <sub>2</sub>	4.22	4.24	4.28
H <sup>6</sup>	CH of CH <sub>2</sub>	4.28	4.34	4.38
H <sup>8</sup>	CHP	3.97	4.90	5.19
H <sup>9</sup>	CHN	4.72	4.70	4.67

The chemical shifts of compounds 4, 5 and 6 are given in Table 3.26. As seen in section 3.2.2 in the hand analysis of the diethyl phosphonate series 4-6 and 27-34, the upfield signals assigned to the methyl protons vary within the series whereas the downfield signals assigned to the other methyl protons are very similar and fall in the range 1.40 to 1.44 ppm. This could imply that any effect due to the aromatic substituent is affecting one methyl group (the upfield methyl signals) and having little effect on the other, or that the effect on the other methyl protons (the downfield signals) is the same within the series. The trend is not as easy to follow in the signals due to the methylene protons. As might be expected the signal assigned to the methine proton H<sup>8</sup> is deshielded as the size of the aromatic substituent increases.

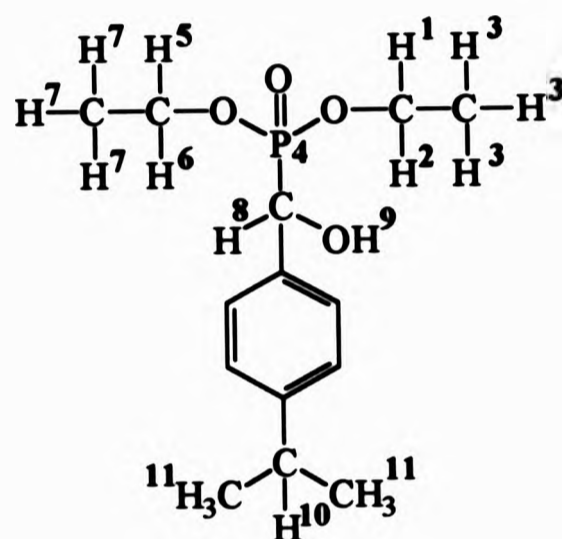
**Table 3.27**  $^1\text{H}$  NMR Linewidth (Hz) of signals for compounds 4, 5 and 6

Nucleus	Group	4	5	6
H <sup>3</sup>	CH <sub>3</sub>	0.83	1.15	0.70
H <sup>7</sup>	CH <sub>3</sub>	0.84	0.96	0.81
H <sup>1</sup>	CH of CH <sub>2</sub>	0.83	1.15	0.70
H <sup>2</sup>	CH of CH <sub>2</sub>	0.83	1.15	0.70
H <sup>5</sup>	CH of CH <sub>2</sub>	0.84	0.96	0.81
H <sup>6</sup>	CH of CH <sub>2</sub>	0.84	0.96	0.81
H <sup>8</sup>	CHP	1.31	4.99	7.50
H <sup>9</sup>	CHN	2.11	2.36	2.42

The linewidths of the signals in compounds 4, 5 and 6 are given in Table 3.27. The signals assigned to the methine protons, H<sup>8</sup> and H<sup>9</sup>, are particularly broad. The broadness can be attributed to these protons coupling to the adjacent NH proton, which is exchanging. The HH-COSY spectrum of compound 6 indicates that the methine proton H<sup>8</sup> couples to the NH proton, this coupling is not apparent in the HH-COSY spectra of compounds 4 and 5. This observation may be attributed to the slower N-H exchange rate in compound 6, which generates the broad signal and the apparent coupling in the HH-COSY spectrum. The proximity of the quadrupolar  $^{14}\text{N}$  nucleus may also be a factor.

### 3.3.5 $^1\text{H}$ NMR Spectrum of Diethyl 1-Hydroxy-1-(4'-isopropylbenzyl)-phosphonate **3**

**Figure 3.42** Numbering scheme used for assigning the  $^1\text{H}$  NMR spectrum of compound **3**



The experimental spectrum (2% w/w solution in  $\text{CDCl}_3$ ) of compound **3** (Figure 3.43) shows two triplets (1.24 and 1.30 ppm) which are assigned to the two methyl groups  $\text{H}^3$  and  $\text{H}^7$  overlapping with a doublet at 1.27 ppm ( $^3J_{\text{H}^{10}-\text{H}^{11}}$  6.9 Hz) assigned to the two methyl group  $\text{H}^{11}$ . There is a septet centred at 2.93 ppm assigned to  $\text{H}^{10}$  and a quartet centred at 3.76 ppm ( $^3J_{\text{H}^8-\text{H}^9}$  5.3 Hz) assigned to the hydroxyl proton  $\text{H}^9$  ( $^3J_{\text{PH}^8}$  10.0 Hz). There is a complex multiplet centred at 4.80 ppm assigned to the four methylene protons ( $\text{H}^1$ ,  $\text{H}^2$ ,  $\text{H}^5$  and  $\text{H}^6$ ) and a the quartet at 5.13 ppm assigned to  $\text{H}^8$  ( $^2J_{\text{PH}^8}$  10.8 Hz). The chemical shifts given above were used as the starting parameters in the simulation.

The fragmentation, simulation and iteration procedure was carried out in exactly the same way as in section 3.3.1. The starting parameters for the procedure were the chemical shifts and coupling constants from the hand analysis of the spectrum; the coupling constants that were not available from the hand analysis were taken from the analysis of compound **4** section 3.3.1 (Table 3.20).

This simulation was unsuccessful; as the multiplet assigned to H<sup>1</sup>, H<sup>2</sup>, H<sup>3</sup> and H<sup>6</sup> could not be satisfactorily simulated, although the rest of the spectrum looks well matched (see Figure 3.44). The multiplet assigned to the methylene protons is more compressed than in the <sup>1</sup>H NMR spectra of the other compounds 4-6 studied, with the multiplets assigned to all four methylene protons overlapping.

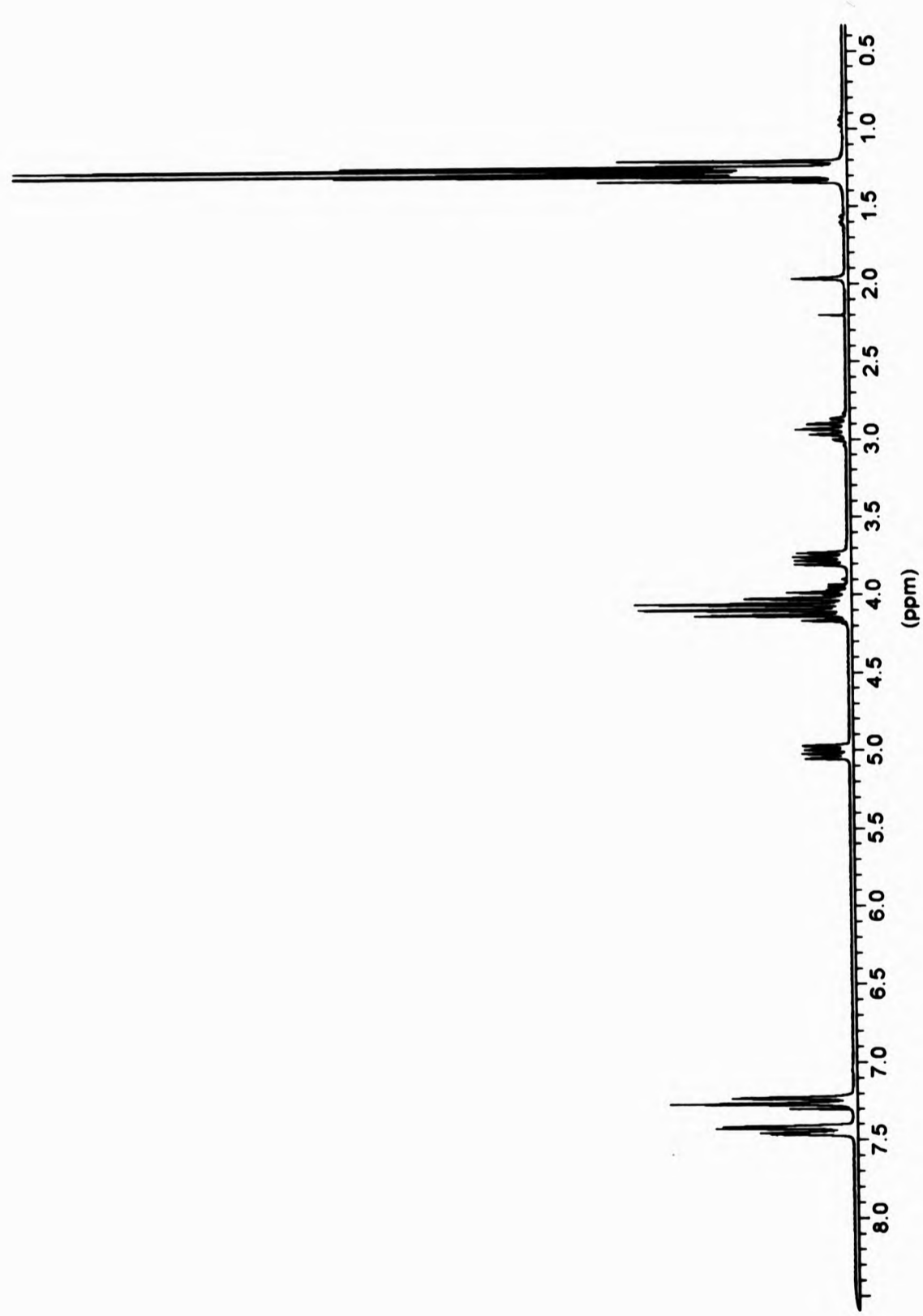
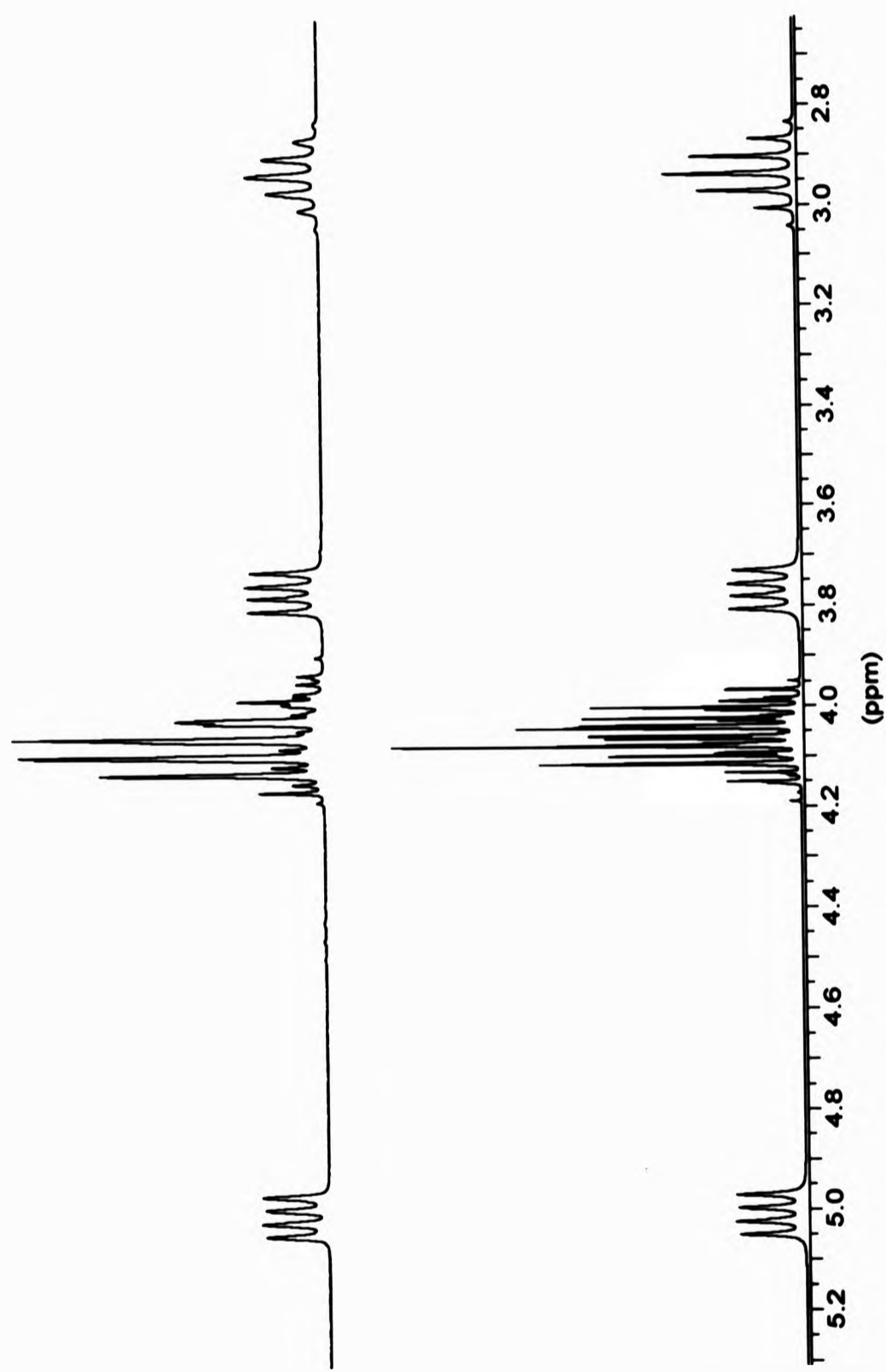


Figure 3.43 Experimental  $^1\text{H}$  NMR spectrum of compound 3 at 200.13 MHz.



**Figure 3.44** <sup>1</sup>H NMR spectra of the methylene, methine and hydroxyl regions of compound **3**.  
The upper trace is the experimental spectrum and the lower trace is the unsatisfactory simulated spectrum.

## CHAPTER FOUR

### PHOSPHONIC ACIDS

#### 4.1 Introduction

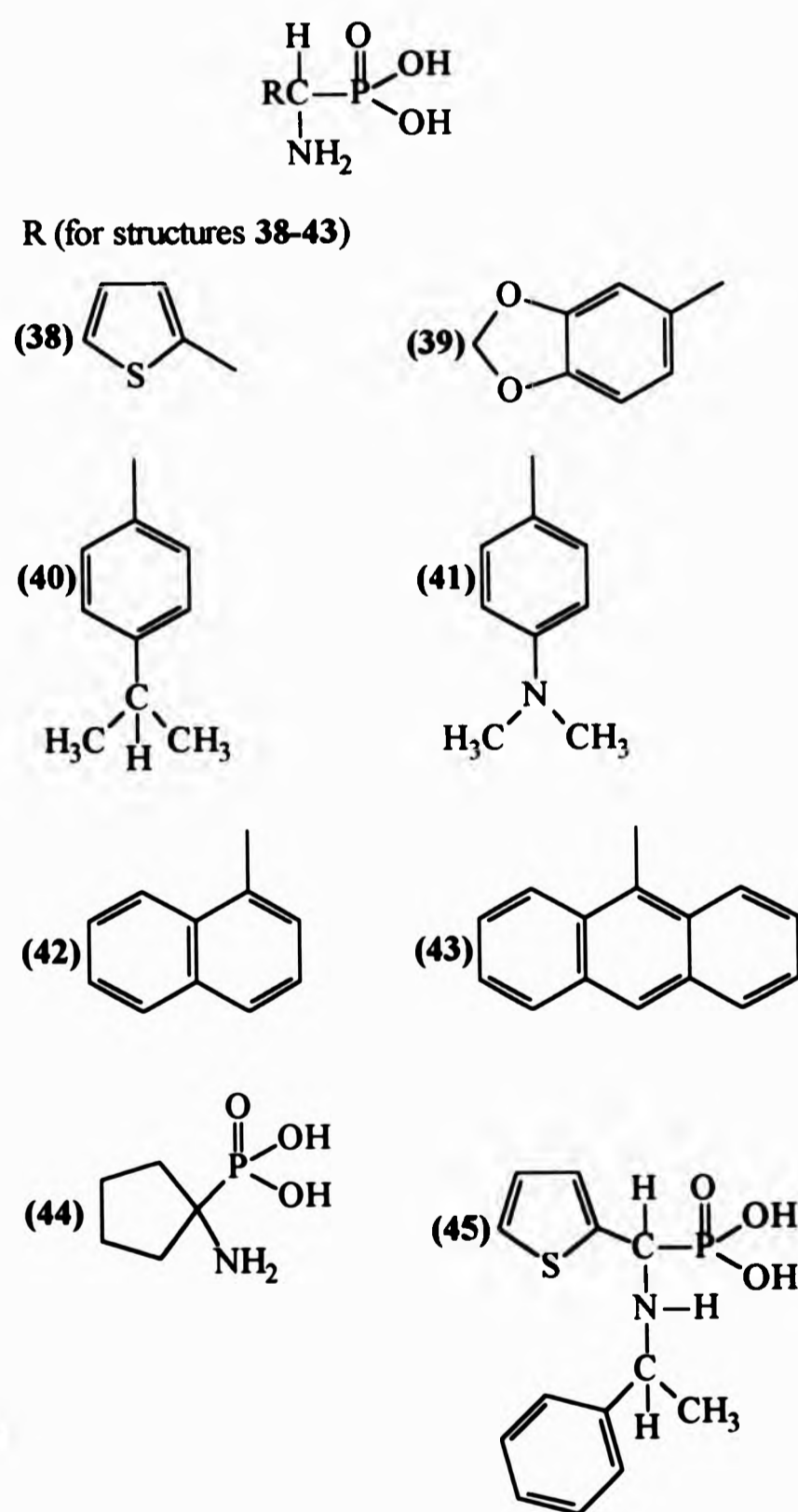
$\alpha$ -Amino-substituted phosphonic acids can be thought of as the phosphorus analogues of the naturally occurring  $\alpha$ -aminocarboxylic acids. The phosphorus analogues of all the common protein amino acids have now been synthesised.<sup>[6, 146, 147]</sup> Phosphonic acids are considered important because of their wide variety of potential biological activities. This chapter describes the synthesis of some novel  $\alpha$ -aminophosphonic acids which could have interesting biological activity. The analysis of the  $^1\text{H}$  NMR spectra of  $\alpha$ -aminopropane-phosphonic and phosphinic acids has also been carried out to gain some insight into the conformations the molecules adopt in solution and which could be important in any biological activity that the molecules have.

#### 4.2 Preparation of Phosphonic Acids from Imine Precursors

The phosphonic acids **38-45** (Figure 4.1) were prepared by heating a 1:1 molar ratio of the imine precursors **10-13**, **15-16**, **18** and **22** (see Chapter 2, Figure 2.1) with diethyl phosphite to give the diethyl phosphonate esters. The phosphonate esters were not isolated, but their formation was confirmed by the presence of a signal at *ca.* 20-30 ppm in the  $^{31}\text{P}$  NMR spectrum of the reaction mixture. The phosphonate esters were hydrolysed by refluxing in concentrated hydrochloric acid for about 3 hours (Scheme 4.1). In the formation of the phosphonic acids **38-44** the ethyl ester groups and the  $\text{CHPh}_2$  group are cleaved in this one step. This same procedure was carried out for the phosphonic acid **45**, but acid-hydrolysis does not cleave the  $\text{CH}(\text{CH}_3)\text{Ph}$  group; in this case only the ethyl ester groups are cleaved. The relative stability of the cations formed by C-N cleavage is an important factor. The cation  $^+\text{CHPh}_2$  has two phenyl rings which delocalise and stabilise the cation charge whereas the cation  $^+[\text{CH}(\text{CH}_3)\text{Ph}]$  has only the one phenyl ring. Cleavage of the C-N bond in the phosphonic acid **45** would require hydrogenolysis rather than just hydrolysis.<sup>[148, 149]</sup> Reaction by-products were removed by washing with toluene

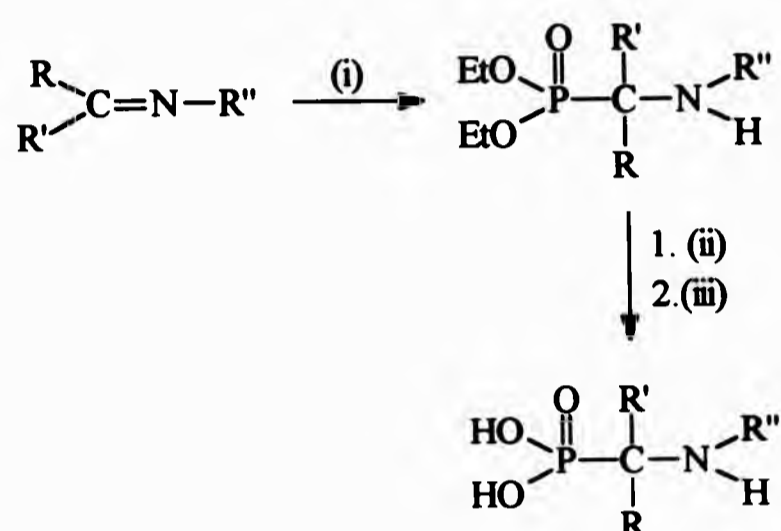
to give the hydrochloride salt of the phosphonic acid. The free phosphonic acid was obtained by dissolving the hydrochloride salt of the phosphonic acid in the minimum amount of warm methanol and adding pre-cooled propylene oxide dropwise until the pH of the reaction mixture reached *ca.* 6, when the free phosphonic acid precipitated.

**Figure 4.1** Phosphonic acids prepared in this work from the imine precursors





**Scheme 4.1** Preparation of  $\alpha$ -aminophosphonic acids from imines



**38-43** R = various substituents R' = H R'' = H

**44** R and R' = part of cyclopentyl ring R'' = H

**45** R = 2'-thienyl substituent R' = H R'' = CH(CH<sub>3</sub>)Ph

*Reagents* (i) HPO(OEt)<sub>2</sub>/Δ (ii) HCl/H<sub>2</sub>O/Δ (iii) Propylene oxide

The phosphonic acids **38-45** were all isolated as microcrystalline solids with high melting points. The yields of the reactions after recrystallisation from hot ethanol and acetone are given in Table 4.1. All the yields are fairly low except for the two phosphonic acids **38** and **45**, which have a 2'-thienyl substituent. The yield of  $\alpha$ -amino- $\alpha$ -cyclopentanephosphonic acid **44** is especially low but this is probably due to the low yield of the phosphonate ester precursor produced (see section 3.2).

**Table 4.1** Yield (%) of phosphonic acids **38-45** after recrystallisation

Compound	% Yield	Compound	% Yield
<b>38</b>	71.5	<b>42</b>	31.8
<b>39</b>	41.6	<b>43</b>	37.4
<b>40</b>	40.7	<b>44</b>	16.2
<b>41</b>	41.1	<b>45</b>	81.7

The imine precursors derived from pyrrole 7, furan 8 and pyrene 17 failed to react to give the phosphonic acid product. The imine derived from pyrrole successfully gave the phosphonate ester (as deduced from the  $^{31}\text{P}$  NMR spectrum, see section 3.2.2) but failed to give the phosphonic acid; the reaction yielded an intractable black tar. The pyrrole derivative was reported to decompose when subjected to prolonged heating in a similar reaction.<sup>[98]</sup> The imine derived from furan successfully gave the phosphonate ester but failed to give the desired phosphonic acid. The furan ring is reported to be acid sensitive and to decompose in the acid conditions.<sup>[150]</sup> The imine derived from pyrene also successfully gave the phosphonate ester but failed to give the desired phosphonic acid product.

The preparation of  $\alpha$ -amino- $\alpha$ -(2'-pyridyl)methanephosphonic acid has been reported to be problematic.<sup>[151]</sup> The conditions required for the acid-hydrolysis of phosphonate ester to the phosphonic acid were reported to lead to dephosphorylation of the molecule and the decomposition of the pyridyl ring. This problem was reported to be overcome by reducing the reaction time of the acid-hydrolysis step, although the product was still isolated in poor yield.<sup>[151]</sup> However, decreasing the concentration of the acid used and/or reducing the length of reaction time failed to give the desired phosphonic acids in the reactions of the pyrrole, furan and pyrene derivatives.

### 4.3 Characterisation of the Phosphonic Acids Prepared from Imine Precursors

#### 4.3.1 Mass Spectrometry of Phosphonic Acids

Liquid secondary ion mass spectrometry (LSIMS) which employs a soft ionisation technique was used for the phosphonic acids. This technique<sup>[152]</sup> was required because the phosphonic acids are involatile and are zwitterionic, so that EI ionisation would be unsuitable.

In most cases the base peak corresponds to either the pseudomolecular ion  $(\text{M}+\text{H})^+$  or the ion formed from this by the elimination of phosphorous acid, a fragment that has been found to be characteristic in the fast atom bombardment (FAB) of aminophosphonic

acids.<sup>[153, 154]</sup> The ion  $[(MH+(G))^+]$  was seen in most of the compounds, where G is a molecule of the glycerol, which is used as the matrix. The important fragments are shown in Table 4.2.

**Table 4.2** Values of m/z and relative abundance (%) for the important fragments in the mass spectra of phosphonic acids **38-45**

Compound	$[MH-(H_3PO_3)]^+$	$[M+H-(OH)]^+$	$(M+H)^+$	$[M+H+(G)]^+$
<b>38</b>	-	-	194 (100)	286 (72)
<b>39</b>	150 (100)	215 (17)	232 (6)	324 (2)
<b>40</b>	148 (100)	-	230 (18)	322 (4)
<b>41</b>	149 (100)	214 (96)	231 (12)	323 (2)
<b>42</b>	-	221 (15)	238 (100)	-
<b>43<sup>†</sup></b>	206 (34)	271 (26)	288 (11)	-
<b>44</b>	-	149 (100)	166 (37)	258 (17)
<b>45</b>	216 (100)	281 (1)	298 (36)	-

<sup>†</sup> Where G is a molecule of glycerol matrix.

<sup>‡</sup> Base peak corresponds to m/z 149.

#### 4.3.2 <sup>1</sup>H and <sup>13</sup>C NMR Spectroscopy of Phosphonic Acids Prepared from Imine Precursors

The <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectra of the phosphonic acids **38-45** were obtained for a saturated solution in an NaOD solution (the NaOD solution itself was prepared by saturating D<sub>2</sub>O with sodium metal under dry nitrogen, then filtering the solution). It was necessary to use NaOD as the solvent as this was the only solvent in which all the compounds were sufficiently soluble. First order analyses of the spectra were carried out by inspection and the results of these analyses (chemical shifts and coupling constants) are given in Appendix IV.

The chemical shifts and coupling constants of H<sup>a</sup> and C<sup>i</sup> (Figure 4.2) can be compared within the series of phosphonic acids prepared (Table 4.3).

The signal assigned to the proton H<sup>a</sup> appears as a doublet in the spectra of all the compounds. Compounds **38** and **45** differ from each other only in the substitution on the nitrogen atom. This clearly has little effect on the chemical shift of the signal assigned to H<sup>a</sup>. The chemical shifts of this signal in compounds **39**, **40** and **41** are very similar (3.73-3.79 ppm). The signal in compounds **42** and **44** is downfield compared to the other compounds due to the shielding effects and/or the aromatic ring current effects of the larger aromatic ring substituents.

The <sup>2</sup>J<sub>P-H<sup>a</sup></sub> coupling in the compounds **38-41** does not differ significantly. The coupling in the other 2'-thienyl derivative (**45**) is significantly larger, but not as large as the coupling in the anthryl derivative (**43**). The coupling in the anthryl derivative is of similar magnitude to the <sup>2</sup>J<sub>PH</sub> coupling observed in the phosphonate ester derivatives. There is evidence of a relationship between dihedral angle and the magnitude of the <sup>2</sup>J<sub>PH</sub> couplings.<sup>[118]</sup> The bulk of the substituent in the anthryl compound, **43**, could affect the dihedral angle and thus the <sup>2</sup>J<sub>PH</sub> coupling. A similar situation could also exist in compound **45**, where the substituents on the nitrogen could affect the dihedral angle.

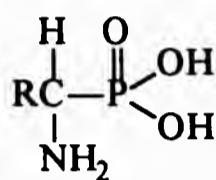
The signal assigned to the carbon atom C<sup>i</sup> appears as a large doublet in all the compounds. The carbon C<sup>i</sup> is the point of substitution so the largest effect of the substituent might be expected here. The signal in the anthryl **43** and naphthyl **42** derivatives is shifted upfield compared to all the other compounds, with compounds **39-41** having similar values. In the two 2'-thienyl derivatives, **38** and **45**, there is a significant difference in chemical shift for the signal assigned to this carbon. In the cyclopentyl derivative **44** the signal is shifted significantly downfield compared to all the other compounds, because the carbon in this compound is quaternary and would be expected to resonate downfield compared to a protonated carbon atom.

The <sup>1</sup>J<sub>PC</sub> coupling observed throughout the series of compounds is known to depend on the percentage s character in the P-C bond.<sup>[124]</sup> The couplings are in the main smaller than the analogous couplings in the phosphonate ester derivatives. The N-protected 2'-thienyl derivative **45** and the cyclopentyl derivative **44** have larger coupling constants than in the

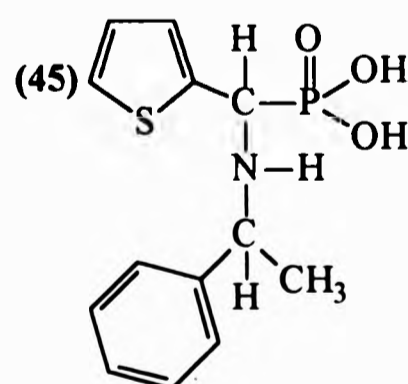
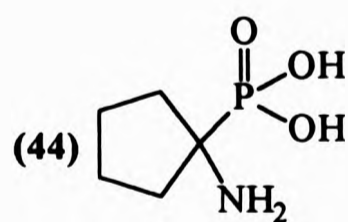
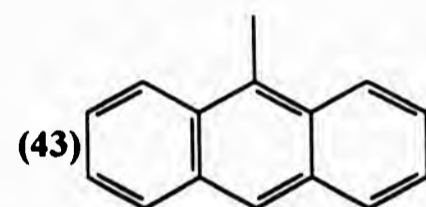
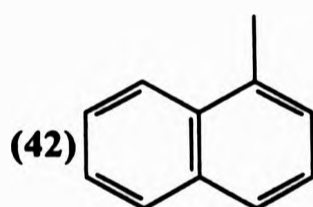
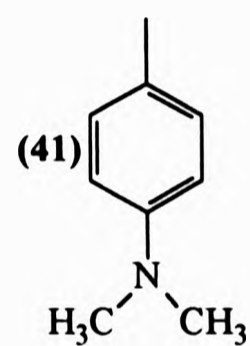
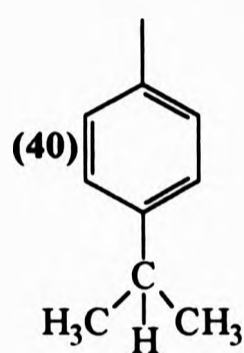
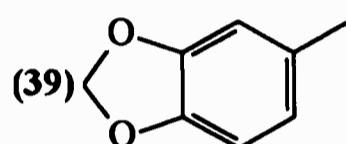
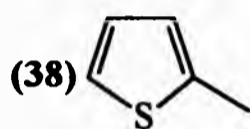
other compounds. The value of the 2'-thienyl phosphonate ester derivative, **30**, has a  $^1J_{PC}$  coupling more in keeping with the values seen for the acid derivatives.

It is known that there is no clear correlation between the electronegativity of substituents and  $^{31}\text{P}$  NMR chemical shift position. The  $^{31}\text{P}$  chemical shift is a function of several effects including  $\pi$ -electron overlap,  $\sigma$ -bond angles, and all the effects that these factors cause, as well as the electronegativity of the substituents.<sup>[129]</sup> The chemical shifts of the singlet in the  $^{31}\text{P}$  NMR spectrum of all the compounds are very similar (18.2-18.8 ppm) except the two 2'-thienyl derivatives **38** and **45**. The  $\delta_P$  in the thienyl derivatives are slightly upfield compared to the other compounds. In the phosphonate ester derivatives the  $\delta_P$  of the cyclo-alkane derivatives was shifted downfield presumably due to the increased steric bulk at the  $\alpha$ -carbon atom. This is not apparent in the acid derivatives, although there is just the one example the cyclopentyl derivative **44**.

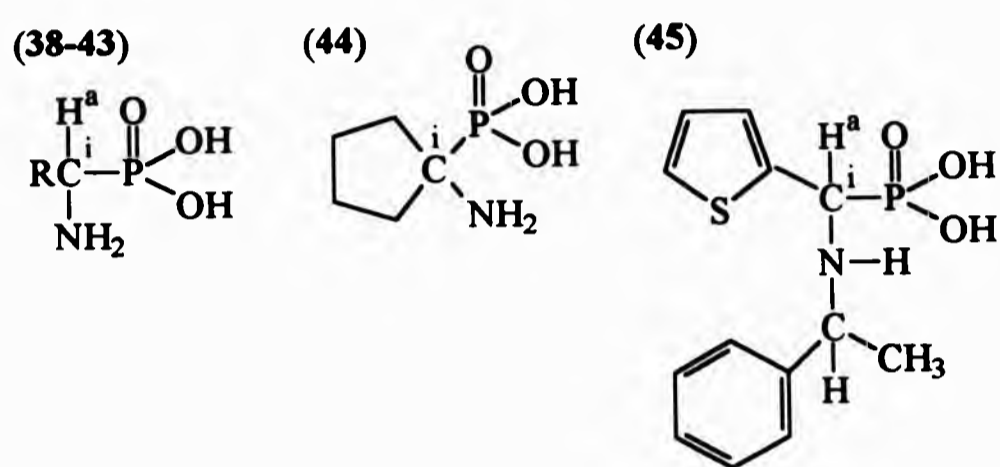
**Table 4.3** Phosphonic acids referred to in Table 4.3



R (for structures 38-43)



**Figure 4.2** Labelling scheme for selected protons and carbon atoms in compounds 38-45



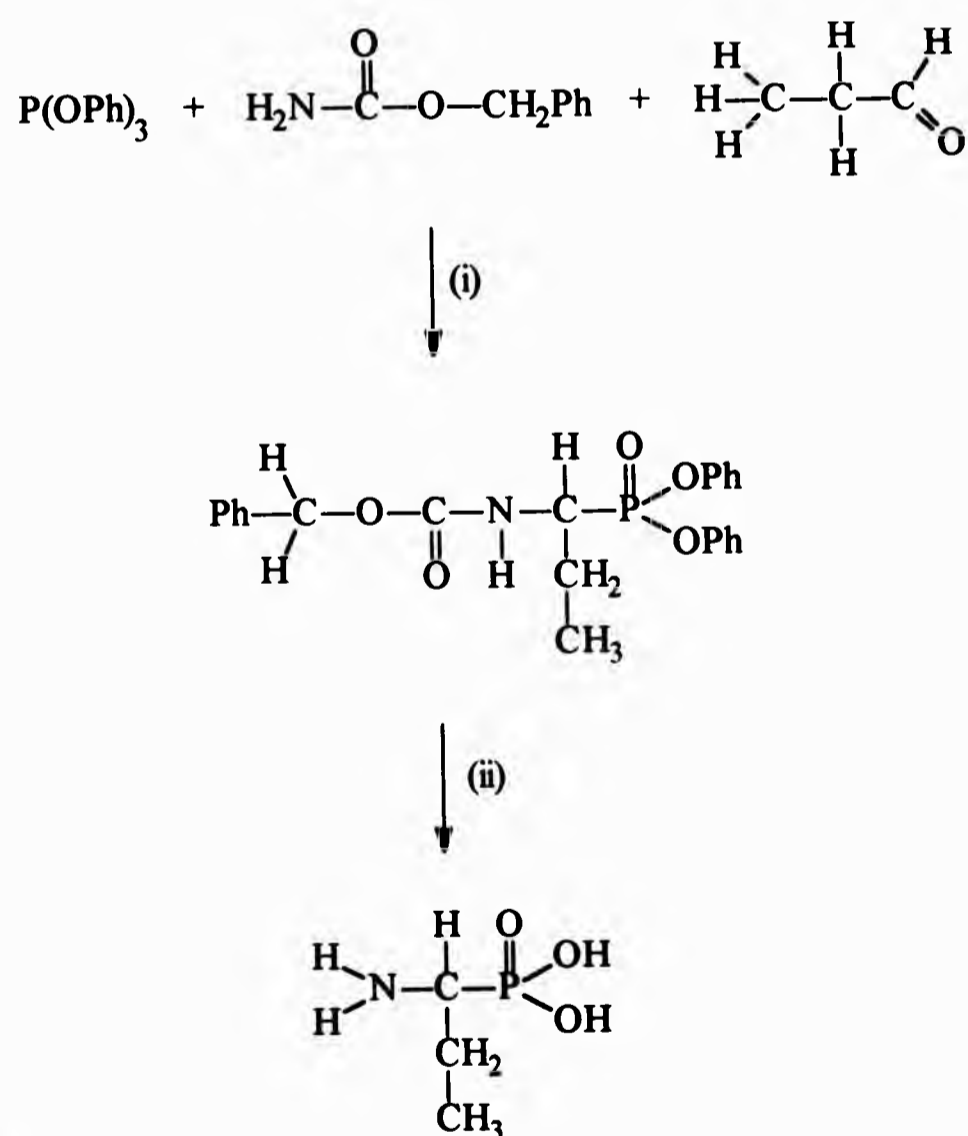
**Table 4.3** Selected  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts (ppm) and coupling constants (Hz) for the phosphonic acids 38-45

Compound	$\delta_{\text{H}^a}$	$^2J_{\text{H}^a\text{-P}}$	$\delta_{\text{C}^i}$	$^1J_{\text{C}^i\text{-P}}$	$\delta_{\text{P}}$
38	4.19	15.1	53.9	133.6	17.3
39	3.73	15.2	58.1	132.5	18.2
40	3.79	15.5	58.0	131.6	18.4
41	3.74	15.0	57.6	132.8	18.6
42	4.76	16.1	52.6	131.1	18.8
43	5.54	22.3	54.3	130.1	18.4
44	-	-	65.1	143.1	18.5
45	4.17	18.6	59.7	136.0	16.1

#### 4.4 Preparation of $\alpha$ -Aminopropanephosphonic Acid

$\alpha$ -Aminopropanephosphonic acid was prepared according to the method of Oleksyszyn and Tyka (Scheme 4.2).<sup>[155]</sup> Triphenyl phosphite, benzyl carbamate and propionaldehyde were refluxed together to give diphenyl  $\alpha$ -(N-benzyloxycarbonylamino)propane phosphonate. Boron trifluorine etherate was used as a Lewis acid catalyst in the reaction.<sup>[47]</sup> The phosphonate ester was then acid-hydrolysed to give the hydrochloride salt of the phosphonic acid which was treated with propylene oxide in methanol to give the free phosphonic acid in moderate yield.

**Scheme 4.2** Procedure for the preparation  $\alpha$ -aminopropanephosphonic acid 1



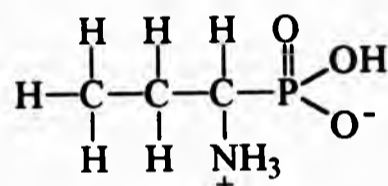
Reagents (i)  $\text{BF}_3 \cdot \text{OEt}_2 / \text{CH}_3\text{COOH}$  (ii)  $\text{HCl} / \text{H}_2\text{O} / \Delta$



#### 4.4.1 Studies of Conformation in Solution of $\alpha$ -Aminopropanephosphonic Acid (1)

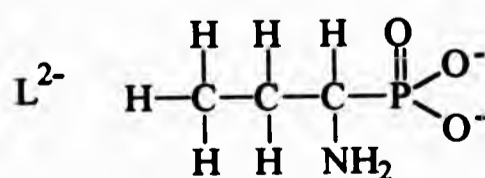
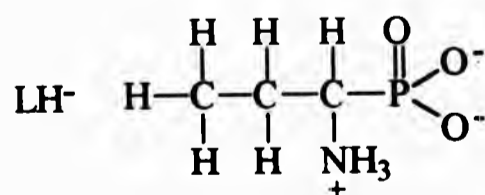
Previous studies have shown that at pH 3.19 the molecules of compound 1 exist primarily in the zwitterionic form  $LH_2$  (Figure 4.3),<sup>[156]</sup> where L is the fully deprotonated molecule. This is the pH obtained for a saturated solution of 1 in  $D_2O$  at room temperature; the concentration of the solution was  $0.42 \text{ mol dm}^{-3}$ . It should be noted that although pH will be quoted the measurements are actually pD ( $pD = \text{pH meter reading} + 0.4$ ).<sup>[157, 158]</sup>

Figure 4.3 Dominant species in solution at pH 3.10 for compound 1 ( $LH_2$ )



From potentiometric studies to determine the  $pK_a$  values together with  $^{31}\text{P}$  NMR titration results it is known that the dominant species at pH 7.54 is  $LH^-$ , while at pH 11.44 the dominant species present will be  $L^{2-}$  (Figure 4.4).<sup>[156]</sup> The  $^1\text{H}$  NMR spectra of these different species were investigated.

