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The Synthesis of Aminophosphonic Acid Derivatives & Related Compounds

by

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A Thesis Submitted in Partial Fulfilment of the Requirements

For the Degree of Doctor of Philosophy

of the Council for National Academic Awards

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I dedicate this thesis to my Wife, Mother and Father in Heaven.

'Where there is no vision, people perish'

Proverbs 29:18

DECLARATION

Whilst registered as a candidate for this degree I have not been registered as a candidate for any other award.

D. St. C. Green

In partial fulfilment of the requirements of the degree I have completed the M.Sc. lectures on: Structural Methods (Infrared, U.V., and N.M.R. Spectroscopy; and Mass Spectrometry); Synthesis of Biologically Active Molecules; Recent Advances in the Chemistry of Synthetic Fine Chemicals. In addition I have attended departmental research colloquia.

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INTRODUCTION

1-Aminoalkanephosphonic acids and their derivatives, have long been claimed to be compounds with a wide variety of application. Numerous examples exist where they have been described as: complex-forming agents with sequestrating properties, extractants, wetting agents, pharmaceutical preparations, ion exchangers, herbicides, compounds with plant growth regulatory activity;[1] inhibitors of amino-peptidases;[2] as structural units in peptide analogues, functioning as antibacterial agents, which inhibit bacterial cell wall biosynthesis;[3,4] as structural units in peptidic phosphonylating agents that irreversibly inhibit a wide variety of serine proteases;[5,6,7] as structural units in butyloxycarbonyl protected phosphonate esters that complex with α-lytic proteases;[8] and as structural units in peptidyl phosphonate diphenyl esters which powerfully inhibit the enzyme thrombin.[9,10]

1-Aminoalkanephosphonic acids in particular, were first shown to have useful fungicidal efficacy, as a result of collaborative work between PNL and KenoGard AB.[11,12] During the course of the present studies, a variety of 1-aminoalkanephosphonic acids, their derivatives, and related compounds have been synthesised, with the intention that they may be of potential use as antifungal agents.

The agrochemical industry has nearly always been faced with the problem of producing prophylactic or therapeutic pesticides that are: metabolically and environmentally stable (although not overly so); have

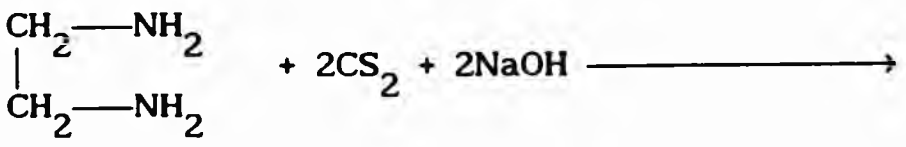
a high degree of biological specificity or potency incorporated into the molecule; have negligible or preferably no mammalian toxicity; and are capable of exerting their biological actions easily at the afflicted site. These compounds should have low application rates, and therefore must be economically cost effective. Potential commercial fungicides are required to fulfill all of these rigorous criteria, before their routine employment may be considered.

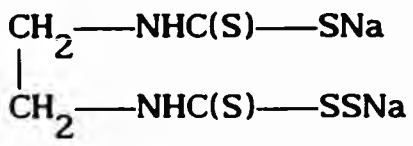
The philosophy that governs the use of certain compounds as fungicides, has thankfully become more precise since the time when inorganic materials such as sulphur, lime-sulphur, copper and mercury compounds, were first used exclusively as prophylatic fungicides. The development of dithiocarbamates and their derivatives was a monumental step forward in the discovery of a novel generation of organic fungicides. Since their introduction by Tisdale and Williams in 1934,[13] a range of these compounds have been developed and used in specific circumstances. For example thiram (1), (*N,N,N',N'* - tetramethylthiuram disulphide), is prepared by the interaction of carbon disulphide and dimethylamine in the presence of sodium hydroxide solution to give sodium dimethyldithiocarbamate which is subsequently oxidised by air, hydrogen peroxide, chlorine, or iodine to the product (Scheme 1).

$$2(CH_3)_2NH + 2CS_2 \xrightarrow{NaOH} 2(CH_3)_2NC(S)SNa \xrightarrow{(oxidation,\ I_2,\ -\ 2NaI)}$$

$(CH_3)_2NC(S)-S-S-C(S)NC(CH_3)_2$ (1) **Scheme 1**

Thiram is used as a seed dressing, demonstrating a contrasting mode of action to the ethylenebisdithiocarbamate, nabam (2), obtained by the reaction of ethylenediamine with carbon disulphide in the presence of sodium hydroxide as shown in Scheme 2.