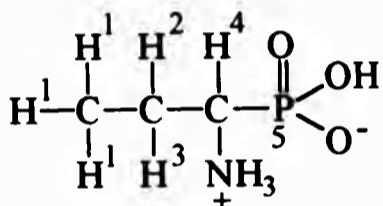
Figure 4.4 Dominant species at pH 7.5 ( $LH^-$ ) and pH 11.4 ( $L^{2-}$ ) for compound 1



#### 4.4.1.1 $^1\text{H}$ NMR Spectrum of $\alpha$ -Aminopropanephosphonic Acid (1) at pH 3.19

The experimental spectrum (Figure 4.6, lower spectrum) shows a doublet of doublet of doublets at 3.2 ppm assigned to the methine proton  $\text{H}^4$ , a complex multiplet centred at  $\sim 1.9$  ppm assigned to the anisochronous methylene protons  $\text{H}^2$  and  $\text{H}^3$  and a broad triplet at  $\sim 1.1$  ppm assigned to the methyl group protons  $\text{H}^1$  (see Figure 4.5 for numbering scheme).

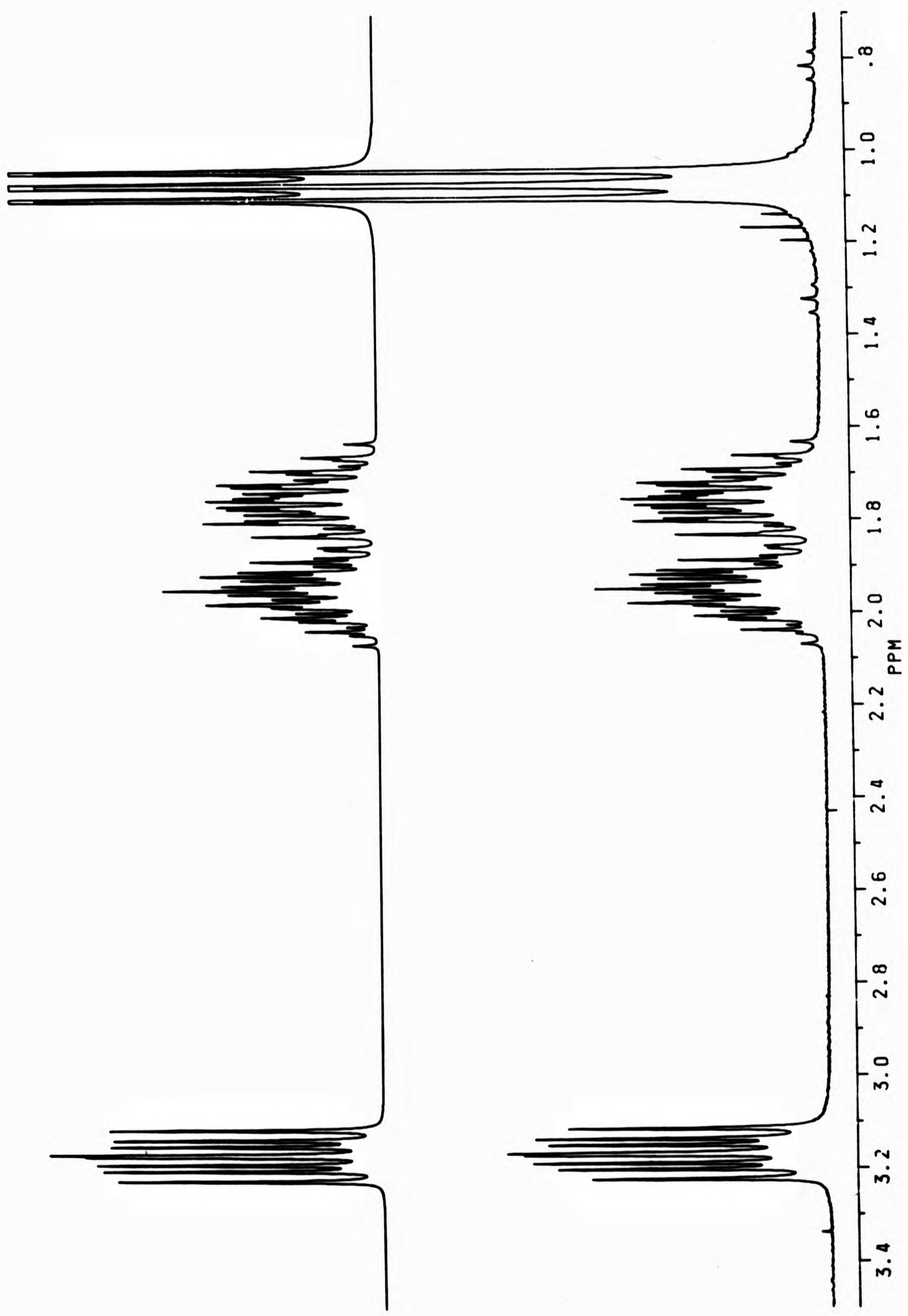
Figure 4.5 Numbering scheme used in assigning the  $^1\text{H}$  NMR spectrum of compound 1



Approximate values for chemical shifts and spin-spin coupling constants involving  $\text{H}^1$  and  $\text{H}^4$  were obtained by a first order analysis of the methyl and methine regions of the spectrum. The complex methylene region did not lend itself to this type of analysis, but the chemical shifts of these protons were taken as the centres of the two distinct halves of the multiplet pattern. The parameters obtained from the first order analysis were: chemical shifts (ppm)  $\text{H}^1$  1.07,  $\text{H}^2$  1.74,  $\text{H}^3$  1.96 and  $\text{H}^4$  3.17; coupling constants (Hz)  $^3\text{J}_{\text{H}^1\text{-H}^2} \sim ^3\text{J}_{\text{H}^1\text{-H}^3} \sim 7.5$  Hz,  $^3\text{J}_{\text{H}^2\text{-H}^4}$  and  $^3\text{J}_{\text{H}^3\text{-H}^4} \sim 5.5$  and  $8.8$  Hz and  $^2\text{J}_{\text{P-H}^4} \sim 13.0$ .

First order analysis does not, of course, give any indication of the signs of the coupling constants. The coupling  $^2\text{J}_{\text{H}^2\text{-H}^3}$  was estimated to be  $-14.0$  Hz ( $^2\text{J}_{\text{HH}}$  for protons attached to  $\text{sp}^3$  carbon falls in the range  $-8$  to  $-20$  Hz).<sup>[159]</sup> The couplings  $^3\text{J}_{\text{H}^2\text{-P}}$  and  $^3\text{J}_{\text{H}^3\text{-P}}$  were estimated to be in the region  $14$  to  $25$  Hz,<sup>[159]</sup> but trial simulations indicated that values of *ca.*  $10$  and  $12$  Hz were more appropriate. The  $^4\text{J}_{\text{H}^1\text{-P}}$  and  $^4\text{J}_{\text{H}^1\text{-H}^4}$  couplings were initially taken as zero. The coupling  $^2\text{J}_{\text{PH}}$  has been shown, both theoretically<sup>[142]</sup> and experimentally,<sup>[141]</sup> to be negative.

**Figure 4.6** <sup>1</sup>H NMR spectra of compound 1 in D<sub>2</sub>O at pH 3.19.  
The upper spectrum is the simulated spectrum with line width 0.85 Hz and the lower spectrum is the experimental spectrum.



[Redacted]

### PANIC Simulation

The initial simulation, using the program PANIC, was carried out assuming an  $ABM_3PX$  ( $H^2H^3H_3^1H^4P$ ) spin system. The phosphorus nucleus was given a chemical shift well removed from the frequencies of the proton signals and hence in keeping with the X-approximation.<sup>[160]</sup> The approximate parameters from the first order analysis, and the estimated coupling constants, gave a calculated spectrum that looked similar to the experimental spectrum in terms of both peak position and intensity. The calculated transition frequencies were then assigned to the experimental transition frequencies, where they matched accurately in terms of position and intensity. The iteration calculation was carried out and the resulting calculated spectrum compared with the experimental spectrum. While reasonable agreement was evident, a better fit was obtained by analysis as an  $ABCD_3X$  spin system. This more second order spin system provided a better match and was used thereafter.

Although small RMS error values were obtained for the agreement between the experimental spectrum and simulations, this parameter cannot on its own be regarded as a satisfactory measure of the agreement between the calculated and experimental spectra. By assigning fewer transitions, or by removing the transition assignments that give rise to the larger differences between the calculated and experimental transition frequencies, the RMS value can be reduced.

To improve the transition assignment procedure, the multiplets were expanded on the VDU screen such that only *ca.* 1 Hz at a time was visible on the screen. The calculated transitions were then assigned in detail using subjective judgements; *e.g.* where several calculated transitions with close, but not identical, frequencies corresponded to an experimental peak, they were assigned to appropriate positions within the experimental peak envelope rather than to the centre of the experimental peak. Having the spectra expanded to this extent also enabled more accurate estimation of the centre of the experimental peaks. A number of shoulders were visible in the experimental spectrum, but the 'centres' of these shoulders could not be estimated with certainty. In these cases the transition in the calculated spectrum that most closely matched the shoulder was used as the position of the shoulder. Initial simulations were carried out assuming that the

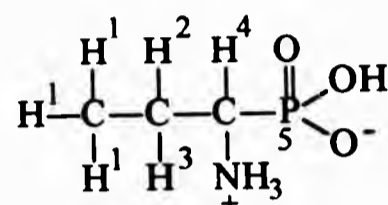
four-bond methyl-phosphorus and methyl-methine couplings were zero. However, the components of the triplet assigned to the methyl protons at 1.07 ppm were broad in comparison to the signals due to ethyl-containing impurity at 1.18 ppm. In an attempt to account for the broadness of the methyl signals, small couplings were introduced for the interactions  $H^1-P^5$  and  $H^1-H^4$ .

For the majority of the experimental peaks the calculated spectrum transitions were assigned to the best estimates of the centres of the experimental peaks. After the iteration calculations, both the differences between the transition frequencies of the experimental and calculated spectra, and the plots of the spectra, were examined. Where any significant discrepancies occurred, adjustments to the assignments were made before further iteration calculations were carried out.

Refinement was considered complete when differences between calculated and experimental frequencies were less than 0.10 Hz, *i.e.* the same order as the digital resolution of both spectra (0.096 Hz per point).

The spectral simulation (*i.e.* assignments and iterations) was carried out with a minimum linewidth (0.19 Hz). After final refinement, the line width was increased to 0.85 Hz in order to approximate more closely the line width in the experimental spectrum (see Figure 4.6). In this way a calculated spectrum was obtained which was a close match to the experimental spectrum. Throughout the analysis all the NMR parameters were varied except the chemical shift of the phosphorus nucleus. The final parameters are given in Table 4.4. A more detailed comparison of the methylene region of the spectrum is given in Figure 4.7.

Numbering scheme of protons referred to in Table 4.4



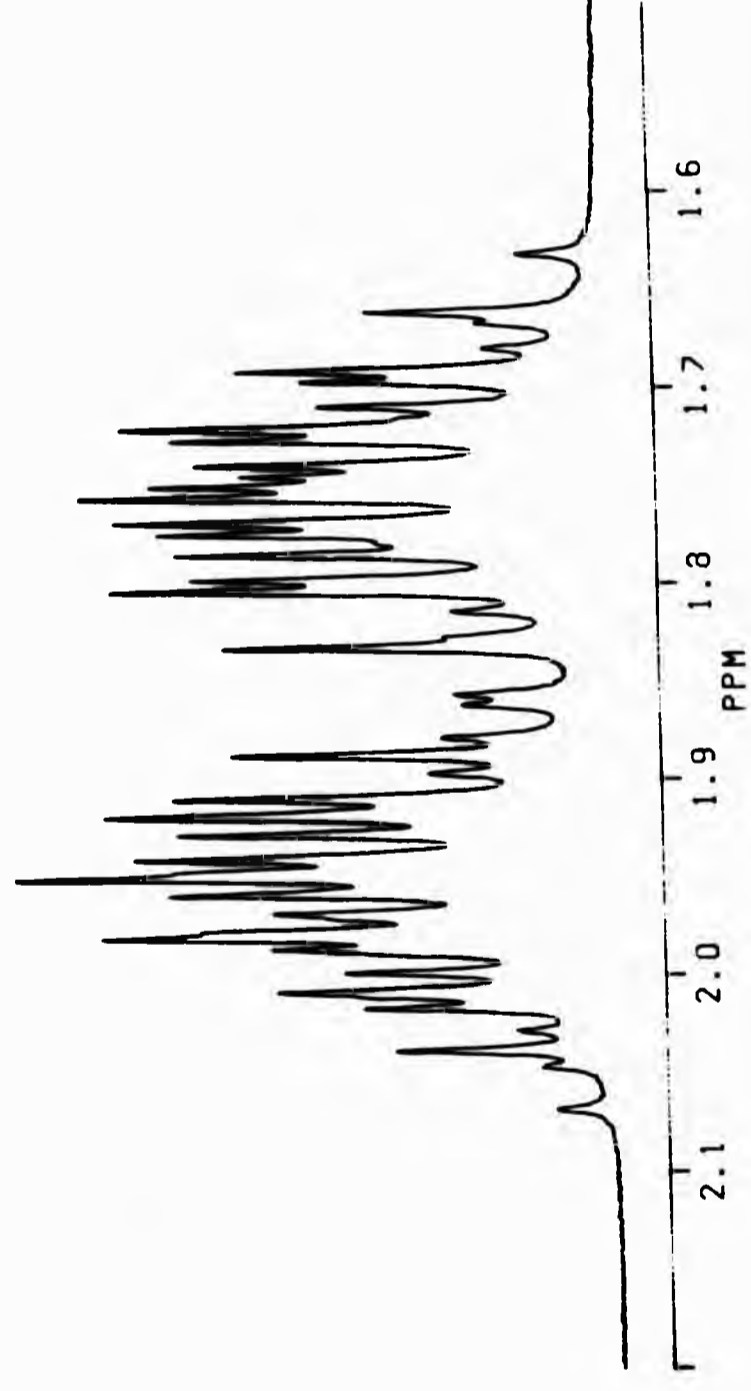
**Table 4.4**  $^1\text{H}$  NMR parameters<sup>†</sup> for compound 1 at pH 3.19 obtained by simulation

	Chemical shift (ppm)		Coupling constant (Hz)
H <sup>1</sup>	1.07 (1)	$^3J_{\text{H}^1-\text{H}^2}$	7.44 (1)
H <sup>2</sup>	1.75 (1)	$^3J_{\text{H}^1-\text{H}^3}$	7.61 (1)
H <sup>3</sup>	1.96 (1)	$^4J_{\text{H}^1-\text{H}^4}$	0.20 (1)
H <sup>4</sup>	3.17 (1)	$^4J_{\text{H}^1-\text{P}}$	0.22 (1)
		$^2J_{\text{H}^2-\text{H}^3}$	-14.64 (1)
		$^3J_{\text{H}^2-\text{H}^4}$	8.86 (1)
		$^3J_{\text{H}^2-\text{P}}$	12.01 (1)
		$^3J_{\text{H}^3-\text{H}^4}$	5.40 (1)
		$^3J_{\text{H}^3-\text{P}}$	9.99 (1)
		$^2J_{\text{H}^4-\text{P}}$	-13.15 (1)

<sup>†</sup> Esd's are given in parentheses.  
RMS of error estimation = 0.032.

**Figure 4.7**  $^1\text{H}$  NMR spectra of the methylene region of compound **1** in  $\text{D}_2\text{O}$  at pH 3.19. The upper trace is simulated spectrum with line width 0.85 Hz and the lower trace is experimental spectrum.





#### 4.4.1.2 Conformational Analysis of $\alpha$ -Aminopropanephosphonic Acid (1) at pH 3.19

The values of  $^3J_{\text{H}_2\text{-H}_4}$  and  $^3J_{\text{H}_3\text{-H}_4}$  obtained from the analysis of the  $^1\text{H}$  NMR spectrum were used to investigate the conformation of 1 in  $\text{D}_2\text{O}$  (pH 3.19).

The Karplus equation relates the vicinal proton-proton coupling constant to the dihedral angle between the coupled protons.<sup>[72]</sup> However the magnitude of the coupling constant has been shown to depend on a variety of other molecular parameters (*e.g.* bond length) apart from the dihedral angle  $\phi$ ,<sup>[161]</sup> the most important of these being the electronegativity and orientation of the substituents attached to the HCCH fragment. The behaviour of the vicinal proton coupling constant can be described by an empirically generalised form of the Karplus equation (Equation 4.1) which includes correction terms for electronegative substituents.<sup>[162]</sup>

##### Equation 4.1

$$^3J_{\text{HH}} = P_1 \cos^2 \phi + P_2 \cos \phi + P_3 + \sum \Delta\chi_i \{P_4 + P_5 \cos^2 (\xi_i \phi + P_6 |\Delta\chi_i|)\}$$

where  $\xi = \pm 1$  depending on substituent orientation

$P_1$  to  $P_6$  are the empirically determined parameters

$\sum \Delta\chi_i$  = the sum of the differences in electronegativity between substituents on the HCCH fragment under study and hydrogen,

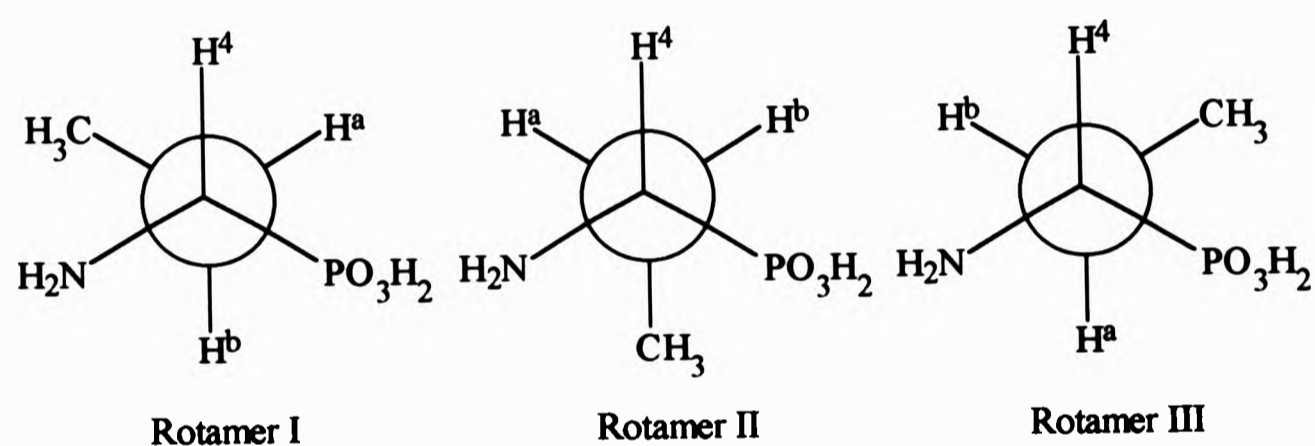
$[\Delta\chi_i = (\chi_{\text{substituent}}) - (\chi_{\text{hydrogen}})]$ .

The six empirical parameters ( $P$ ) in equation 4.1 were derived from 315 coupling constants obtained from 109 different compounds using an iterative least-squares minimising procedure.<sup>[162]</sup> The compounds studied were restricted to conformationally rigid structures, mainly six membered rings containing 'holding groups' to help ensure a single conformation. The data set was therefore biased towards dihedral angles of either  $60^\circ$  or  $180^\circ$  and thus the coupling constants were biased towards 0 to 5.5 Hz and 7.5 to 13 Hz. However, the advantage of equation 4.1 over the standard Karplus relationship<sup>[72]</sup>

is that it accounts for the increase of coupling constant value with the increasing electronegativity of substituents in particular orientations. Equation 4.1, which is utilised in the program ALTONA,<sup>[163]</sup> is thought to be applicable to a wide variety of compounds without further parameterisation being necessary.<sup>[162]</sup>

Assuming staggered conformations (Figure 4.8), there are three possible rotamers for each of the enantiomers; for example the *S* enantiomer has the rotamers:

**Figure 4.8** The three staggered rotamers of compound 1, the *S* enantiomer<sup>†</sup>



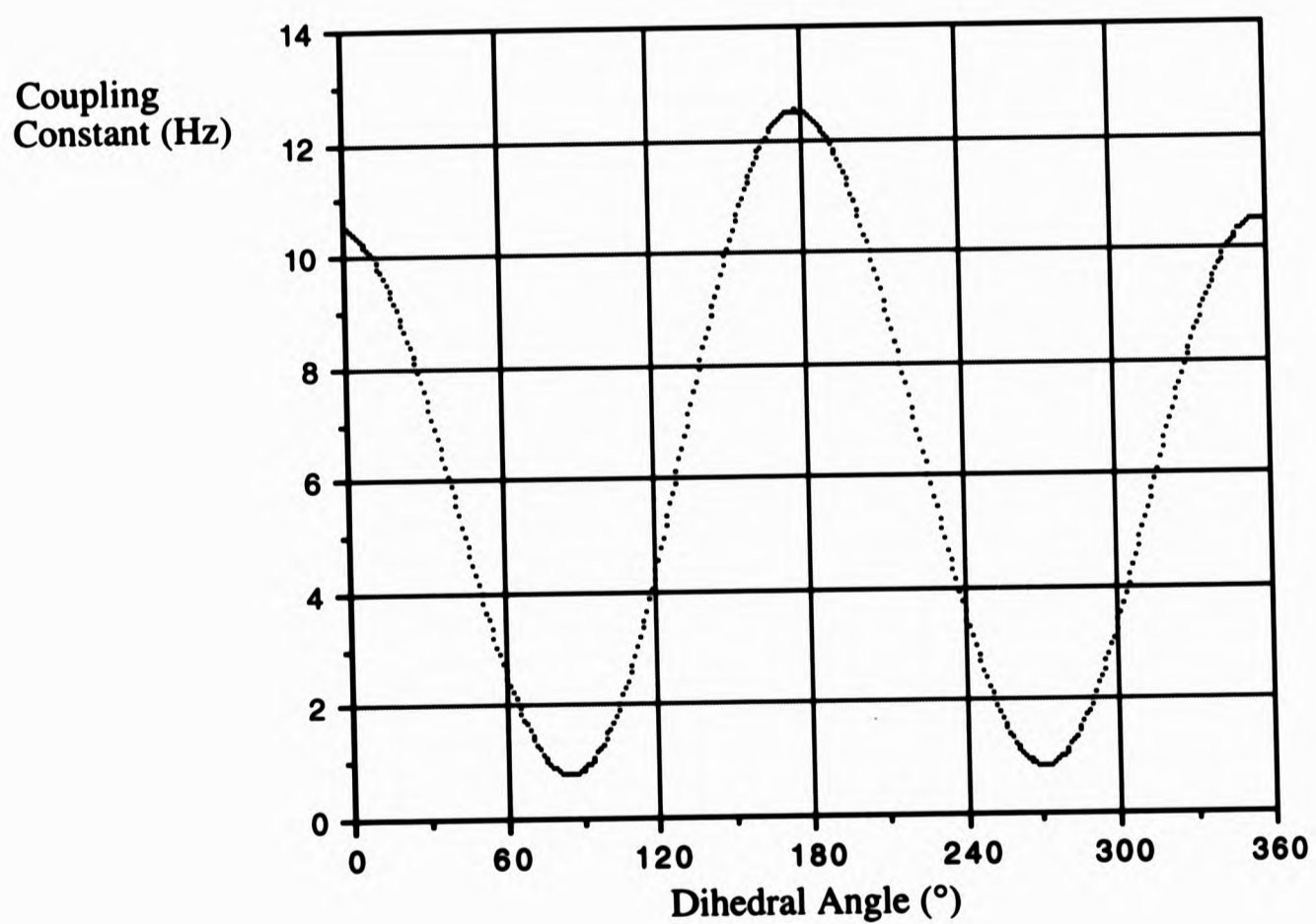
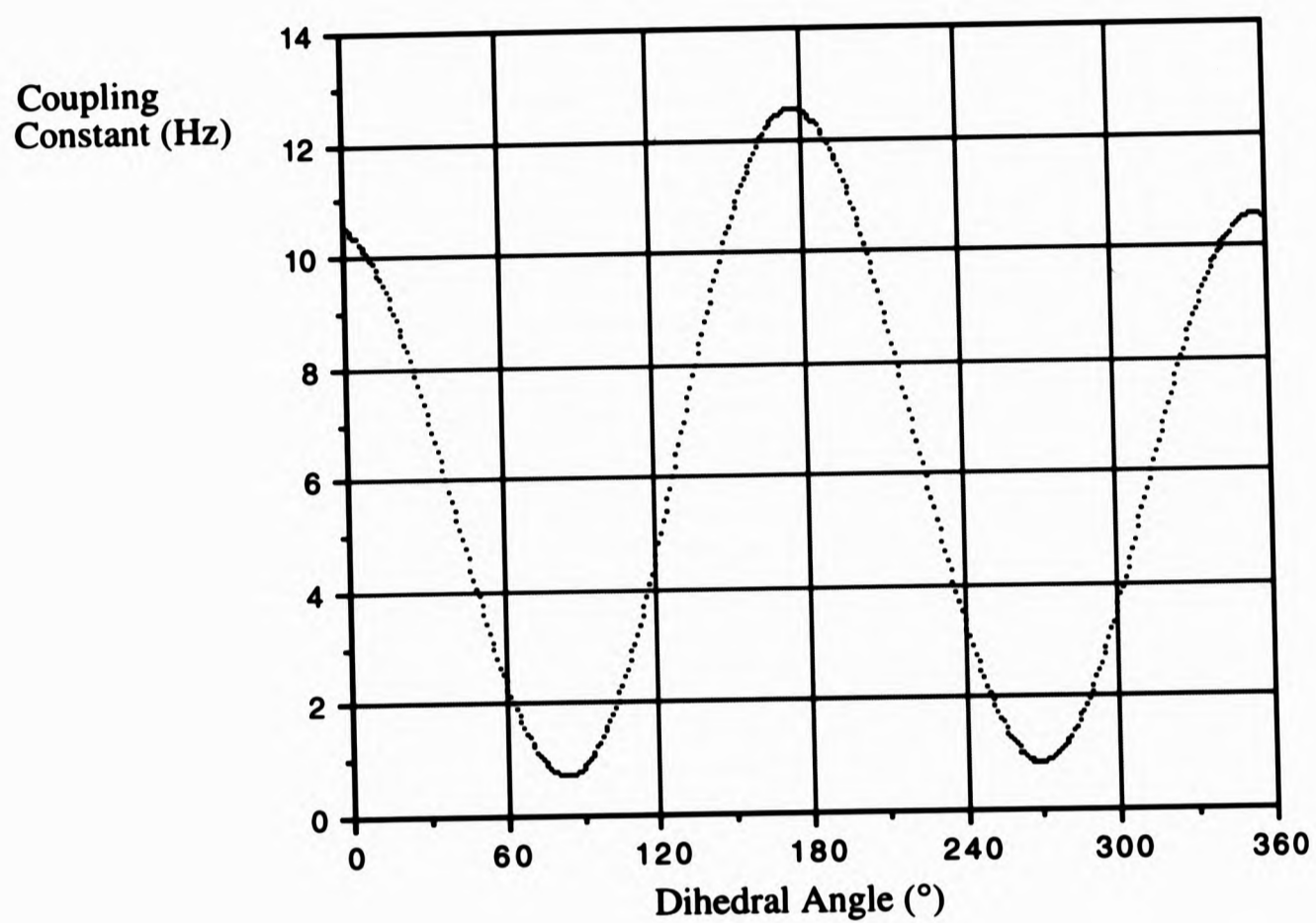
The dihedral angles between the methine proton and the methylene protons,  $H^a$  and  $H^b$  respectively, were assumed to determine the values of  $^3J_{H^b-H^4}$  and  $^3J_{H^a-H^4}$ . The program ALTONA<sup>[163]</sup> was used to calculate the relationship between the dihedral angles  $H^aCCH^4$ ,  $H^bCCH^4$ , and the vicinal coupling constants  $^3J_{H^a-H^4}$  and  $^3J_{H^b-H^4}$  respectively. The calculation takes into account the electronegativity and orientation of the substituents. The number of substituents (atoms other than hydrogen) attached to the HCCH fragment, and type of atom attached one bond away from the considered fragment must be specified. The orientation ( $\pm 1$ ) of the substituents is also considered following the given convention.<sup>[162]</sup> (In the Newman projection the vicinal protons are set in an *anti* conformation with the front proton in the upper position. The substituents on the right side of the molecule are considered positive while those on the left are negative).

<sup>†</sup> The methylene protons are now labelled  $H^a$  and  $H^b$  because it is not possible to assign  $H^2$  and  $H^3$  individually to  $H^a$  or  $H^b$ .

The calculated relationships for  ${}^3J_{\text{H}^a\text{H}^d}$  and  ${}^3J_{\text{H}^b\text{H}^d}$  are plotted in Figure 4.9, and the predicted values for the vicinal coupling constants for each rotamer are given in Table 4.5.

**Table 4.5** Vicinal coupling constants (Hz) associated with a dihedral angle ( $^\circ$ ) in rotamers of the *S* enantiomer of compound 1 at pH 3.19

	$R_I$		$R_{II}$		$R_{III}$	
	$\phi$	J	$\phi$	J	$\phi$	J
$\text{H}^a\text{H}^d$	60	2.63	300	3.41	180	12.50
$\text{H}^b\text{H}^d$	180	12.50	60	2.40	300	3.64



**Figure 4.9** Plots of Karplus-type relationships between vicinal coupling constants and dihedral angle in the *S* enantiomer of compound 1. The upper trace is for  ${}^3J_{H^aH^4}$  and the lower trace is for  ${}^3J_{H^bH^4}$ .

The observed vicinal coupling constants  ${}^3J_{H^a-H^4}$  and  ${}^3J_{H^b-H^4}$  are average values determined by the relative populations of the three rotamers which are rapidly interconverting through rotation about the C-C bond. The relative population of each rotamer was determined by solving the following simultaneous equations.

Assignment (1)

If  $H^a = H^2$  and  $H^b = H^3$  (i.e.  ${}^3J_{H^2-H^4} = 8.855$  Hz and  ${}^3J_{H^3-H^4} = 5.404$  Hz)

$$8.855 = P_I(2.63) + P_{II}(3.41) + P_{III}(12.50)$$

$$5.404 = P_I(12.50) + P_{II}(2.40) + P_{III}(3.64)$$

$$P_I + P_{II} + P_{III} = 1$$

where P represents the population in the rotamer.

Assignment (2)

If  $H^a = H^3$  and  $H^b = H^2$  (i.e.  ${}^3J_{H^2-H^4} = 5.404$  Hz and  ${}^3J_{H^3-H^4} = 8.855$  Hz)

$$8.855 = P_I(12.50) + P_{II}(2.40) + P_{III}(3.64)$$

$$5.404 = P_I(2.63) + P_{II}(3.41) + P_{III}(12.50)$$

$$P_I + P_{II} + P_{III} = 1$$

The results of this analysis are shown in Table 4.6.

**Table 4.6** Relative rotamer populations (normalised to 1) for the alternative assignments of the methylene protons (*S* enantiomer) in compound 1 at pH 3.19

	$P_I$	$P_{II}$	$P_{III}$
$H^a=H^2, H^b=H^3$	0.22	0.16	0.62
$H^a=H^3, H^b=H^2$	0.61	0.12	0.27

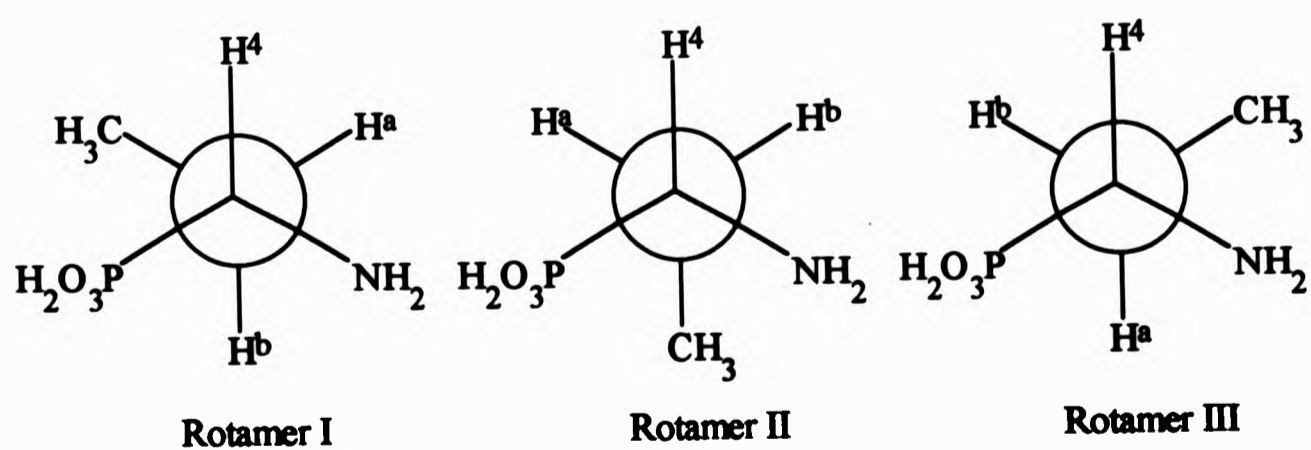
Of the three rotamers, rotamer II is present in the lowest proportion in both assignments ( $H^a = H^2$  or  $H^a = H^3$ ). This is probably because it has two *gauche* pairs involving the three most bulky groups (i.e. the groups  $PO_3H_2$ ,  $CH_3$  and  $NH_2$  are in close proximity). Assignment 1 has rotamer III in the highest proportion, while assignment 2 has rotamer I in the highest proportion.

Clearly, it is necessary to distinguish between the two assignments. One approach might be on the basis of chemical shift using the method of Bhacca and Williams<sup>[164]</sup> who investigated a variety of electronegative groups in axial or equatorial positions and the effect which they have on the chemical shift of the axial or equatorial proton on the adjacent carbon atom. These shifts are rationalised in terms of anisotropic effects, bond rotation, or van der Waals' interactions, although these results seemed to be derived from a fairly limited number of examples.

In rotamer I (Figure 4.8), H<sup>a</sup> has a deshielding *anti* interaction with the electronegative NH<sub>2</sub> group,<sup>[164]</sup> and it also has a shielding *gauche* interaction with the electronegative PO<sub>3</sub>H<sub>2</sub> group. H<sup>b</sup> has shielding *gauche* interactions with both the electronegative groups. In rotamer III, H<sup>a</sup> has shielding *gauche* interactions with both the electronegative groups, while H<sup>b</sup> has a shielding *gauche* interaction with the NH<sub>2</sub> group and a deshielding *anti* interaction with the PO<sub>3</sub>H<sub>2</sub> group. Clearly this analysis does not help in any way to determine the assignment of H<sup>a</sup> or H<sup>b</sup>.

The variation of the vicinal coupling constants with dihedral angle was calculated by the same procedure for the three possible staggered conformations of the *R* enantiomer (Figure 4.10) which has the following rotamers:

Figure 4.10 The three staggered rotamers of compound 1, the *R* enantiomer



The predicted values for the vicinal coupling constants for each rotamer are given in Table 4.7.

These results (Table 4.7) are, of course, essentially the same as for the *S* enantiomer, e.g. *S* enantiomer rotamer I is the enantiomorph of the *R* enantiomer rotamer III.

**Table 4.7** Vicinal coupling constants (Hz) associated with a dihedral angle ( $^{\circ}$ ) in rotamers of the *R* enantiomer in compound 1 at pH 3.19

	<b>R<sub>I</sub></b>		<b>R<sub>II</sub></b>		<b>R<sub>III</sub></b>	
	$\phi$	J	$\phi$	J	$\phi$	J
H <sup>a</sup> H <sup>d</sup>	60	3.64	300	2.40	180	12.50
H <sup>b</sup> H <sup>d</sup>	180	12.50	60	3.41	300	2.63

The rotamer populations were calculated by solving three simultaneous equations as follows:

Assignment (1)

If H<sup>a</sup> = H<sup>2</sup> and H<sup>b</sup> = H<sup>3</sup>

$$8.855 = P_I(3.64) + P_{II}(2.40) + P_{III}(12.50)$$

$$5.404 = P_I(12.50) + P_{II}(3.41) + P_{III}(2.63)$$

$$P_I + P_{II} + P_{III} = 1$$

Assignment (2)

If H<sup>a</sup> = H<sup>3</sup> and H<sup>b</sup> = H<sup>2</sup>

$$5.404 = P_I(3.64) + P_{II}(2.40) + P_{III}(12.50)$$

$$8.855 = P_I(12.50) + P_{II}(3.41) + P_{III}(2.63)$$

$$P_I + P_{II} + P_{III} = 1$$

The results of this analysis are shown in Table 4.8.



**Table 4.8** Relative rotamer populations (normalised to 1) for the alternative assignments of the methylene protons (*R* enantiomer) in compound 1 at pH 3.19

	P <sub>I</sub>	P <sub>II</sub>	P <sub>III</sub>
H <sup>a</sup> =H <sup>2</sup> , H <sup>b</sup> =H <sup>3</sup>	0.27	0.12	0.61
H <sup>a</sup> =H <sup>3</sup> , H <sup>b</sup> =H <sup>2</sup>	0.62	0.16	0.22

Naturally, the results for the rotamer populations for the *R* enantiomer are the 'mirror image' of those for the *S* enantiomer. Therefore of the three rotamers in assignments 1 and 2, rotamer II is present in the smallest proportion. Assignment 1 has rotamer III in the highest proportion, while assignment 2 has rotamer I in the highest proportion. It follows that attempts to distinguish between the two assignments on the basis of shielding arguments<sup>[164]</sup> proved unsuccessful.

The molecular modelling program ALCHEMY II<sup>[165]</sup> was used to investigate whether any of the rotamers considered are associated with a lower energy value. This would indicate a preferential conformation and thus allow the assignment of H<sup>a</sup> and H<sup>b</sup>. The overall energy calculated by the program ALCHEMY represents the sum of the potential energy functions corresponding to the following interactions:<sup>[166]</sup> bond stretching, angle bending, torsional deformations, Van der Waals' interactions and out of plane bending. Then, *via* an iterative process, the conformation is altered to minimise this total energy value. The program did not appear to be sensitive enough to the small energy differences in the rotamers considered. The energies obtained for the rotamers were between the -6.6 and -6.9 kcal mol<sup>-1</sup>. The calculation suggests there is little barrier to rotation and the molecule is freely rotating in solution.

#### 4.4.1.3 $^1\text{H}$ NMR Spectrum of $\alpha$ -Aminopropanephosphonic Acid (1) at pH 7.54

The experimental spectrum (Figure 4.11, lower spectrum) shows a doublet of doublet of doublets at 2.96 ppm assigned to the methine proton  $\text{H}^4$ ; two distinct multiplets are assigned to the methylene protons  $\text{H}^2$  and  $\text{H}^3$ , one centred at 1.96 ppm and the other at 1.70 ppm, and the methyl protons  $\text{H}^1$  give rise to a triplet at 1.06 ppm.

The spectrum at this pH looks very similar to the spectrum at pH 3.19; the most obvious change is in the chemical shifts of the multiplets rather than the appearance of the multiplets. The multiplets due to the methylene protons are now shifted further apart.

The starting parameters were obtained by first order hand analysis of the spectrum, but also using the information from the analysis at pH 3.19, the chemical shifts are (ppm)  $\text{H}^1$  1.06,  $\text{H}^2$  1.70,  $\text{H}^3$  1.97 and  $\text{H}^4$  2.96; and the coupling constants are  $^3J_{\text{H}^1-\text{H}^2} \sim ^3J_{\text{H}^1-\text{H}^3} \sim 7.50$ ,  $^4J_{\text{H}^1-\text{H}^4} \sim ^4J_{\text{H}^1-\text{P}} \sim 0.2$ ,  $^3J_{\text{H}^2-\text{H}^3} \sim -14$ ,  $^3J_{\text{H}^2-\text{H}^4} \sim 9.7$ ,  $^3J_{\text{H}^2-\text{P}} \sim ^3J_{\text{H}^3-\text{P}} \sim 11$ ,  $^3J_{\text{H}^3-\text{H}^4} \sim 5$  and  $^2J_{\text{H}^4-\text{P}} \sim -12$ .

#### PANIC simulation

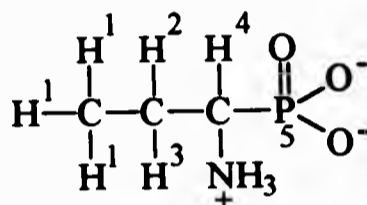
The simulation was carried out using the same spin system as in the previous simulation. The procedure for this simulation is exactly the same as for the  $\alpha$ -aminopropanephosphonic acid at pH 3.19 (see section 4.4.1.1).

Refinement was considered complete when the transitions matched in terms of peak position and intensity, and when the frequency difference between the experimental and calculated frequency was less than the digital resolution of the experimental spectrum.

The spectral simulation was carried out using a minimum linewidth (0.116 Hz). After refinement the linewidth was increased to 0.85 Hz (Figure 4.11, upper spectrum) in order to approximate the linewidth of the experimental spectrum.

The final parameters are given in Table 4.9. A more detailed comparison of the methylene region is shown in Figure 4.12.