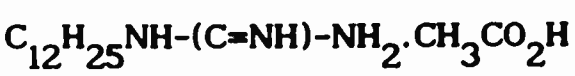


(2)

Scheme 2

Nabam is water-soluble, possessing a distinctive spectrum of activity against various types of fungi.[14]

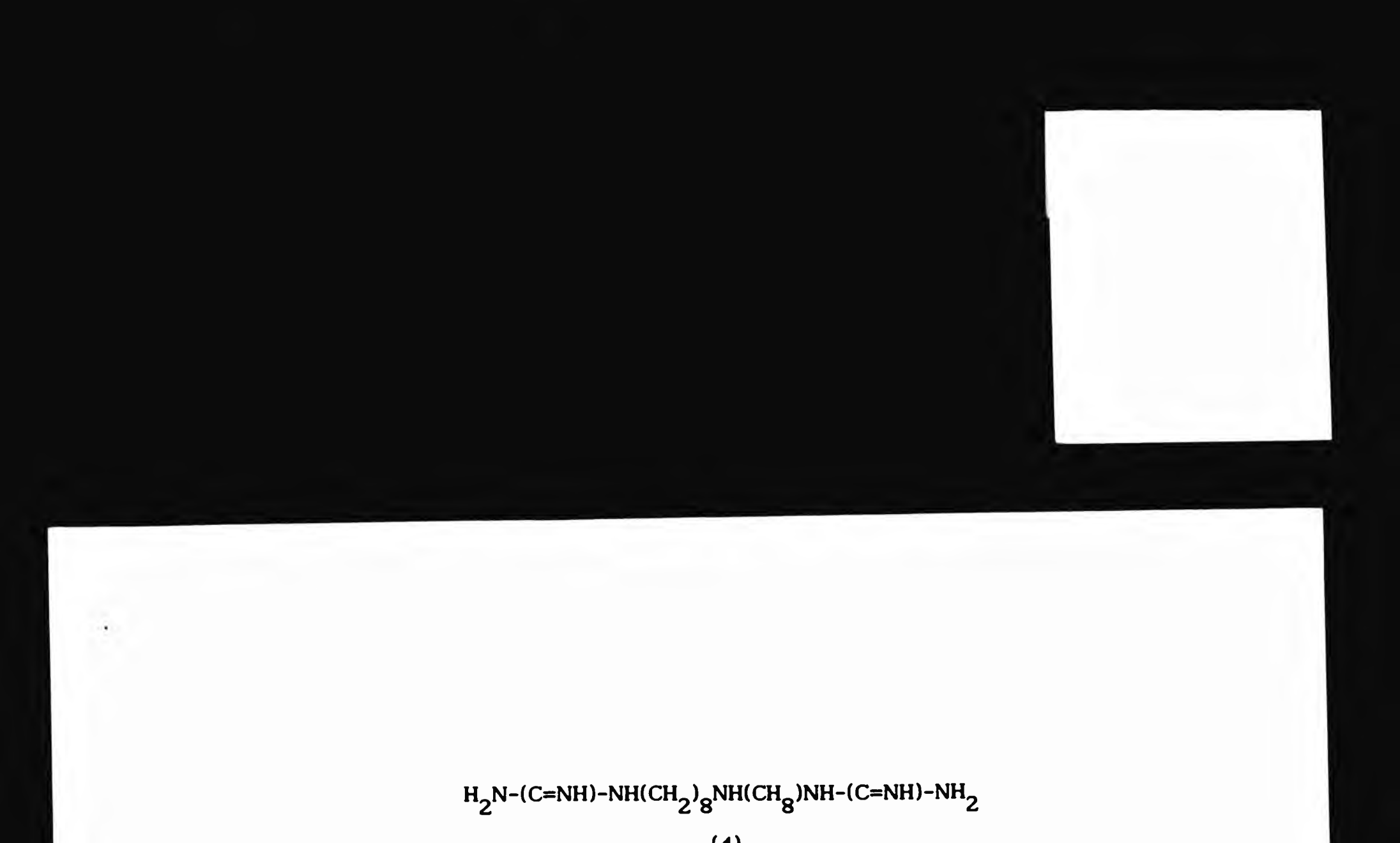
This systematic approach to manufacturing organic antifungal compounds that act selectively without damaging the host plant, was further exemplified by the production of the n-alkyl monoguanidine derivative, 1-dodecylguanidinium acetate or 'dodine' (3).



(3)

Introduced by the American Cyanamid Company in 1956, this first commericial guanidine assumed economic popularity in the control of fungal pathogens of commericial crops. With particularly good activity against *Venturia inaequalis* and *Venturia pirina* (apple and pear scab), the compound shows negligible or no phytotoxicity.[15] Combination of dodine with dithiocarbamates and phthalimides, potentiates the effect of these protective fungicides. Also sterol biosynthesis-inhibiting fungicides, have improved protectant and eradicant action, after mixing them with dodine.[16] Dodine has been found to affect the fungi at various stages of its life cycle, interfering with the fungal cell wall, to initiate loss of important metabolites, and vital cellular components. Mitochondrial function is also impaired through inhibition of enzymes, as a result of lysis of the cell wall. Pressman (1963) demonstrated that dodine's effects were not restricted to one type of cellular membrane. His experiments showed that the compound caused 50 % inhibition of electron transport in isolated rat liver mitochondria at a concentration of 80 μmol dm^{-3}.[17] This highlighted that the compound was acting as an inhibitor of oxidative phosphorylation; a property shared by other alkylguanidines.

The precedent established by dodine may have been helpful in releasing the polyalkylene-polyamine derivative, guazatine (4) (1,17-bis-guanidino-9-azaheptadecane), into the commericial arena.



(4)

As the acetate salt, guazatine has been shown to have a broad spectrum of activity against seed borne fungi.[15] A commericial preparation called Panoctine, derived from the combination of a range of guandino-acetates, has achieved considerable success in the control of *Geotrichum candidum*, *Piricularia oryzae*, *Helminthosporium oryzae* and *Gaeumannomyces graminis* (the pathogen of 'take-all' disease). Eradication of *Drechslera oryzae* is achieved when the compound is mixed with dichloromethane, and applied to affected rice seeds.[15]

Murphey and Gerner (1987) showed that so-called guazatine, is a powerful inhibitor of mammalian polyamine oxidase, which catalyses the production of deoxyhypusine, an important precursor of the rare amino acid, hypusine.[18] The mechanism of action is thought to be the same as that which is involved when guazatine powerfully inhibits polyamine oxidase in higher plants.[19] This demonstrates the wide range of properties that the molecule possesses, and may go some way towards attempting to fully understand the mode of action that it is able to exert.

It has been acknowledged that the biological properties of antifungal molecules, are intimately related to their inherent chemical and physical attributes. Considerable progress has been made in rationalising the structure-activity relationships that govern

biological efficacy of these molecules.[20,21] Consideration of properties such as hydrophobicity, hydrophilicity and lipophilicity, mediate the routes taken to synthesise new fungicides. Often these characteristics have a bearing on how successfully biological activity is delivered to the required site of action.

Straight chain aminoalkanephosphonic acids such as the naturally occurring 2-aminoethanephosphonic acid, 2-AEP (5),

$$(HO)_2P(O)CH_2CH_2NH_2 \quad (5)$$

found in a wide variety of organisims, have been known to fulfill important biological functions.[22] The isolation of (5) from ciliated protozoa in 1960 provided the 1st example of a P-C bond in nature. First synthesised by Finkelstein (1946), this aminophosphonic acid has also been isolated from the hydrolysates of insoluble proteinaceous residues from the sea anemone *Metridium dianthus*, from bovine brain (free and lipid-bound) and human tissue, including brain and human aorta, indicating that phosphonic acids may have an important role to play in their integration into macromolecular material. Since the discovery of 2-AEP, and the synthesis of other phosphonic acid derivatives of biological importance, these compounds have generated considerable interest, as amino acid analogues. 1-Aminoalkanephosphonic acids and their derivatives, were first shown to have marked fungitoxicity as a result of the collaborative work between PNL and

KenoGard AB. The investigations carried out during the course of this association showed that these compounds could be of potential use in the agrochemical industry.[11,12]

In-depth study has shown that optimum fungicidal activity occurs as in the case for example of 1-aminopropanephosphonic acid, when the molecule is 1-substituted and contains moderately short alkane branches.[23] *In vivo* tests carried out by applying 2 cm^3 of a 20 % concentration of a 1-aminoalkanephosphonic acid to 1 kg of barley or oat seeds infected with *Drechslera teres, Drechslera gramineum* or *Septoria nodorum*, (the causative organisms of the net blotch of barley, leaf stripe of barley and glume blotch respectively), gave good control results. The seedlings were examined and the percentage control of the disease was evaluated. As indicated in Table 1 & Table 2, the compounds showed marked activity against *Drechslera teres*. 1-Aminopropanephosphonic acid showed particularly good activity against *Drechslera teres* and *Septoria nodorum*. The compound also gave 76 - 100 % growth inhibition of *Drechslera sativa in vitro*.[12] Any attempt to modify the 1-aminoalkanephosphonic acids, by for example, branching of the 1-alkane chain, effected a significant drop in their performance against *Drechslera teres*. The mode of action of these types of compound has not been elucidated, although it is possible that they may interfere in some way with peptide synthesis, by virtue of their structural resemblance to amino acids. This process is crucial to the propagation and proliferation of fungi.

TABLE 1. THE EFFECT OF SUBSTITUTION WITH α-CHAIN OF INCREASING LENGTH ON THE STRUCTURE-ACTIVITY RELATIONSHIPS OF AMINOALKANEPHOSPHONIC ACIDS $(HO)_2P(O)CH(NH_2)R$[23]

PNL	R	ACTIVITY(%) AGAINST *D. teres*
53	H	21
84	Methyl	52
62	Ethyl	91
209	Propyl	87
211	Butyl	82
212	Pentyl	67
80	Heptyl	12

TABLE 2. THE EFFECT OF BRANCHING OF THE α-ALKYL CHAIN AND REPLACING THE α-HYDROGEN BY AN ALKYL GROUP $(HO)_2P(O)CR(NH_2)R'$[23]

PNL	R	R'	ACTIVITY(%) AGAINST *D. teres*	*S. nodorum*
62	H	Ethyl	91	90
85	Methyl	Methyl	23	7
209	H	Propyl	87	*
86	H	Isopropyl	65	64
215	Methyl	Isopropyl	6	*