Numbering scheme of protons referred to in Table 4.9

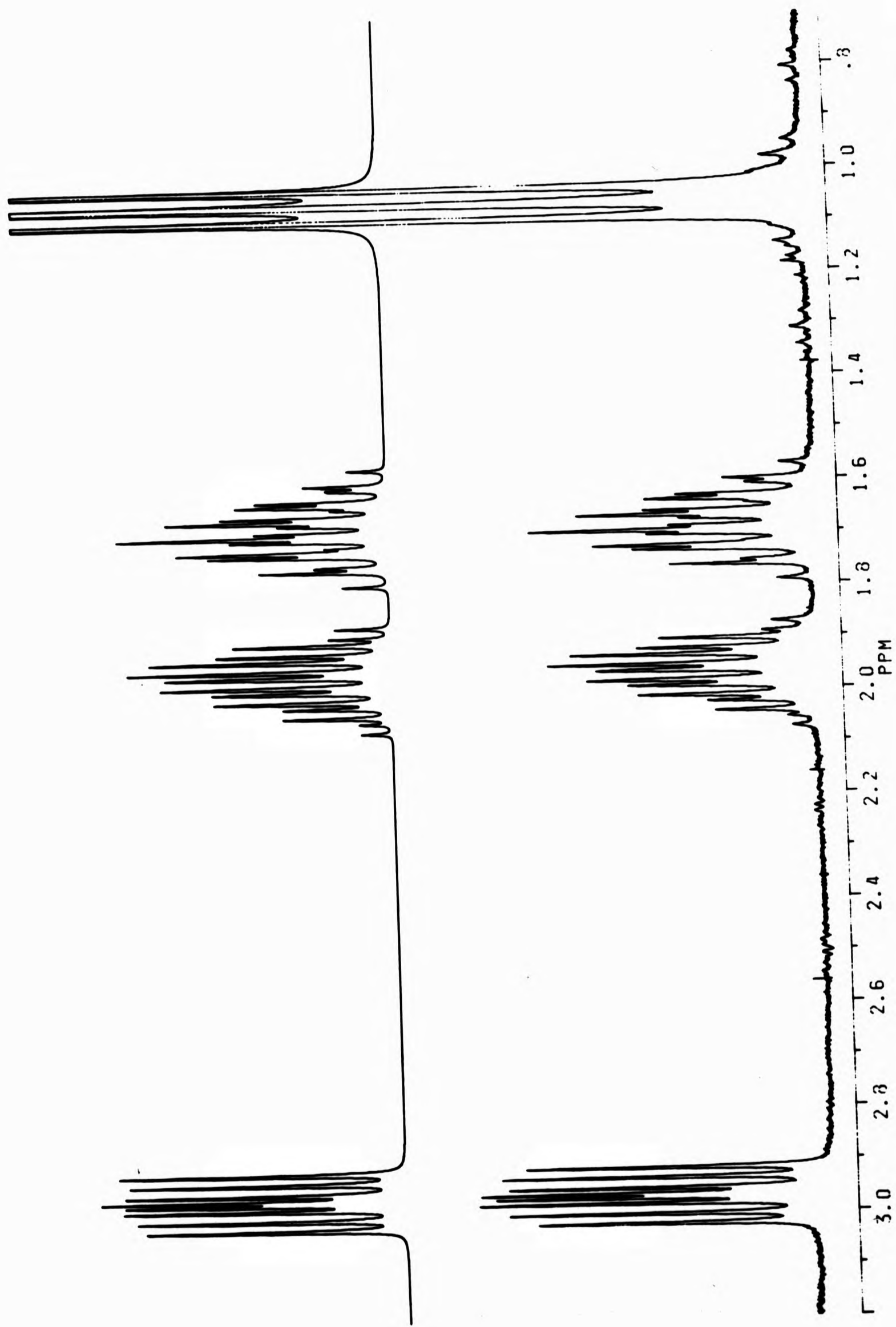


**Table 4.9**  $^1\text{H}$  NMR parameters<sup>†</sup> for compound 1 at pH 7.54 obtained by simulation

	Chemical shifts (ppm)	Coupling constants (Hz)	
H <sup>1</sup>	1.06 (1)	$^3J_{\text{H1-H2}}$	7.38 (1)
H <sup>2</sup>	1.68 (1)	$^3J_{\text{H1-H3}}$	7.63 (1)
H <sup>3</sup>	1.97 (1)	$^4J_{\text{H1-H4}}$	0.27 (1)
H <sup>4</sup>	2.96 (1)	$^4J_{\text{H1-P}}$	0.27 (1)
		$^2J_{\text{H2-H3}}$	-14.81 (1)
		$^3J_{\text{H2-H4}}$	9.71 (1)
		$^3J_{\text{H2-P}}$	9.12 (1)
		$^3J_{\text{H3-H4}}$	4.58 (1)
		$^3J_{\text{H3-P}}$	8.01 (1)
		$^2J_{\text{H4-P}}$	-12.40 (1)

<sup>†</sup> Esd's are given in parentheses.  
RMS for error estimation = 0.25.

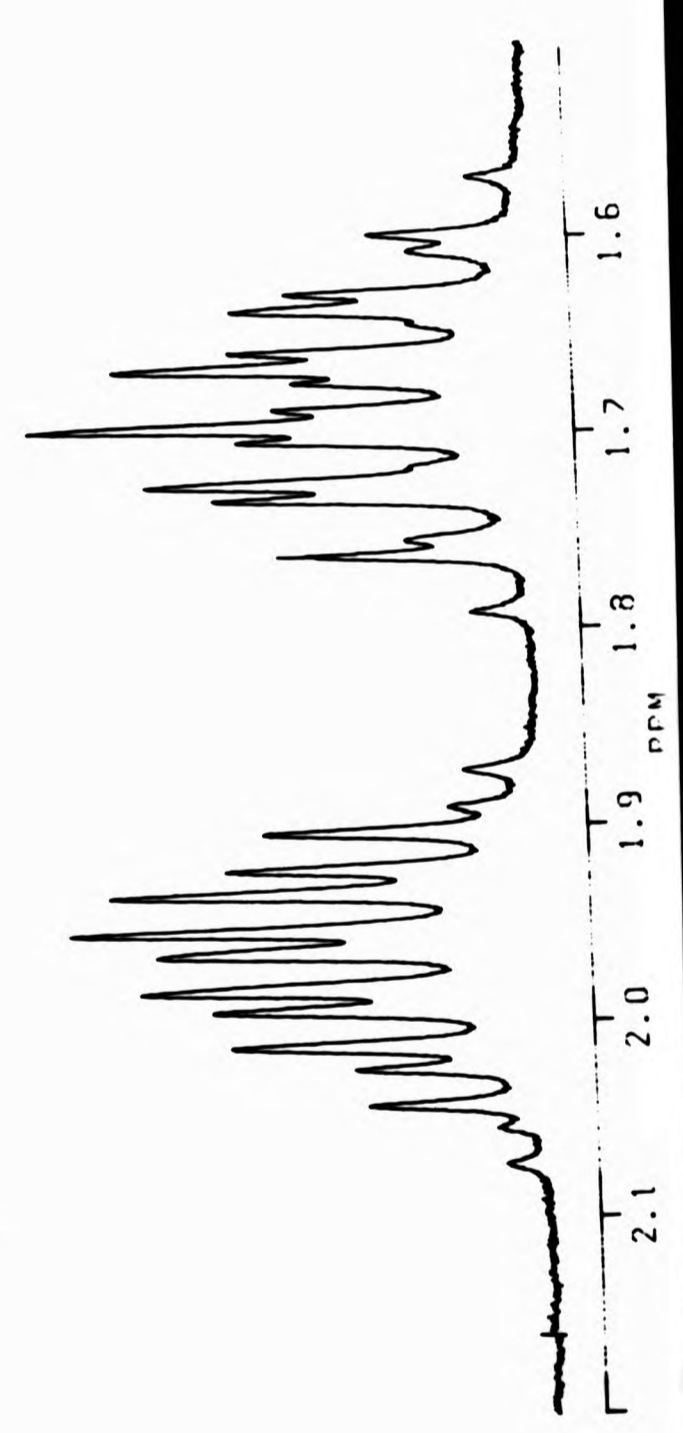
**Figure 4.11**  $^1\text{H}$  NMR spectra of compound **1** in  $\text{D}_2\text{O}$  at pH 7.54.  
The upper spectrum is the simulated spectrum with line width 0.85 Hz and the lower spectrum is the experimental spectrum.



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<sup>1</sup>H NMR spectra of the methylene region of compound **1** in D<sub>2</sub>O at pH 7.54.  
The upper spectrum is the simulated spectrum with line width 0.85 Hz and the lower spectrum is the experimental spectrum.

**Figure 4.12**



#### 4.4.1.4 Conformational Analysis of $\alpha$ -Aminopropanephosphonic Acid (1) at pH 7.54

The values of the  $^3J_{\text{HH}}$  coupling constants from the proton NMR analysis were used to investigate the conformation of the molecule at pH 7.54. The program ALTONA was used to determine the relative populations of the three rotamers for each enantiomer in exactly the same way as for the molecule at pH 3.19 (see section 4.4.1.2). The results are given in Table 4.10.

**Table 4.10** Relative rotamer populations (normalised to 1) for the alternative assignments of the methylene protons for compound 1 at pH 7.54

	$P_{\text{I}}$	$P_{\text{II}}$	$P_{\text{III}}$
<i>S</i> Enantiomer			
$\text{H}^{\text{a}}=\text{H}^2, \text{H}^{\text{b}}=\text{H}^3$	0.13	0.17	0.70
$\text{H}^{\text{a}}=\text{H}^3, \text{H}^{\text{b}}=\text{H}^2$	0.70	0.11	0.19
<i>R</i> Enantiomer			
$\text{H}^{\text{a}}=\text{H}^2, \text{H}^{\text{b}}=\text{H}^3$	0.19	0.11	0.70
$\text{H}^{\text{a}}=\text{H}^3, \text{H}^{\text{b}}=\text{H}^2$	0.70	0.17	0.13

Again the most abundant rotamer depends on the assignment of  $\text{H}^{\text{a}}$  and  $\text{H}^{\text{b}}$  to either  $\text{H}^1$  or  $\text{H}^2$ .

#### 4.4.1.5 $^1\text{H}$ NMR Spectrum of $\alpha$ -Aminopropanephosphonic Acid (1) at pH 11.44

The experimental spectrum (Figure 4.13, lower spectrum) shows a doublet of doublet of doublets 2.70 ppm assigned to the methine proton  $\text{H}^4$ , two separate multiplets assigned to the methylene protons  $\text{H}^2$  and  $\text{H}^3$ , one centred at 1.88 ppm and the other at 1.54 ppm and finally the methyl protons  $\text{H}^1$  give rise to a triplet at 1.03 ppm. The starting parameters were obtained by first order hand analysis of the spectrum, but also using the information from the analysis at pH 3.19, the chemical shifts were (ppm):  $\text{H}^1$  1.03,  $\text{H}^2$  1.54,  $\text{H}^3$  1.88 and  $\text{H}^4$  2.70, and the coupling constants were  $^3J_{\text{H}^1\text{H}^2} \sim ^3J_{\text{H}^1\text{H}^3} \sim 7.50$ ,  $^4J_{\text{H}^1\text{H}^4} \sim ^4J_{\text{H}^1\text{P}} \sim 0.2$ ,  $^3J_{\text{H}^2\text{H}^3} \sim -14$ ,  $^3J_{\text{H}^2\text{H}^4} \sim 9.9$ ,  $^3J_{\text{H}^2\text{P}} \sim ^3J_{\text{H}^3\text{P}} \sim 11$ ,  $^3J_{\text{H}^3\text{H}^4} \sim 4$  and  $^2J_{\text{H}^4\text{P}} \sim -11.4$ .



The spectrum at this pH looks very similar to the spectra at the previous pH values, the most obvious change is in the chemical shifts of the multiplets rather than the appearance of the multiplets.

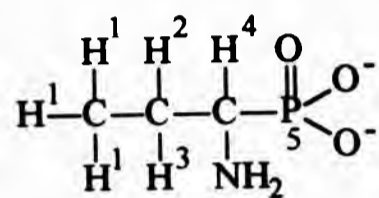
#### **PANIC simulation**

The simulation was carried out using the same spin system as in the previous simulation. The coupling constants and chemical shift values used to start the analysis differed from the previous simulation.

The procedure employed was the same as in the other simulations, and was again considered complete when the transitions matched in terms of peak position and intensity, and when the frequency difference between the experimental and calculated frequency was less than the digital resolution of the experimental spectrum.

The spectral simulation was carried out using a minimum linewidth (0.116 Hz). After the final refinement this was increased to 0.85 Hz (Figure 4.13, upper spectrum) to approximate the line width of the experimental spectrum, with an expansion of the methylene region in Figure 4.14. The final parameters are given in Table 4.11.

Numbering scheme for protons referred to in Table 4.11



**Table 4.11**  $^1\text{H}$  NMR parameters<sup>†</sup> for compound **1** at pH 11.44 obtained by simulation

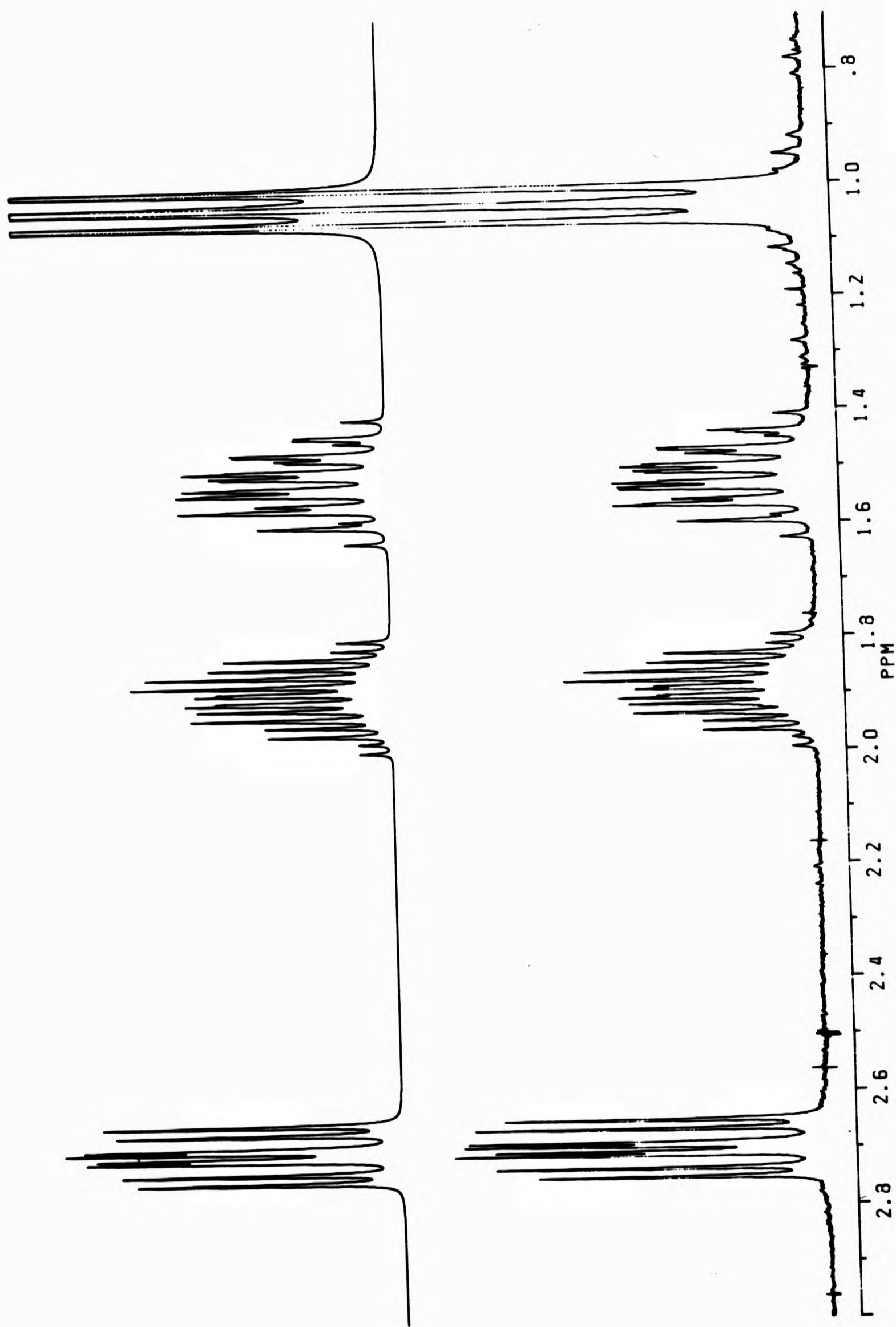
	Chemical shifts (ppm)	Coupling constants (Hz)	
H <sup>1</sup>	1.03 (1)	$^3J_{\text{H}1-\text{H}2}$	7.37 (1)
H <sup>2</sup>	1.52 (1)	$^3J_{\text{H}1-\text{H}3}$	7.68 (1)
H <sup>3</sup>	1.71 (1)	$^4J_{\text{H}1-\text{H}4}$	0.20 (1)
H <sup>4</sup>	2.70 (1)	$^4J_{\text{H}1-\text{P}}$	0.23 (1)
		$^2J_{\text{H}2-\text{H}3}$	-14.47 (1)
		$^3J_{\text{H}2-\text{H}4}$	10.00 (1)
		$^3J_{\text{H}2-\text{P}}$	8.10 (1)
		$^3J_{\text{H}3-\text{H}4}$	4.01 (1)
		$^3J_{\text{H}3-\text{P}}$	7.82 (1)
		$^2J_{\text{H}4-\text{P}}$	-11.37 (1)

<sup>†</sup> Esd's are given in parentheses.  
RMS for error estimation = 0.22.

**Figure 4.13** <sup>1</sup>H NMR spectra of compound **1** in D<sub>2</sub>O at pH 11.44.  
The upper spectrum is the simulated spectrum with line width 0.85 Hz and the lower spectrum is the experimental spectrum.

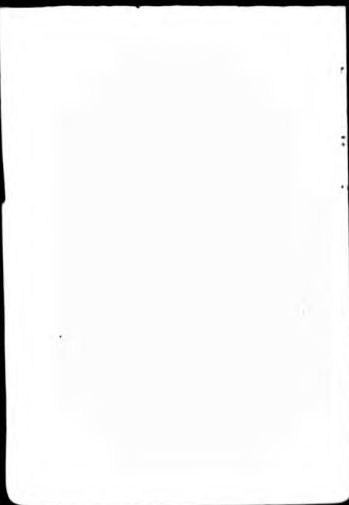
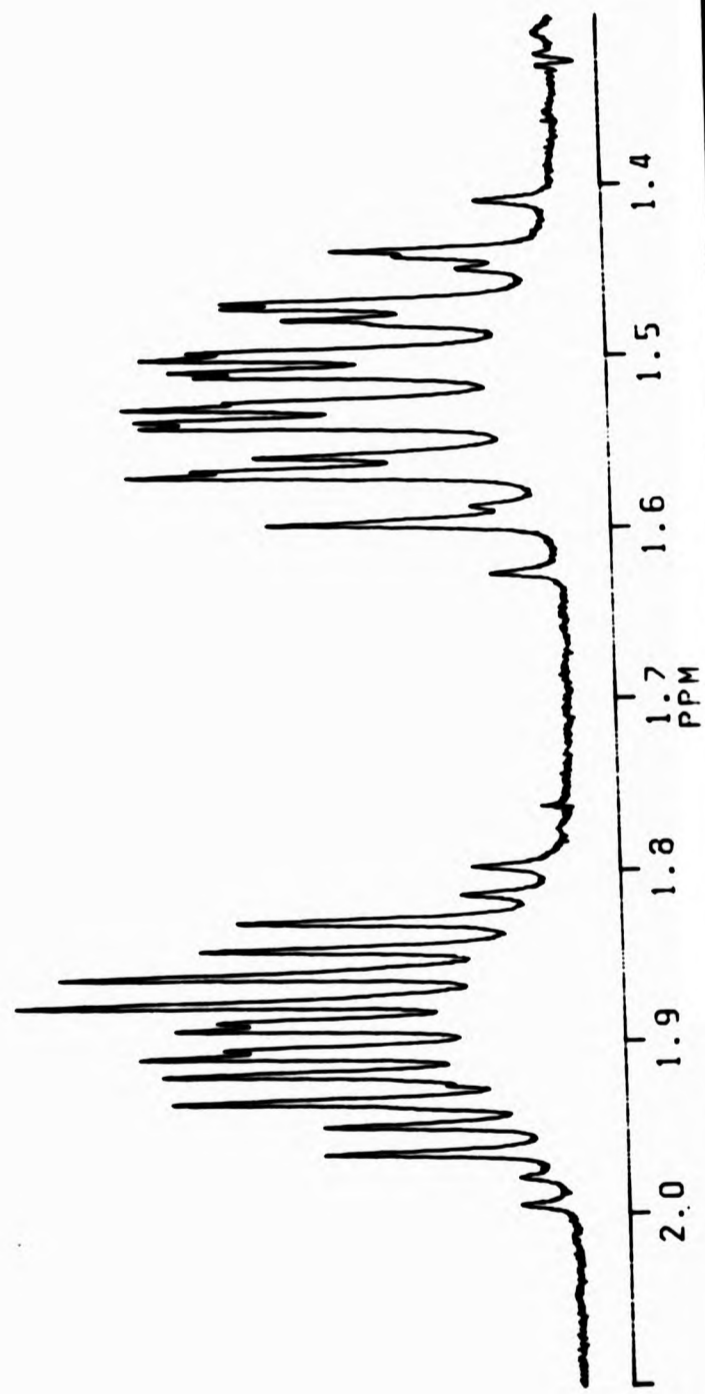
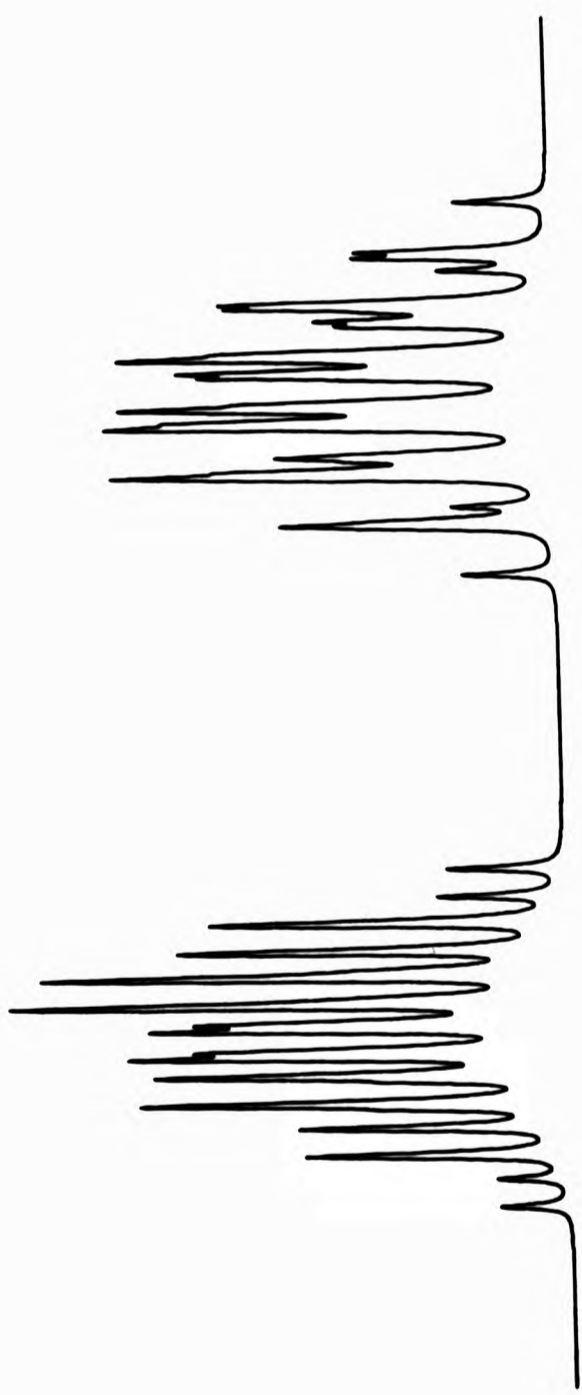


**Figure 4.13** <sup>1</sup>H NMR spectra of compound 1 in D<sub>2</sub>O at pH 11.44.  
The upper spectrum is the simulated spectrum with line width 0.85 Hz and the lower spectrum is the experimental spectrum.



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**Figure 4.14**  $^1\text{H}$  NMR spectra of the methylene region of compound **1** in  $\text{D}_2\text{O}$  at pH 11.44. The upper spectrum is the simulated spectrum with line width 0.85 Hz and the lower spectrum is the experimental spectrum.



#### 4.4.1.6 Conformational Analysis of $\alpha$ -Aminopropanephosphonic Acid (1) at pH 11.44

The values of the  $^3J_{\text{HH}}$  coupling constants from the proton NMR analysis were used again to investigate the conformation of the molecule at pH 11.44. The program ALTONA<sup>[163]</sup> was used to determine the relative populations of the three rotamers for each enantiomer. The results are given in Table 4.12.

**Table 4.12** Relative rotamer populations (normalised to 1) for the alternative assignments of the methylene protons in compound 1 at pH 11.44

	$P_{\text{I}}$	$P_{\text{II}}$	$P_{\text{III}}$
<i>S</i> Enantiomer			
$\text{H}^{\text{a}}=\text{H}^2, \text{H}^{\text{b}}=\text{H}^3$	0.07	0.20	0.73
$\text{H}^{\text{a}}=\text{H}^3, \text{H}^{\text{b}}=\text{H}^2$	0.74	0.13	0.13
<i>R</i> Enantiomer			
$\text{H}^{\text{a}}=\text{H}^2, \text{H}^{\text{b}}=\text{H}^3$	0.13	0.13	0.74
$\text{H}^{\text{a}}=\text{H}^3, \text{H}^{\text{b}}=\text{H}^2$	0.73	0.20	0.07

Again, the most abundant rotamer depends on the assignment of the geminal protons.

#### 4.4.2 Comparison of the $^1\text{H}$ NMR Spectra of $\alpha$ -Aminopropanephosphonic Acid at the Different pH Values

The proton NMR spectra of the different species were as expected quite similar in appearance, the major differences being the change in the chemical shift of the protons (see Tables 4.13 and 4.14).



**Table 4.13** Chemical shifts (ppm) of compound 1 at different pH values

	pH 3.19	pH 7.54	pH 11.44
	$\begin{array}{c} \text{H} & \text{H} & \text{H} & \text{O} & \text{OH} \\   &   &   &    & / \\ \text{H}-\text{C} & -\text{C} & -\text{C} & -\text{P} & \\   &   &   & \backslash & \backslash \\ \text{H} & \text{H} & \text{NH}_3^+ & \text{O}^- & \end{array}$	$\begin{array}{c} \text{H} & \text{H} & \text{H} & \text{O} & \\   &   &   &    & \\ \text{H}-\text{C} & -\text{C} & -\text{C} & -\text{P} & \\   &   &   & \backslash & \backslash \\ \text{H} & \text{H} & \text{NH}_3^+ & \text{O}^- & \text{O}^- \end{array}$	$\begin{array}{c} \text{H} & \text{H} & \text{H} & \text{O} & \\   &   &   &    & \\ \text{H}-\text{C} & -\text{C} & -\text{C} & -\text{P} & \\   &   &   & \backslash & \backslash \\ \text{H} & \text{H} & \text{NH}_2 & \text{O}^- & \text{O}^- \end{array}$
H <sup>1</sup>	1.07	1.06	1.03
H <sup>2</sup>	1.75	1.68	1.52
H <sup>3</sup>	1.96	1.97	1.71
H <sup>4</sup>	3.17	2.96	2.70

The chemical shift of the signals assigned to H<sup>1</sup>, H<sup>2</sup> and H<sup>4</sup> all move upfield as the pH increases. The chemical shift of the signal assigned to H<sup>3</sup> is the same at pH 3.2 and 7.5, but moves upfield at pH 11.4. This can be explained in terms of the dominant species in solution at the different pH values (see Figure 4.3 and 4.4). At pH 3.2 and 7.5 the amino group, in the dominant species, is protonated (NH<sub>3</sub><sup>+</sup>). At pH 11.4 the amino group in the dominant species is neutral (NH<sub>2</sub>). The magnitude of this upfield shift of the signals is smallest for H<sup>1</sup>, the methyl protons, which are distal to the amine or phosphonic group. The magnitude of this upfield shift is largest for H<sup>4</sup>, the methine protons, which are proximal to the amine and phosphonic groups.

The coupling constants also vary with pH (see Table 4.14). The four bond couplings, <sup>4</sup>J<sub>H1-H4</sub> and <sup>4</sup>J<sub>H1-P</sub>, do not vary a great deal with the change in pH. The magnitude of the vicinal <sup>3</sup>J<sub>H1-H2</sub> coupling decreases with the increase in pH, while the vicinal <sup>3</sup>J<sub>H1-H3</sub> coupling increases. The changes in the magnitude of these couplings are very small. More significant differences in the magnitude of the couplings with the change in pH are seen in the vicinal <sup>3</sup>J<sub>H2-H4</sub> and <sup>3</sup>J<sub>H3-H4</sub> couplings. Again one coupling (<sup>3</sup>J<sub>H3-H4</sub>) decreases with the increase in pH, while the other coupling (<sup>3</sup>J<sub>H2-H4</sub>) increases with the increase in pH. The differences in the couplings with the change in pH are larger when the coupling is to the methine proton H<sup>4</sup> which is closest to the groups (amino and phosphonic groups) that are deprotonated with the change in pH. The couplings involving the phosphorus atom, <sup>3</sup>J<sub>H2-P</sub>,

$^3J_{\text{HB-P}}$  and  $^2J_{\text{H4-P}}$  all decrease in magnitude as the pH value increases. The largest change in magnitude of the coupling is seen as the pH value increases from 3.2 to 7.5 as this is where the phosphonic group is deprotonated (see Figure 4.3 and 4.4). There is a much smaller change in coupling as the pH value increases from 7.5 to 11.4 because the phosphonic group does not change here.

**Table 4.14** Coupling constants (Hz) of compound 1 at different pH values

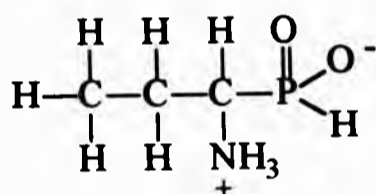
	pH 3.19	pH 7.54	pH 11.44
	$\begin{array}{c} \text{H} & \text{H} & \text{H} & \text{O} \\   &   &   & // \\ \text{H}-\text{C}-\text{C}-\text{C}-\text{P} & & & \text{OH} \\   &   &   & \backslash \\ \text{H} & \text{H} & \text{NH}_3^+ & \text{O}^- \end{array}$	$\begin{array}{c} \text{H} & \text{H} & \text{H} & \text{O} \\   &   &   & // \\ \text{H}-\text{C}-\text{C}-\text{C}-\text{P} & & & \text{O}^- \\   &   &   & \backslash \\ \text{H} & \text{H} & \text{NH}_3^+ & \text{O}^- \end{array}$	$\begin{array}{c} \text{H} & \text{H} & \text{H} & \text{O} \\   &   &   & // \\ \text{H}-\text{C}-\text{C}-\text{C}-\text{P} & & & \text{O}^- \\   &   &   & \backslash \\ \text{H} & \text{H} & \text{NH}_2 & \text{O}^- \end{array}$
$^3J_{\text{H1-H2}}$	7.44	7.38	7.37
$^3J_{\text{H1-H3}}$	7.61	7.63	7.68
$^4J_{\text{H1-H4}}$	0.20	0.27	0.24
$^4J_{\text{H1-P}}$	0.22	0.27	0.23
$^2J_{\text{H2-H3}}$	-14.64	-14.81	-14.47
$^3J_{\text{H2-H4}}$	8.86	9.71	10.00
$^3J_{\text{H2-P}}$	12.01	9.12	8.10
$^3J_{\text{H3-H4}}$	5.40	4.58	4.01
$^3J_{\text{H3-P}}$	9.99	8.01	7.82
$^2J_{\text{H4-P}}$	-13.15	-12.40	-11.37

The question of which rotamer I or III is dominant remains unresolved because of the problem encountered assigning the methylene protons. It is worth noting that the changes in the protonation of the phosphonic acids group ( $\text{PO}_3\text{H}$ ,  $\text{PO}_3^{2-}$ ) and the amino group ( $\text{NH}_3^+$ ,  $\text{NH}_2$ ) cannot be accounted for by the program ALTONA.

#### 4.5 Studies of Conformation in Solution of $\alpha$ -Aminopropanephosphinic Acid (2) at pH 3.10

By analogy with the work already carried out on  $\alpha$ -aminopropanephosphonic acid it might be expected that at pH 3.10 the  $\alpha$ -aminopropanephosphinic molecule will also exist primarily in the zwitterionic form.<sup>[156]</sup> This is the pH obtained for a solution of concentration  $0.42 \text{ mol dm}^{-3}$  in  $\text{D}_2\text{O}$  (the same concentration as a saturated solution of  $\alpha$ -aminopropanephosphonic acid at room temperature).

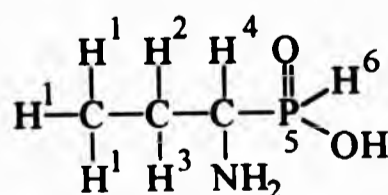
Figure 4.15 Dominant species in solution at pH 3.1 for compound 2 ( $\text{LH}_2$ )



##### 4.5.1 $^1\text{H}$ NMR Spectrum of $\alpha$ -Aminopropanephosphinic Acid (2) at pH 3.10

The experimental spectrum (Figure 4.17, lower spectrum) shows a large doublet assigned to the methine proton  $\text{H}^6$  centred at about 6.8 ppm, and a doublet of doublet of doublets at 2.8 ppm assigned to the methine proton  $\text{H}^4$ ; the anisochronous methylene protons  $\text{H}^3$  and  $\text{H}^2$  give rise to a complex multiplet centred at about 1.6 ppm, and the isochronous methyl protons  $\text{H}^1$  give rise to a triplet at  $\sim 0.9$  ppm (See Figure 4.16).

Figure 4.16 Numbering scheme used in assigning the  $^1\text{H}$  NMR spectrum of compound 2



The approximate values for the chemical shifts and spin-spin coupling constants were obtained from first order hand analysis of the spectrum and the knowledge gained from  $\alpha$ -aminopropanephosphonic acid.

#### **PANIC simulation**

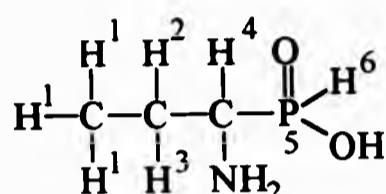
The procedure for the simulation is exactly the same as for the simulations of  $\alpha$ -aminopropanephosphonic acid (see Section 4.4.1.1)

The simulation was carried out assuming the spin system to be  $A_3BCDMX$  ( $CH_3^1CH^2CH^3CH^4P^5PH^6$ ), with the methyl, methylene and methine protons strongly coupled together, then weakly coupled to the proton on the phosphorus and weakly coupled to the phosphorus itself. The phosphorus nucleus was given a chemical shift well removed from the chemical shifts of the protons.

The refinement was considered complete when the differences between the calculated and experimental frequencies were less than 0.1 Hz, *i.e.* the same order as the digital resolution of both spectra (the digital resolution is 0.115 Hz).

After the final resolution the linewidth was increased to 0.5 Hz in order to approximate the experimental spectrum more closely (Figure 4.17, upper spectrum). The final parameters are given in Table 4.15, an expansion of the methylene region of the spectrum is shown in Figure 4.18.

Numbering scheme for the protons referred to in Table 4.15



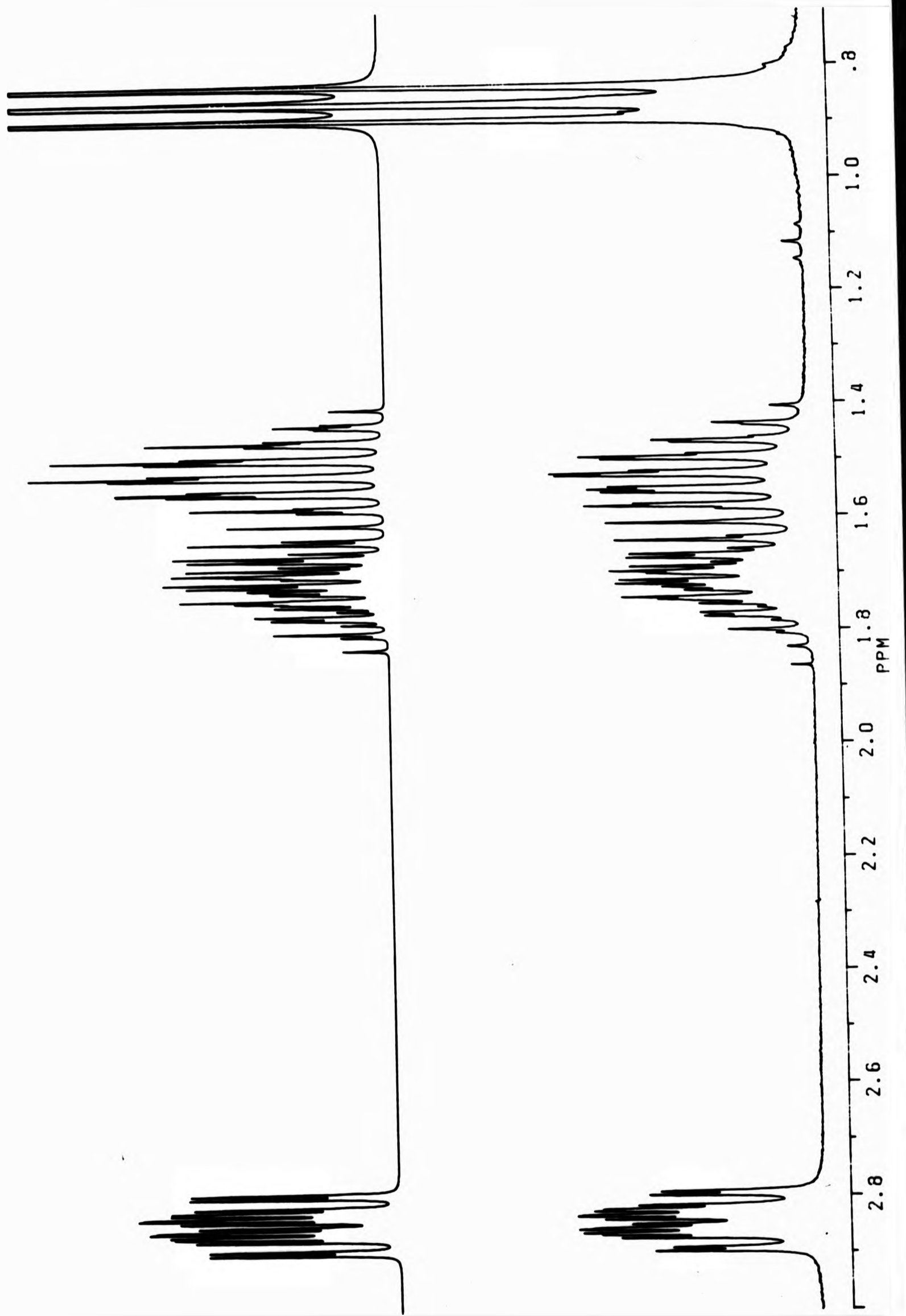
**Table 4.15**  $^1\text{H}$  NMR parameters<sup>†</sup> at pH 3.1 for compound 2

	Chemical shift (ppm)	Coupling constants (Hz)	
H <sup>1</sup>	0.86 (1)	$^3J_{\text{H}1-\text{H}2}$	7.40 (4)
H <sup>2</sup>	1.51 (1)	$^3J_{\text{H}1-\text{H}3}$	7.62 (3)
H <sup>3</sup>	1.72 (1)	$^4J_{\text{H}1-\text{H}4}$	0.22 (6)
H <sup>4</sup>	2.84 (1)	$^4J_{\text{H}1-\text{P}}$	0.24 (8)
H <sup>6</sup>	6.78 (1)	$^5J_{\text{H}1-\text{H}6}$	-
		$^2J_{\text{H}2-\text{H}3}$	-14.62 (5)
		$^3J_{\text{H}2-\text{H}4}$	8.36 (5)
		$^3J_{\text{H}2-\text{P}}$	5.99 (7)
		$^4J_{\text{H}2-\text{H}6}$	-
		$^3J_{\text{H}3-\text{H}4}$	5.98 (5)
		$^3J_{\text{H}3-\text{P}}$	11.62 (6)
		$^4J_{\text{H}3-\text{H}6}$	-
		$^2J_{\text{H}4-\text{P}}$	-10.55 (8)
		$^3J_{\text{H}4-\text{H}6}$	1.50 (5)
		$^1J_{\text{P}-\text{H}6}$	531.82 (6)

<sup>†</sup> Esd's are given in parentheses  
RMS of error estimation = 0.029.

**Figure 4.17**  $^1\text{H}$  NMR spectra of compound **2** in  $\text{D}_2\text{O}$  at pH 3.10.  
The upper spectrum is the simulated spectrum with line width 0.85 Hz and the lower spectrum is the experimental spectrum.