* Not tested

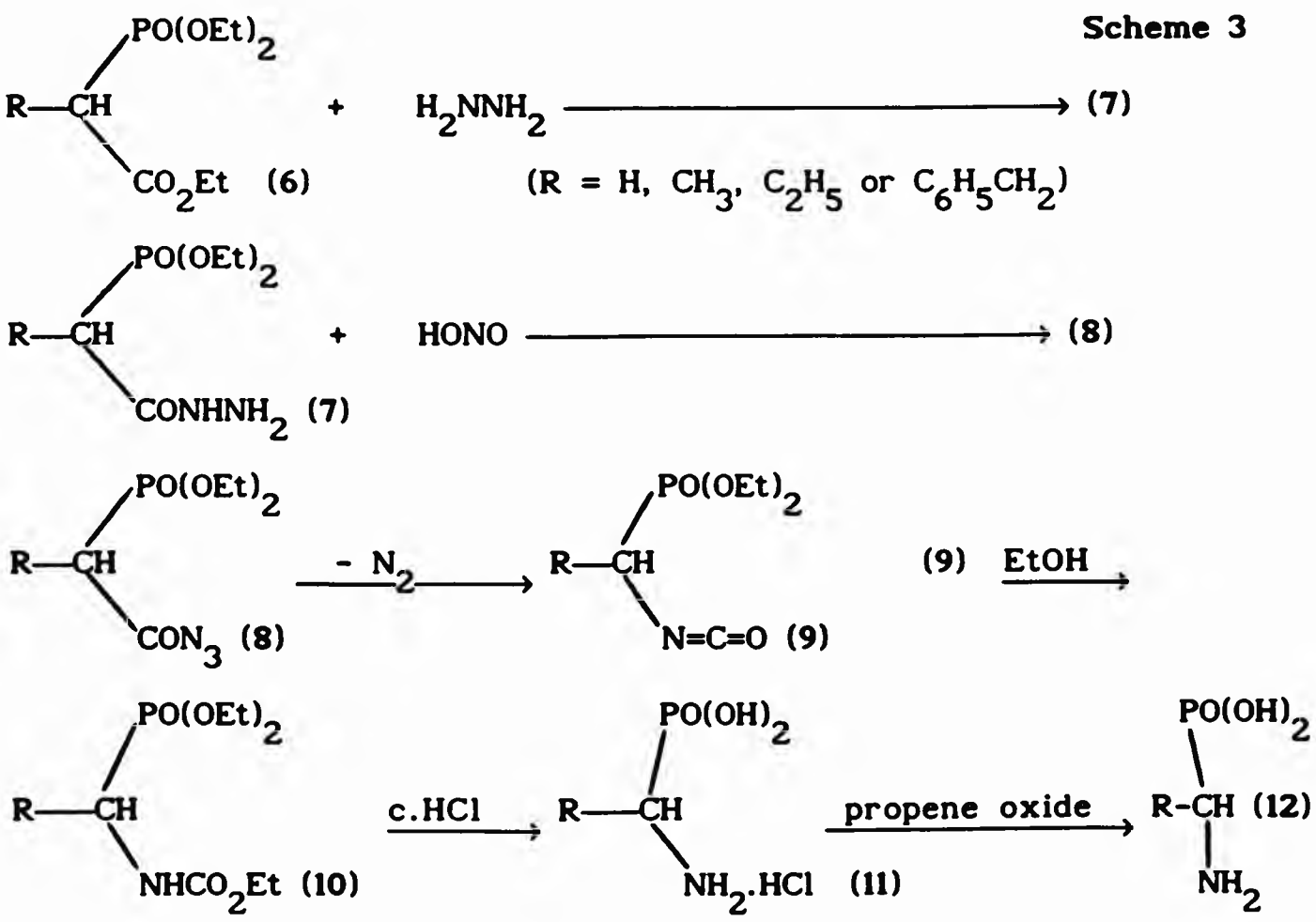
A wide variety of 1-aminoalkanephosphonic acid derivatives and related compounds have been synthesised during the course of the present work. ^{1}H, ^{13}C, ^{31}P and where appropriate ^{19}F N.M.R. spectroscopy, has been used extensively in the characterisation of these molecules. Where applicable, Fast Atom Bombardment (FAB) mass spectrometry was employed to give confirmatory evidence of the identity of the compound being analysed, revealing the abundant $[M+H]^+$ ion (normally the base peak), and other characteristic fragmentations. An additional mass spectrometric technique, LSIMS ionisation, where involatile materials are bombarded with caesium ions, was also used on certain aminoalkanephosphonic acid derivatives for the first time. The fragmentation patterns were generally much simpler, generating the $[M+H]^+$ ion, as the most abundant species in those molecules examined. Electron impact mass spectrometry and infrared spectroscopy were used in the most amenable cases, as qualitative methods of identification. In accompaniment with elemental analysis, very useful information was acquired as to the presence and purity of the molecule being tested.