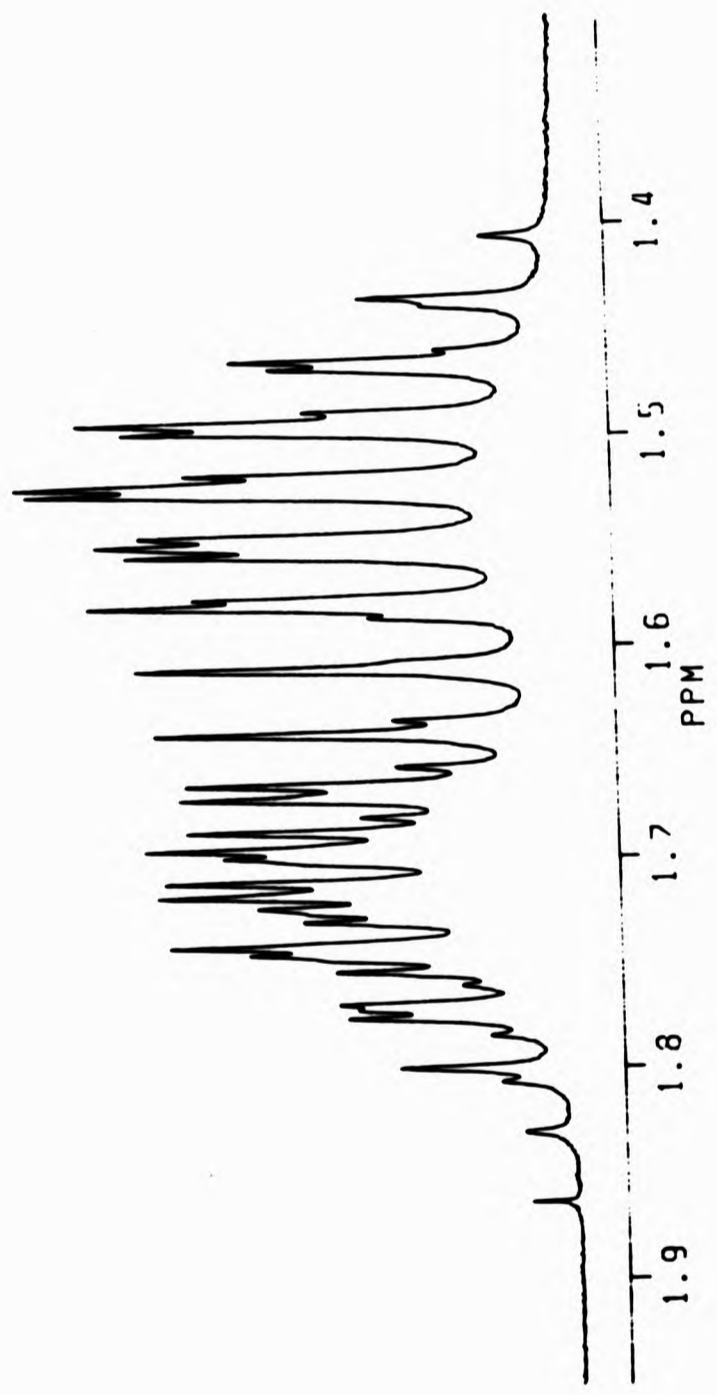




[Blank white box]

**Figure 4.18**  $^1\text{H}$  NMR spectra of methylene region of compound 2 in  $\text{D}_2\text{O}$  at pH 3.10.  
The upper spectrum is the simulated spectrum with line width 0.85 Hz and the lower spectrum is the experimental spectrum.





#### 4.5.2 Conformational Analysis of $\alpha$ -Aminopropanephosphinic Acid (2) at pH 3.10

The values of the  $^3J_{\text{HH}}$  coupling constants from the proton NMR analysis were used again to investigate the conformation of the molecule at pH 3.10. The program ALTONA<sup>[163]</sup> was used to determine the relative populations of the three rotamers for each enantiomer (see section 4.4.1.2). The results are given in Tables 4.16.

**Table 4.16** Relative rotamer populations (normalised to 1) for the alternative assignments of the methylene protons in compound 2

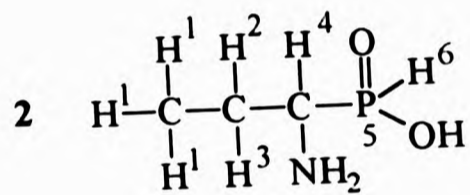
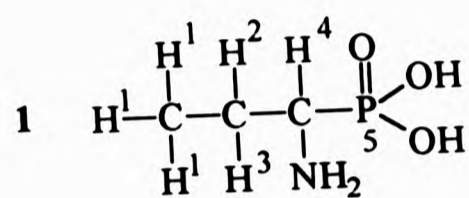
	$P_I$	$P_{II}$	$P_{III}$
<i>S</i> Enantiomer			
$H^a=H^2, H^b=H^3$	0.28	0.15	0.57
$H^a=H^3, H^b=H^2$	0.55	0.12	0.33
<i>R</i> Enantiomer			
$H^a=H^2, H^b=H^3$	0.33	0.12	0.55
$H^a=H^3, H^b=H^2$	0.57	0.15	0.28

Again the most abundant rotamer depends on the assignment of the geminal protons.

#### 4.6 Comparison of the $^1\text{H}$ NMR parameters of $\alpha$ -Aminopropanephosphonic Acid (1) and $\alpha$ -Aminopropanephosphinic Acid (2)

Assuming that the same dominant species exists for both compounds in solution, the coupling constants and chemical shifts of  $\alpha$ -aminopropanephosphonic acid (pH 3.19) and  $\alpha$ -aminopropanephosphinic acid (pH 3.10) can be compared (see Tables 4.17 and 4.18).

Numbering scheme for the protons referred to in Tables 4.17 and 4.18



**Table 4.17** Chemical shifts (ppm) of  $\alpha$ -aminopropanephosphonic acid 1 and  $\alpha$ -aminopropanephosphinic acid 2

	1	2
H <sup>1</sup>	1.07	0.86
H <sup>2</sup>	1.75	1.51
H <sup>3</sup>	1.96	1.72
H <sup>4</sup>	3.17	2.84
H <sup>6</sup>	-	6.78

The signals of the protons in the phosphinic acid 2 are approximately 0.2 ppm upfield of the comparable proton signals in the phosphonic acid 1. This difference is slightly larger (0.3 ppm) for the methine proton H<sup>4</sup>. This is probably because the methine proton is proximal to the phosphonic/phosphinic group. Alternatively, these small differences in chemical shifts could perhaps be attributed to the slight differences in pH value.

**Table 4.18** Coupling constants (Hz) of  $\alpha$ -aminopropanephosphonic acid 1 and  $\alpha$ -aminopropanephosphinic acid 2

	1	2
<sup>3</sup> J <sub>H1-H2</sub>	7.44	7.40
<sup>3</sup> J <sub>H1-H3</sub>	7.61	7.62
<sup>4</sup> J <sub>H1-H4</sub>	0.20	0.22
<sup>4</sup> J <sub>H1-P</sub>	0.22	0.24
<sup>2</sup> J <sub>H2-H3</sub>	-14.64	-14.62
<sup>3</sup> J <sub>H2-H4</sub>	8.86	8.36
<sup>3</sup> J <sub>H2-P</sub>	12.01	5.99
<sup>3</sup> J <sub>H3-H4</sub>	5.40	5.98
<sup>3</sup> J <sub>H3-P</sub>	9.99	11.62
<sup>2</sup> J <sub>H4-P</sub>	-13.15	-10.55

In both the compounds the couplings involving the methyl protons,  $H^1$ , and the vicinal couplings  ${}^3J_{H2-H3}$  are all very similar. The couplings  ${}^3J_{H2-H4}$  and  ${}^3J_{H3-H4}$  are of similar magnitude. The vicinal  ${}^3J_{H2-H4}$  coupling is larger in the phosphonic compound **1**, while the vicinal  ${}^3J_{H3-H4}$  coupling is larger in the phosphinic compound **2**. The couplings that differ more between the two compounds are the couplings involving the phosphorus nucleus.

## CHAPTER FIVE

### EXPERIMENTAL

#### 5.1 Instrumental Analysis

##### (i) NMR Spectra

$^1\text{H}$  NMR spectra were obtained on a Bruker AM250 spectrometer operating at 250.133 MHz unless otherwise stated.  $^{13}\text{C}$  NMR spectra, broad band proton decoupled, DEPT-135 and DEPT-90, were obtained on a Bruker AM250 spectrometer operating at 62.896 MHz. The samples were dissolved in  $\text{CDCl}_3$  or DMSO containing tetramethylsilane (TMS) as the internal reference, or in  $\text{D}_2\text{O}$  or  $\text{NaOD}/\text{D}_2\text{O}$  containing sodium 3-trimethylsilylpropionate- $\text{d}_4$  ( $\text{Me}_3\text{SiCD}_2\text{CD}_2\text{CO}_2\text{Na}$ ) (TSP) as the internal reference.  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra were obtained on a Bruker AM250 spectrometer operating at 101.256 MHz, and a Bruker WP80-SY spectrometer operating at 32.44 MHz. The samples were dissolved in  $\text{CDCl}_3$ ,  $\text{D}_2\text{O}$ , DMSO or  $\text{NaOD}/\text{D}_2\text{O}$  with  $\text{H}_3\text{PO}_4$  as the external reference. The chemical shifts of the nuclei are given in ppm and the coupling constants are given in Hertz (Hz).

The numbering schemes used for annotating the NMR spectra throughout this chapter are given in the Appendices II (imine precursors), III (phosphonate esters) and IV (phosphonic acids).

##### (ii) Elemental Analysis

Analyses for carbon, hydrogen, nitrogen and sulfur content of samples were obtained using a Carlo Erba 1106 Elemental Analyzer.

##### (iii) Mass Spectra

Low resolution electron impact mass spectra were obtained using a Kratos Profile HV3 spectrometer with 70 eV ionizing energy. LSIMS mass spectra were obtained on the same

instrument using a glycerol matrix and with a primary beam of caesium ions generated in an ion-gun operating at 10 kV.

#### (iv) Melting Points

Melting points were recorded on an Electrothermal digital melting point apparatus and are uncorrected.

### 5.2 Synthesis of the Imine Precursors

#### 5.2.1 Synthesis of Imine Precursors using Aminodiphenylmethane and Aldehydes

##### Preparation of N-(2'-Pyrrolylmethylidene)-1,1-diphenylmethanamine (7)

A mixture of pyrrole-2-carboxaldehyde (5.57 g, 0.058 mol) and aminodiphenylmethane hydrochloride (12.81 g, 0.058 mol) was stirred in dichloromethane (50 cm<sup>3</sup>) with anhydrous potassium carbonate (5 g, 0.036 mol) at room temperature for 6 hours. The potassium chloride and excess potassium carbonate were removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow crystalline solid. Recrystallisation from toluene and petroleum spirit (b.p. 40-60°C) gave N-(2'-pyrrolylmethylidene)-1,1-diphenylmethanamine as a yellow crystalline solid (8.30 g, 55.3%); m.p. 160-162°C; (Found: C, 82.9; H, 6.3; N, 10.9. C<sub>19</sub>H<sub>16</sub>N requires: C, 83.0; H, 6.2; N, 10.8%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 5.56 (1H, s, 7-H), 6.22 (1H, dd, <sup>3</sup>J<sub>H3-H4</sub> 3.65 and <sup>3</sup>J<sub>H4-H5</sub> 2.56, 4-H), 6.51 (1H, dd, <sup>4</sup>J<sub>H3-H5</sub> 1.10, 3-H), 6.84 (1H, dd, 5-H), 7.18-7.35 (10H, m, 2 x Ph-H), 8.13 (1H, s, 6-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 77.66 (s, 7-C), 110.16 (s, 4-C), 115.54 (s, 3-C), 122.68 (s, 5-C), 127.10 (s, 11-C), 127.82 (s, 10-C), 128.47 (s, 9-C), 129.76 (s, 8-C), 143.37 (s, 2-C), 151.34 (s, 6-C); EI ms: m/z 260 (M<sup>+</sup>, 21.7%).

A mixture of pyrrole-2-carboxaldehyde (5.57 g, 0.058 mol) and aminodiphenylmethane (10.73 g, 0.058 mol) was stirred in diethyl ether (50 cm<sup>3</sup>) with anhydrous potassium carbonate (5 g, 0.036 mol) at room temperature for 6 hours. The excess potassium carbonate was removed by filtration. The diethyl ether was removed *in vacuo* to yield a

yellow crystalline solid which was recrystallised from toluene and petroleum spirit (b.p. 40-60°C) to give N-(2'-pyrrolylmethylidene)-1,1-diphenylmethanamine as a yellow crystalline solid (10.73 g, 71.2%); (Found: C, 82.9; H, 6.2; N, 10.9%).

#### Preparation of N-Furfurylidene-1,1-diphenylmethanamine (8)

A mixture of furfural (9.6 g, 0.1 mol) and aminodiphenylmethane hydrochloride (22.0 g, 0.1 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.072 mol) at room temperature for 6 hours. The potassium chloride and excess potassium carbonate were removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow solid which was recrystallised from toluene and petroleum spirit (b.p. 30-40°C) to give the product as a pale yellow crystalline solid (21.0 g, 80.4%); m.p. 110-112°C; (Found: C, 82.8; H, 5.8; N, 5.4. C<sub>18</sub>H<sub>15</sub>NO requires: C, 82.7; H, 5.8; N, 5.4%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 5.53 (1H, s, 7-H), 6.36 (1H, dd, <sup>3</sup>J<sub>H4-H3</sub> 3.42 and <sup>3</sup>J<sub>H4-H5</sub> 1.75, 4-H), 6.72 (1H, dd, <sup>4</sup>J<sub>H3-H5</sub> 0.67, 3-H), 7.17-7.37 (10H, m, 2 x Ph), 7.44 (CH, dd, 5-H), 8.13 (1H, s, 6-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 77.92 (s, 7-C), 111.61 (s, 4-C), 114.5 (s, 3-C), 126.99 (s, 11-C), 127.73 (s, 10-C), 128.38 (s, 9-C), 143.27 (s, 8-C), 144.79 (s, 5-C), 149.63 (s, 6-C), 151.54 (s, 2-C); EI ms: m/z 261 (M<sup>+</sup>, 61.9).

A mixture of furfural (2.62 g, 0.027 mol) and aminodiphenylmethane (5.0 g, 0.027 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (4 g, 0.029 mol) at room temperature for 6 hours. The potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow solid which was recrystallised from toluene and petroleum spirit (b.p. 30-40°C) to give the product as a pale yellow crystalline solid (6.01 g, 85.2%); (Found: C, 82.6; H, 5.8; N, 5.5%).

A mixture of furfural (9.6 g, 0.1 mol) and aminodiphenylmethane (18.3 g, 0.1 mol) was refluxed in toluene (150 cm<sup>3</sup>) with the azeotropic removal of water for 36 hours. The toluene was removed *in vacuo* to yield a pale brown solid which was recrystallised from toluene and petroleum spirit (b.p. 40-60°C) to give the desired product as a yellow crystalline solid (24.77 g, 94.9%); (Found: C, 82.7; H, 5.8; N, 5.4%).



**Preparation of N-(3'-Thienylmethylidene)-1,1-diphenylmethanamine (9)**

A mixture of thiophen-3-carboxaldehyde (5.0 g, 0.044 mol) and aminodiphenylmethane hydrochloride (9.8 g, 0.044 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (8 g, 0.058 mol) at room temperature for 6 hours. The potassium chloride and excess potassium carbonate were removed by filtration. The dichloromethane was removed *in vacuo* to yield a brown oil that solidified on standing. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave the desired product (6.0 g, 49.6%); m.p. 80-81°C; (Found: C, 77.9; H, 5.4; N, 5.0; S, 11.7. C<sub>18</sub>H<sub>15</sub>NS requires: C, 77.9; H, 5.4; N, 5.0; S, 11.6%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 5.52 (1H, s, 7-H), 7.14-7.38 (11H, m, 2 x Ph-H and 5-H), 7.55 (1H, dd, 4-H), 7.63 (1H, dd, 2-H), 8.35 (1H, s, 6-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 77.63 (s, 7-C), 125.95 (s, 5-C), 126.10 (s, 4-C), 126.85 (s, 11-C), 127.58 (s, 10-C), 128.31 (s, 9-C), 128.63 (s, 2-C), 140.51 (s, 8-C), 143.70 (s, 3-C), 154.98 (s, 6-C); EI ms: m/z 277 (M<sup>+</sup>, 23.0%).

A mixture of thiophen-3-carboxaldehyde (5.0 g, 0.044 mol) and aminodiphenylmethane (8.1 g, 0.044 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (8 g, 0.058 mol) at room temperature for 6 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to yield a brown oil that solidified on standing. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave the desired product (8.2 g, 67.0%); (Found: C, 77.9; H, 5.5; N, 5.0%).

**Preparation of N-(2'-Thienylmethylidene)-1,1-diphenylmethanamine (10)**

A mixture of thiophen-2-carboxaldehyde (5.0 g, 0.044 mol) and aminodiphenylmethane hydrochloride (9.8 g, 0.044 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (8 g, 0.058 mol) at room temperature for 6 hours. The potassium chloride and excess potassium carbonate were removed by filtration. The dichloromethane was removed *in vacuo* to yield a brown oil that solidified on standing. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave the desired product (4.30 g, 35.3%); m.p. 95°C; (Found: C, 77.9; H, 5.4; N, 5.0; S, 11.7. C<sub>18</sub>H<sub>15</sub>NS requires: C, 77.9; H, 5.4; N, 5.0; S, 11.6%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 5.57 (1H, s, 7-H), 7.01 (1H, dd, <sup>2</sup>J<sub>H3-H4</sub> 5.00 and <sup>2</sup>J<sub>H4-H5</sub> 3.62, 4-H), 7.17-7.38 (12H, m, 2 x Ph-H, 3-H and 5-H), 8.43 (1H,

s, 6-H);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 77.21 (s, 7-C), 127.09 (s, 11-C), 127.41 (s, 4-C), 127.82 (s, 10-C), 128.54 (s, 9-C), 129.25 and 130.77 (2 x s, 3-C and 5-C), 142.85 (s, 2-C), 143.76 (s, 8-C), 154.12 (s, 6-C); EI ms:  $m/z$  277 ( $M^+$ , 80.7%).

A mixture of thiophen-2-carboxaldehyde (12.30 g, 0.11 mol) and aminodiphenylmethane (20.09 g, 0.11 mol) was stirred in ether (100  $\text{cm}^3$ ) with anhydrous potassium carbonate (12 g, 0.14 mol) at room temperature for 8 hours. The excess potassium carbonate was removed by filtration. The ether was removed *in vacuo* to yield a yellow oil that solidified on standing. Recrystallisation from dichloromethane and petroleum spirit (b.p. 30-40°C) gave the desired product (17.92 g, 58.8%); (Found: C, 77.9; H, 5.4; N, 5.0; S, 11.5%).

**Preparation of N-(4'-Dimethylaminobenzylidene)-1,1-diphenylmethanamine<sup>[64]</sup> (11)**

A mixture of 4-dimethylaminobenzaldehyde (14.9 g, 0.1 mol) and aminodiphenylmethane hydrochloride (22.0 g, 0.1 mol) was stirred in dichloromethane (100  $\text{cm}^3$ ) with anhydrous potassium carbonate (10 g, 0.072 mol) at room temperature for 6 hours. The potassium chloride and excess potassium carbonate were removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow liquid that solidified on standing. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave the desired product as an orange crystalline solid (28.98 g 92.3%); m.p. 140-141°C; (Found: C, 84.0; H, 7.1; N, 8.9. Calculated for  $\text{C}_{22}\text{H}_{22}\text{N}_2$ : C, 84.0; H, 7.0; N, 8.9%);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.92 (6H, s, 2 x  $\text{CH}_3$ ), 5.51 (1H, s, 6-H), 6.64 (2H, d, 3-H), 7.13-7.40 (10H, m, 2 x Ph-H), 7.69 (2H, d, 2-H), 8.82 (1H, s, 5-H);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 40.12 (s, 2 x  $\text{CH}_3$ ), 77.69 (s, 6-C), 111.49 (s, 3-C), 124.61 (s, 4-C), 126.68 (s, 10-C), 127.74 (s, 9-C), 128.26 (s, 8-C), 129.79 (s, 2-C), 144.47 (s, 7-C), 152.07 (s, 1-C), 160.56 (s, 5-C); EI ms:  $m/z$  314 ( $M^+$ , 20.7%).

A mixture of 4-dimethylaminobenzaldehyde (14.9 g, 0.1 mol) and aminodiphenylmethane (18.3 g, 0.1 mol) was stirred in dichloromethane (100  $\text{cm}^3$ ) with anhydrous potassium carbonate (10 g, 0.072 mol) at room temperature for 6 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow liquid that solidified on standing. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave the desired product as an orange crystalline solid (16.96 g, 54.0%); (Found: C, 84.0; H, 7.1; N, 8.9%).

#### Preparation of N-Piperonylidene-1,1-diphenylmethamine (12)

A mixture of piperonal (15.0 g, 0.1 mol) and aminodiphenylmethane hydrochloride (22.0 g, 0.1 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.72 mol) at room temperature for 6 hours. The potassium chloride and excess potassium carbonate were removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow oil which solidified on standing. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave the product as a white crystalline solid (16.73 g, 53.1%); m.p. 115-116°C; (Found: C, 80.1; H, 5.4; N, 4.4. C<sub>21</sub>H<sub>17</sub>NO<sub>2</sub> requires: C, 80.0; H, 5.4; N, 4.4%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 5.55 (1H, s, 9-H), 5.97 (2H, s, 7-CH<sub>2</sub>), 6.80 (1H, d, <sup>3</sup>J<sub>H5-H6</sub> 7.99, 5-H), 7.14 (1H, dd, <sup>4</sup>J<sub>H2-H6</sub> 1.57, 6-H), 7.18-7.40 (10H, m, 2 x Ph-H) 7.52 (1H, d, 2-H), 8.29 (1H, s, 8-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 77.63 (s, 9-C), 101.41 (s, 7-C), 106.92 and 107.96 (2 x s, 5-C and 6-C), 124.73 (s, 2-C), 126.93 (s, 13-C), 127.65 (s, 12-C), 128.41 (s, 11-C) 131.27 (s, 10-C) 144.07 (s, 1-C), 148.22 and 149.94 (2 x s, 3-C and 4-C), 159.83 (s, 8-C); EI ms: m/z 315 (M<sup>+</sup>, 29%).

A mixture of piperonal (15.0 g, 0.1 mol) and aminodiphenylmethane (18.3 g, 0.1 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.72 mol) at room temperature for 6 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow oil which solidified on standing. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave the product as crystalline white solid (26.9 g, 85.4%); (Found: C, 80.1; H, 5.4; N, 4.4%).

#### Preparation of N-(4'-Isopropylbenzylidene)-1,1-diphenylmethamine<sup>[64, 167]</sup> (13)

A mixture of 4-isopropylbenzaldehyde (14.8 g, 0.1 mol) and aminodiphenylmethane hydrochloride (22.0 g, 0.1 mol) was stirred in dichloromethane (50 cm<sup>3</sup>) with anhydrous potassium carbonate (15 g, 0.11 mol) at room temperature for 6 hours. The potassium chloride and excess potassium carbonate were removed by filtration. The dichloromethane was removed *in vacuo* to yield a white crystalline solid. Recrystallisation from toluene and petroleum spirit (b.p. 40-60°C) gave N-(4'-isopropylbenzylidene)-1,1-diphenylmethamine as a white crystalline solid (16.54 g, 52.8%); m.p. 63-64°C; (Found: C, 88.2; H, 7.5; N, 4.4. Calculated for C<sub>23</sub>H<sub>23</sub>N: C, 88.1; H, 7.4; N, 4.5%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.21 (6H, d,

$^3J_{\text{HH}}$  6.81, 2 x CH<sub>3</sub>), 2.87 (1H, septet, CHCH<sub>3</sub>), 5.55 (1H, s, 6-H), 7.13-7.76 (14H, m, Ar H), 8.34 (1H, s, 5-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 23.79 (s, 2 x CH<sub>3</sub>), 34.08 (s, CHCH<sub>3</sub>), 77.79 (s, 6-C), 123.58 (s, 3-C), 126.86 (s, 10-C), 127.67 (s, 9-C), 128.34 (s, 8-C), 128.52 (s, 2-C), 134.13 (s, 7-C), 143.99 (s, 4-C), 151.86 (s, 1-C), 160.59 (s, 5-C); EI ms: m/z 313 (M<sup>+</sup>, 48.8%).

A mixture of 4-isopropylbenzaldehyde (14.8 g, 0.1 mol) and aminodiphenylmethane (18.3 g, 0.1 mol) was stirred in diethyl ether (50 cm<sup>3</sup>) with anhydrous potassium carbonate (15 g, 0.11 mol) at room temperature for 6 hours. The potassium carbonate was removed by filtration. The diethyl ether was removed *in vacuo* to yield a white crystalline solid. Recrystallisation from toluene and petroleum spirit (b.p. 40-60°C) gave N-(4'-isopropylbenzylidene)-1,1-diphenylmethylamine as a white crystalline solid (23.41 g, 74.8%); (Found: C, 88.2; H, 7.5; N, 4.4%).

#### Preparation of N-Benzylidene-1,1-diphenylmethylamine<sup>[64]</sup> (14)

A mixture of benzaldehyde (2.89 g, 0.027 mol) and aminodiphenylmethane (5.0 g, 0.027 mol) was stirred in ether (50 cm<sup>3</sup>) with anhydrous potassium carbonate (5 g, 0.036 mol) at room temperature for 8 hours under a nitrogen atmosphere. The potassium carbonate was removed by filtration. The ether was removed *in vacuo* to yield a white crystalline solid. Recrystallisation from dichloromethane and petroleum spirit (b.p. 40-60°C) gave the product as a white crystalline solid (4.89 g, 66.7%); m.p. 104-105°C; (Found: C, 88.5; H, 6.4; N, 5.2. Calculated for C<sub>20</sub>H<sub>17</sub>N: C, 88.5; H, 6.3; N, 5.2%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 5.59 (1H, s, 6-H), 7.17-7.42 (13H, m, Ph-H, 3-H and 4-H), 7.81-7.85 (2H, m, 2-H), 8.40 (1H, s, 5-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 77.77 (s, 6-C), 126.88 and 128.34 (2 x s, 8-C, 9-C and 10-C), 127.58 and 128.40 (2 x s, 3-C and 2-C), 130.63 (s, 4-C), 136.18 (s, 1-C), 143.83 (s, 7-C), 160.63 (s, 5-C); EI ms: m/z 271 (M<sup>+</sup>, 66.7%).

#### Preparation of N-(1'-Naphthylmethylidene)-1,1-diphenylmethylamine (15)

A mixture of 1-naphthaldehyde (15.6 g, 0.1 mol) and aminodiphenylmethane (18.3 g, 0.1 mol) was stirred in ether (100 cm<sup>3</sup>) with anhydrous potassium carbonate (20 g, 0.145 mol) at room temperature for 9 hours. The potassium carbonate was removed by filtration. The ether was removed *in vacuo* to yield a yellow orange oil which solidified on

standing. Recrystallisation from dichloromethane and petroleum spirit (b.p. 40-60°C) gave the desired product as crystalline yellow solid (29.71 g, 92.2%); m.p. 109-110°C; (Found: C, 89.8; H, 6.0; N, 4.3.  $C_{24}H_{19}N$  requires: C, 89.7; H, 6.0; N, 4.4%);  $\delta_H$  ( $CDCl_3$ ) 5.59 (1H, s, 12-H), 7.12-7.52 (14H, m, 2 x Ph-H, 3-H, 7-H, 8-H and 9-H), 7.71-7.75 (2H, 2 x dd,  $^3J_{HH}$  and  $^3J_{HH}$  8.36 and 8.10, 4-H and 6-H), 8.92 (1H, s, 11-H) 9.09 (1H, d,  $^3J_{HH}$  8.56, 2-H);  $\delta_C$  ( $CDCl_3$ ) 79.23 (s, 12-C), 124.66 and 125.05 (2 x s, 7-C and 8-C), 125.93 (s, 9-C) 126.92 (s, 16-C), 127.14 (s, 4-C), 127.61 (s, 15-C), 128.43 (s, 14-C), 128.48 (s, 6-C), 129.78 (s, 3-C), 131.14 (s, 2-C), 131.28 and 131.37 (2 x s, 5-C and 10-C), 133.72 (s, 1-C), 143.97 (s, 13-C), 160.85 (s, 11-C); EI ms: m/z 321 ( $M^+$ , 21.81%).

#### Preparation of N-(9'-Anthrylmethylidene)-1,1-diphenylmethanamine (16)

A mixture of 9-anthraldehyde (20.62 g, 0.1 mol) and aminodiphenylmethane (18.3 g, 0.1 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (20 g, 0.145 mol) at room temperature for 6 hours. The potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow orange oil which solidified on standing. Recrystallisation from toluene and petroleum spirit (b.p. 40-60°C) gave the product as crystalline yellow solid (6.45 g, 87%); m.p. 139°C; (Found: C, 90.3; H, 5.6; N, 3.7.  $C_{28}H_{21}N$  requires: C, 90.5; H, 5.7; N, 3.8%);  $\delta_H$  ( $CDCl_3$ ) 5.83 (1H, s, 16-H), 7.20-7.41 (10H, m, 2 x Ph-H), 7.50-7.53 (4H, m, 3-H, 6-H, 10-H and 13-H), 7.86-7.90 (2H, m, 5-H and 11-H), 8.33 (1H, s, 8-H) 8.37-8.43 (2H, m, 4-H and 12-H), 9.49 (1H, s, 15-H);  $\delta_C$  ( $CDCl_3$ ) 80.29 (s, 16-C), 125.01 (s, 5-C and 11-C), 125.35 (s, 4-C and 12-C), 126.82 (s, 6-C and 10-C), 127.32 (s, 3-C and 13-C), 127.94 (s, 19-C), 128.80 (s, 18-C), 128.98 (s, 20-C), 129.69 (s, 8-C), 130.29 (s, 17-C), 131.39 (s, 2-C, 7-C, 9-C and 14-C), 143.94 (s, 1-C), 160.70 (s, 15-C); EI ms: m/z 371 ( $M^+$  22.8%).

#### Preparation of N-(1'-Pyrenylmethylidene)-1,1-diphenylmethanamine (17)

A mixture of 1-pyrenecarboxaldehyde (23.72 g, 0.1 mol) and aminodiphenylmethane (18.3 g, 0.1 mol) was stirred in ether (100 cm<sup>3</sup>) with anhydrous potassium carbonate (20 g, 0.145 mol) at room temperature for 6 hours under a nitrogen atmosphere. The potassium carbonate was removed by filtration. The ether was removed *in vacuo* to yield a yellow oil which solidified on standing. Recrystallisation from dichloromethane and petroleum spirit (b.p. 40-60°C) gave the product as crystalline yellow solid (26.85 g,

67.9%); m.p. 180-181 °C; (Found: C, 90.9; H, 5.6; N, 3.4. C<sub>28</sub>H<sub>21</sub>N requires: C, 91.1; H, 5.4; N, 3.5%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 5.80 (1H, s, 18-H), 7.23-7.57 (10H, m, 2 x Ph-H), 7.98-8.18 (5H, m, 6-H, 7-H, 8-H, 10-H and 11-H), 8.14 (1H, d, <sup>3</sup>J<sub>HH</sub> 8.07, 13-H), 8.20 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.21, 4-H) 8.65 (1H, d, 14-H), 9.01 (1H, d, 3-H), 9.42 (1H, s, 17-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 79.27 (s, 18-C), 122.84, 124.84, 125.64, 125.87, 126.08, 127.10, 127.43 and 128.70 (8 x s, 3-C, 4-C, 6-C, 7-C, 8-C, 10-C, 11-C, 13-C and 14-C), 127.04 (s, 22-C), 127.74 (s, 21-C), 128.70 (s, 20-C), 124.59, 130.02, 130.57, 131.22 and 132.91 (5 x s, 1-C, 2-C, 5-C, 9-C and 12-C), 144.14 (s, 19-C), 159.84 (s, 17-C); EI ms: m/z 395 (M<sup>+</sup>, 2.0%).

### 5.2.2 Synthesis of Imines Precursor using Aminodiphenylmethane and Ketones

#### Preparation of N-Cyclopentylidene-1,1-diphenylmethanamine (18)

A mixture of cyclopentanone (8.4 g, 0.1 mol) and aminodiphenylmethane hydrochloride (22.0 g, 0.1 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.072 mol) at room temperature for 8 hours. The potassium chloride and excess potassium carbonate were removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow liquid which, on the addition of petroleum spirit (b.p. 30-40°C) gave the product as a pale yellow powder. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave N-cyclopentylidene-1,1-diphenylmethanamine as a yellow crystalline solid (5.03 g, 20.2%); m.p. 95°C; Found: C, 86.8; H, 7.7; N, 5.6. C<sub>18</sub>H<sub>19</sub>N requires: C, 86.7; H, 7.7; N, 5.6%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.64-1.77 (4H, m, 3-CH<sub>2</sub> and 4-CH<sub>2</sub>), 2.21-2.27 and 2.41-2.47 (4H, 2 x m, 2-CH<sub>2</sub> and 5-CH<sub>2</sub>), 5.46 (1H, s, 6-H), 7.12-7.36 (10H, m, 2 x Ph-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 24.11 and 24.93 (2 x s, 3-C and 4-C), 29.43 and 36.72 (2 x s, 2-C and 5-C), 70.58 (s, 6-C), 126.66 (s, 10-C), 127.60 (s, 9-C), 128.32 (s, 8-C), 144.27 (s, 7-C), 180.80 (s 1-C); EI ms: m/z 249 (M<sup>+</sup>, 19.4%).

A mixture of cyclopentanone (8.4 g, 0.1 mol) and aminodiphenylmethane (18.3 g, 0.1 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.072 mol) at room temperature for 6 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow oil which solidified on standing to give the product as a pale yellow powder. Recrystallisation from toluene and petroleum spirit (b.p. 30-40°C) gave N-cyclopentylidene-1,1-

diphenylmethanamine as a yellow crystalline solid (19.97 g, 80.2%); (Found: C, 86.6; H, 7.6; N, 5.6%).

#### Preparation of N-Cyclohexylidene-1,1-diphenylmethanamine (19)

A mixture of cyclohexanone (9.81 g, 0.1 mol) and aminodiphenylmethane (18.32 g, 0.1 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.072 mol) at room temperature for 14 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to yield a yellow oil which, solidified on standing to give the product as a yellow powder. Recrystallisation from toluene and petroleum spirit (b.p 40-65°C) gave N-cyclohexylidene-1,1-diphenylmethanamine as a sticky yellow solid (11.12 g, 42.2%); Found: C, 86.4; H, 7.9; N, 5.4. C<sub>19</sub>H<sub>21</sub>N requires: C, 86.6; H, 8.0; N, 5.3%;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.61-1.90 (6H, m, 3-CH<sub>2</sub>, 4-CH<sub>2</sub>, and 5-CH<sub>2</sub>), 2.36-2.58 (4H, m, 2-CH<sub>2</sub> and 6-CH<sub>2</sub>), 5.91 (1H, s, 7-H), 7.26-7.51 (10H, m, 2 x Ph-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 25.94 (s, 4-C), 26.83 and 27.78 (2 x s, 3-C and 5-C), 29.83 (s, 6-C), 40.26 (s, 2-C), 66.49 (s, 7-C), 126.46 (s, 11-C), 127.57 (s, 10-C), 128.26 (s, 9-C), 144.93 (s, 8-C), 173.20 (s, 1-C); EI ms: m/z 263 (M<sup>+</sup>, 32.6%).

#### Reaction between Camphor and Aminodiphenylmethane (20)

Aminodiphenylmethane (1.8 g, 0.01 mol) was dissolved in toluene (sodium dried, 10 cm<sup>3</sup>) under nitrogen and cooled to -20°C. Titanium tetrachloride (0.1 g, 0.005 mol) dissolved in toluene (sodium dried, 1 ml) was added dropwise and allowed to mix for 1 hour. Camphor (1.5 g, 0.01 mol) was added and the reaction mixture allowed to reach room temperature. The mixture was refluxed for 2 hours and stirred at room temperature for a further 72 hours. The titanium oxide precipitate was filtered off and the toluene was removed *in vacuo* to yield an orange coloured oil (1.10 g). A portion of this oil (0.5 g) was taken and purified by chromatography [silica column; elution with dichloromethane - b.p. petroleum spirit 40-60°C (2:5)] to give a colourless oil (0.1 g); Found: C, 87.4; H, 8.4; N, 4.4. C<sub>22</sub>H<sub>23</sub>N requires: C, 87.1; H, 8.3; N, 4.6%;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.62 and 0.90 (2 x 3H, 2 x s, 2 x CH<sub>3</sub>), 1.08 (3H, s, 10-CH<sub>3</sub>), 1.23-1.42 (2H, m, 4-CH<sub>2</sub>), 1.59-2.05 (4H, m, 3-H, 5-CH<sub>2</sub> and 1H of 2-CH<sub>2</sub>), 2.25-2.36 (1H, m, 2-CH<sub>2</sub>), 5.43 (1H, s, 11-H), 7.09-7.40 (10H, m, 2 x Ph-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 11.54 (s, 10-C), 19.00 and 19.48 (2 x s, 8-C and 9-C), 27.41 (s, 4-C), 31.95 (s, 5-C), 35.83 (s, 2-C), 42.99 (s, 3-C), 47.03 (s, 7-C), 53.93 (s,

6-C), 68.18 (s, 11-C), 126.34 (s, 15-C and 15'-C), 127.39 (s, 14-C and 14'-C), 128.35 and 128.43 (2 x s, 13-C and 13'-C), 144.91 and 145.00 (2 x s, 12-C and 12'-C), 181.36 (s, 1-C); EI ms:  $m/z$  317 ( $M^+$ , 9.9%).

### 5.2.3 Attempted Preparations of Imine Precursors using Aminodiphenylmethane and Aldehydes (See Figure 2.2)

#### General Procedure (5.2.3)

A mixture of the aldehyde (0.01 mol) and aminodiphenylmethane (1.83 g, 0.01 mol) was stirred in dichloromethane (25 cm<sup>3</sup>) with anhydrous potassium carbonate (2 g, 0.014 mol) at room temperature for between 6 and 8 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo*.

#### Attempted Reactions of Aldehydes and Aminodiphenylmethane

The aldehydes (1*R*)-(-)-myretal (i), *S*-(-)-perillaldehyde (ii) and 2-methyl-3-(2-furyl)propenal (iii) were reacted according to the general procedure (5.2.3). The <sup>1</sup>H NMR spectra of residues obtained showed signals corresponding to the starting materials.

#### Attempted reaction of 5-Norborene-2-carboxaldehyde (iv) and Aminodiphenylmethane

The reaction was carried out according to the general procedure (5.2.3). The <sup>1</sup>H NMR spectrum of the brown oil obtained showed signals corresponding to a mixture of the starting materials as well as signals corresponding to the desired product identified by the observation of the molecular ion in the mass spectrum EI ms:  $m/z$  287 ( $M^+$ , 5.6). Attempts to isolate the product by chromatography resulted in isolation of the starting materials only.



## 5.2.4 Attempted Preparations of Imine Precursors using Aminodiphenylmethane and Ketones (See Figure 2.2)

### General Procedure (5.2.4)

A mixture of the ketone (0.01 mol) and aminodiphenylmethane (1.83 g, 0.01 mol) was stirred in dichloromethane (25 cm<sup>3</sup>) with anhydrous potassium carbonate (2 g, 0.014 mol) at room temperature for between 6 and 8 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo*.

### Attempted Reactions of Ketones and Aminodiphenylmethane

The ketones dimedone (v), dicyclopropylketone (vi), xanthrone (vii) and anthrone (viii) were reacted according to the general procedure (5.2.4). The <sup>1</sup>H NMR spectra showed signals corresponding to the starting materials only.

### Attempted reaction of Ketones and aminodiphenylmethane

The ketones 2-adamantanone (ix) and (-)-thujone (x) were reacted according to the general procedure (5.2.4). The <sup>1</sup>H NMR spectra showed signals corresponding to the starting materials as well as signals corresponding to the desired products which were identified by the observation of the molecular ion in the mass spectrum EI ms: *m/z* 315 (*M*<sup>+</sup>, 65.1%) and *m/z* 317 (*M*<sup>+</sup>, 11.6) respectively. Attempts to isolate the products by chromatography resulted in the isolation of the starting materials only.

### Attempted reaction of Aminodiphenylmethane hydrochloride with menthone (xi)

The reaction was carried out according to the general procedure (5.2.4). GC-MS showed the residue, a pale yellow oil, was a mixture of 3 components, menthone EI ms: *m/z* *M*<sup>+</sup> 154, aminodiphenylmethane EI ms: *m/z* *M*<sup>+</sup> 183 and the desired product which could not be isolated EI ms: *m/z* 319 *M*<sup>+</sup>.