CHAPTER 1

1.1. THE SYNTHESIS OF 1-AMINOALKANEPHOSPHONIC ACIDS - HISTORICAL

A review of the literature shows that 1-aminoalkanephosphonic acids may be synthesised in a variety of ways. One of the earlier methods used, involved the Curtius degradation of substituted diethyl phosphonoacetylhydrazides, formed by the mildly exothermic condensation of hydrazine with a phosphonoacetic ester. Acid hydrolysis of the unisolable intermediate, followed by work-up with propene oxide, is a route that may afford up to 80 % of the desired product, based on the parent phosphonoacetic ester used as the substrate for the reaction.[24] The reactions (Scheme 3) are given below.

Scheme 3



Treatment with propene oxide affords the corresponding aminophosphonic acid (12) from the hydrochloride precursor (11). Compounds (7) to (10) are unisolable intermediates. This method is comparatively less convenient than the so-called '1-pot' procedure, to be discussed later.

Another method used in the present work, involved subjecting Schiff's bases, prepared from benzylamine and aliphatic or aromatic aldehydes or ketones to the nucleophilic addition reaction of dialkyl phosphites. Catalytic hydrogenolysis of the so-formed isolable *O,O*-dialkyl 1-benzylaminoalkanephosphonate derivative, followed by acid hydrolysis of the subsequently produced crude, *O,O*-dialkyl 1-aminoalkanephosphonate and treatment with propene oxide as described,[25] liberated the corresponding 1-aminoalkanephosphonic acid as a white, water soluble, high melting point, crystalline material.[26] The reactions (Scheme 4) are shown below.

1. $R'RCO + C_6H_5CH_2NH_2 \xrightarrow{[Et_2O/K_2CO_3\ (anhyd)\ -H_2O,\ 0\ ^oC,\ R.T.]}$

$R'RC{=}NCH_2C_6H_5$

(13)

2. (13) + $(R''O)_2P(O)H$ $(0\ ^oC,\ R.T.) \longrightarrow$

$(R''O)_2P(O)CR(NHCH_2C_6H_5)R'$

(14)

(14) $\xrightarrow{H_2,\ Pd/C \text{ in AcOH, } 80\ ^{o}C}$

$(R''O)_2P(O)CR(NH_2)R'$

(15)

(15) $\xrightarrow{\text{(i) HCl, (ii) propene oxide at } 40\text{-}50\ ^{o}C}$

$(HO)_2P(O)CR(NH_2)R'$

(12)

(R = H, alkyl; R' = alkyl, aryl; R'' = CH_3, CH_3CH_2)

Scheme 4

If ethyl hydrogen alkylphosphonites are used in place of dialkyl phosphites, in the nucleophilic addition reaction, the corresponding 1-aminoalkanephosphinic acids (16) may be synthesised.

$R(HO)P(O)CR(NH_2)R'$

(16)

1-Aminoalkanephosphinic acid, R = alkyl

J.Lukszo and R.Tyka showed that when the benzylamine is highly branched, so that the amino group resides on a tertiary benzylic carbon atom (benzylic carbinamines), it is readily able to form Schiff's bases.

When these Schiff's bases react with diethyl phosphite, forming the corresponding phosphonate derivatives, these intermediates may be converted to the free 1-aminoalkanephosphonic acids, upon acid hydrolysis, accompanied with simultaneous formation of unsaturated hydrocarbons.[27] The reactions (Scheme 5) are illustrated below.

$$R'RCO + C_6H_5\text{-}C(CH_2R'')R'''NH_2 \xrightarrow{\text{heat, toluene/}K_2CO_3\text{(anhyd) - }H_2O}$$

$$C_6H_5\text{-}C(CH_2R'')(R''')N{=}CRR'$$

(17)

$$\textbf{(17)} + (CH_3CH_2O)_2P(O)H \text{ (at 120 - 140 } ^oC) \longrightarrow$$

$$(CH_3CH_2O)_2P(O)CR[NHC(CH_2R'')(R''')C_6H_5]R'$$

(18)

$$\textbf{(18)} \xrightarrow{\text{(i) HCl, (ii) propene oxide}}$$

$$(HO)_2P(O)CR(NH_2)R' + R''CH{=}CR'''C_6H_5$$

(12) **(19)**

(R = H or alkyl, R' = alkyl or aryl, R'' = H or alkyl, R''' = alkyl)

Scheme 5

This Scheme represented the move toward a more convenient '1-pot' operation without isolation of the intermediates (17) and (18). Although the reaction is relatively straightforward to operate, generating the starting material, 1,1-disubstituted benzylamine, tends to be laborious.[28,29,30]

Numerous cases have been documented in the literature, where the addition of hypophosphorous acid, H_3PO_2, to a variety of Schiff's bases in solvents such as ethanol, gives rise to the corresponding phosphonous acid (20).[31] The general reaction (Scheme 6) is given below.

$$RN{=}CR'R'' + H_3PO_2 \longrightarrow H(HO)P(O)CR'(NHR)R''$$

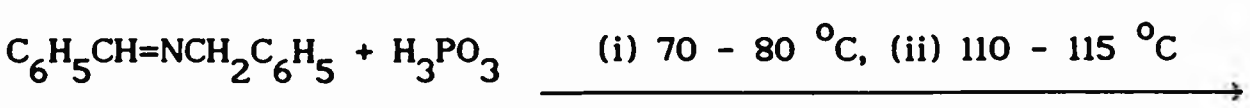
(20)

(R = CH_3, CH_3CH_2, t-C_4H_9, $C_6H_5CH_2$; R'' = C_6H_5, 4-ClC_6H_4, $CH(CH_3)_2$, 2-HOC_6H_4; R' = H)

Scheme 6

In similar fashion, Redmore attempted to add phosphorous acid to Schiff's bases, but gained no success in the preparation of the corresponding free phosphonic acid this way. Although heating equimolar amounts of various Schiff's bases and phosphorous acid in the absence of solvent, yielded white crystalline products, basification of these solids liberated benzylamine, showing that the solids were benzylamine salts. However he did show that controlled heating of a 1:1 mixture of

N-benzylidenebenzylamine and phosphorous acid gave an almost quantitative yield of *N*-benzyl 1-aminobenzylphosphonic acid (21), as the reaction (Scheme 7) below shows.



$(HO)_2P(O)CH(NHCH_2C_6H_5)C_6H_5$

(21)

Scheme 7

A variety of *N*-benzyl 1-aminobenzylphosphonic acid derivatives were synthesised in good yield, ranging from 40 - 98 %. By contrast it was observed that when Schiff's bases were obtained from aliphatic aldehydes or dialkyl ketones, only moderate yields of the corresponding aminophosphonic acids were afforded. A possible explanation for this, was that reduction of the Schiff's base to the corresponding amine was a competing reaction.[32]

I.A.Gandurina *et. al.*, synthesised a series of aminoalkane-phosphonic acid derivatives, by firstly subjecting the acid chloride of a carboxylic acid to reaction with tribenzyl phosphite at a temperature of - 10 to + 20 °C in the medium of an organic solvent. After removal of benzyl chloride, produced as a by-product of the initial reaction, the reaction product (22) that formed was subjected to catalytic hydrogenolysis in absolute methanol at 20 - 30 °C. The 1-ketophosphonic

acid (23) produced as a result of this reaction, was treated with sodium borohydride in the presence of aqueous ammonia or any other primary amine at 0 - 20 ^{o}C, to generate the corresponding 1-aminophosphonic acid derivative.[33] The reactions (Scheme 8) are illustrated below.

$(C_6H_5CH_2O)_3P$: + R'COCl ⟶

$(C_6H_5CH_2O)_2P(O)C(O)R'$ (22) + $C_6H_5CH_2Cl$ ⟶

(22) $\xrightarrow{H_2 \text{ / abs. } CH_3OH, \text{ Pd/C at 20 - 30 } ^{o}C, \text{ - toluene}}$

$(HO)_2P(O)C(O)R'$ (23) $\xrightarrow{NaBH_4 \text{ in Aq.}NH_3 \text{ or R''-}NH_2 \text{ at 0 - 20 } ^{o}C}$

$(HO)_2P(O)CH(NHR'')R'$ (12) (R' = alkyl or aryl, R'' = H or alkyl)

Scheme 8

The method described above, enabled the workers to synthesise 1-aminoalkanephosphonic acids from readily accessible reagents without the separation of intermediate products.This significantly reduced the number of stages required to isolate the desired product.

The synthesis of 1-aminoalkanephosphonic acids was greatly improved by the so-called '1-pot' approach of Oleksyszyn and Tyka. They showed that the condensation of ethyl carbamate, with aldehydes and triphenyl phosphite in the presence of glacial acetic acid, followed by

acid hydrolysis of the crude condensation products (24), could afford fair yields of the aminophosphonic acids.[34] This method was used with considerable effect in the present work. The modification of condensing benzyl carbamate with aldehydes and triphenyl phosphite in the presence of a catalytic amount of boron trifluoride etherate, using toluene as the solvent for the reaction, followed by acid hydrolysis of the crude condensation products (25), roughly afforded twice as much of the aminophosphonic acid as compared with the former condensation procedure.[35] The reactions (Schemes 9 & 10) are shown below.

1. $(C_6H_5O)_3P:$ + R'RCO + $CH_3CH_2OCONH_2$ $\xrightarrow{100\ ^oC \text{ for } 1 \text{ h/HOAc}}$

$(C_6H_5O)_2P(O)CR(NHOCOCH_2CH_3)R'$ (24)

(24) $\xrightarrow{\text{(i) HCl / 6 h, (ii) propene oxide at 40 - 50 } ^oC}$

$(HO)_2P(O)CR(NH_2)R'$ (12)

Scheme 9

2. $(C_6H_5O)_3P:$ + R'RCO + $C_6H_5CH_2OCONH_2$

$\xrightarrow{\text{(reflux 1 h, } BF_3\text{-}Et_2O \text{ / toluene)}}$ $(C_6H_5O)_2P(O)CR(NHOCOCH_2C_6H_5)R'$ (25)

(25) (i) c.HCl / 6 h, (ii) propene oxide at 40 - 50 ^{o}C

$(HO)_2P(O)CR(NH_2)R'$ (12) (R = H or alkyl, R' = alkyl)