## 5.2.5 Synthesis of Imines Precursors using $\alpha$ -Methylbenzylamine and Aldehydes

### Preparation of N-(2'-Pyrrolylmethylidene)-1-phenylethylamine (21)

A mixture of pyrrole-2-carboxaldehyde (0.71 g, 0.0075 mol) and  $\alpha$ -methylbenzylamine (0.90 g, 0.0075 mol) was stirred in ether (25 cm<sup>3</sup>) with anhydrous potassium carbonate (1.4 g, 0.01 mol) at room temperature for 6 hours. The excess potassium carbonate was removed by filtration. The ether was removed *in vacuo* to yield the desired product as a brown oil (1.36 g, 91.4%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.54 (3H, d, <sup>3</sup>J<sub>MeH7</sub> 6.68, CH<sub>3</sub>), 4.46 (1H, q, 7-H), 6.15 (1H, dd, <sup>3</sup>J<sub>H4-H5</sub> 3.16 and <sup>3</sup>J<sub>H4-H5</sub> 3.34, 4-H), 6.46 (1H, dd, <sup>4</sup>J<sub>H3-H5</sub> 1.63, 5-H), 6.62 (1H, dd, 3-H), 7.18-7.35 (5H, m, Ph-H), 8.14 (1H, s, 6-H), 9.40 (1H, br s, 1-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 24.24 (s, CH<sub>3</sub>), 68.87 (s, 7-C), 109.49 (s, 4-C), 114.63 (s, 5-C), 122.09 (s, 3-C), 126.64 (s, 11-C), 126.81 (s, 12-C), 128.37 (s, 10-C), 130.06 (s, 9-C), 144.88 (s, 2-C), 150.76 (s, 6-C); EI ms: m/z 198 (M<sup>+</sup>, 85.9%).

### Preparation of N-(2'-Thienylmethylidene)-1-phenylethylamine (22)

A mixture of thiophene-2-carboxaldehyde (9.60 g, 0.085 mol) and  $\alpha$ -methylbenzylamine (10.37 g, 0.085 mol) was stirred in ether (50 cm<sup>3</sup>) with anhydrous potassium carbonate (8 g, 0.06 mol) at room temperature for 18 hours. The excess potassium carbonate was removed by filtration. The ether was removed *in vacuo* to give the desired product as a brown oil (11.0 g, 60.2%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.50 (3H, d, <sup>3</sup>J<sub>MeH7</sub> 6.70, CH<sub>3</sub>), 4.38 (1H, q, 7-H), 6.85 (1H, dd, <sup>3</sup>J<sub>H3H4</sub> 4.95 and <sup>3</sup>J<sub>H4H5</sub> 3.67, 4-H), 7.10-7.41 (7H, m, Ph-H, 3-H and 5-H), 8.24 (1H, s, 6-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 24.76 (s, CH<sub>3</sub>), 68.90 (s, 7-C), 126.49 (s, 11-C), 126.69 (s, 4-C), 127.14 (s, 12-C), 128.28 (s, 10-C), 128.63 (s, 3-C), 130.29 (s, 5-C), 142.58 (s, 9-C), 144.90 (s, 2-C), 152.48 (s, 6-C); EI ms: m/z 215 (M<sup>+</sup>, 63.0%).

### Preparation of N-Furfurylidene-1-phenylethylamine (23)

A mixture of furfural (9.60 g, 0.1 mol) and  $\alpha$ -methylbenzylamine (12.12 g, 0.1 mol) was refluxed in toluene (100 cm<sup>3</sup>) with the azeotropic removal of water for 8 hours. The toluene was removed *in vacuo* to yield the desired product as a brown oil (15.47 g, 77.6%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.60 (3H, d, <sup>3</sup>J<sub>MeH7</sub> 6.69, CH<sub>3</sub>), 3.00 (1H, q, 7-H), 6.40 (1H, dd, <sup>3</sup>J<sub>H3H4</sub> 3.42 and <sup>3</sup>J<sub>H4H5</sub> 1.80, 4-H), 6.69 (1H, dd, 3-H), 7.14-7.40 (5H, m, Ph-H), 7.46 (1H, dd, 5-H), 8.10 (1H, s, 6-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 24.46 (s, 8-C), 69.61 (s, 7-C), 111.56 (s, 4-C),

114.28 (s, 3-C), 126.70 (s, 11-C), 126.80 (s, 12-C), 128.50 (s, 10-C), 144.56 (s, 9-C), 144.67 (s, 5-C), 148.35 (s, 6-C), 151.55 (s, 2-C); EI ms: m/z 199 ( $M^+$ , 39.8%).

**Preparation of N-(4'-Isopropylbenzylidene)-1-phenylethylamine (24)**

A mixture of 4-isopropylbenzaldehyde (14.82 g, 0.1 mol) and  $\alpha$ -methylbenzylamine (12.12 g, 0.1 mol) was stirred in dichloromethane (100 cm<sup>3</sup>) with anhydrous potassium carbonate (14 g, 0.01 mol) at room temperature for 6 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to yield the desired product as a yellow liquid (17.45 g, 69.4%);  $\delta_H$  (CDCl<sub>3</sub>) 1.21 (6H, d, <sup>3</sup>J<sub>H5-H6</sub> 6.85, 6-H), 1.56 (3H, d, <sup>3</sup>J<sub>H9-H8</sub> 6.65, 9-H), 2.87 (1H, septet, 5-H), 4.48 (1H, q, 8-H), 7.06-7.38 (5H, m, Ph-H), 7.41 (2H, d, <sup>3</sup>J<sub>H2-H3</sub> 7.11, 3-H), 7.70 (2H, d, 2-H), 8.29 (1H, s, 7-H);  $\delta_C$  (CDCl<sub>3</sub>) 23.79 (s, 6-C), 24.05 (s, 9-C), 34.05 (s, 5-C), 69.57 (s, 8-C), 126.68 (s, 13-C), 126.88 (s, 11-C and 12-C), 128.31 (s, 2-C and 3-C), 134.19 (s, 4-C), 145.29 (s, 10-C), 156.00 (s, 1-C), 159.21 (s, 7-C); EI ms: m/z 251 ( $M^+$ , 61.5%).

**Preparation of N-Piperonylidene-1-phenylethylamine (25)**

A mixture of piperonal (15.01 g, 0.1 mol) and  $\alpha$ -methylbenzylamine (12.12 g, 0.1 mol) was stirred in dichloromethane (50 cm<sup>3</sup>) with anhydrous potassium carbonate (15 g, 0.11 mol) at room temperature for 6 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to give the desired product as a yellow oil (18.54 g, 73.2%);  $\delta_H$  (CDCl<sub>3</sub>) 1.54 (3H, d, <sup>3</sup>J<sub>Me-H9</sub> 6.64, 10-H), 4.43 (1H, q, 9-H), 5.83 (2H, s, 7-H), 6.73 (1H, d, <sup>3</sup>J<sub>H5-H6</sub> 7.93, 5-H), 7.04 (1H, dd, <sup>4</sup>J<sub>H2-H6</sub> 1.61, 6-H), 7.18 (1H, m, 14-H), 7.29 (2H, m, 13-H), 7.37 (3H, m, 2-H and 12-H), 8.16 (1H, s, 8-H);  $\delta_C$  (CDCl<sub>3</sub>) 24.93 (s, 10-C), 69.34 (s, 9-C), 101.26 (s, 7-C), 106.68 and 107.85 (2 x s, 5-C and 6-C), 124.30 (s, 14-C), 126.54 (s, 13-C), 126.70 (s, 2-C), 128.34 (s, 12-C), 131.23 (s, 11-C), 145.35 and 149.69 (2 x s, 3-C and 4-C), 148.13 (s, 1-C), 158.39 (s, 8-C); EI ms: m/z 253 ( $M^+$ , 15.1%).

## 5.2.6 Synthesis of Imine Precursors using $\alpha$ -Methylbenzylamine and Ketones

### Preparation of N-Cyclopentylidene-1-phenylethylamine (26)

A mixture of cyclopentanone (8.41 g, 0.1 mol) and  $\alpha$ -methylbenzylamine (12.18 g, 0.1 mol) was stirred in ether (50 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.07 mol) at room temperature for 18 hours. The excess potassium carbonate was removed by filtration. The ether was removed *in vacuo* to give the desired product as a yellow oil (9.09 g, 48.6%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.46 (3H, d, <sup>3</sup>J<sub>MeH</sub> 6.60, CH<sub>3</sub>), 1.60-2.51 (8H, m, 2-H, 3-H, 4-H and 5-H), 4.40 (1H, q, 6-H), 7.18-7.35 (5H, m, Ph-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 24.69 (s, CH<sub>3</sub>), 24.07 and 24.95 (2 x s, 3-C and 4-C), 28.86 and 36.59 (2 x s, 2-C and 5-C), 61.96 (s, 6-C), 126.51 (s, 11-C), 126.59 (s, 10-C), 128.30 (s, 9-C), 145.67 (s, 8-C), 179.06 (s, 1-C); EI ms: m/z 187 (M<sup>+</sup>, 57.5%).

## 5.2.7 Attempted preparation of Imines Precursors using *tert*-Butylamine and Aldehydes

### Attempted Reaction between *tert*-Butylamine and Furfural

A mixture of furfural (9.60 g, 0.1 mol) and *tert*-butylamine (7.31 g, 0.1 mol) was stirred in ether (50 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.07 mol) at room temperature for 18 hours. The excess potassium carbonate was removed by filtration. The ether was removed *in vacuo* to give a brown oil. The <sup>1</sup>H NMR spectrum showed signals corresponding to the two starting materials only.

### Attempted Reaction between *tert*-Butylamine and Propional

A mixture of propional (5.81 g, 0.1 mol) and *tert*-butylamine (7.31 g, 0.1 mol) was stirred in ether (50 cm<sup>3</sup>) with anhydrous potassium carbonate (10 g, 0.07 mol) at room temperature for 18 hours. The excess potassium carbonate was removed by filtration. The ether was removed *in vacuo* to give a pale yellow oil. The <sup>1</sup>H NMR spectrum showed signals corresponding to the two starting materials.

#### **Attempted Reaction between *tert*-Butylamine and Piperonal**

A mixture of piperonal (15.0 g, 0.1 mol) and *tert*-butylamine (7.31 g, 0.1 mol) was refluxed in toluene (48 hours) with the azeotropic removal of any water that formed (*c.a.* 0.1 cm<sup>3</sup> 0.005 mol). The toluene was removed *in vacuo* to give a pale yellow oil. The <sup>1</sup>H NMR spectrum showed signals corresponding to the two starting materials.

#### **5.2.8 Attempted Preparation of Imine Precursors using Benzylamine and Ketones**

##### **Attempted Reaction between Menthone (xi) and Benzylamine**

A mixture of menthone (4.32 g, 0.026 mol) and benzylamine (16.7 g, 0.15 mol) was refluxed in toluene (24 hours) with the azeotropic removal of any water that formed (0.35 cm<sup>3</sup> 0.02 mol). The toluene was removed *in vacuo* to give a pale yellow oil. The <sup>1</sup>H NMR spectrum showed signals corresponding to the two starting materials as well as the desired product which was identified by the mass spectrum EI ms: *m/z* 243 (*M*<sup>+</sup>, 9.6%). Attempts to isolate the desired product by chromatography resulted in the isolation of the starting materials.

##### **Attempted Reaction Between 2-Adamantanone (ix) and Benzylamine**

A mixture of 2-adamantanone (0.92 g, 0.006 mol) and benzylamine (0.65 g, 0.006 mol) was stirred in dichloromethane (40 cm<sup>3</sup>) with anhydrous potassium carbonate (1 g, 0.007 mol) at room temperature for 18 hours. The excess potassium carbonate was removed by filtration. The dichloromethane was removed *in vacuo* to give a pale yellow oil. The <sup>1</sup>H NMR spectrum showed signals corresponding to the two starting materials as well as the desired product which was identified by the mass spectrum EI ms: *m/z* 239 (*M*<sup>+</sup>, 9.3%).

##### **Attempted Reaction between Camphor and Benzylamine**

A mixture of camphor (5.89 g, 0.038 mol) and benzylamine (24.65 g, 0.23 mol) was refluxed in toluene (24 hours) with the azeotropic removal of any water that formed (0.2 cm<sup>3</sup> 0.01 mol). The toluene was removed *in vacuo* to give a pale yellow oil. The <sup>1</sup>H NMR spectrum showed signals corresponding to the two starting materials as well as the desired product which was identified by the mass spectrum EI ms: *m/z* 241 (*M*<sup>+</sup>, 29.3%).

Attempts to isolate the desired product by chromatography resulted in the isolation of the starting materials only.

### 5.3 Synthesis of Dialkyl Phosphonate Esters

#### 5.3.1 Synthesis of Diethyl Phosphonate Esters from Imines Prepared from Aldehydes

##### Preparation of Diethyl 1-(2'-Pyrrolyl)-1-(diphenylmethylamino)methane-phosphonate (27)

Diethyl phosphite (1.06 g, 0.008 mol) and N-(2'-pyrrolylmethylidene)-1,1-diphenylmethylamine 7 (2.0 g, 0.008 mol) were heated (100°C) for 6 hours to give a pale yellow oil. A pale yellow precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate yielded the desired product as a pale yellow crystalline solid (1.88 g, 59.2%); m.p. 88-90°C; (Found: C, 66.3; H, 6.8; N, 7.0. C<sub>22</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub>P requires: C, 66.3; H, 6.8; N, 7.0%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.01 (3H, t, <sup>3</sup>J<sub>HH</sub> 6.96, CH<sub>3</sub>), 1.33 (3H, t, <sup>3</sup>J<sub>HH</sub> 7.06, CH<sub>3</sub>), 2.67 (1H, br s, NH), 3.41-3.51 (1H, m, CH<sub>2</sub>), 3.67-3.76 (1H, m, CH<sub>2</sub>), 3.94 (1H, d, <sup>2</sup>J<sub>PH</sub> 22.52, H-6), 4.00-4.21 (2H, m, CH<sub>2</sub>), 4.81 (1H, s, 7-H), 6.01 (1H, m, 4-H), 6.13 (1H, m, 3-H), 6.76 (1H, m, 5-H), 7.13-7.41 (10H, m, 2 x Ph-H), 9.78 (1H, br s, 1-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 16.14 (d, <sup>3</sup>J<sub>PC</sub> 6.89, CH<sub>3</sub>), 16.56 (d, <sup>3</sup>J<sub>PC</sub> 6.16, CH<sub>3</sub>), 51.53 (d, <sup>1</sup>J<sub>PC</sub> 161.83, 6-C), 62.68 (d, <sup>2</sup>J<sub>PC</sub> 6.79, CH<sub>2</sub>), 63.07 (d, <sup>2</sup>J<sub>PC</sub> 6.79, CH<sub>2</sub>), 63.87 (d, <sup>3</sup>J<sub>PC</sub> 17.17, 7-C), 107.68 (s, 4-C), 109.52 (d, <sup>4</sup>J<sub>CP</sub> 9.56, 3-C), 118.62 (s, 5-C), 125.27 (d, <sup>2</sup>J<sub>CP</sub> 3.40, 2-C), 126.88 and 127.16 (2 x s, 11-C and 11'-C), 127.29 and 127.90 (2 x s, 10-C and 10'-C), 128.24 and 128.48 (2 x s, 9-C and 9'-C), 142.56 and 144.16 (2 x s, 8-C and 8'-C);  $\delta_{\text{P}}$  (CDCl<sub>3</sub>) 23.96; EI ms: m/z 398 (M<sup>+</sup>, 19.8%).

##### Preparation of Diethyl 1-Furfuryl-1-(diphenylmethylamino)methane-phosphonate (28)

Diethyl phosphite (4.23 g, 0.031 mol) and N-(furfurylidene)-1,1-diphenylmethylamine 8 (8.0 g, 0.031 mol) were heated (100°C) for 6 hours to give a brown oil. A pale yellow precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate yielded the desired product

as a white crystalline solid (10.64 g, 87%); m.p. 82-84°C; (Found: C, 66.4; H, 6.6; N, 3.5.  $C_{22}H_{26}NO_4P$  requires: C, 66.2; H, 6.7; N, 3.5%);  $\delta_H$  ( $CDCl_3$ ) 1.15 (3H, t,  $^3J_{HH}$  6.97,  $CH_3$ ), 1.36 (3H, t,  $^3J_{HH}$  7.19,  $CH_3$ ), 2.53 (1H, br s, NH), 3.80-4.00 (1H, m,  $CH_2$ ), 4.01-4.09 (1H, m,  $CH_2$ ), 4.04 (1H, d,  $^2J_{PH}$  23.79, 6-H), 4.17-4.33 (2H, m,  $CH_2$ ), 4.74 (1H, s, 7-H), 6.29 (1H, m, 4-H), 6.38 (1H, m, 3-H), 7.15-7.44 (11H, m, 2 x Ph and 5-H);  $\delta_C$  ( $CDCl_3$ ) 16.28 (d,  $^3J_{PC}$  5.85,  $CH_3$ ), 16.55 (d,  $^3J_{PC}$  6.35,  $CH_3$ ), 52.02 (d,  $^1J_{PC}$  163.0, 6-C), 62.19 (d,  $^2J_{PC}$  6.86,  $CH_2$ ), 62.53 (d,  $^2J_{PC}$  6.79,  $CH_2$ ), 64.42 (d,  $^3J_{PC}$  16.29, 7-C), 109.48 (d,  $^3J_{PC}$  7.86, 3-C), 110.54 (s, 4-C), 127.22 (s, 5-C), 127.38 and 127.77 (2 x s, 11-C and 11-C), 128.46 and 128.58 (2 x s, 10-C and 10'-C), 142.38 and 142.68 (2 x s, 9-C and 9'-C) 141.89 and 143.59 (s, 8-C and 8'-C) 149.88 (d,  $^2J_{PC}$  2.70, 2-C);  $\delta_P$  ( $CDCl_3$ ) 21.00; EI ms: m/z 399 ( $M^+$ , 8.4%).

**Preparation of Diethyl 1-(3'-Thienyl)-1-(diphenylmethylamino)methane-phosphonate (29)**

Diethyl phosphite (3.82 g, 0.028 mol) and N-(3'-thienylmethylidene)-1,1-diphenylmethylamine **9** (7.68 g, 0.028 mol) were heated (100°C) for 6 hours to give a brown oil. A pale brown precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate yielded the desired product as a cream crystalline solid (5.77 g, 50.2%); m.p. 90-92°C; (Found: C, 63.7; H, 6.3; N, 3.4; S, 7.6.  $C_{22}H_{26}NO_3PS$  requires: C, 63.6; H, 6.3; N, 3.4; S, 7.7%);  $\delta_H$  ( $CDCl_3$ ) 1.11 (3H, d of t,  $^3J_{HH}$  7.05 and  $^4J_{PH}$  0.47,  $CH_3$ ), 1.36 (3H, d of t,  $^3J_{HH}$  7.05 and  $^4J_{PH}$  0.46,  $CH_3$ ), 2.33 (1H, br s, NH), 3.69-3.84 (1H, m,  $CH_2$ ), 3.88-4.03 (1H, m,  $CH_2$ ), 4.05 (1H, d,  $^2J_{PH}$  22.01, 6-H), 4.10-4.33 (2H, m,  $CH_2$ ), 4.74 (1H, s, 7-H), 7.07-7.40 (13H, m, 2 x Ph, 2-H, 4-H and 5-H);  $\delta_C$  ( $CDCl_3$ ) 16.35 (d,  $^3J_{PC}$  6.14,  $CH_3$ ), 16.69 (d,  $^3J_{PC}$  5.82,  $CH_3$ ), 53.74 (d,  $^1J_{PC}$  157.90, 6-C), 62.79 (d,  $^2J_{PC}$  6.82,  $CH_2$ ), 63.20 (d,  $^2J_{PC}$  6.84,  $CH_2$ ), 64.05 (d,  $^3J_{PC}$  16.35, 7-C), 123.90 (d,  $^3J_{PC}$  10.38, 2-C), 126.16 (s, 5-C), 127.29 and 127.37 (2 x s, 11-C and 11'-C), 127.37 and 127.91 (2 x s, 10-C and 10'-C), 127.56 (d,  $^3J_{PC}$  3.84, 4-C) 128.55 and 128.72 (2 x s, 9-C and 9'-C), 137.08 (s, 3-C), 142.21 and 143.77 (2 x s, 8-C and 8'-C);  $\delta_P$  ( $CDCl_3$ ) 23.18; EI ms: m/z 415 ( $M^+$ , 3.4%).

**Preparation of Diethyl 1-(2'-Thienyl)-1-(diphenylmethylamino)methane-phosphonate (30)**

Diethyl phosphite (0.75 g, 0.005 mol) and N-(2'-thienylmethylidene)-1,1-diphenylmethylamine 10 (1.50 g, 0.05 mol) were heated (100°C) for 8 hours to give a yellow oil. A pale yellow precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate and ether yielded the desired product as a pale yellow crystalline solid (1.96 g, 87.5%); m.p. 93-95°C; (Found: C, 63.7; H, 6.2; N, 3.4; S, 7.6.  $C_{22}H_{26}NO_3PS$  requires: C, 63.6; H, 6.3; N, 3.4; S, 7.7%);  $\delta_H$  ( $CDCl_3$ ) 1.15 (3H, t,  $^3J_{HH}$  7.01,  $CH_3$ ), 1.35 (3H, t,  $^3J_{HH}$  7.17,  $CH_3$ ), 2.76 (1H, br s, NH), 3.80-3.93 (1H, m,  $CH_2$ ), 3.97-4.09 (1H, m,  $CH_2$ ), 4.21 (1H, d,  $^2J_{PH}$  22.40, 6-H), 4.13-4.30 (2H, m,  $CH_2$ ), 4.86 (1H, s, 7-H), 6.98-7.02 (2H, m, 3-H and 4-H), 7.02-7.41 (11H, m, Ph-H and 5-H);  $\delta_C$  ( $CDCl_3$ ), 16.26 (d,  $^3J_{PC}$  6.23,  $CH_3$ ), 16.55 (d,  $^3J_{PC}$  6.23,  $CH_3$ ), 53.45 (d,  $^1J_{PC}$  130.51, 6-C), 62.96 (d,  $^2J_{PC}$  6.73,  $CH_2$ ), 63.31 (d,  $^2J_{PC}$  6.98,  $CH_2$ ), 63.79 (d,  $^3J_{PC}$  15.79, 7-C), 125.51 (d,  $^3J_{PC}$  3.21, 3-C), 126.96 and 127.21 (2 x s, 11-C and 11'-C), 127.08 (s, 4-C), 127.43 (s, 5-C), 127.88 and 128.65 (2 x s, 10-C and 10'-C), 128.43 and 128.85 (2 x s, 9-C and 9'-C) 139.64 (s, 2-C), 141.80 and 143.45 (2 x s, 8-C and 8'-C);  $\delta_P$  ( $CDCl_3$ ) 21.93; EI ms: m/z 415 ( $M^+$ , 4.5%).

**Preparation of Diethyl 1-(4'-Dimethylaminobenzyl)-1-(diphenylmethylamino)-phosphonate (31)**

Diethyl phosphite (4.22 g, 0.03 mol) and N-(4'-dimethylaminobenzylidene)-1,1-diphenylmethylamine 11 (10 g, 0.03 mol) were heated (100°C) for 6 hours to give a yellow oil. An orange precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate and ether yielded the desired product as a red-orange crystalline solid (12.09 g, 87.6%); m.p. 108-109°C; Found: C, 69.3; H, 7.3; N, 6.3.  $C_{26}H_{33}N_2O_3P$  requires: C, 69.1; H, 7.4; N, 6.2%);  $\delta_H$  ( $CDCl_3$ ) 1.07 (3H, t,  $^3J_{HH}$  7.11,  $CH_3$ ), 1.35 (3H, t,  $^3J_{HH}$  7.05,  $CH_3$ ), 2.92 (6H, s,  $N(CH_3)_2$ ), 3.62-3.75 (1H, m,  $CH_2$ ), 3.85-3.95 (1H, m,  $CH_2$ ), 3.83 (1H, d,  $^2J_{PH}$  22.05, 5-H), 4.14-4.29 (2H, m,  $CH_2$ ), 4.72 (1H, s, 6-H), 6.70 (2H, d,  $^3J_{H_2-H_3}$  8.56, 3-H), 7.13-7.38 (12H, m, 2 x Ph-H and 2-H);  $\delta_C$  ( $CDCl_3$ ), 16.26 (d,  $^3J_{PC}$  5.79,  $CH_3$ ), 16.57 (d,  $^3J_{PC}$  5.91,  $CH_3$ ), 40.40 (s,  $N(CH_3)_2$ ), 57.22 (d,  $^1J_{PC}$  157.36, 5-C), 62.54 (d,  $^2J_{PC}$  6.86,  $CH_2$ ), 62.80 (d,  $^2J_{PC}$  6.86,  $CH_2$ ), 63.35 (d,  $^3J_{PC}$  17.23, 6-C), 112.37 (d,  $^4J_{PC}$  1.76, 3-C), 122.86



(d,  $^3J_{PC}$  1.50, 4-C), 126.99 and 127.16 (2 x s, 10-C and 10'-C), 127.27 and 127.88 (2 x s, 9-C and 9'-C), 128.32 and 128.48 (2 x s, 8-C and 8'-C) 129.38 (d,  $^3J_{PC}$  6.54, 2-C), 142.25 and 143.98 (2 x s, 7-C and 7'-C), 150.17 (d,  $^2J_{PC}$  1.87, 1-C);  $\delta_P$  (CDCl<sub>3</sub>) 25.12; EI ms: m/z 452 ( $M^+$ , 3.0%).

**Preparation of Diethyl 1-(Piperonyl)-1-(diphenylmethylamino)methane-phosphonate (32)**

Diethyl phosphite (6.2 g, 0.0448 mol) and N-piperonylidene-1,1-diphenylmethylamine 12 (14.1 g, 0.0448 mol) were heated (100°C) for 6 hours to give an orange oil. A white precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate yielded the desired product as a white crystalline solid (18.9 g, 93.0%); m.p. 119-120°C; (Found: C, 66.4; H, 6.4; N, 3.0. C<sub>25</sub>H<sub>28</sub>NO<sub>5</sub>P requires: C, 66.2; H, 6.2; N, 3.1%);  $\delta_H$  (CDCl<sub>3</sub>) 1.12 (3H, d of t,  $^3J_{HH}$  7.03 and  $^4J_{PH}$  0.43, CH<sub>3</sub>), 1.35 (3H, d of t,  $^3J_{HH}$  6.98 and  $^4J_{PH}$  0.43, CH<sub>3</sub>), 2.52 (1H, br s, NH), 3.76-3.90 (1H, m, CH<sub>2</sub>), 3.84 (1H, d,  $^2J_{PC}$  20.07, 8-H) 3.93-4.14 (1H, m, CH<sub>2</sub>), 4.19-4.23 (2H, m, CH<sub>2</sub>), 4.70 (1H, s, 9-H), 5.93 (2H, s, 7-CH<sub>2</sub>), 6.74-6.80 (2H, m, 5-H and 6-H), 6.90 (1H, m, 2-H), 7.15-7.35 (10H, m, 2 x Ph);  $\delta_C$  (CDCl<sub>3</sub>) 16.28 (d,  $^3J_{PC}$  5.79, CH<sub>3</sub>), 16.57 (d,  $^3J_{PC}$  5.85, CH<sub>3</sub>), 57.69 (d,  $^1J_{PC}$  156.70, 8-C), 62.65 (d,  $^2J_{PC}$  7.25, CH<sub>2</sub>), 63.02 (d,  $^2J_{PC}$  7.33, CH<sub>2</sub>), 63.56 (d,  $^3J_{PC}$  16.86, 9-C), 101.92 (s, 7-CH<sub>2</sub>), 108.22 (d,  $^4J_{PC}$  1.76, 5-C), 108.71 (d,  $^3J_{PC}$  5.41, 6-C), 122.23 and 122.35 (2 x s, 13-C and 13'-C), 127.15 and 127.25 (2 x s, 12-C and 12'-C), 127.34 and 127.85 (2 x s, 11-C and 11'-C) 128.51 (d,  $^3J_{PC}$  12.39, 2-C), 129.68 (s, 1-C), 142.01 and 143.69 (2 x s, 10-C and 10'-C), 147.96 (s, 4-C), 147.99 (s, 3-C);  $\delta_P$  (CDCl<sub>3</sub>) 23.67; EI ms: m/z 453 ( $M^+$ , 4.5%).

**Preparation of Diethyl 1-(4'-Isopropylbenzyl)-1-(diphenylmethylamino)-phosphonate (33)**

Diethyl phosphite (7.18 g, 0.052 mol) and N-(4'-isopropylbenzylidene)-1,1-diphenylmethylamine 13 (16.30 g, 0.052 mol) were heated (100°C) for 5 hours to give a pale yellow oil. A pale yellow precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate yielded the desired product as a white crystalline solid (14.6 g, 62.4%); m.p. 88-90°C; (Found: C, 71.9; H, 7.6; N, 3.1. C<sub>27</sub>H<sub>34</sub>NO<sub>3</sub>P requires: C, 71.8; H, 7.6; N, 3.1%);

$\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.01 (3H, t,  $^3J_{\text{HH}}$  7.07, CH<sub>3</sub>), 1.25 (6H, d,  $^3J_{\text{HH}}$  7.01 CH<sub>3</sub>CH), 1.33 (3H, t,  $^3J_{\text{HH}}$  7.05, CH<sub>3</sub>), 2.59 (1H, br s, NH), 2.89 (1H, septet, CHCH<sub>3</sub>), 3.61-3.77 (1H, m, CH<sub>2</sub>), 3.82-3.97 (1H, m, CH<sub>2</sub>), 3.91 (1H, d,  $^2J_{\text{PH}}$  22.01, 5-H), 4.07-4.27 (2H, m, CH<sub>2</sub>), 4.71 (1H, s, 6-H), 7.10-7.37 (14H, m, 2 x Ph-H, 2-H and 3-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 16.42 (d,  $^3J_{\text{PC}}$  5.84, CH<sub>3</sub>), 16.84 (d,  $^3J_{\text{PC}}$  5.99, CH<sub>3</sub>), 24.0 (s, CH<sub>3</sub>CH), 33.62 (s, CH<sub>3</sub>CH), 57.75 (d,  $^1J_{\text{PC}}$  155.6, 5-C), 62.86 (d,  $^2J_{\text{PC}}$  6.37, CH<sub>2</sub>), 63.21 (d,  $^2J_{\text{PC}}$  7.20, CH<sub>2</sub>), 63.89 (d,  $^3J_{\text{PC}}$  17.05, 6-C), 126.87 (d,  $^3J_{\text{PC}}$  2.14, 2-C), 127.37 (s, 3-C) 127.56 and 128.18, (2 x s, 10-C and 10'-C), 128.66 and 128.76 (2 x s, 9-C and 9'-C), 128.83 and 128.86 (2 x s, 8-C and 8'-C), 133.33 (s, 4-C), 142.47 and 144.10 (2 x s 7-C and 7'-C), 148.82 (d,  $^2J_{\text{CP}}$  3.14, 1-C);  $\delta_{\text{P}}$  (CDCl<sub>3</sub>) 24.63; EI ms: m/z 451 (M<sup>+</sup>, 7.0%).

**Preparation of Diethyl 1-Phenyl-1-(diphenylmethylamino)methanephosphonate (4)**

Diethyl phosphite (1.65 g, 0.012 mol) and N-benzylidene-1,1-diphenylmethylamine 14 (3.25 g, 0.012 mol) were heated (100°C) for 4 hours to give a yellow oil. A white precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate yielded the desired product as a white crystalline solid (3.52 g, 71.6%); m.p. 98-99°C; (Found: C, 70.4; H, 6.9; N, 3.3. C<sub>24</sub>H<sub>28</sub>NO<sub>3</sub>P requires: C, 70.4; H, 6.9; N, 3.3%);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.07 (3H, d of t,  $^3J_{\text{HH}}$  7.06 and  $^4J_{\text{PH}}$  0.57, CH<sub>3</sub>), 1.36 (3H, d of t,  $^3J_{\text{HH}}$  7.07 and  $^4J_{\text{PH}}$  0.56, CH<sub>3</sub>), 2.56 (1H, br s, NH), 3.62-3.78 (1H, m, CH<sub>2</sub>), 3.83-3.99 (1H, m, CH<sub>2</sub>), 3.93 (1H, d,  $^2J_{\text{PH}}$  22.47, 5-H), 4.12-4.29 (2H, m, CH<sub>2</sub>), 4.68 (1H, d,  $^4J_{\text{PH}}$  1.13, 6-H), 7.14-7.40 (15H, m, 2 x Ph-H);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 16.14 (d,  $^3J_{\text{PC}}$  6.23, CH<sub>3</sub>), 16.29 (d,  $^3J_{\text{PC}}$  6.29, CH<sub>3</sub>), 57.99 (d,  $^1J_{\text{PC}}$  155.29, 5-C), 62.59 (d,  $^2J_{\text{PC}}$  6.92, CH<sub>2</sub>), 62.97 (d,  $^2J_{\text{PC}}$  7.23, CH<sub>2</sub>), 63.65 (d,  $^3J_{\text{PC}}$  17.04, 6-C), 127.11 and 127.29 (2 x s, 3-C and 3'-C), 127.92 (s, 4-C), 128.38 (s, 10-C), 128.56 (s, 9-C), 128.50 and 128.66 (2 x s, 2-C and 2'-C), 135.89 (d,  $^2J_{\text{PC}}$  1.57, 1-C), 142.00 and 143.66 (2 x s, 7-C and 7'-C);  $\delta_{\text{P}}$  (CDCl<sub>3</sub>) 23.70; EI ms: m/z 409 (M<sup>+</sup>, 9.7%).

**Preparation of Diethyl 1-(1'-Naphthyl)-1-(diphenylmethylamino)methanephosphonate (5)**

Diethyl phosphite (10.27 g, 0.074 mol) and N-(1'-naphthylmethylidene)-1,1-diphenylmethylamine 15 (23.97 g, 0.074 mol) were heated (100°C) for 10 hours to give a yellow

oil. A yellow precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate yielded the desired product as a white crystalline solid (18.12 g, 53.3%); m.p. 102-103°C; (Found: C, 73.3; H, 6.7; N, 3.0.  $C_{28}H_{30}NO_3P$  requires: C, 73.2; H, 6.6; N, 3.0%);  $\delta_H$  ( $CDCl_3$ ) 0.76 (3H, t,  $^3J_{HH}$  7.06,  $CH_3$ ), 1.36 (3H, t,  $^3J_{HH}$  7.06,  $CH_3$ ), 2.74 (1H, br s, NH), 3.34-3.43 (1H, m,  $CH_2$ ), 3.70-3.79 (1H, m,  $CH_2$ ), 4.14-4.35 (2H, m,  $CH_2$ ), 4.65 (1H, s, 12-H), 4.86 (1H, br d,  $^2J_{PH}$  23.01, 11-H), 7.13-7.87 (17H, m, Ar-H);  $\delta_C$  ( $CDCl_3$ ) 15.73 (d,  $^3J_{PC}$  5.85,  $CH_3$ ), 16.43 (d,  $^3J_{PC}$  6.10,  $CH_3$ ), 52.05 (d,  $^1J_{PC}$  155.03, 11-C), 62.46 (d,  $^2J_{PC}$  6.98,  $CH_2$ ), 62.90 (d,  $^2J_{PC}$  6.92,  $CH_2$ ), 63.76 (d,  $^3J_{PC}$  16.67, 12-C), 122.99 (s, 2-C), 125.36 (d,  $^4J_{PC}$  3.33, 3-C), 125.46 and 125.77 (2 x s, 7-C and 8-C), 128.28 (s, 9-C), 126.48 and 127.19 (2 x s, 16-C and 16'-C), 127.03 and 127.84 (2 x s, 15-C and 15'-C), 128.25 and 128.36 (2 x s, 14-C and 14'-C), 128.53 and 128.55 (2 x s, 4-C and 6-C), 132.14 (s, 1-C), 132.24 (s, 5-C), 133.55 (d, 10-C), 142.09 and 143.50 (2 x s, 13-C and 13'-C);  $\delta_P$  ( $CDCl_3$ ) 23.90; EI ms: m/z 459 ( $M^+$ , 1.4%).

**Preparation of Diethyl 1-(9'-Anthryl)-1-(diphenylmethylamino)methane-phosphonate (34)**

Diethyl phosphite (11.1 g, 0.08 mol) and N-(9'-anthrylmethylidene)-1,1-diphenylmethylamine 16 (29.9 g, 0.08 mol) were heated (100°C) for 8 hours to give an orange oil. A yellow precipitate was obtained when the oil was triturated with ethyl acetate. The solid was washed with diethyl ether. Recrystallisation from ethyl acetate yielded the desired product as a white crystalline solid (21.14 g, 51.9%); m.p. 122-123°C; (Found: C, 75.3; H, 6.1; N, 2.6.  $C_{32}H_{32}NO_3P$  requires: C, 75.4; H, 6.3; N, 2.7%);  $\delta_H$  ( $CDCl_3$ ) 0.62 (3H, t,  $^3J_{HH}$  7.10,  $CH_3$ ), 1.35 (3H, t,  $^3J_{HH}$  7.12,  $CH_3$ ), 3.04 (1H, br s, NH), 3.27-3.37 (1H, m,  $CH_2$ ), 3.61-3.71 (1H, m,  $CH_2$ ), 4.12-4.31 (2H, m,  $CH_2$ ), 4.41 (1H, s, 16-H), 5.62 (1H, d,  $^2J_{PH}$  26.78, 15-H), 7.00-7.57 (15H, m, Ar-H), 7.93-7.98 (2H, 2 x d, 6-H and 10-H), 8.39 (1H, d,  $^3J_{HH}$  2.45, 13-H) 9.33 (1H, d,  $^3J_{HH}$  9.02, 3-H);  $\delta_C$  ( $CDCl_3$ ) 15.90 (d,  $^3J_{PC}$  5.72,  $CH_3$ ), 16.68 (d,  $^3J_{PC}$  5.98,  $CH_3$ ), 53.84 (d,  $^1J_{PC}$  157.24, 15-C), 62.64 (d,  $^2J_{PC}$  6.98,  $CH_2$ ), 62.78 (d,  $^2J_{PC}$  7.42,  $CH_2$ ), 64.53 (d,  $^3J_{PC}$  15.41, 16-C), 123.47, 124.80, 125.36, 125.99 and 126.13 (5 x s, 4-C, 5-C, 8-C, 11-C and 12-C), 127.05 (d, 3-C), 127.09 and 127.48 (2 x s, 20-C and 20'-C), 127.52 and 128.30 (2 x s, 19-C and 19'-C), 128.26 and 128.62 (2 x s, 18-C and 18'-C), 128.97 (d,  $^4J_{PC}$  4.09, 13-C), 129.36 (br s, 10-C and 6-C), 130.90 (d,

$^2J_{PC}$  4.09, 1-C), 131.35 (d,  $^3J_{PC}$  1.95, 14-C), 131.68 and 131.83 (2 x s, 7-C and 9-C), 131.95 (d,  $^3J_{PC}$  3.40, 2-C), 142.09 and 143.39 (2 x s, 17-C and 17'-C);  $\delta_P$  (CDCl<sub>3</sub>) 25.60; EI ms: m/z 509 (M<sup>+</sup>, 37.9%).

**Preparation of Diethyl 1-(1'-Pyrenyl)-1-(diphenylmethylamino)methane-phosphonate (6)**

Diethyl phosphite (0.35 g, 0.0025 mol) and N-(1'-pyrenylmethylidene)-1,1-diphenylmethylamine 17 (1.0 g, 0.0025 mol) were heated (140°C) for 4 hours to give a green oil. The product was purified by chromatography [silica column; elution with dichloromethane - petroleum spirit b.p. 40-60°C (1:1)] to give a yellow oil. A white precipitate was obtained when the oil was triturated with ethyl acetate. Recrystallisation from ethyl acetate yielded the desired product as a white crystalline solid (0.93 g, 69.7%); m.p. 107-108°C; (Found: C, 76.5; H, 6.1; N, 2.5. C<sub>34</sub>H<sub>32</sub>NO<sub>3</sub>P requires: C, 76.5; H, 6.0; N, 2.6%);  $\delta_H$  (CDCl<sub>3</sub>) 0.75 (3H, t,  $^3J_{HH}$  7.05, CH<sub>3</sub>), 1.38 (3H, t,  $^3J_{HH}$  7.04, CH<sub>3</sub>), 3.02 (1H, br s, NH), 3.35-3.45 (1H, m, CH<sub>2</sub>), 3.67-3.80 (1H, m, CH<sub>2</sub>), 4.18-4.39 (2H, m, CH<sub>2</sub>), 4.61 (1H, s, 18-H), 5.41 (1H, br dd,  $^2J_{PH}$  22.80, 17-H), 7.10-7.33 (10H, m, 2 x Ph-H), 7.76 (1H, br m, 3-H), 7.93 (1H, br d, 4-H), 7.96 (t,  $^3J_{HH}$  7.61, 7-H), 8.05 (2H, m, 10-H and 11-H), 8.13 (2H, m, 6-H and 8-H), 8.26 (1H, br d,  $^3J_{HH}$  7.97, 13-H), 8.45 (1H, br m, 14-H);  $\delta_C$  (CDCl<sub>3</sub>) 16.15 (d,  $^3J_{PC}$  5.66, CH<sub>3</sub>), 16.77 (d,  $^3J_{PC}$  5.91, CH<sub>3</sub>), 52.95 (br d,  $^1J_{PC}$  158.37, 17-C), 62.83 (d,  $^2J_{PC}$  6.79, CH<sub>2</sub>), 63.35 (d,  $^2J_{PC}$  6.98, CH<sub>2</sub>), 64.09 (d,  $^3J_{PC}$  16.98, 18-C), 122.65 (br s, 3-C), 124.86 (s, 4-C), 124.95 (br s, 14-C), 125.15, 125.42, 125.62 and 126.12 (4 x s, 6-C, 7-C, 11-C and 13-C), 127.28 and 127.55 (2 x s, 22-C and 22'-C), 127.63 and 127.70 (2 x s, 8-C and 10-C), 127.34 and 128.23 (2 x s, 21-C and 21'-C), 128.55 and 128.74 (2 x s, 20-C and 20'-C), 130.02 and 130.80 (2 x s, 5-C and 12-C), 130.17 (d,  $^2J_{PC}$  7.67, 1-C), 131.02 (d,  $^3J_{PC}$  2.70, 2-C), 131.48 (s, 9-C), 142.26 and 143.75 (2 x s, 19-C and 19'-C);  $\delta_P$  (CDCl<sub>3</sub>) 23.74; EI ms: m/z 534 (M<sup>+</sup>, 3.0%).