Scheme 10

In a very similar fashion, Kudzin and Stec, showed that 1-aminoalkanephosphonic acids may be synthesised via the acid hydrolysis of *O,O*-diphenyl thioureidoalkanephosphonates (26) in 59 - 98 % yield.[36] Reaction between *N*-monosubstituted thiourea, an aldehyde and triphenyl phosphite in glacial acetic acid solution proceeds smoothly at room temperature with slight exothermicity. Addition of water leads to formation of crystalline compounds identified as the corresponding thioureidophosphonate derivatives (26) in 70 - 94 % yield. The reaction (Scheme 11) is given below.

$$RNHC(S)NH_2 + R'CHO + (C_6H_5O)_3P: \xrightarrow{HOAc}$$

$(C_6H_5O)_2P(O)CHR'NHC(S)NHR$ (26)

O,O-Diphenyl thioureidoalkanephosphonate

Scheme 11

Treatment of thioureidophosphonates when R = C_6H_5 (27) in acetic acid solution with hydrochloric acid under reflux causes degradation of the substrate, and 1-aminoalkanephosphonic

acid-hydrochlorides are formed. Neutralisation with propene oxide gives the desired free aminophosphonic acids. In the case of thioureidophosphonates when R = C_6H_5-CH(CH_3)-, (28) more drastic degradation conditions are required. Most favourable results were obtained when the substrate was refluxed in acetic anhydride/acetic acid solution for a few hours and then treated with hydrobromic acid, to liberate the desired aminophosphonic acid. The reaction (Scheme 12) is shown below.

(27), (28) $\xrightarrow{\text{(i) HOAc / } Ac_2O,\ \text{(ii) HBr, (iii) propene oxide}}$ $(HO)_2P(O)CH(NH_2)R'$ (12) (R = C_6H_5 or C_6H_5-CH(CH_3)-; R' = alkyl)

Scheme 12

It was found that treatment of the unisolated product of the reaction between thiourea, aldehyde and triphenyl phosphite with acetic anhydride/hydrobromic acid or concentrated hydrochloric acid, gave the desired aminophosphonic acid in moderate to high yield, thereby localising the preparation to a '1-pot' operation.[36]

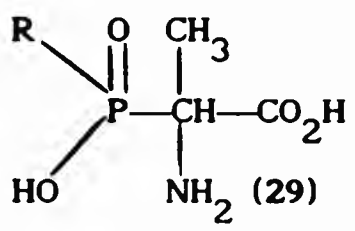
The biological activity of a variety of aminophosphonic acid derivatives has always stimulated interest in the synthesis of phosphonic analogues of carboxylic amino acids.[37,38,39] Especially interesting are the glutamic and aspartic acid analogues for which strong neuroactive, antibiotic, antiviral and other biological activity

has been demonstrated.[38] Oleksyszyn *et al.*,[38] showed that 1-amino-phosphonic acid analogues of 1-methylaspartic, glutamic and pyroglutamic acids can be readily obtained by applying the general procedure of reacting carbonyl compounds, amides and trivalent phosphorus chlorides.

They found that the reaction of ethyl acetoacetate with benzyl carbamate and phosphorus trichloride or dichlorophosphines gave the analogues of 1-methylaspartic acid (29), as shown (Scheme 13) below.

$$CH_3COCH_2CO_2CH_2CH_3 + C_6H_5CH_2OCONH_2 + R'\text{-}PCl_2$$

$$\xrightarrow{\text{(i) AcOH, (ii) HCl/H}_2\text{O}}$$



(29)

(R = OH, C_6H_5, CH_3 or CH_3CH_2

R' = H or alkyl)

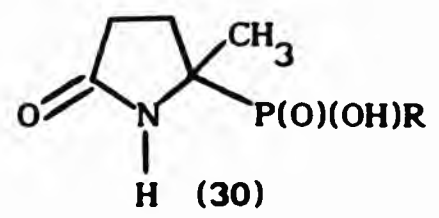
Scheme 13

Similar reaction with ethyl levulinate gave the cyclic products representing the phosphonic analogues of 1-methylpyroglutamic acid (30)