### 5.3.2 Synthesis of Diethyl Phosphonate Esters from Imines Prepared from Ketones

#### Preparation of Diethyl [1-(Diphenylmethylamino)cyclopentyl]phosphonate (35)

Diethyl phosphite (0.55 g, 0.004 mol) and N-cyclopentylidene-1,1-diphenylmethanamine 18 (1 g, 0.004 mol) were heated (100°C) for 1.5 hours to give a black oil. Column chromatography [silica column; elution with ethyl acetate - petroleum spirit 40-60°C (4:1)] gave a pale brown oil containing a phosphonate (assumed to be the desired product  $\delta_P$  31.4) and an unidentified impurity ( $\delta_P$  4.0).

#### Preparation of Diethyl [1-(Diphenylmethylamino)cyclohexyl]phosphonate (36)

Diethyl phosphite (0.83 g, 0.007 mol) and N-cyclohexylidene-1,1-diphenylmethanamine 19 (1.75 g, 0.007 mol) were heated (100°C) for 3 hours to give a brown oil. The product was purified by chromatography [silica column; elution with ethyl acetate - petroleum spirit 40-60°C (3:1)] gave the desired product as a sticky yellow solid (0.23 g, 8.2%); (Found: C, 68.9; H, 8.1; N, 3.5.  $C_{23}H_{32}NO_3P$  requires: C, 68.8; H, 8.0; N, 3.5%);  $\delta_H$  (CDCl<sub>3</sub>) 1.17 (6H, t,  $^3J_{HH}$  7.09, 2 x CH<sub>3</sub>), 1.20 (2H, m, 4-CH<sub>2</sub>), 1.45-1.49 (3H, m, from 3-CH<sub>2</sub> and 5-CH<sub>2</sub>), 1.62-1.70 (5H, m, 2-CH<sub>2</sub>, 6-CH<sub>2</sub>, and 1H from 3-CH<sub>2</sub> or 5-CH<sub>2</sub>), 3.99 (4H, m, 2 x OCH<sub>2</sub>), 5.53 (1H, d,  $^4J_{P-H}$  2.67, 7-H), 7.08-7.14 (2H, m, Ph-H), 7.19-7.22 (4H, m, Ph-H), 7.45-7.49 (4H, m, Ph-H);  $\delta_C$  (CDCl<sub>3</sub>) 16.51 (d,  $^3J_{PC}$  5.60, 2 x CH<sub>3</sub>), 20.15, 20.32 (2 x s, 3-C and 5-C), 25.49 (s, 4-C), 30.49, 30.54 (2 x s, 2-C and 6-C), 58.60 (d,  $^1J_{PC}$  138.81, 1-C), 61.20 (s, 7-C), 61.64 (d,  $^2J_{PC}$  8.18, 2 x OCH<sub>2</sub>), 126.49 (s, 11-C), 127.47 (s, 10-C), 128.23 (s, 9-C), 146.27 (s, 8-C);  $\delta_P$  (CDCl<sub>3</sub>) 30.90; EI ms: m/z 401 (M<sup>+</sup>, 5.3%).

### 5.3.3 Synthesis of Dimethyl Phosphonate Esters from Imines Prepared from Ketones

#### Preparation of Dimethyl [1-(Diphenylmethylamino)cyclopentyl]phosphonate (37)

Dimethyl phosphite (0.88 g, 0.008 mol) and N-cyclopentylidene-1,1-diphenylmethanamine 19 (2.00 g, 0.008 mol) were heated (100°C) for 15 minutes to give a brown oil. A yellow solid was obtained when the oil triturated with ethyl acetate. Recrystallisation from ethyl

acetate and petroleum spirit (40-65°C) gave the desired product as a crystalline yellow solid (2.05 g, 55.8%); m.p. 97-99°C; (Found: C, 66.8; H, 7.4; N, 3.8.  $C_{20}H_{26}NO_3P$  requires: C, 66.8; H, 7.3; N, 3.9%);  $\delta_H$  ( $CDCl_3$ ) 1.57 (8H, m, 2- $CH_2$ , 3- $CH_2$ , 4- $CH_2$  and 5- $CH_2$ ), 3.73 (6H, d,  $^3J_{PH}$  10.21, 2 x  $OCH_3$ ), 5.45 (1H, d,  $^4J_{PH}$  2.46, 6-H), 7.13-7.19 (2H, m, Ph-H), 7.23-7.30 (4H, m, Ph-H), 7.39-7.44 (4H, m, Ph-H);  $\delta_C$  ( $CDCl_3$ ) 24.34, 24.54 (2 x s, 3-C and 4-C), 34.52, 34.64 (2 x s, 2-C and 5-C), 52.79 (d,  $^2J_{PC}$  7.67, 2 x  $CH_3$ ), 62.11 (s, 6-C), 64.95 (d,  $^1J_{PC}$  143.91, 1-C), 126.67 (s, 10-C), 127.41 (s, 9-C), 128.36 (s, 8-C), 145.89 (s, 7-C);  $\delta_P$  ( $CDCl_3$ ) 33.67; EI ms: m/z 359 ( $M^+$ , 9.3%).

#### 5.3.4 Synthesis of Diethyl $\alpha$ -Hydroxyphosphonate Ester

##### Preparation of Diethyl 1-Hydroxy-1-(4'-isopropylbenzyl)phosphonate<sup>[168]</sup> (3)

Potassium fluoride (2.90 g, 0.05 mol) was added to a stirred mixture of diethyl phosphite (1.38 g, 0.01 mol) and 4-isopropylbenzaldehyde (1.48 g, 0.01 mol). The reagents were completely adsorbed onto the potassium fluoride. After 20 hours the product was extracted with dichloromethane (2 x 50 cm<sup>3</sup>). The solid potassium fluoride was filtered off and the dichloromethane evaporated under reduced pressure to yield the crude diethyl 1-hydroxy-4'-isopropylbenzylphosphonate as a thick colourless oil which solidified on standing. Recrystallisation from hot petroleum ether (b.p. 30-40°C) gave a white crystalline solid (2.51 g, 87.8%); m.p. 43-44°C; (Found: C, 58.9; H, 8.2. Calculated for  $C_{14}H_{23}O_4P$ : C, 58.7; H, 8.1%);  $\delta_H$  ( $CDCl_3$ ) 1.16-1.31 (12H, m, 2 x  $CHCH_3$  and 2 x  $CH_2CH_3$ ), 2.87 (1H, septet,  $^3J_{HH}$  6.95, 6-H), 3.78 (1H, dd,  $^3J_{HH}$  5.03, OH) 3.87-4.13 (4H, m, 2 x  $CH_2$ ), 4.96 (1H, dd,  $^2J_{PH}$  10.38, 1-H), 7.18-7.48 (4H, m, Ar-H);  $\delta_C$  ( $CDCl_3$ ) 16.30 (d,  $^3J_{PC}$  5.53,  $CH_3CH_2$ ), 16.35 (d,  $^3J_{PC}$  5.53,  $CH_3CH_2$ ), 23.98 (s,  $CH_3CH$ ), 33.83 (s,  $CHCH_3$ ), 62.96 (d,  $^2J_{PC}$  7.42,  $CH_2$ ), 63.14 (d,  $^2J_{PC}$  6.86,  $CH_2$ ), 70.43 (d,  $^1J_{PC}$  161.52,  $CHOH$ ), 126.14 (d,  $^4J_{PC}$  2.45, 4-C), 127.28 (d,  $^3J_{PC}$  5.79, 3-C), 134.55 (s, 5-C), 148.42 (d,  $^2J_{PC}$  3.02, 2-C);  $\delta_P$  ( $CDCl_3$ ) 22.45 (s); EI ms: m/z 286 ( $M^+$ , 16.3%).

#### 5.4 Analysis of $^1H$ NMR Spectra of the Diethyl Phosphonate Esters (4, 5, 6)

The  $^1H$  NMR spectrum of the compounds studied (4, 5, 6) was obtained at 200.131 MHz on a Bruker DRX 200 spectrometer using WIN-NMR on a silicon graphic INDY

computer using the IRIX 5.3 operating system. The temperature at which the spectra were measured was 300 K. The solvent used was  $\text{CDCl}_3$  with TMS as an internal reference. The typical acquisition and processing conditions used were receiver gain 256, pulse width 6  $\mu\text{sec}$ ., relaxation delay 1 sec., line broadening 0.10 Hz, gaussian broadening 0. The data was processed using 16K. The program WIN-DAISY was used to simulate the spectra.

#### **5.4.1 Diethyl Phenyl-1-(diphenylmethylamino)methanephosphonate (4)**

The purity of the sample was determined by elemental analysis and  $^1\text{H}$  NMR spectroscopy. (Found: C, 70.4; H, 6.9; N, 3.3. Calculated for  $\text{C}_{24}\text{H}_{28}\text{NO}_3\text{P}$ . C, 70.4; H, 6.9; N, 3.3%). The  $^1\text{H}$  NMR spectrum was obtained in  $\text{CDCl}_3$  at a concentration of  $0.070 \text{ mol dm}^{-3}$ . The digital resolution of the spectrum was 0.115 Hz per point.

#### **5.4.2 Diethyl 1-(1'-Naphthyl)-1-(diphenylmethylamino)methanephosphonate (5)**

The purity of the sample was determined by elemental analysis and  $^1\text{H}$  NMR spectroscopy. (Found: C, 73.3; H, 6.7; N, 3.0.  $\text{C}_{28}\text{H}_{30}\text{NO}_3\text{P}$  requires. C, 73.2; H, 6.6; N, 3.0%). The  $^1\text{H}$  NMR spectrum was obtained in  $\text{CDCl}_3$  at a concentration of  $0.073 \text{ mol dm}^{-3}$ . The digital resolution of the spectrum was 0.115 Hz per point.

#### **5.4.3 Diethyl 1-(1'-Pyrenyl)-1-(diphenylmethylamino)methanephosphonate (6)**

The purity of the sample was determined by elemental analysis and  $^1\text{H}$  NMR spectroscopy. (Found: C, 76.5; H, 6.1; N, 2.5.  $\text{C}_{34}\text{H}_{32}\text{NO}_3\text{P}$  requires. C, 76.5; H, 6.0; N, 2.6%). The  $^1\text{H}$  NMR spectrum was obtained in  $\text{CDCl}_3$  at a concentration of  $0.060 \text{ mol dm}^{-3}$ . The digital resolution of the spectrum was 0.121 Hz per point.

### **5.5 Preparation of Phosphonic Acids**

#### **5.5.1 Synthesis of $\alpha$ -Aminophosphonic Acids from Imines**

##### **Preparation of $\alpha$ -Amino- $\alpha$ -(2'-thienyl)methanephosphonic Acid (38)**

N-(2'-thienylmethylidene)-1,1-diphenylamine 10 (7.41 g, 0.027 mol) was heated with diethyl phosphite (3.69 g, 0.027 mol) at  $120^\circ\text{C}$  for 4 hours to yield diethyl 1-(2'-thienyl)-1-

(diphenylmethylamino)methanephosphonate **30** as a yellow oil. Concentrated hydrochloric acid (27 cm<sup>3</sup>) was added and the mixture was refluxed for 3 hours to give a yellow solution. The solution was extracted with toluene (3 x 50 cm<sup>3</sup>). The aqueous layer was evaporated *in vacuo* to give a yellow solid. The solid was dissolved in methanol and heated to 50°C. The solution was treated with propylene oxide (pre-cooled in ice) to yield a precipitate. The precipitate was filtered off and washed with acetone. Recrystallisation from water and acetone yielded the desired product as a pale pink solid (3.74 g, 71.5%); m.p.250-252°C; (Found: C, 30.2; H, 4.4; N, 6.9. Calculated for C<sub>3</sub>H<sub>4</sub>NO<sub>3</sub>PS.<sup>1</sup>/<sub>3</sub>H<sub>2</sub>O: C, 30.2; H, 4.4; N, 7.0%); δ<sub>H</sub> (D<sub>2</sub>O/NaOD) 4.19 (1H, d, <sup>2</sup>J<sub>P-H6</sub> 15.11, 6-H), 7.04 (1H, dd, <sup>3</sup>J<sub>H4-H5</sub> 5.04 and <sup>3</sup>J<sub>H4-H3</sub> 3.56, 4-H), 7.11 (1H, dd, <sup>4</sup>J<sub>H3-H5</sub> 1.12, 3-H), 7.35 (1H, dd, 5-H); δ<sub>C</sub> (D<sub>2</sub>O/NaOD) 53.93 (d, <sup>1</sup>J<sub>PC</sub> 133.59, 6-C), 127.44 (d, <sup>4</sup>J<sub>PC</sub> 1.38, 4-C), 128.40 (d, <sup>3</sup>J<sub>PC</sub> 6.29, 3-C), 129.58 (d, <sup>4</sup>J<sub>PC</sub> 1.45, 5-C), 145.94 (d, <sup>2</sup>J<sub>PC</sub> 3.08, 2-C); δ<sub>P</sub> (D<sub>2</sub>O/NaOD) 17.31; ms LSIMS: m/z 194 (MH<sup>+</sup>, 100%).

#### Preparation of α-Amino-α-piperonylphosphonic Acid (**39**)

N-Piperonylidene-1,1-diphenylamine **12** (5.00 g, 0.016 mol) was heated with diethyl phosphite (2.17 g, 0.016 mol) at 110°C for 2 hours to yield diethyl 1-piperonyl-1-(diphenylmethylamino)methanephosphonate **32** as a orange oil. Concentrated hydrochloric acid (16 cm<sup>3</sup>) was added and the mixture was refluxed for 3 hours to give a brown solution. The solution was extracted with toluene (3 x 50 cm<sup>3</sup>). The aqueous layer was evaporated *in vacuo* to give a brown solid. The solid was dissolved in methanol and heated to 50°C. The solution was treated with propylene oxide (pre-cooled in ice) to yield a precipitate. The precipitate was filtered off and washed with acetone. Recrystallisation from water and acetone yielded the desired product as a cream solid (1.54 g, 41.6%); m.p.242-245°C; (Found: C, 41.1; H, 4.4; N, 5.0. Calculated for C<sub>8</sub>H<sub>10</sub>NO<sub>3</sub>P: C, 41.6; H, 4.4; N, 5.1%); δ<sub>H</sub> (D<sub>2</sub>O/NaOD) 3.73 (1H, d, <sup>2</sup>J<sub>PH8</sub> 15.18, 8-H), 5.95 (2H, s, 7-CH<sub>2</sub>), 6.86-6.97 (3H, m, 2-H, 5-H and 6-H); δ<sub>C</sub> (D<sub>2</sub>O/NaOD) 58.08 (d, <sup>1</sup>J<sub>PC</sub> 132.46, 8-C), 103.54 (s, CH<sub>2</sub>), 110.76 (d, <sup>4</sup>J<sub>PC</sub> 1.82, 5-C), 111.17 (d, <sup>3</sup>J<sub>PC</sub> 4.59, 6-C), 123.77 (d, <sup>3</sup>J<sub>PC</sub> 5.79, 2-C), 139.07 (d, <sup>5</sup>J<sub>PC</sub> 2.33, 4-C), 148.07 (d, <sup>4</sup>J<sub>PC</sub> 2.83, 3-C), 149.34 (d, <sup>2</sup>J<sub>PC</sub> 1.89, 1-C); δ<sub>P</sub> (D<sub>2</sub>O/NaOD) 18.23; ms LSIMS: m/z 232 (MH<sup>+</sup>, 5.5), 150 [MH<sup>+</sup>-(H<sub>3</sub>PO<sub>3</sub>), 100].



**Preparation of  $\alpha$ -Amino- $\alpha$ -(4'-isopropylbenzyl)phosphonic Acid (40)**

N-(4-isopropylbenzylidene)-1,1-diphenylamine **13** (8.0 g, 0.025 mol) was heated with diethyl phosphite (3.52 g, 0.025 mol) at 120°C for 3.5 hours to yield diethyl 1-(4'-isopropylbenzyl)-1-(diphenylmethylamino)phosphonate **33** as a dark yellow oil. Concentrated hydrochloric acid (25 cm<sup>3</sup>) was added and refluxed for 3 hours to give a purple solution. The solution was extracted with toluene (3 x 50 cm<sup>3</sup>). The aqueous layer was evaporated *in vacuo* to give a pale yellow solid. The solid was dissolved in methanol and heated to 50°C. The solution was treated with propylene oxide (pre-cooled in ice) to yield a precipitate. The precipitate was filtered and washed with acetone. Recrystallisation from ethanol and acetone yielded the desired product as a white solid (2.33 g, 40.7%); m.p.308°C (decomp.); (Found: C, 52.5; H, 7.0; N, 6.0. Calculated for C<sub>10</sub>H<sub>16</sub>NO<sub>3</sub>P: C, 52.4; H, 7.0; N, 6.1%);  $\delta_{\text{H}}$  (D<sub>2</sub>O/NaOD) 1.23 (6H, d, <sup>3</sup>J<sub>HH</sub> 6.90, 2 x CH<sub>3</sub>), 2.92 (1H, septet, 5-H), 3.79 (1H, d, <sup>2</sup>J<sub>P-H6</sub> 15.49, 1-H), 7.29 (2H, d, 3-H), 7.35 (2H, dd, <sup>3</sup>J<sub>H2-H3</sub> 8.30 and <sup>4</sup>J<sub>P-H2</sub> 1.50, 2-H);  $\delta_{\text{C}}$  (D<sub>2</sub>O/NaOD) 26.15 (s, 2 x CH<sub>3</sub>), 35.82 (s, 5-C), 57.95 (d, <sup>1</sup>J<sub>PC</sub> 131.58, 6-C), 128.66 (d, <sup>4</sup>J<sub>PC</sub> 1.38, 3-C), 130.48 (d, <sup>3</sup>J<sub>PC</sub> 4.90, 2-C), 142.35 (d, <sup>5</sup>J<sub>PC</sub> 2.45, 4-C), 150.12 (d, <sup>2</sup>J<sub>PC</sub> 2.64, 1-C);  $\delta_{\text{P}}$  (D<sub>2</sub>O/NaOD) 18.40; ms LSIMS: m/z 230 (MH<sup>+</sup>, 17.7), 148 [MH<sup>+</sup>-(H<sub>3</sub>PO<sub>3</sub>), 100].

**Preparation of  $\alpha$ -Amino- $\alpha$ -(4'-dimethylaminobenzyl)phosphonic Acid (41)**

N-(4-dimethylaminobenzylidene)-1,1-diphenylmethylamine **11** (6.78 g, 0.015 mol) was heated with diethyl phosphite (2.07 g, 0.015 mol) at 100°C for 3 hours to yield diethyl 1-(4'-dimethylaminobenzyl)-1-(diphenylmethylamino)phosphonate **31** as a brown oil. Concentrated hydrochloric acid (16 cm<sup>3</sup>) was added and the mixture was refluxed for 3 hours to give a dark brown solution. The solution was extracted with toluene (3 x 50 cm<sup>3</sup>). The aqueous layer was evaporated *in vacuo* to give a brown-yellow solid. The solid was dissolved in methanol and heated to 50°C. The solution was treated with propylene oxide (pre-cooled in ice) to yield a precipitate. The precipitate was filtered off and washed with acetone. Recrystallisation from water and acetone yielded the desired product as a pale yellow solid (1.42 g, 41.1%); m.p.230-234°C; (Found: C, 44.9; H, 7.0; N, 11.4. Calculated for C<sub>9</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>P.<sup>3</sup>/<sub>4</sub>H<sub>2</sub>O: C, 44.4; H, 6.8; N, 11.5%);  $\delta_{\text{H}}$  (D<sub>2</sub>O/NaOD) 2.83 (6H, s, 2 x CH<sub>3</sub>), 3.74 (1H, d, <sup>2</sup>J<sub>PH</sub> 15.03, 5-H), 7.01 (2H, d, <sup>3</sup>J<sub>H2-H3</sub> 8.68, 3-H), 7.34 (2H, dd, <sup>4</sup>J<sub>P-H2</sub> 1.83, 2-H);  $\delta_{\text{C}}$  (D<sub>2</sub>O/NaOD) 44.35 (s, 2 x CH<sub>3</sub>), 57.56 (d, <sup>1</sup>J<sub>PC</sub> 132.77,

5-C), 118.44 (d,  $^4J_{PC}$  1.45, 3-C), 131.21 (d,  $^3J_{PC}$  5.03, 2-C), 136.27 (d,  $^2J_{PC}$  2.70, 1-C), 152.64 (d,  $^5J_{PC}$  1.95, 4-C);  $\delta_P$  ( $D_2O/NaOD$ ) 18.65; ms LSIMS: m/z 231 ( $MH^+$ , 12.3%), 149 [ $MH^+-(H_3PO_3)$ , 100%].

**Preparation of  $\alpha$ -Amino- $\alpha$ -(1'-naphthyl)methanephosphonic Acid (42)**

N-(1'-naphthylmethylidene)-1,1-diphenylamine 15 (24.30 g, 0.08 mol) was heated with diethyl phosphite (10.44 g, 0.08 mol) at 100°C for 14 hours to yield diethyl 1-(1'-naphthyl)-1-(diphenylmethylamino)methanephosphonate 5 as a yellow oil. Concentrated hydrochloric acid (80 cm<sup>3</sup>) was added and the mixture was refluxed for 3 hours to give an orange solution. The solution was extracted with toluene (3 x 50 cm<sup>3</sup>). The aqueous layer was evaporated *in vacuo* to give a red solid. The solid was dissolved in methanol and heated to 50°C. The solution was treated with propylene oxide (pre-cooled in ice) to yield a precipitate. The precipitate was filtered off and washed with acetone. Recrystallisation from water and acetone yielded the desired product as a white solid (7.54 g, 31.8%); m.p. 257°C; (Found: C, 55.6; H, 5.1; N, 5.7.  $C_{11}H_{12}NO_3P$  requires: C, 55.7; H, 5.1; N, 5.9%);  $\delta_H$  ( $D_2O/NaOD$ ) 4.76 (1H, d,  $^2J_{PH11}$  16.06, 11-H), 7.52-7.65 (3H, m, 3-H, 7-H and 8-H), 7.71 (1H, d,  $^3J_{HH}$  7.45, 9-H), 7.84 (1H, d,  $^3J_{HH}$  8.15, 6-H), 7.94 (1H, d,  $^3J_{HH}$  7.90, 4-H), 8.31 (1H, d,  $^3J_{HH}$  8.38, 2-H);  $\delta_C$  ( $D_2O/NaOD$ ) 52.65 (d,  $^1J_{PC}$  131.08, 11-C), 127.19, 128.34 and 128.52 (3 x s, 3-C, 7-C and 8-C), 128.56 (s, 9-C), 128.62 and 129.25 (2 x s, 4-C and 6-C), 131.27 (s, 2-C), 134.23 (d,  $^2J_{PC}$  5.66, 1-C), 136.06 and 141.56 (2 x s, 5-C and 10-C);  $\delta_P$  ( $D_2O/NaOD$ ) 18.77; ms LSIMS: m/z 238 ( $MH^+$ , 100).

**Preparation of  $\alpha$ -Amino- $\alpha$ -(9'-anthryl)methanephosphonic Acid (43)**

N-(9'-anthrylmethylidene)-1,1-diphenylamine 16 (17.4 g, 0.047 mol) was heated with diethyl phosphite (6.47 g, 0.047 mol) at 100°C for 6 hours to yield diethyl 1-(9'-anthryl)-1-(diphenylmethylamino)methanephosphonate 34 as a yellow oil. Concentrated hydrochloric acid (47 cm<sup>3</sup>) was added and the mixture was refluxed for 3 hours to give an orange solution. The solution was extracted with toluene (3 x 50 cm<sup>3</sup>). The aqueous layer was evaporated *in vacuo* to give a orange yellow oil. The oil was dissolved in methanol and heated to 50°C. The solution was treated with propylene oxide (pre-cooled in ice) to yield a precipitate. The precipitate was filtered off and washed with acetone. Recrystallisation from water and acetone yielded the desired product as a yellow solid

(10.74 g, 37.4%); m.p.286-287°C (decomp.); (Found: C, 62.0; H, 5.1; N, 4.5. Calculated for C<sub>15</sub>H<sub>14</sub>NO<sub>3</sub>P: C, 62.7; H, 4.9; N, 4.9%);  $\delta_{\text{H}}$  (D<sub>2</sub>O/NaOD) 5.54 (1H, d, <sup>2</sup>J<sub>PH15</sub> 22.25, 15-H), 7.49-7.65 (4H, m, 4-H, 5-H, 11-H and 12-C), 8.04 (2H, d, <sup>3</sup>J<sub>HH</sub> 7.30, 6-H and 10-H), 8.42 (1H, s, 8-H), 8.49 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.02, 13-H), 8.96 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.71, 3-H);  $\delta_{\text{C}}$  (D<sub>2</sub>O/NaOD) 54.32 (d, <sup>1</sup>J<sub>PC</sub> 130.13, 15-C), 127.30, 127.72, 127.78, 127.88 (4 x s, 4-C, 5-C, 11-C and 12-C), 129.19 and 129.24 (2 x s, 6-C and 10-C), 130.96 (s, 8-C), 131.59 (s, 13-C), 131.85 (s, 3-C), 132.20 and 134.09 (2 x s, 7-C and 9-C), 132.84 (d, <sup>2</sup>J<sub>PC</sub> 7.48, 1-C), 134.54 (d, <sup>3</sup>J<sub>PC</sub> 2.77, 14-C), 139.12 (s, 2-C);  $\delta_{\text{P}}$  (D<sub>2</sub>O/NaOD) 18.44; ms LSIMS: m/z 288 (MH<sup>+</sup>, 11.4), 206 [MH<sup>+</sup>-(H<sub>3</sub>PO<sub>3</sub>), 34%].

#### Preparation of $\alpha$ -Amino- $\alpha$ -cyclopentanephosphonic Acid (44)

N-cyclopentylidene-1,1-diphenylamine 18 (2.30 g, 0.009 mol) was heated with diethyl phosphite (1.27 g, 0.009 mol) at 120°C for 4 hours to yield diethyl 1-cyclopentyl-1-(diphenylmethylamino)methanephosphonate 35 (not isolated and characterised) as a thick brown oil. Concentrated hydrochloric acid (10 cm<sup>3</sup>) was added and the mixture was refluxed for 2 hours to give a brown solution. The solution was extracted with toluene (3 x 50 cm<sup>3</sup>). The aqueous layer was evaporated *in vacuo* to give a brown solid. The solid was dissolved in methanol and heated to 50°C. The solution was treated with propylene oxide (pre-cooled in ice) to yield a precipitate. The precipitate was filtered off and washed with acetone. Recrystallisation from water and acetone yielded the desired product as a cream solid (0.24 g, 16.15%); m.p.205-208°C;  $\delta_{\text{H}}$  (D<sub>2</sub>O/NaOD) 1.64-1.76 (6H, m, 3-CH<sub>2</sub>, 4-CH<sub>2</sub> and 2H from 2-CH<sub>2</sub> and 5-CH<sub>2</sub>), 2.16 (2H, m, 2H from 2-CH<sub>2</sub> and 5-CH<sub>2</sub>);  $\delta_{\text{C}}$  (D<sub>2</sub>O/NaOD) 27.72 (d, <sup>3</sup>J<sub>PC</sub> 7.48, 3-C and 4-C), 37.56 (d, <sup>2</sup>J<sub>PC</sub> 1.51, 2-C and 5-C), 65.10 (d, <sup>1</sup>J<sub>PC</sub> 143.08, 1-C);  $\delta_{\text{P}}$  (D<sub>2</sub>O/NaOD) 18.48; ms LSIMS: m/z 166 (MH<sup>+</sup>, 36.8), 149 [MH<sup>+</sup>-(OH), 100].

#### 5.5.2 Attempted Synthesis of $\alpha$ -Aminophosphonic Acids from Imines

The same general procedure was carried out using the imine precursors N-(2'-pyrrolylidene)-1,1-diphenylamine 7, N-furfurylidene-1,1-diphenylamine 8 and N-(1'-pyrenylmethylidene)-1,1-diphenylamine 17 but the desired products were not obtained.

### 5.5.3 Synthesis of N-protected Phosphonic Acid from Imines

#### Preparation of $\alpha$ -(Phenylethylamino)- $\alpha$ -(2'-thienyl)methanephosphonic Acid (45)

N-(2'-thienylmethylidene)-1,1-phenylethylamine **22** (15 g, 0.07 mol) was heated with diethyl phosphite (9.63 g, 0.07 mol) at 100°C for 16 hours to yield diethyl 1-(2'-thienyl)-1-(phenylethylamino)methane phosphonate (not isolated and characterized) as a dark orange oil. Concentrated hydrochloric acid (70 cm<sup>3</sup>) was added and the mixture was refluxed for 3 hours to give a yellow solution. The solution was extracted with toluene (3 x 50 cm<sup>3</sup>). The aqueous layer was evaporated *in vacuo* to give a yellow solid. The solid was dissolved in methanol and heated to 50°C. The solution was treated with propylene oxide (pre-cooled in ice) to yield a precipitate. The precipitate was filtered off and washed with acetone. Recrystallisation from water and acetone yielded the desired product as a pale pink solid (17.01 g, 81.7%); m.p. 210-212°C; (Found: C, 51.0; H, 5.2; N, 4.7. Calculated for C<sub>13</sub>H<sub>16</sub>NO<sub>3</sub>PS: C, 52.5; H, 5.4; N, 4.7%);  $\delta_{\text{H}}$  (D<sub>2</sub>O/NaOD) 1.37 (3H, d, <sup>3</sup>J<sub>HH</sub> 6.60, 8-H), 3.88 (1H, q, 7-H), 4.17 (1H, d, <sup>2</sup>J<sub>PH</sub> 18.64, 6-H), 6.92-6.97 (2H, m, 3-H and 4-H), 7.14-7.22 (6H, m, Ph-H and 5-H);  $\delta_{\text{C}}$  (D<sub>2</sub>O/NaOD) 23.46 (s, 8-C), 58.94 (d, <sup>3</sup>J<sub>PC</sub> 10.00, 7-C), 59.68 (d, <sup>1</sup>J<sub>PC</sub> 135.98, 6-C), 126.77 (s, 12-C), 128.66 (d, <sup>3</sup>J<sub>PC</sub> 7.30, 3-C), 129.67 (s, 4-C), 129.81 (s, 11-C), 131.28 (s, 10-C), 131.40 (s, 5-C);  $\delta_{\text{P}}$  (D<sub>2</sub>O/NaOD) 16.11; ms LSIMS: m/z 298 [(M+1)<sup>+</sup>, 35.8]. 216 [MH<sup>+</sup>-(H<sub>3</sub>PO<sub>3</sub>), 100].

### 5.5.4 Synthesis of $\alpha$ -Aminopropanephosphonic Acid (1) using Benzyl Carbamate<sup>[155]</sup>

Triphenyl phosphite (26.7 g, 0.086 mol), benzyl carbamate (13.0 g, 0.086 mol) and propanal (5.0 g, 0.086 mol) were mixed together in sodium dried toluene (80 cm<sup>3</sup>). Boron trifluoride etherate (2.5 cm<sup>3</sup>), in toluene (50 cm<sup>3</sup>), was added dropwise with stirring. The mixture was heated under reflux (5 hours). The toluene was removed *in vacuo* to yield a pale yellow oil. Concentrated hydrochloric acid (120 cm<sup>3</sup>) was added to the residue and the mixture was heated under reflux (8 hours). Phenol and the other by-products were removed by extraction with toluene (3 x 20 cm<sup>3</sup>), and the aqueous layer was removed *in vacuo* to yield a yellow oil. The yellow oil was dissolved in methanol (45 cm<sup>3</sup>) and heated under reflux. Propylene oxide (25 cm<sup>3</sup>) was added to give an immediate precipitate. The

precipitate was filtered off, washed with acetone (15 cm<sup>3</sup>) and dried in a vacuum oven at 60°C to give the crude  $\alpha$ -aminopropanephosphonic acid (5.27 g, 44.1%). Recrystallisation from water and ethanol yielded  $\alpha$ -aminopropanephosphonic acid as a crystalline white solid (5.03 g, 42.1%); m.p. 258-260°C (Lit.<sup>[155]</sup> m.p. 264-265°C); (Found: C, 25.8; H, 7.1; N, 9.9. Calculated for C<sub>3</sub>H<sub>10</sub>NO<sub>3</sub>P: C, 25.9; H, 7.3; N, 10.1%);  $\delta_{\text{H}}$  (D<sub>2</sub>O) 1.07 (3H, t, <sup>3</sup>J<sub>HH</sub> 7.52, CH<sub>3</sub>), 1.67-2.04 (2H, m, CH<sub>2</sub>), 3.17 (1H, ddd, CH);  $\delta_{\text{C}}$  (D<sub>2</sub>O) 13.13 (d, <sup>3</sup>J<sub>PC</sub> 9.33, CH<sub>3</sub>), 24.75 (s, CH<sub>2</sub>), 53.66 (d, <sup>1</sup>J<sub>PC</sub> 143.1, CH);  $\delta_{\text{P}}$  (D<sub>2</sub>O) 14.19 (s).

#### 5.6 Analysis of <sup>1</sup>H NMR Spectra of $\alpha$ -Aminopropanephosphonic Acid (1) and $\alpha$ -Aminopropanephosphinic Acid (2)

The proton NMR spectra of compounds 1 and 2 were obtained at 250.133 MHz at a temperature of 300 K, on a Bruker AM250 spectrometer. The solvent used was either D<sub>2</sub>O or D<sub>2</sub>O/NaOD depending on the required pH, with TSP as internal reference. The typical conditions used were: Receiver gain 16, pulse width 4.0  $\mu$ s, relaxation delay 5.0 s, line broadening 0 and gaussian broadening 0. The data was processed using 32 k data points zero-filled from 16 k.

The spectral analysis program 'Parameter Adjusted NMR Iteration Calculation' (PANIC)<sup>[73]</sup> was used on the Bruker AM250 spectrometer to simulate the proton spectrum and, through iterative procedures, achieve a good match to the experimental spectrum in terms of both peak position and intensity. The digital resolution used for the simulation of the spectrum was the same as for the experimental spectrum.

#### Analysis of conformation

Conformational analysis of the molecule was carried out using the program ALTONA.<sup>[163]</sup> The program is an implementation of the empirically generalised relationship between the vicinal coupling constant <sup>3</sup>J(HH) and the dihedral angle.<sup>[162]</sup>

### 5.6.1 $\alpha$ -Aminopropanephosphonic acid 1

The purity of the sample was determined by elemental analysis, and  $^1\text{H}$  NMR spectroscopy. Found: C, 25.8; H, 7.1; N, 9.9. Calculated for  $\text{C}_3\text{H}_9\text{NO}_3\text{P}$ : C, 25.9; H, 7.3; N, 10.1%. A small quantity (<1%) of ethyl-containing impurity was indicated by the presence of signals at 1.33 and 1.18 ppm in the  $^1\text{H}$  NMR spectrum.

Proton NMR spectra were obtained;

- (a) in  $\text{D}_2\text{O}$  at a concentration of  $0.42 \text{ mol dm}^{-3}$  and pH 3.19;  
the digital resolution of the spectrum was 0.096 Hz per point;
- (b) in  $\text{D}_2\text{O}$  and NaOD at a concentration of  $0.14 \text{ mol dm}^{-3}$  and pH 7.54;  
the digital resolution of the spectrum was 0.058 Hz per point;
- (c) in  $\text{D}_2\text{O}$  and NaOD at a concentration of  $0.17 \text{ mol dm}^{-3}$  and pH 11.44;  
the digital resolution of the spectrum was 0.058 Hz per point.

### 5.6.2 $\alpha$ -Aminopropanephosphonic acid 2

The purity of the sample provided within the department was determined by elemental analysis and  $^1\text{H}$  NMR spectroscopy. (Found: C, 29.2; H, 8.1; N, 11.2. Calculated for  $\text{C}_3\text{H}_9\text{NO}_2\text{P}$ : C, 29.8; H, 8.2; N, 11.3%).

A proton NMR spectrum was obtained in  $\text{D}_2\text{O}$  at a concentration of  $0.42 \text{ mol dm}^{-3}$  and pH 3.10, the digital resolution of the spectrum was 0.115 Hz per point.

## SUMMARY

This project achieved its two general aims. The first objective was to synthesise a range of new  $\alpha$ -aminophosphonic acids and their phosphonate ester derivatives. The second aim was to investigate the conformation of a number of these compounds in solution using the coupling constants obtained from the full analysis of the  $^1\text{H}$  NMR spectrum.

A range of diethyl 1-substituted-1-(diphenylmethylamino)methanephosphonates (section 3.2) and  $\alpha$ -amino- $\alpha$ -substituted phosphonic acids (section 4.2) were prepared and characterised.  $^1\text{H}$  NMR spectral analysis was carried out on key compounds in the series of compounds prepared in this work and some related known compounds.

Imine precursors were successfully prepared, isolated and characterised (Chapter 2) using standard procedures. Problems were encountered in reactions where the carbonyl compound was of low reactivity. This problem was overcome by modification of the standard procedure to use titanium tetrachloride as a water scavenger. The modified procedure allowed the isolation of the imine derived from camphor and aminodiphenylmethane.

Diethyl phosphonate esters were successfully prepared, isolated and characterised (Chapter 3). The diethyl phosphonate esters which have a chiral  $\alpha$ -carbon atom and prochiral phosphorus atom gave rise to complex multiplets within the  $^1\text{H}$  NMR spectra. The signals arising from the methylene protons are particularly interesting. The  $^1\text{H}$  NMR spectra of the phenyl, naphthyl and pyrenyl substituted diethyl phosphonate esters were analysed and simulated. The effects of bulky aromatic substituents on the  $\alpha$ -carbon atom were investigated. It was envisaged that larger substituents on the  $\alpha$ -carbon atom would bring about a larger chemical shift non-equivalence of the ethoxy group protons due to aromatic ring current effects. Although a distinct pattern did not emerge in this study (probably due to the limited number of examples investigated), the results justify further investigation with more compounds.

$\alpha$ -Amino- $\alpha$ -substituted phosphonic acids were successfully prepared, isolated and characterised (Chapter 4). The aminophosphonic acids prepared in this work generally had large aromatic substituents, and the  $^1\text{H}$  NMR spectra of these compounds were not simulated.

The  $^1\text{H}$  NMR spectra of  $\alpha$ -aminopropanephosphonic and  $\alpha$ -aminopropanephosphinic acid were analysed and simulated. The  $^1\text{H}$  NMR spectra of these compounds gave rise to complex multiplets assigned to the methylene protons due to the chiral carbon atom the molecule contains. The data obtained from the analyses of the spectra revealed information about the conformation of the molecules in solution, but this was not fully satisfactory because of the problem in assigning the methylene protons.

$\alpha$ -Aminopropanephosphonic acid has fungicidal activity. The new phosphonate esters and phosphonic acids prepared in this work may possess similar activity and biological screening is planned for these compounds.

In conclusion, this thesis describes the synthesis of a range of new phosphonic acids and their phosphonate ester derivatives and the analysis and simulation of the  $^1\text{H}$  NMR spectra of key compounds.



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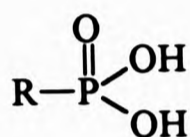
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## APPENDIX I

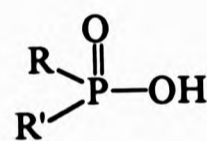
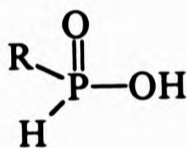
### Nomenclature

#### Pentavalent Phosphorus

Phosphonic Acid



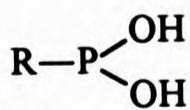
Phosphinic Acid or Alkylphosphinic Acid



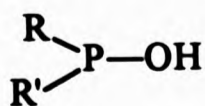
Phosphinic acids are also referred to as alkylphosphonous acids<sup>[6]</sup> but phosphonous implies that the phosphorus is in a trivalent state so the term phosphinic acid<sup>[7]</sup> is more correct and in accord with the IUPAC nomenclature.

#### Trivalent Phosphorus

Phosphonous Acid



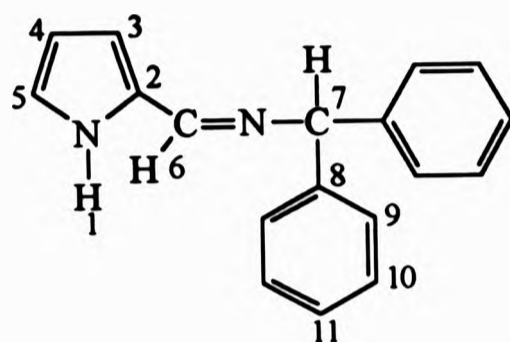
Phosphinous Acid



## APPENDIX II

### <sup>1</sup>H and <sup>13</sup>C NMR Spectral Data of the Imines Structures

7



**Table II.1** <sup>1</sup>H NMR chemical shifts (ppm) and coupling constants (Hz) for 7 in CDCl<sub>3</sub>

Proton	Chemical shifts, Coupling constants
7-H	5.56, (s)
4-H	6.22, (dd), <sup>3</sup> J <sub>H3-H4</sub> 3.65, <sup>3</sup> J <sub>H4-H5</sub> 2.56
3-H	6.51, (dd), <sup>4</sup> J <sub>H3-H5</sub> 1.10
5-H	6.84, (dd)
Ph-H	7.18-7.35, (m)
6-H	8.13, (s)

**Table II.2** <sup>13</sup>C NMR chemical shifts (ppm) and coupling constants (Hz) for 7 in CDCl<sub>3</sub>

Carbon	Chemical shifts, Coupling constants
7-C	77.66 (s)
4-C	110.16 (s)
3-C	115.54 (s)
5-C	122.68 (s)
11-C	127.10 (s)
10-C	127.82 (s)
9-C	128.47 (s)
8-C	129.76 (s) <sup>†</sup>
2-C	143.37 (s) <sup>†</sup>
6-C	151.34 (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

8

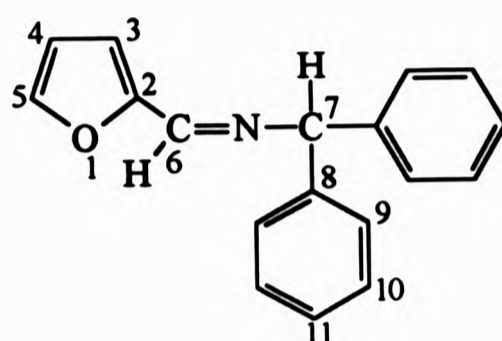


Table II.3

<sup>1</sup>H NMR chemical shifts (ppm) and coupling constants (Hz) for **8** in CDCl<sub>3</sub>

Proton	Chemical shifts, Coupling constants
7-H	5.53, (s)
4-H	6.36, (dd), <sup>3</sup> J <sub>H4-H3</sub> 3.42, <sup>3</sup> J <sub>H4-H5</sub> 1.75.
3-H	6.72, (dd), <sup>4</sup> J <sub>H3-H5</sub> 0.67
Ph-H	7.17-7.37, (m)
5-H	7.44, (dd)
6-H	8.13, (s)

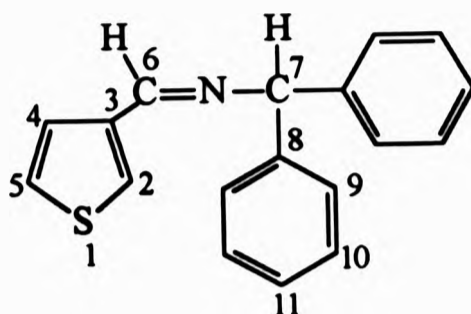
Table II.4

<sup>13</sup>C NMR chemical shifts (ppm) and coupling constants (Hz) for **8** in CDCl<sub>3</sub>

Carbon	Chemical shifts, Coupling constants
7-C	77.92, (s)
4-C	111.61, (s)
3-C	114.50, (s)
11-C	126.99, (s)
10-C	127.73, (s)
9-C	128.38, (s)
8-C	143.27, (s) <sup>†</sup>
5-C	144.79, (s)
6-C	149.63, (s)
2-C	151.54, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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**Table II.5**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **9** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
7-H	5.52, (s)
5-H, Ph-H	7.14-7.38, (m)
4-H	7.55, (dd) <sup>†</sup>
2-H	7.63, (dd) <sup>†</sup>
6-H	8.35, (s)

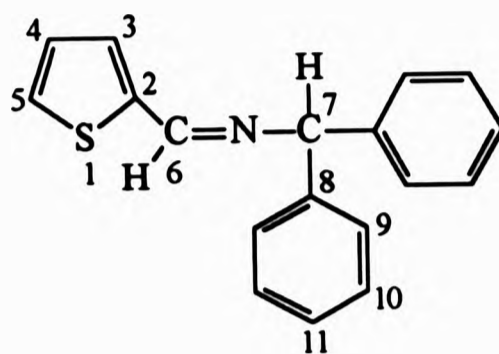
<sup>†</sup> The spectrum was not resolved well enough to measure the coupling constants

**Table II.6**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **9** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
7-C	77.63 (s)
5-C	125.95 (s)
4-C	126.10 (s)
11-C	126.85 (s)
10-C	127.58 (s)
9-C	128.31 (s)
2-C	128.63 (s)
8-C	140.51 (s) <sup>†</sup>
3-C	143.70 (s) <sup>†</sup>
6-C	154.98 (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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**Table II.7**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **10** in  $\text{CDCl}_3$

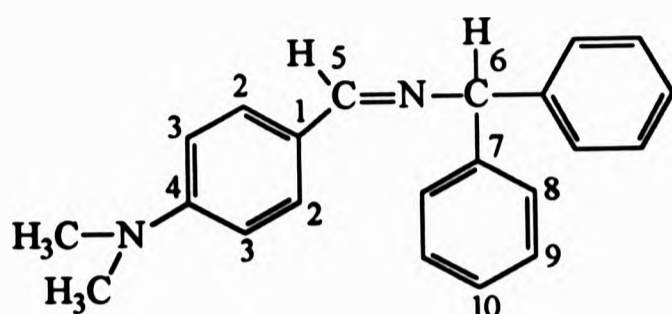
Proton	Chemical shifts, Coupling constants
7-H	5.57, (s)
4-H	7.01 (dd), $^3J_{\text{H3-H4}}$ 5.00, $^3J_{\text{H4-H5}}$ 3.62
Ph-H, 3-H, 5-H	7.17-7.38, (m)
6-H	8.43, (s)

**Table II.8**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **10** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
7-C	77.21, (s)
11-C	127.09, (s)
4-C	127.41, (s)
10-C	127.82, (s)
9-C	128.54, (s)
3-C <sup>†</sup>	129.25, (s)
5-C <sup>‡</sup>	130.77, (s)
2-C	142.85, (s) <sup>†</sup>
8-C	143.76, (s) <sup>†</sup>
6-C	154.12, (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

<sup>‡</sup> These carbons signals could be assigned the other way round



**Table II.9**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for 11 in  $\text{CDCl}_3$

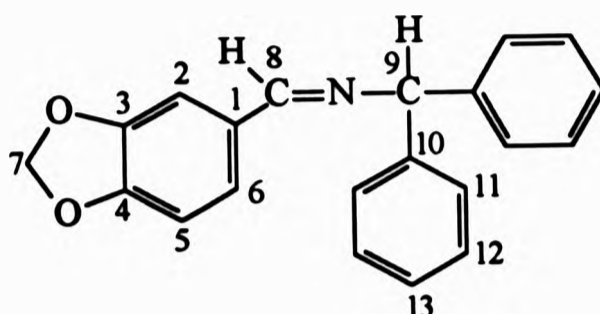
Proton	Chemical shifts, Coupling constants
2 x $\text{CH}_3$	2.92, (s)
6-H	5.51, (s)
3-H	6.64, (m)
Ph-H	7.13-7.40, (m)
2-H	7.69, (m)
5-H	8.28, (s)

**Table II.10**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for 11 in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
2 x $\text{CH}_3$	40.12, (s)
C-6	77.69, (s)
3-C	111.49, (s)
4-C	124.61, (s) <sup>†</sup>
10-C	126.68, (s)
9-C	127.74, (s)
8-C	128.26, (s)
2-C	129.79, (s)
7-C	144.47, (s) <sup>†</sup>
1-C	152.07, (s) <sup>†</sup>
5-C	160.56, (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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**Table II.11**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for 12 in  $\text{CDCl}_3$

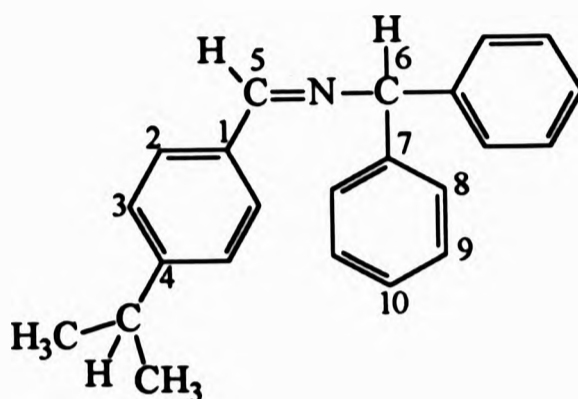
Proton	Chemical shifts, Coupling constants
9-H	5.55, (s)
7- $\text{CH}_2$	5.97, (s)
5-H	6.80, (d), $^3J_{\text{H}5-\text{H}6}$ 7.99
6-H	7.14, (dd), $^4J_{\text{H}2-\text{H}6}$ 1.57
Ph-H	7.18-7.40, (m)
2-H	7.52, (d)
8-H	8.29, (s)

**Table II.12**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for 12 in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
9-C	77.63 (s)
7- $\text{CH}_2$	101.41(s)
5-C, 6-C	106.92, 107.96 (2 x s)
2-C	124.73 (s)
13-C	126.93 (s)
12-C	127.65 (s)
11-C	128.41 (s)
10-C	131.27 (s) <sup>†</sup>
1-C	144.07 (s) <sup>†</sup>
3-C, 4-C	148.22, 149.94 (2 x s) <sup>†</sup>
8-C	159.83 (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment





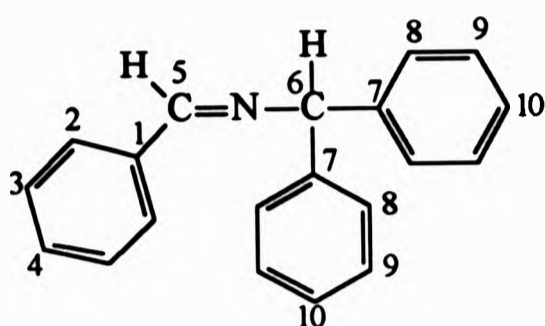
**Table II.13**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **13** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
2 x $\text{CH}_3$	1.21, (d), $^3J_{\text{HH}}$ 6.91
$\text{CHCH}_3$	2.87, (septet)
6-H	5.55, (s)
Ar-H	7.13-7.76, (m)
5-H	8.34, (s)

**Table II.14**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **13** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
2 x $\text{CH}_3$	23.79, (s)
CH	34.08, (s)
6-C	77.79, (s)
3-C	123.58, (s)
10-C	126.86, (s)
9-C	127.67, (s)
8-C	128.34, (s)
2-C	128.52, (s)
7-C	134.13, (s) <sup>†</sup>
1-C	143.99, (s) <sup>†</sup>
4-C	151.86, (s) <sup>†</sup>
5-C	160.59, (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table II.15**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **14** in  $\text{CDCl}_3$

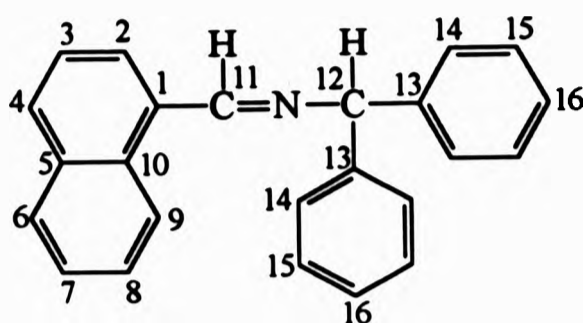
Proton	Chemical shifts, Coupling constants
6-H	5.59, (s)
3-H, 4-H, 2 x Ph-H	7.17-7.42, (m)
2-H	7.18-7.85, (m)
5-H	8.40, (s)

**Table II.16**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **14** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
6-C	77.77 (s)
8-C, 9-C, 10-C	126.88, 128.34, (2 x s)
3-C, 2-C	127.58, 128.40, (2 x s)
4-C	130.63 (s)
1-C	136.18 (s) <sup>†</sup>
7-C	143.83 (s) <sup>†</sup>
5-C	160.63 (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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**Table II.17**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **15** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
12-H	5.59, (s)
2 x Ph-H, 3-H, 7-H, 8-H, 9-H	7.12-7.52, (m)
4-H, 6-H	7.71-7.75, (2 x dd), $^3J_{\text{HH}}$ 8.36 and 8.10 <sup>†</sup>
11-H	8.92, (s)
2-H	9.09, (d), $^3J_{\text{HH}}$ 8.56

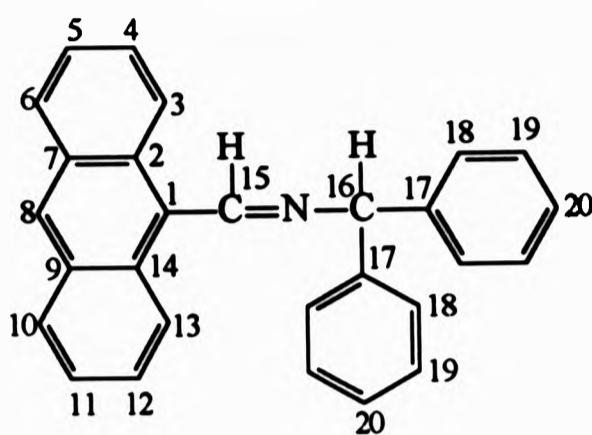
<sup>†</sup> The doublet of doublets was not resolved well enough to measure the smaller coupling constant

**Table II.18**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **15** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
12-C	79.23, (s)
7-C, 8-C	124.63, 125.05, (2 x s)
9-C	125.93, (s)
16-C	126.92, (s)
4-C	127.14, (s)
15-C	127.61, (s)
14-C	128.43, (s)
6-C	128.48, (s)
3-C	129.78, (s)
2-C	131.14, (s)
5-C, 10-C	131.28, 131.37, (2 x s) <sup>†</sup>
1-C	133.72(s) <sup>†</sup>
13-C	143.97(s) <sup>†</sup>
11-C	160.85(s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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**Table II.19**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **16** in  $\text{CDCl}_3$

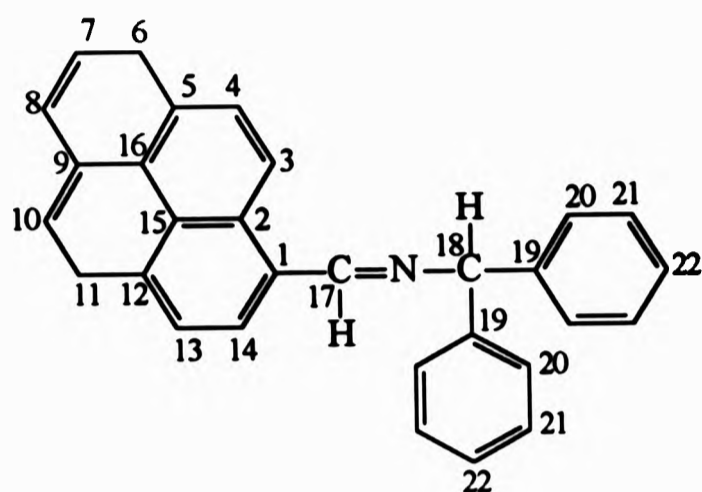
Proton	Chemical shifts, Coupling constants
16-H	5.83, (s)
2 x Ph-H	7.20-7.41, (m)
3-H, 6-H, 10-H, 13-H	7.50-7.53, (m)
5-H, 11-H	7.86, 7.90, (m)
8-H	8.33, (s)
4-H, 12-H	8.37, 8.43, (m)
15-H	9.49, (s)

**Table II.20**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **16** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
16-C	80.29, (s)
5-C, 11-C	125.01, (s)
4-C, 12-C	125.35, (s)
6-C, 10-C	126.82, (s)
3-C, 13-C	127.32, (s)
19-C	127.94, (s)
18-C	128.80, (s)
20-C	128.98, (s)
8-C	129.69, (s)
17-C	130.29, (s) <sup>†</sup>
2-C, 7-C, 9-C, 14-C	121.39, (s) <sup>†</sup>
1-C	143.94, (s) <sup>†</sup>
15-C	160.70, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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**Table II.21**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for 17 in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
H-18	5.80, (s)
2 x Ph-H	7.23-7.57, (m)
6-H, 7-H, 8-H, 10-H, 11-H	7.98-8.18, (m)
13-H	8.14, (d), $^3J_{\text{HH}}$ 8.07
4-H	8.20, (d), $^3J_{\text{HH}}$ 9.21
14-H	8.65, (d)
3-H	9.01, (d)
17-H	9.42 (s)

**Table II.22**  $^{13}\text{C}$  NMR chemical shifts<sup>†</sup> (ppm) and coupling constants (Hz) for 17 in  $\text{CDCl}_3$

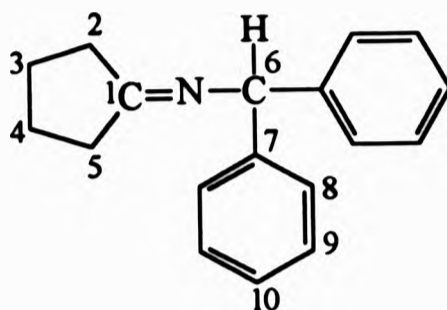
Carbon	Chemical shifts, Coupling constants
18-C	79.27, (s)
3-C, 4-C, 6-C, 7-C, 8-C, 10-C, 11-C, 13-C, 14-C	122.84, 124.84, 125.64, 125.87, 126.08, 127.10, 127.43, 128.70, (8 x s)
22-C	127.04, (s)
21-C	127.74, (s)
20-C	128.70, (s)
1-C, 2-C, 5-C, 9-C, 12-C	124.59, 130.02, 130.57, 131.22, 132.91, (5 x s) <sup>‡</sup>
19-C	144.14, (s) <sup>‡</sup>
17-C	159.84, (s)

<sup>†</sup> Assuming 15-C and 16-C have long relaxation times and were not observed

<sup>‡</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



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**Table II.23**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **18** in  $\text{CDCl}_3$

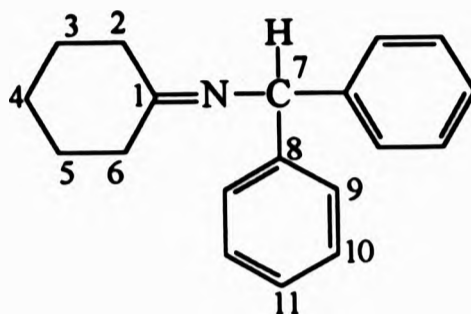
Proton	Chemical shifts, Coupling constants
3- $\text{CH}_2$ , 4- $\text{CH}_2$	1.64-1.77, (m)
2- $\text{CH}_2$ , 5- $\text{CH}_2$	2.21-2.27, 2.41-2.47, (2 x m)
6-H	5.46, (s)
Ph-H	7.12-7.36, (m)

**Table II.24**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **18** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
3-C, 4-C	24.11, 24.93, (2 x s)
2-C, 5-C	29.43, 36.72, (2 x s)
6-C	70.58, (s)
10-C	126.66, (s)
9-C	127.60, (s)
8-C	128.32, (s)
7-C	144.27, (s) <sup>†</sup>
1-C	180.80, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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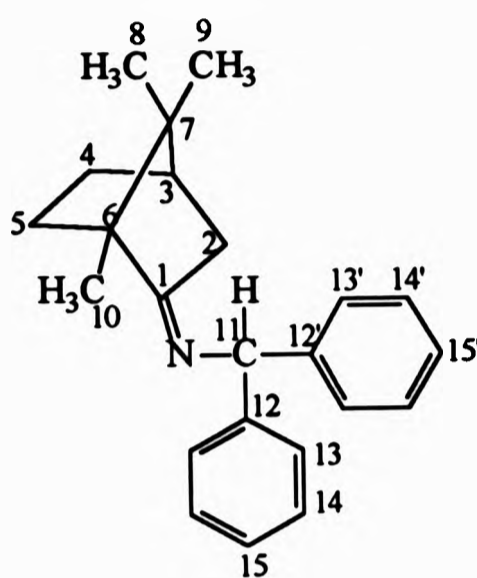
**Table II.25**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **19** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
3- $\text{CH}_2$ , 4- $\text{CH}_2$ , 5- $\text{CH}_2$	1.61-1.90, (m)
2- $\text{CH}_2$ , 6- $\text{CH}_2$	2.36-2.58, (m)
7-H	5.91, (s)
2x Ph-H	7.26-7.51, (m)

**Table II.26**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **19** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
4-C	25.94, (s)
3-C, 5-C	26.83, 27.78, (2 x s)
6-C	29.83, (s)
2-C	40.26, (s)
7-C	66.49, (s)
11-C	126.46, (s)
10-C	127.57, (s)
9-C	128.26, (s)
8-C	144.93, (s) <sup>†</sup>
1-C	173.20, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table II.27**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **20** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
8- $\text{CH}_3$ , 9- $\text{CH}_3$	0.62, 0.90, (2 x s)
10- $\text{CH}_3$	1.08, (s)
4- $\text{CH}_2$	1.23-1.42, (m)
3-CH, 5- $\text{CH}_2$ 1H of 2- $\text{CH}_2$	1.59-20.5, (m)
1H of 2- $\text{CH}_2$	2.25-2.36, (m)
11-H	5.43, (s)
2 x Ph-H	7.09-7.40, (m)

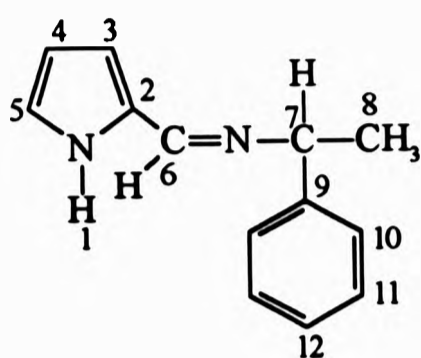
**Table II.28**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **20** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
10- $\text{CH}_3$	11.54, (s)
8- $\text{CH}_3$ , 9- $\text{CH}_3$	19.00, 19.48, (2 x s)
4-C	27.41, (s)
5-C	31.95, (s)
2-C	35.83, (s)
3-C	42.99, (s) <sup>†</sup>
7-C	47.03, (s)
6-C	53.93, (s)
11-C	68.18, (s) <sup>†</sup>
15-C, 15'-C	126.34, (s)
14-C, 14'-C	127.39, (s)
13-C, 13'-C	128.35, 128.43, (2 x s)
12-C, 12'-C	145.00, 144.91, (2 x s) <sup>†</sup>
1-C	181.36, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

<sup>‡</sup> CH carbons signals were identified by a DEPT-90 experiment

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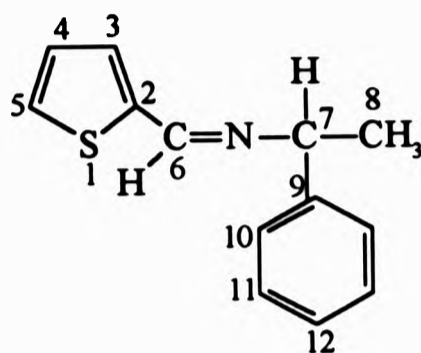
**Table II.29**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **21** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
$\text{CH}_3$	1.54, (d), $^3J_{\text{MeH}}$ 6.68
7-H	4.46, (q)
4-H	6.15, (dd), $^3J_{\text{H4-H5}}$ 3.16, $3J_{\text{H3-H4}}$ 3.34
5-H	6.46, (dd), $^4J_{\text{H3-H5}}$ 1.63
3-H	6.62, (dd)
Ph-H	7.18-7.35, (m)
6-H	8.14, (s)
1-H	9.40, (br s)

**Table II.30**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **21** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
$\text{CH}_3$	24.24, (s)
7-C	68.87, (s)
4-C	109.49, (s)
5-C	114.63, (s)
3-C	122.09, (s)
11-C	126.64, (s)
12-C	126.81, (s)
10-C	128.37, (s)
9-C	130.06, (s) <sup>†</sup>
2-C	144.88, (s) <sup>†</sup>
6-C	150.76, (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



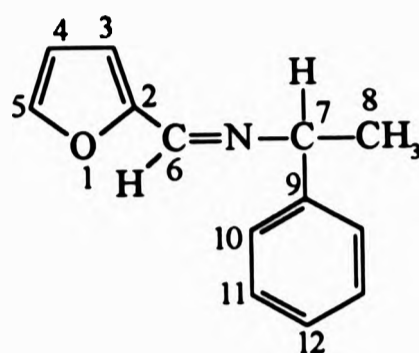
**Table II.31**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **22** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
$\text{CH}_3$	1.50, (d), $^3J_{\text{MeH7}}$ 6.70
7-H	4.38, (q)
4-H	6.85, (dd), $^3J_{\text{H3-H4}}$ 4.95 and $^3J_{\text{H4-H5}}$ 3.67
Ph-H, 3-H, 5-H	7.10-7.41, (m)
6-H	8.24, (s)

**Table II.32**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **22** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
$\text{CH}_3$	24.76, (s)
7-C	68.90, (s)
11-C	126.49, (s)
4-C	126.69, (s)
12-C	127.14, (s)
10-C	128.28, (s)
3-C	128.63, (s)
5-C	130.29, (s)
9-C	142.58, (s) <sup>†</sup>
2-C	144.90, (s) <sup>†</sup>
6-C	152.48, (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table II.33**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **23** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
$\text{CH}_3$	1.60, (d) $^3J_{\text{MeH7}}$ 6.69
7-H	3.00, (q)
4-H	6.40, (dd), $^3J_{\text{H3-H4}}$ 3.42 and $^3J_{\text{H4-H5}}$ 1.80
3-H	6.69, (dd) <sup>†</sup>
Ph-H	7.14-7.40, (m)
5-H	7.46, (dd) <sup>†</sup>
6-H	8.10, (s)

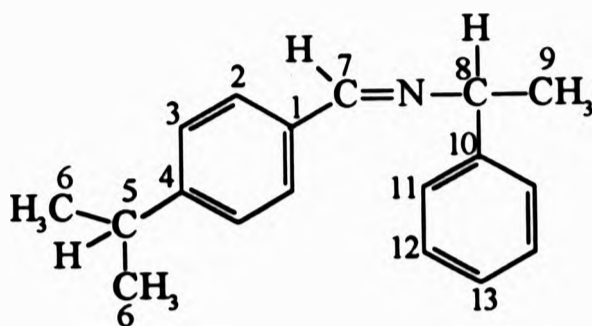
<sup>†</sup> The spectrum was not resolved well enough to measure the coupling constants



**Table II.34**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **23** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
$\text{CH}_3$	24.46, (s)
7-C	69.61, (s)
4-C	111.56, (s)
3-C	114.28, (s)
11-C	126.70, (s)
12-C	126.80, (s)
10-C	128.50, (s)
9-C	144.56, (s) <sup>†</sup>
5-C	144.67, (s)
6-C	148.35, (s)
2-C	151.55, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



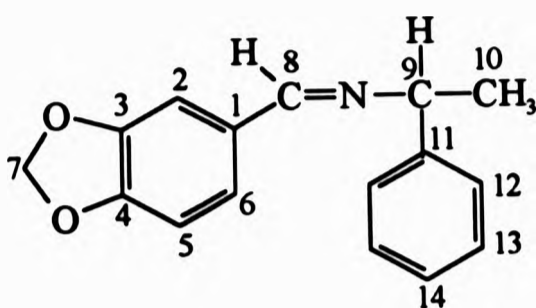
**Table II.35**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **24** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
2 x 6- $\text{CH}_3$	1.21, (d), $^3J_{\text{MeH}}$ 6.85
9- $\text{CH}_3$	1.56, (d), $J_{\text{H8-H9}}$ 6.65
5-H	2.87, (septet)
8-H	4.48, (q)
Ph-H	7.06-7.38, (m)
3-H	7.41, (d), $J_{\text{H2-H3}}$ 7.11
2-H	7.70, (d)
7-H	8.29, (s)

**Table II.36**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **24** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
6-C	23.79, (s)
9-C	24.05, (s)
5-C	34.05, (s)
8-C	69.57, (s)
13-C	126.68, (s)
11-C, 12-C	126.88, (s)
2-C, 3-C	128.31, (s)
4-C	134.19, (s) <sup>†</sup>
10-C	145.29, (s) <sup>†</sup>
1-C	156.00 (s) <sup>†</sup>
7-C	159.21, (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



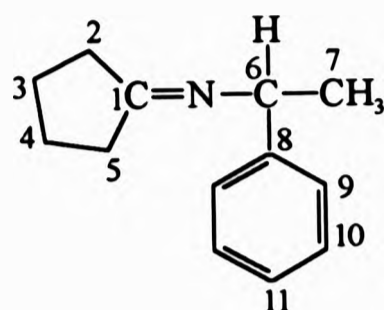
**Table II.37**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **25** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
10-H	1.54, (d), $^3J_{\text{MeH}}$ 6.64
9-H	4.43, (q)
7-H	5.83, (s)
5-H	6.73, (d), $J_{\text{H5-H6}}$ 7.93
6-H	7.04, (dd), $J_{\text{H2-H6}}$ 1.61
14-H	7.18, (m)
13-H	7.29, (m)
2-H, 12-H	7.37, (m)
8-H	8.16, (s)

**Table II.38**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **25** in  $\text{CDCl}_3$

Carbon	Chemical shifts, Coupling constants
10-C	24.93, (s)
9-C	69.34, (s)
7-C	101.26, (s)
5-C, 6-C	106.68, 107.85, (2 x s)
14-C	124.30, (s)
13-C	126.54, (s)
2-C	126.70, (s)
12-C	128.34, (s)
11-C	131.23, (s) <sup>†</sup>
3-C, 4-C	145.35, 149.69 (2 x s) <sup>†</sup>
1-C	148.13, (s) <sup>†</sup>
8-C	158.39, (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table II.39**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **26** in  $\text{CDCl}_3$

Proton	Chemical shifts, Coupling constants
$\text{CH}_3$	1.46, (d), $^3J_{\text{MeH6}}$ 6.60
2-H, 3-H, 4-H, 5-H	1.60-2.51, (m)
6-H	4.40, (q)
Ph-H	7.18-7.35, (m)

**Table II.40**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **26** in  $\text{CDCl}_3$

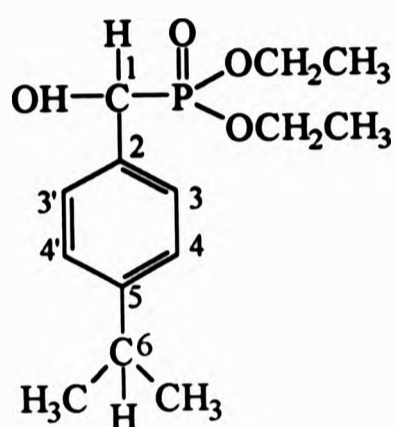
Carbon	Chemical shifts, Coupling constants
$\text{CH}_3$	24.69, (s)
3-C, 4-C	24.07, 24.95, (2 x s)
2-C, 5-C	28.86, 36.59, (2 x s)
6-C	61.96, (s)
11-C	126.51, (s)
10-C	126.59, (s)
9-C	128.30, (s)
8-C	145.67, (s) <sup>†</sup>
1-C	179.06, (s)

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

## APPENDIX III

### <sup>1</sup>H and <sup>13</sup>C NMR Spectral Data of the Diethyl Phosphonate Esters

3



**Table III.1**

<sup>1</sup>H NMR chemical shifts (ppm) and coupling constants (Hz) for **3** in CDCl<sub>3</sub>

Proton	Chemical shift, Coupling constant
2 x CHCH <sub>3</sub> and 2 x CH <sub>2</sub> CH <sub>3</sub>	1.16-1.31, (m)
6-H	2.87, (septet), <sup>3</sup> J <sub>HH</sub> 6.95
OH	3.78, (dd), <sup>3</sup> J <sub>HH</sub> 5.03
2 x CH <sub>2</sub>	3.87-4.13, (m)
1-H	4.96, (dd), <sup>2</sup> J <sub>PH</sub> 10.38
Ph-H	7.18-7.48, (m)

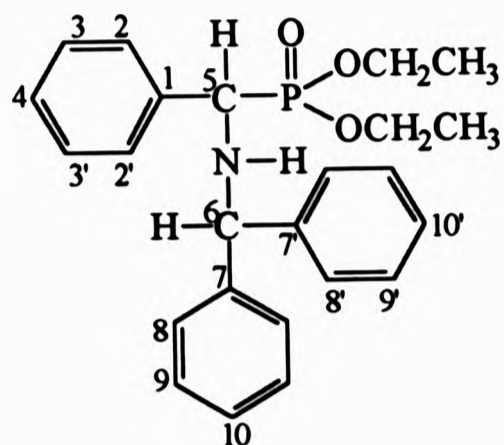
**Table III.2**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **3** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.30, (d), $^3J_{\text{PC}}$ 5.53
$\text{CH}_3$	16.35, (d), $^3J_{\text{PC}}$ 5.53
$\text{CH}_2\text{CH}$	23.98, (s)
$\text{CHCH}_3$	33.83, (s)
$\text{CH}_2$	62.96, (d), $^4J_{\text{PC}}$ 6.68
$\text{CH}_2$	63.14, (d), $^4J_{\text{PC}}$ 7.42
CHOH	70.43, (d), $^1J_{\text{PC}}$ 161.52
4-C, 4'-C	126.14, (d), $^4J_{\text{PC}}$ 2.45
3-C, 3'-C	127.28, (d), $^3J_{\text{PC}}$ 5.79
5-C	134.55, (s) <sup>†</sup>
1-C	148.42, (d), $^2J_{\text{PC}}$ 3.02 <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



4



**Table III.3**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **4** in  $\text{CDCl}_3$

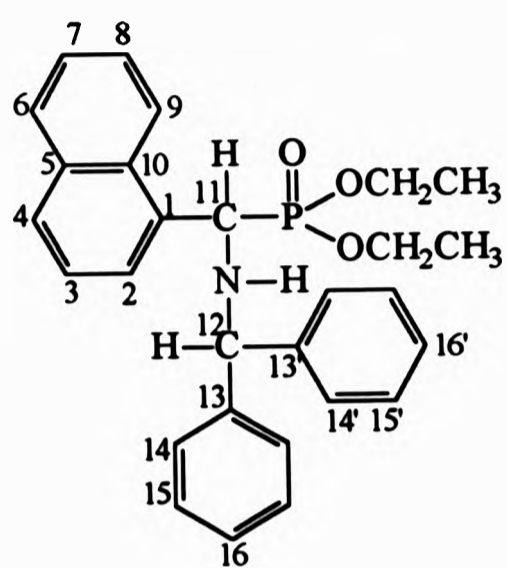
Proton	Chemical shift, Coupling constant
$\text{CH}_3$	1.07, (d of t), $^3J_{\text{HH}}$ 7.06 and $^4J_{\text{PH}}$ 0.57
$\text{CH}_3$	1.36, (d of t), $^3J_{\text{HH}}$ 7.07 and $^4J_{\text{PH}}$ 0.56
NH	2.56, (br s)
H of $\text{CH}_2$	3.62-3.78, (m)
H of $\text{CH}_2$	3.83-3.99, (m)
5-H	3.93, (d), $^2J_{\text{HP}}$ 22.47
$\text{CH}_2$	4.12-4.29, (m)
6-H	4.68, (d), $^2J_{\text{PH}}$ 1.13
Ar-H	7.14-7.40, (m)

**Table III.4**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **4** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.14, (d), $^3J_{\text{PC}}$ 6.23
$\text{CH}_3$	16.29, (d), $^3J_{\text{PC}}$ 6.29
5-C	57.99, (d), $^1J_{\text{PC}}$ 155.29
$\text{CH}_2$	62.59, (d), $^2J_{\text{PC}}$ 6.92
$\text{CH}_2$	62.97, (d), $^2J_{\text{PC}}$ 7.23
6-C	63.56, (d), $^3J_{\text{PC}}$ 17.04
3-C, 3'-C	127.11, 127.29 (2 x s)
4-C	127.92, (s)
10-C	128.38, (s)
9-C	128.56, (s)
2-C, 2'-C	128.50, 128.66, (2 x s)
1-C	135.89, (d), $^2J_{\text{PC}}$ 1.57 <sup>†</sup>
7-C, 7'-C	142.00, 143.66, (2 x s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

5



**Table III.5**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **5** in  $\text{CDCl}_3$

Proton	Chemical shift, Coupling constant
$\text{CH}_3$	0.76, (t), $^3J_{\text{HH}}$ 7.06
$\text{CH}_3$	1.36, (t), $^3J_{\text{HH}}$ 7.06
NH	2.74, (br s)
H of $\text{CH}_2$	3.34-3.43, (m)
H of $\text{CH}_2$	3.70-3.79, (m)
$\text{CH}_2$	4.14-4.35, (m)
12-H	4.65, (s)
11-H	4.86, (br d), $^2J_{\text{HP}}$ 23.01
Ar-H	7.13-7.87, (m)

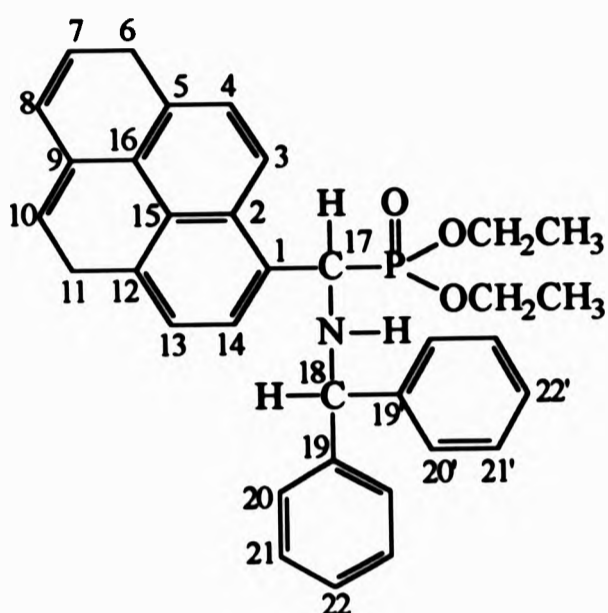
**Table III.6**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **5** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	15.73, (d), $^3J_{\text{PC}}$ 5.85
$\text{CH}_3$	16.43, (d), $^3J_{\text{PC}}$ 6.10
11-C	52.05, (d), $^1J_{\text{PC}}$ 155.03
$\text{CH}_2$	62.46, (d), $^2J_{\text{PC}}$ 6.98
$\text{CH}_2$	62.90, (d), $^2J_{\text{PC}}$ 6.92
12-C	63.76, (d), $^3J_{\text{PC}}$ 16.67
2-C	122.99, (s)
3-C	125.36, (d), $^4J_{\text{PC}}$ 3.33
7-C, 8-C	125.46, 125.77, (2 x s)
9-C	128.28, (s)
16-C, 16'-C	126.48, 127.19, (2 x s)
15-C, 15'-C	127.03, 127.84, (2 x s)
14-C, 14'-C	128.25, 128.36, (2 x s)
4-C, 6-C	128.53, 128.55, (2 x s)
1-C	132.14, (s) <sup>†</sup>
5-C	132.24, (s) <sup>†</sup>
10-C	133.55 (d) <sup>†‡</sup>
13-C, 13'-C	142.09, 143.50. (2 x s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

<sup>‡</sup> The spectrum was not resolved well enough to measure the coupling constant

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**Table III.7**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **6** in  $\text{CDCl}_3$

Proton	Chemical shift, Coupling constant
$\text{CH}_3$	0.75, (t), $^3J_{\text{HH}}$ 7.05
$\text{CH}_3$	1.38, (t), $^3J_{\text{HH}}$ 7.04
NH	3.02, (br s)
H of $\text{CH}_2$	3.35-3.45, (m)
H of $\text{CH}_2$	3.67-3.80, (m)
$\text{CH}_2$	4.18-4.39, (m)
18-H	4.61, (s)
17-H	5.41, (br dd), $^2J_{\text{PH}}$ 22.80 <sup>†</sup>
2 x Ph-H	7.10-7.33, (m)
3-H	7.76, (br m)
4-H	7.93, (br d) <sup>a</sup>
7-H	7.96, (t), $^3J_{\text{HH}}$ 7.61
10-H, 11-H	8.05, (m)
6-H, 8-H	8.13, (m)
13-H	8.26, (br d), $^3J_{\text{HH}}$ 7.97
14-H	8.45, (br m)

<sup>†</sup> The spectrum was not resolved well enough to measure the coupling constant

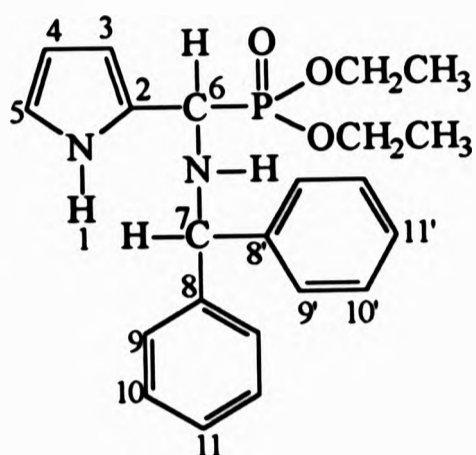
**Table III.8**  $^{13}\text{C}$  NMR chemical shifts<sup>†</sup> (ppm) and coupling constants (Hz) for **6** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.15, (d), $^3J_{\text{PC}}$ 5.66
$\text{CH}_3$	16.77, (d), $^3J_{\text{PC}}$ 5.91
17-C	52.95, (br d), $^1J_{\text{PC}}$ 158.37
$\text{CH}_2$	62.83, (d), $^2J_{\text{PC}}$ 6.79
$\text{CH}_2$	63.35, (d), $^2J_{\text{PC}}$ 6.98
18-C	64.09, (d), $^3J_{\text{PC}}$ 16.98
3-C	122.65, (br s)
4-C	124.86, (s)
14-C	124.95, (br s)
6-C, 7-C, 11-C, 13-C	125.15, 125.42, 125.62, 126.12, (4 x s)
22-C, 22'-C	127.28, 127.55, (2 x s)
8-C, 10-C	127.63, 127.70, (2 x s)
21-C, 21'-C	127.34, 128.23, (2 x s)
20-C, 20'-C	128.55, 128.74, (2 x s)
12-C, 5-C	130.02, 130.80, (2 x s) <sup>‡</sup>
1-C <sup>§</sup>	130.17, (d), $^2J_{\text{PC}}$ 7.67 <sup>‡</sup>
2-C <sup>§</sup>	131.02, (d), $^3J_{\text{PC}}$ 2.70 <sup>‡</sup>
9-C	131.48, (s) <sup>‡</sup>
19-C, 19'-C	142.26, 143.75 (2 x s) <sup>‡</sup>

<sup>†</sup> Assuming the 15-C and 16-C have very long relaxation times and were not observed

<sup>‡</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

<sup>§</sup> These two carbon signals could be assigned the other way round



**Table III.9**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **27** in  $\text{CDCl}_3$

Proton	Chemical shift, Coupling constant
$\text{CH}_3$	1.01, (t), $^3J_{\text{HH}}$ 6.96
$\text{CH}_3$	1.33, (t), $^3J_{\text{HH}}$ 7.06
NH	2.67, (br s)
H of $\text{CH}_2$	3.41-3.51, (m)
H of $\text{CH}_2$	3.67-3.76, (m)
6-H	3.94, (d), $^2J_{\text{PH}}$ 22.52
$\text{CH}_2$	4.00-4.21, (m)
7-H	4.81, (s)
4-H	6.01, (m) <sup>†</sup>
3-H	6.13, (m) <sup>†</sup>
5-H	6.76, (m) <sup>†</sup>
2 x Ph-H	7.13-7.41, (m)
1-H	9.78, (br s)

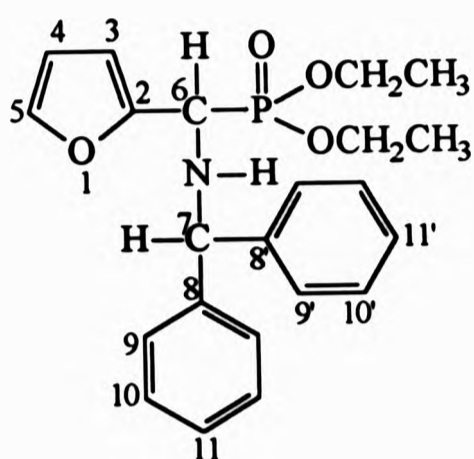
<sup>†</sup> The spectrum was not resolved well enough to measure the coupling constants

**Table III.10**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **27** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.14, (d), $^3J_{\text{PC}}$ 6.89
$\text{CH}_3$	16.56, (d), $^3J_{\text{PC}}$ 6.16
6-C	51.53, (d), $^1J_{\text{PC}}$ 161.83
$\text{CH}_2$	62.68, (d), $^2J_{\text{PC}}$ 6.79
$\text{CH}_2$	63.07, (d), $^2J_{\text{PC}}$ 6.79
7-C	63.87, (d), $^3J_{\text{PC}}$ 17.17
4-C	107.68, (s)
3-C	109.52, (d), $^4J_{\text{PC}}$ 9.56
5-C	118.62, (s)
2-C	125.27, (d), $^2J_{\text{PC}}$ 3.40 <sup>†</sup>
11-C, 11'-C	126.88, 127.16, (2 x s)
10-C, 10'-C	127.29, 127.90, (2 x s)
9-C, 9'-C	128.24, 128.48, (2 x s)
8-C, 8'-C	142.56, 144.16, (2 x s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment





**Table III.11**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **28** in  $\text{CDCl}_3$

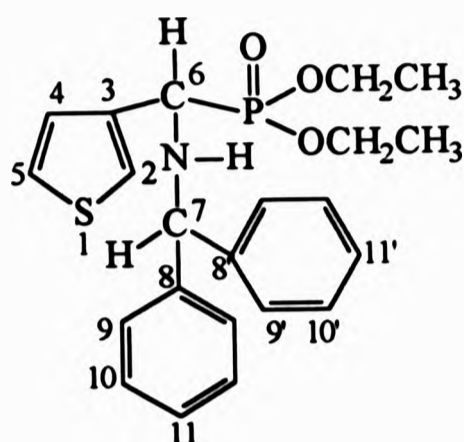
Proton	Chemical shift, Coupling constant
$\text{CH}_3$	1.15, (t), $^3J_{\text{HH}}$ 6.97
$\text{CH}_3$	1.36, (t), $^3J_{\text{HH}}$ 7.19
NH	2.53, (br s)
H of $\text{CH}_2$	3.80-4.00, (m)
H of $\text{CH}_2$	4.01-4.09, (m)
6-H	4.04, (d), $^2J_{\text{HP}}$ 23.73
$\text{CH}_2$	4.17-4.33, (m)
7-H	4.74, (s)
4-H	6.29, (m) <sup>†</sup>
3-H	6.38, (m) <sup>†</sup>
2 x Ph-H, 5-H	7.15-7.44, (m)

<sup>†</sup> The spectrum was not resolved well enough to measure the coupling constants

**Table III.12**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **28** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.28, (d), $^3J_{\text{PC}}$ 5.85
$\text{CH}_3$	16.55, (d), $^3J_{\text{PC}}$ 6.35
6-C	52.02, (d), $^1J_{\text{PC}}$ 163.0
$\text{CH}_2$	62.19, (d), $^2J_{\text{PC}}$ 6.86
$\text{CH}_2$	62.53, (d), $^2J_{\text{PC}}$ 6.79
7-C	64.47, (d), $^3J_{\text{PC}}$ 16.29
3-C	109.48, (d), $^3J_{\text{PC}}$ 7.86
4-C	110.54, (s)
5-C	127.22, (s)
11-C, 11'-C	127.38, 127.77, (2 x s)
10-C, 10'-C	128.46, 128.58, (2 x s)
9-C, 9'-C	142.38, 142.68, (2 x s)
8-C, 8'-C	141.89, 143.59, (2 x s) <sup>†</sup>
2-C	149.88 (d), $^2J_{\text{PC}}$ 2.70 <sup>†</sup>

<sup>†</sup> Quaternary carbons were identified by a DEPT-135 experiment



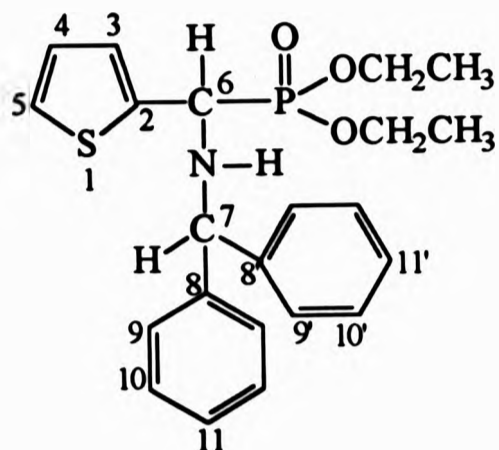
**Table III.13**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **29** in  $\text{CDCl}_3$

Proton	Chemical shift, Coupling constant
$\text{CH}_3$	1.11, (d of t), $^3J_{\text{HH}}$ 7.05 and $^4J_{\text{PH}}$ 0.47
$\text{CH}_3$	1.36, (d of t), $^3J_{\text{HH}}$ 7.05 and $^4J_{\text{PH}}$ 0.46
NH	2.33, (br s)
H of $\text{CH}_2$	3.69-3.84, (m)
H of $\text{CH}_2$	3.88-4.03, (m)
6-H	4.05 (d), $^2J_{\text{PH}}$ 22.01
$\text{CH}_2$	4.10-4.33, (m)
7-H	4.74, (s)
Ph-H, 5-H, 4-H, 2-H	7.07-7.40, (m)

**Table III.14**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **29** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.35, (d), $^3J_{\text{PC}}$ 6.14
$\text{CH}_3$	16.69, (d), $^3J_{\text{PC}}$ 5.82
6-C	53.74, (d), $^1J_{\text{PC}}$ 157.9
$\text{CH}_2$	62.79, (d), $^2J_{\text{PC}}$ 6.82
$\text{CH}_2$	63.20, (d), $^2J_{\text{PC}}$ 6.84
7-C	64.05, (d), $^3J_{\text{PC}}$ 16.35
2-C	123.90, (d), $^3J_{\text{PC}}$ 10.38
5-C	126.16, (s)
11-C, 11'-C	127.29, 127.44, (2 x s)
10-C, 10'-C	127.37, 127.91, (2 x s)
4-C	127.56, (d), $^3J_{\text{PC}}$ 3.84
9-C, 9'-C	128.55, 128.72, (2 x s)
3-C	137.08 (s) <sup>†</sup>
8-C and 8'-C	142.21 and 143.77 (2 x s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table III.15**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **30** in  $\text{CDCl}_3$

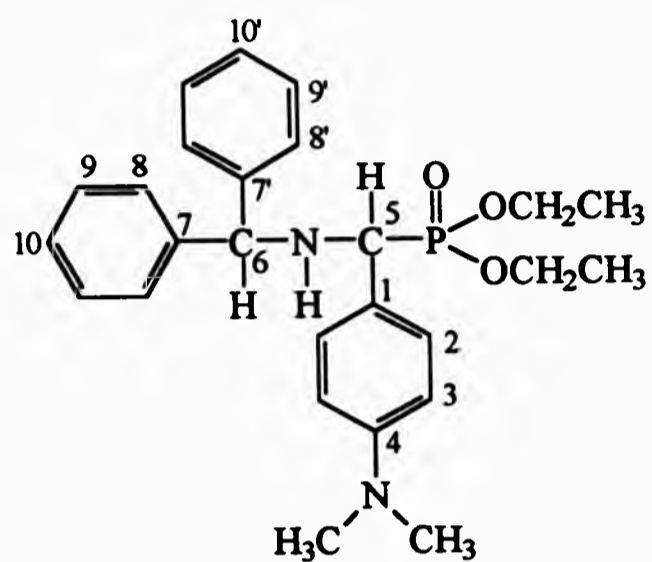
Proton	Chemical shift, Coupling constant
$\text{CH}_3$	1.15, (t), $^3J_{\text{HH}}$ 7.01
$\text{CH}_3$	1.35, (t), $^3J_{\text{HH}}$ 7.12
NH	2.76, (br s)
H of $\text{CH}_2$	3.80-3.93, (m)
H of $\text{CH}_2$	3.97-4.09, (m)
6-H	4.21, (d), $^2J_{\text{PH}}$ 22.40
$\text{CH}_2\text{CH}_3$	4.13-4.30, (m)
7-H	4.86, (s)
3-H and 4-H	6.98-7.02, (m)
2 x Ph-H and 5-H	7.02-7.41, (m)

**Table III.16**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **30** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.26, (d), $^3J_{\text{PC}}$ 6.23
$\text{CH}_3$	16.55, (d), $^3J_{\text{PC}}$ 6.23
6-C	53.45, (d), $^1J_{\text{PC}}$ 130.51
$\text{CH}_2$	62.96, (d), $^2J_{\text{PC}}$ 6.73
$\text{CH}_2$	63.31, (d), $^2J_{\text{PC}}$ 6.98
7-C	63.79, (d), $^3J_{\text{PC}}$ 15.79
3-C	125.51, (d), $^3J_{\text{PC}}$ 3.21
11-C, 11'-C	126.96, 127.21 (2 x s)
4-C	127.08, (s)
5-C	127.43, (s)
10-C, 10'-C	127.88, 128.65 (2 x s)
9-C, 9'-C	128.43, 128.85 (2 x s)
2-C	139.64, (s) <sup>†</sup>
8-C, 8'-C	141.81, 143.45 (2 x s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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**Table III.17**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **31** in  $\text{CDCl}_3$

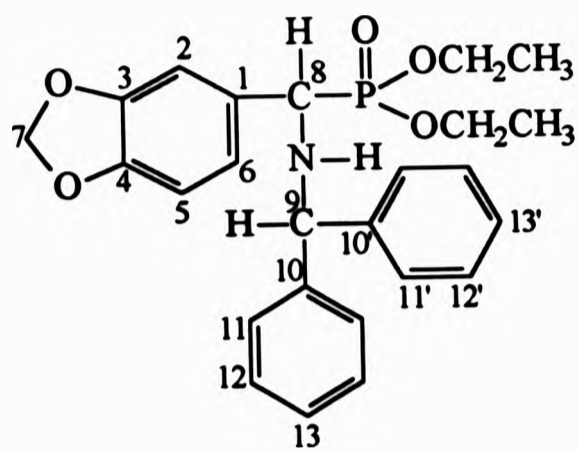
Proton	Chemical shift, Coupling constant
$\text{CH}_3$	1.07, (t), $^3J_{\text{HH}}$ 7.11
$\text{CH}_3$	1.35, (t), $^3J_{\text{HH}}$ 7.05
$\text{N}(\text{CH}_3)_2$	2.92, (s)
H of $\text{CH}_2$	3.62-3.75, (m)
5-H	3.83, (d), $^2J_{\text{HP}}$ 22.05
H of $\text{CH}_2$	3.85-3.95, (m)
$\text{CH}_2$	4.14-4.29, (m)
6-H	4.72, (s)
3-H	6.70, (d), $^3J_{\text{H}_2\text{-H}_3}$ 8.56
2 x Ph-H, 2-H	7.13-7.38, (m)

**Table III.18**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **31** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.26, (d), $^3J_{\text{PC}}$ 5.79
$\text{CH}_3$	16.57, (d), $^3J_{\text{PC}}$ 5.91
$\text{N}(\text{CH}_3)_2$	40.40, (s)
5-C	57.22, (d), $^1J_{\text{PC}}$ 157.36
$\text{CH}_2$	62.54, (d), $^2J_{\text{PC}}$ 6.86
$\text{CH}_2$	62.80, (d), $^2J_{\text{PC}}$ 6.86
6-C	63.35, (d), $^3J_{\text{PC}}$ 17.23
3-C	112.37, (d), $^4J_{\text{PC}}$ 1.76 <sup>†</sup>
4-C	122.86, (d), $^5J_{\text{PC}}$ 1.50 <sup>†</sup>
10-C, 10'-C	126.99, 127.16, (2 x s)
9-C, 9'-C	127.27, 127.88, (2 x s)
8-C, 8'-C	128.32, 128.48, (2 x s)
2-C	129.38, (d), $^3J_{\text{PC}}$ 6.54
7-C, 7'-C	142.25, 143.98 (2 x s)
1-C	150.17, (d), $^2J_{\text{PC}}$ 1.87 <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment





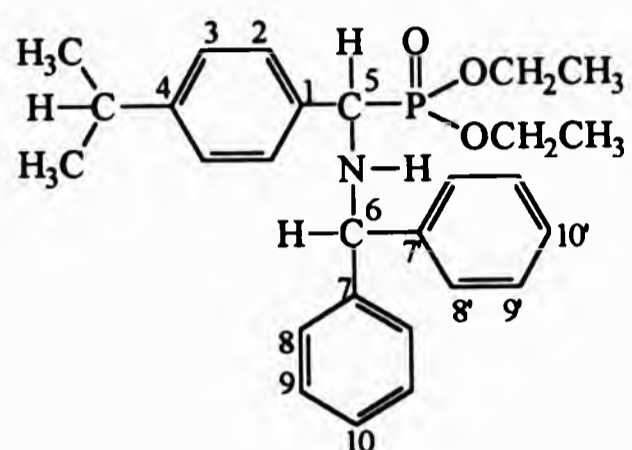
**Table III.19**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) **32** in  $\text{CDCl}_3$

Proton	Chemical shift, Coupling constant
$\text{CH}_3$	1.12, (d of t), $^3J_{\text{HH}}$ 7.03 and $^4J_{\text{PH}}$ 0.43
$\text{CH}_3$	1.35, (d of t), $^3J_{\text{HH}}$ 6.98 and $^4J_{\text{PH}}$ 0.43
NH	2.52, (br s)
H of $\text{CH}_2$	3.76-3.90, (m)
8-H	3.84 (d), $^2J_{\text{HP}}$ 20.07
H of $\text{CH}_2$	3.93-4.14, (m)
$\text{CH}_2$	4.19-4.23, (m)
9-H	4.70, (s)
7- $\text{CH}_2$	5.93, (s)
5-H, 6-H	6.74-6.80, (m)
2-H	6.90, (m)
2 x Ph-H	7.15-7.35, (m)

**Table III.20**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **32** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.28, (d), $^3J_{\text{PC}}$ 5.97
$\text{CH}_3$	16.57, (d), $^3J_{\text{PC}}$ 5.85
8-C	57.69, (d), $^1J_{\text{PC}}$ 156.70
$\text{CH}_2$	62.65, (d), $^2J_{\text{PC}}$ 7.25
$\text{CH}_2$	63.02, (d), $^2J_{\text{PC}}$ 7.33
9-C	63.56, (d), $^3J_{\text{PC}}$ 16.86
7- $\text{CH}_2$	101.92, (s)
5-C	108.22, (d), $^4J_{\text{PC}}$ 1.76
6-C	108.71, (d), $^3J_{\text{PC}}$ 5.41
13-C, 13'-C	122.23, 122.35, (2 x s)
12-C, 12'-C	127.15, 127.25, (2 x s)
11-C, 11'-C	127.34, 127.85, (2 x s)
2-C	128.51, (d), $^3J_{\text{PC}}$ 12.39
1-C	129.68, (s) <sup>†</sup>
10-C, 10'-C	142.01, 143.69, (2 x s) <sup>†</sup>
4-C	147.96 (s) <sup>†</sup>
3-C	147.99 (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table III.21**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **33** in  $\text{CDCl}_3$

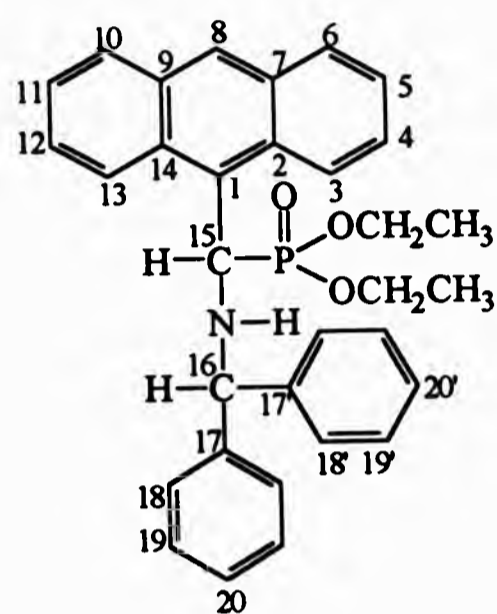
Proton	Chemical shift, Coupling constant
$\text{CH}_3$	1.01, (t), $^3J_{\text{HH}}$ 7.07
$\text{CHCH}_3$	1.25, (d), $^3J_{\text{HH}}$ 7.01
$\text{CH}_3$	1.33, (t), $^3J_{\text{HH}}$ 7.05
NH	2.59, (br s)
$\text{CHCH}_3$	2.89, (septet)
H of $\text{CH}_2$	3.61-3.77, (m)
H of $\text{CH}_2$	3.82-3.97, (m)
5-H	3.91, (d), $^2J_{\text{PH}}$ 22.01
$\text{CH}_2$	4.07-4.27, (m)
6-H	4.71, (s)
2-H, 3-H, 2 x Ph-H	7.10-7.37, (m)

**Table III.22**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **33** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	16.42, (d), $^3J_{\text{PC}}$ 5.84
$\text{CH}_3$	16.84, (d), $^3J_{\text{PC}}$ 5.99
$\text{CH}(\text{CH}_3)_2$	24.00, (s)
$\underline{\text{C}}\text{H}(\text{CH}_3)_2$	33.62, (s)
5-C	57.75 (d), $^1J_{\text{PC}}$ 155.6
$\text{CH}_2$	62.86, (d), $^2J_{\text{PC}}$ 6.37
$\text{CH}_2$	63.21, (d), $^2J_{\text{PC}}$ 7.20
6-C	63.89, (d), $^3J_{\text{PC}}$ 17.05
2-C	126.87, (d), $^3J_{\text{PC}}$ 2.14
3-C	127.37, (s)
10-C, 10'-C	127.56, 128.18, (2 x s)
9-C, 9'-C	128.66, 128.76, (2 x s)
8-C, 8'-C	128.83, 128.86, (2 x s)
4-C	133.33, (s) <sup>†</sup>
7-C, 7'-C	142.47, 144.10 (2 x s) <sup>†</sup>
1-H	148.82, (d), $^2J_{\text{PC}}$ 3.14 <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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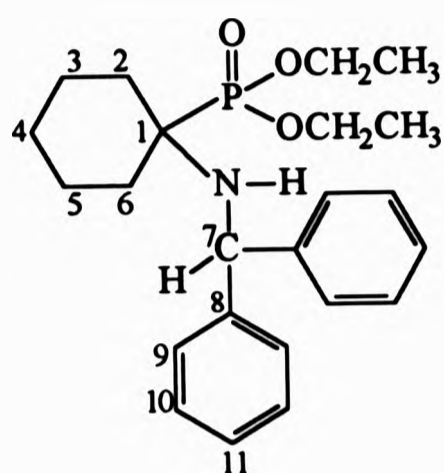
**Table III.23**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **34** in  $\text{CDCl}_3$

Proton	Chemical shift, Coupling constant
$\text{CH}_3$	0.62, (t), $^3J_{\text{HH}}$ 7.10
$\text{CH}_3$	1.35, (t), $^3J_{\text{HH}}$ 7.12
NH	3.04, (br s)
H of $\text{CH}_2$	3.27-3.37, (m)
H of $\text{CH}_2$	3.61-3.71, (m)
$\text{CH}_2$	4.12-4.31, (m)
16-H	4.41, (s)
15-H	5.62, (d), $^2J_{\text{PH}}$ 26.78
Ar-H	7.00-7.57, (m)
6-H, 10-H	7.93-7.98, (2 x d)
13-H	8.39, (d), $^3J_{\text{HH}}$ 2.45
3-H	9.33, (d), $^3J_{\text{HH}}$ 9.02

**Table III.24**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **34** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
$\text{CH}_3$	15.90, (d), $^3J_{\text{PC}}$ 5.72
$\text{CH}_3$	16.68, (d), $^3J_{\text{PC}}$ 5.98
15-C	53.84, (d), $^1J_{\text{PC}}$ 157.25
$\text{CH}_2$	62.64, (d), $^2J_{\text{PC}}$ 6.98
$\text{CH}_2$	62.78, (d), $^2J_{\text{PC}}$ 7.42
16-C	64.53, (d), $^3J_{\text{PC}}$ 15.41
4-C, 5-C, 8-C, 11-C, 12-C	123.47, 124.80, 125.36, 125.99, 126.13 (5 x s)
3-C	127.05 (d)
20-C, 20'-C	127.09, 127.48, (2 x s)
19-C, 19'-C	127.52, 128.30, (2 x s)
18-C, 18'-C	128.26, 128.62, (2 x s)
13-C	128.97, (d), $^4J_{\text{PC}}$ 4.09
6-C, 10-C	129.36, (br s)
1-C	130.90, (d), $^2J_{\text{PC}}$ 4.09 <sup>†</sup>
14-C	131.35, (d), $^3J_{\text{PC}}$ 1.95 <sup>†</sup>
7-C, 9-C	131.83, 131.68, (2 x s) <sup>†</sup>
2-C	131.95, (d), $^3J_{\text{PC}}$ 3.40 <sup>†</sup>
17-C, 17'-C	142.09, 143.39 (2 x s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table III.25**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **36** in  $\text{CDCl}_3$

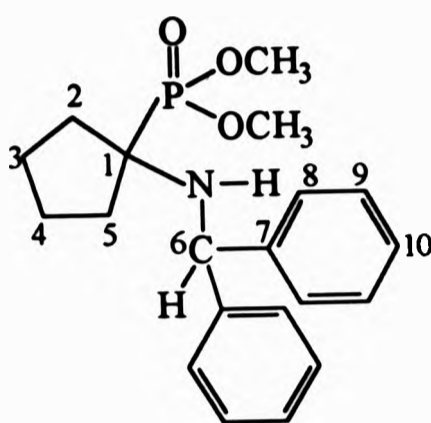
Proton	Chemical shift, Coupling constant
2 x $\text{CH}_3$	1.17, (t), $^3J_{\text{HH}}$ 7.09
4- $\text{CH}_2$	1.20, (m)
3H from 3- $\text{CH}_2$ and 5- $\text{CH}_2$	1.45-1.49, (m)
2- $\text{CH}_2$ , 6- $\text{CH}_2$ , and 1H from 3- $\text{CH}_2$ or 5- $\text{CH}_2$	1.62-1.70, (m)
2 x $\text{OCH}_2$	3.99, (m)
7-H	5.53, (d), $^4J_{\text{PH}}$ 2.67
2 x Ph-H	7.08-7.49, (m)

**Table III.26**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **36** in  $\text{CDCl}_3$

Carbon	Chemical shift, Coupling constant
2 x $\text{CH}_3$	16.51, (t), $^3J_{\text{PC}}$ 5.60
3-C, 5-C	20.15, 20.32, (2 x s)
4-C	25.49, (s)
2-C, 6-C	30.49, 30.54, (2 x s)
1-C	58.60, (d), $^1J_{\text{PC}}$ 138.10 <sup>†</sup>
7-C	61.20, (s)
2 x $\text{OCH}_2$	61.64, (d), $^2J_{\text{PC}}$ 8.18
11-C	126.49, (s)
10-C	127.47, (s)
9-C	128.23, (s)
8-C	146.27, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment





**Table III.27**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **37** in  $\text{CDCl}_3$

Proton	Chemical shift, Coupling constant
2- $\text{CH}_2$ , 3- $\text{CH}_2$ , 4- $\text{CH}_2$ , 5- $\text{CH}_2$	1.57, (m)
2 x $\text{CH}_3$	3.73, (d), $^2J_{\text{PH}}$ 10.21
6-H	5.45, (d), $^4J_{\text{PH}}$ 2.46
2 x Ph-H	7.13-7.44, (m)

**Table III.28**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **37** in  $\text{CDCl}_3$

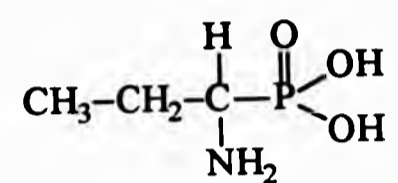
Carbon	Chemical shift, Coupling constant
3-C, 4-C	24.34, 24.54, (2 x s)
2-C, 5-C	34.52, 34.64, (2 x s)
2 x $\text{CH}_3$	62.65, (d), $^2J_{\text{PC}}$ 7.67
6-C	62.11, (s)
1-C	64.95, (d), $^1J_{\text{PC}}$ 143.91 <sup>†</sup>
10-C	126.67, (s)
9-C	127.41, (s)
8-C	128.36, (s)
7-C	145.89, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

## APPENDIX IV

### <sup>1</sup>H and <sup>13</sup>C NMR Spectral Data for the Phosphonic and Phosphinic Acid structures

1

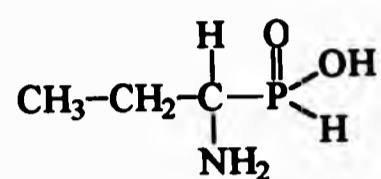


**Table IV.1** <sup>1</sup>H NMR chemical shifts (ppm) and coupling constants (Hz) for **1** in D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
CH <sub>3</sub>	1.07, (t), <sup>3</sup> J <sub>HH</sub> 7.52
CH <sub>2</sub>	1.67-2.04, (m)
CH	3.17, (ddd)

**Table IV.2** <sup>13</sup>C NMR chemical shifts (ppm) and coupling constants (Hz) for **1** in D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
CH <sub>3</sub>	13.13, (d), <sup>3</sup> J <sub>PC</sub> 9.33
CH <sub>2</sub>	24.75, (s)
CH	53.66, (d), <sup>1</sup> J <sub>PC</sub> 143.10

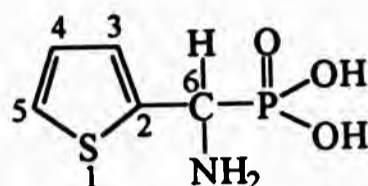


**Table IV.3**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **2** in  $\text{D}_2\text{O}$

Proton	Chemical shift, Coupling constants
$\text{CH}_3$	1.07, (t), $^3J_{\text{HH}}$ 7.52
$\text{CH}_2$	1.67-2.04, (m)
CH	3.17, (ddd)

**Table IV.4**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **2** in  $\text{D}_2\text{O}$

Carbon	Chemical shift, Coupling constants
$\text{CH}_3$	12.71, (d), $^3J_{\text{PC}}$ 8.95
$\text{CH}_2$	22.65, (s)
CH	54.79, (d), $^1J_{\text{PC}}$ 92.58



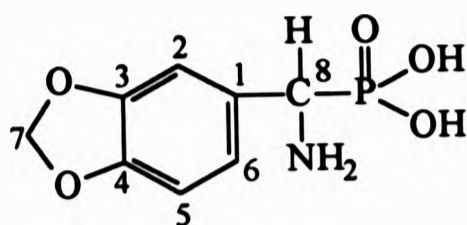
**Table IV.7**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **38** in NaOD/D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
6-H	4.19, (d), $^2J_{\text{PH6}}$ 15.11
4-H	7.04, (dd), $^3J_{\text{H4-H5}}$ 5.04 and $^3J_{\text{H4-H3}}$ 3.56
3-H	7.11, (dd), $^4J_{\text{H3-H5}}$ 1.12
5-H	7.35, (dd)

**Table IV.8**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **38** in NaOD/D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
6-C	53.93, (d), $^1J_{\text{PC}}$ 133.59
4-C	127.44, (d), $^4J_{\text{PC}}$ 1.38
3-C	128.40, (d), $^3J_{\text{PC}}$ 6.29
5-C	129.58, (d), $^4J_{\text{PC}}$ 1.45
2-C	145.94, (d), $^2J_{\text{PC}}$ 3.08 <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



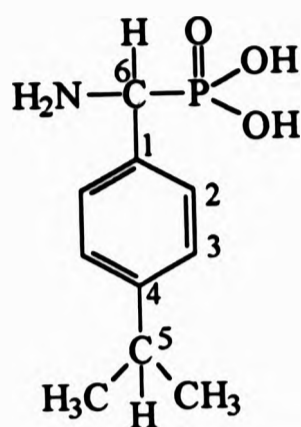
**Table IV.9**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **39** in NaOD/D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
8-H	3.73, (d), $^2J_{\text{PH8}}$ 15.18
CH <sub>2</sub>	5.95, (s)
2-H, 5-H, 6-H	6.86-6.97, (m)

**Table IV.10**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **39** in NaOD/D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
8-C	58.08, (d), $^1J_{\text{PC}}$ 132.46
7-CH <sub>2</sub>	103.54, (s)
5-C	110.76, (d), $^4J_{\text{PC}}$ 1.82
6-C	111.17, (d), $^3J_{\text{PC}}$ 4.59
2-C	123.77, (d), $^3J_{\text{PC}}$ 5.79
4-C	139.07, (d), $^5J_{\text{PC}}$ 2.33 <sup>†</sup>
3-C	148.07, (d), $^4J_{\text{PC}}$ 2.83 <sup>†</sup>
1-C	149.34, (d), $^2J_{\text{PC}}$ 1.89 <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



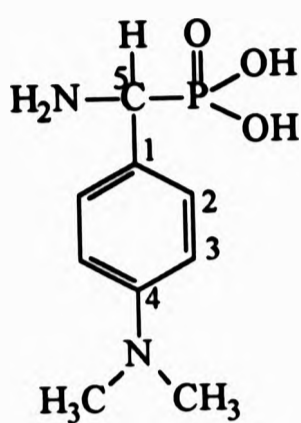
**Table IV.11**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **40** in NaOD/D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
2 x CH <sub>3</sub>	1.23, (d), $^3J_{\text{HH}}$ 6.90
5-H	2.92, (septet)
1-H	3.79, (d), $^2J_{\text{PH}}$ 15.49
3-H	7.29, (d)
2-H	7.35, (dd), $^3J_{\text{H2-H3}}$ 8.30 and $^4J_{\text{PH2}}$ 1.50

**Table IV.12**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **40** in NaOD/D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
2 x CH <sub>3</sub>	26.15, (s)
5-C	35.82, (s)
6-C	57.95, (d), $^1J_{\text{PC}}$ 131.58
3-C	128.66, (d), $^4J_{\text{PC}}$ 1.38
2-C	130.48, (d), $^3J_{\text{PC}}$ 4.90
4-C	142.35, (d), $^5J_{\text{PC}}$ 2.45 <sup>†</sup>
1-C	150.12, (d), $^2J_{\text{PC}}$ 2.64 <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



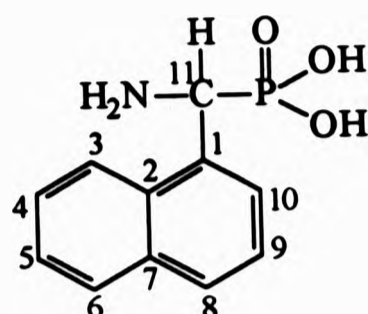
**Table IV.13**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **41** in NaOD/D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
2 x CH <sub>3</sub>	2.83, (s)
5-H	3.74, (d), $^2J_{\text{PH}}$ 15.03
3-H	7.01, (d), $^3J_{\text{H2-H3}}$ 8.68
2-H	7.34, (dd), $^4J_{\text{PH2}}$ 1.83

**Table IV.14**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **41** in NaOD/D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
2 x CH <sub>3</sub>	44.35, (s)
5-C	57.56, (d), $^1J_{\text{PC}}$ 132.77
3-C	118.44, (d), $^4J_{\text{PC}}$ 1.45
2-C	131.21, (d), $^3J_{\text{PC}}$ 5.03
1-C	136.27, (d), $^2J_{\text{PC}}$ 2.70 <sup>†</sup>
4-C	152.64, (d), $^5J_{\text{PC}}$ 1.95 <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table IV.15**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **42** in NaOD/D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
11-C	4.76, (d), $^2J_{\text{PH}}$ 16.06
3-C, 7-C, 8-C	7.52-7.65, (m)
9-H	7.71, (d), $^3J_{\text{HH}}$ 7.45
6-H <sup>†</sup>	7.84, (d), $^3J_{\text{HH}}$ 8.15
4-H <sup>†</sup>	7.94, (d), $^3J_{\text{HH}}$ 7.90
2-H	8.31, (d), $^3J_{\text{HH}}$ 8.38

<sup>†</sup> These proton could be assigned the other way around

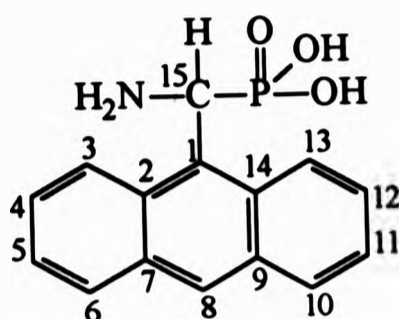
**Table IV.16**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **42** in NaOD/D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
11-C	52.65, (d), $^1J_{\text{PC}}$ 131.08
3-C, 7-C, 8-C	127.19, 128.34, 128.52 (3 x s)
9-C	128.56, (s)
6-C <sup>‡</sup>	128.62, (s)
4-C <sup>‡</sup>	129.25, (s)
2-C	131.27, (s)
1-C	134.23, (d), $^2J_{\text{PC}}$ 5.66 <sup>†</sup>
5-C	136.06, (s) <sup>†</sup>
10-C	141.56, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

<sup>‡</sup> These carbons signals could be assigned the other way around





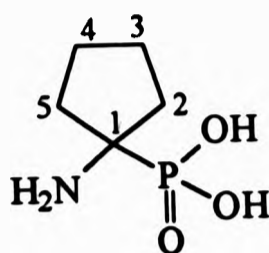
**Table IV.17**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **43** in NaOD/D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
15-H	5.54, (d), $^2J_{\text{PH}}$ 22.25
4-H, 5-H, 11-H, 12-H	7.49-7.65, (m)
6-H, 10-H	8.04, (d), $^3J_{\text{HH}}$ 7.30
8-H	8.42, (s)
13-H	8.49, (d), $^3J_{\text{HH}}$ 9.02
3-H	8.96, (d), $^3J_{\text{HH}}$ 9.71

**Table IV.18**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **43** in NaOD/D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
15-C	54.32, (d), $^1J_{\text{PC}}$ 130.13
4-C, 5-C, 11-C, 12-C	127.30, 127.72, 127.78, 128.88, (4 x s)
6-C, 10-C	129.19, 129.24, (2 x s)
8-C	130.96, (s)
13-C	131.59, (s)
3-C	131.85, (s)
7-C, 9-C	132.20, 134.09, (2 x s) <sup>†</sup>
1-C	132.84, (d), $^2J_{\text{PC}}$ 7.48 <sup>†</sup>
14-C	134.54, (d), $^3J_{\text{PC}}$ 2.77 <sup>†</sup>
2-C	139.12, (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



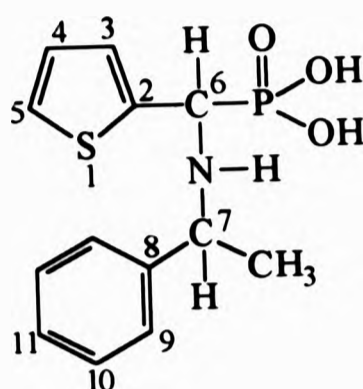
**Table IV.19**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **44** in NaOD/D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
3-CH <sub>2</sub> , 4-CH <sub>2</sub> and 2H from 5-CH <sub>2</sub> and 2-CH <sub>2</sub>	1.64-1.76, (m)
2H from 2-CH <sub>2</sub> and 5-CH <sub>2</sub>	2.16, (m)

**Table IV.20**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **44** in NaOD/D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
3-CH <sub>2</sub> , 4-CH <sub>2</sub>	27.72, (d), $^3J_{\text{PC}}$ 7.48
2-CH <sub>2</sub> , 5-CH <sub>2</sub>	37.56, (d), $^2J_{\text{PC}}$ 1.51
1-C	65.10, (d), $^1J_{\text{PC}}$ 143.08 <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment



**Table IV.21**  $^1\text{H}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **45** in NaOD/D<sub>2</sub>O

Proton	Chemical shift, Coupling constants
CH <sub>3</sub>	1.37, (d), $^3J_{\text{HH}}$ 6.60
7-H	3.88, (q)
6-H	4.17, (d), $^2J_{\text{PH}}$ 18.64
3-H, 4-H	6.92-6.97, (m)
Ph-H, 5-H	7.14-7.22, (m)

**Table IV.22**  $^{13}\text{C}$  NMR chemical shifts (ppm) and coupling constants (Hz) for **45** in NaOD/D<sub>2</sub>O

Carbon	Chemical shift, Coupling constants
CH <sub>3</sub>	23.46, (s)
7-C	58.94, (d), $^3J_{\text{PC}}$ 10.00
6-C	59.68, (d), $^1J_{\text{PC}}$ 135.98
12-C	126.77, (s)
3-C	128.66, (d), $^3J_{\text{PC}}$ 7.30
4-C	129.67, (s)
11-C	129.81, (s)
10-C	131.28, (s)
5-C	131.40, (s)
8-C	147.88 (s) <sup>†</sup>

<sup>†</sup> Quaternary carbon signals were identified by a DEPT-135 experiment

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