$$CH_3CO(CH_2)_2CO_2CH_2CH_3 + C_6H_5CH_2OCONH_2 + R'\text{-}PCl_2$$

$$\xrightarrow{\text{(i) AcOH, (ii) HCl/H}_2\text{O}}$$

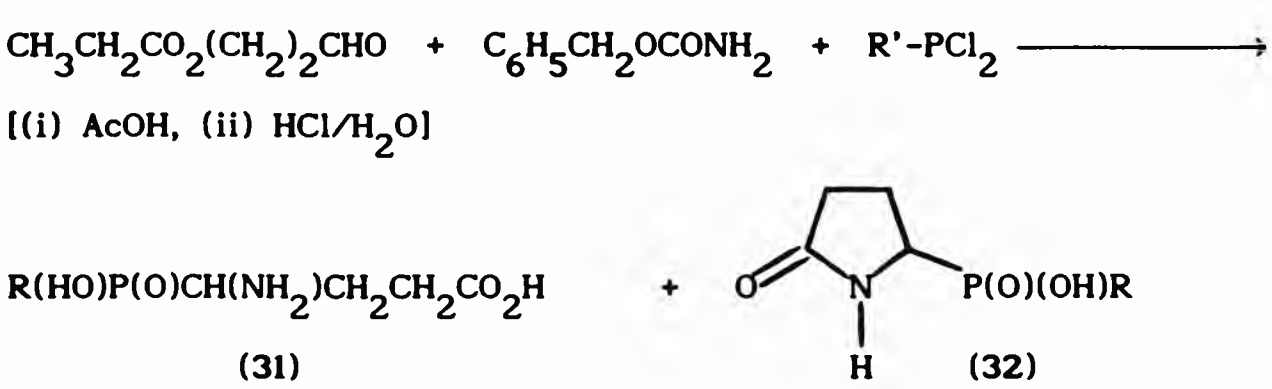
(R = OH or C_6H_5)



(30)

Scheme 14

By contrast the reaction of ethyl succinate semialdehyde[82] under the same conditions, produced the open-chain derivative (31) in moderate yield with only trace amounts of the cyclic product (32).

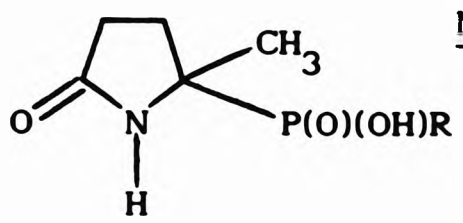


Scheme 15

Due to the reasonably successful use of ethyl succinate semialdehyde in the above reaction,[38] numerous attempts were made in the current work to synthesise this aldehyde[82] and use it in the '1-pot' condensation reaction with carbamate and triphenyl phosphite, to synthesise 1-amino-3-carboxypropanephosphonic acid, a compound that had been claimed to have useful biological activity,[81] and which was required in the present work for a study of the effect of carboxy substitution on the fungicidal activity of 1-aminopropanephosphonic acid. It had also been claimed that the 3-carboxy compound possessed insectidal, herbicidal and other biological activity, but no mention of fungitoxicity had been made.[33] However when the product expected to be

succinic semialdehyde was used in the "one-pot" reaction to synthesise the corresponding aminophosphonic acid, the desired product was not formed.

When the phosphonic acid analogues of 1-methylpyroglutamic acid are hydrolysed in sodium hydroxide solution, salts of the open chain products (33) may be obtained.[38]



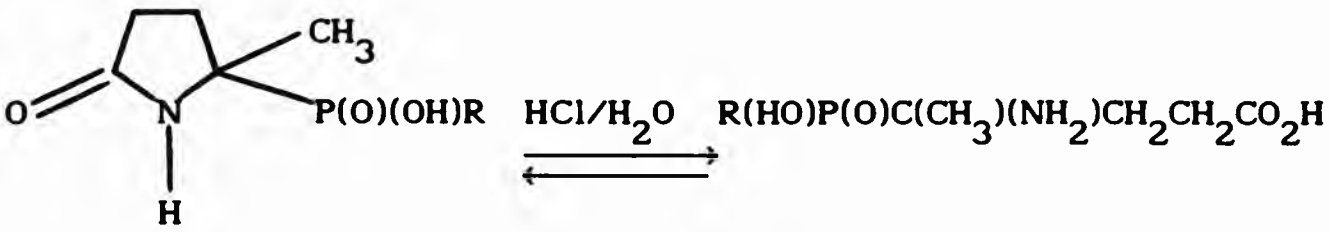
$$\xrightarrow{NaOH/H_2O} NaO(R)P(O)CCH_3(NH_2)CH_2CH_2CO_2Na$$

(33)

(R = ONa, C_6H_5)

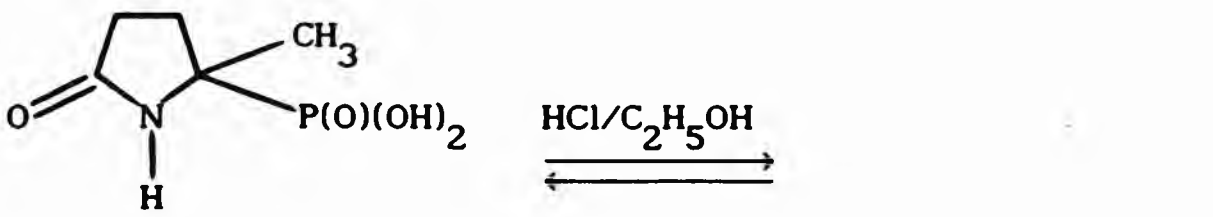
Scheme 16

At low pH, the situation is more complicated, as an equilibrium exists between the ring and open chain compounds. After prolonged heating of 1-methylpyroglutamic acid analogues in hydrochloric acid, mixtures of cyclic and open chain products were obtained. A similar effect was observed when the substrate was ring-opened with ethanol and hydrogen chloride, producing a mixture of open chain product and unchanged substrate. The product obtained in the above instance was the same as that isolated when 1-amino-1-methyl-3-carboxypropanephosphonic acid (34) was esterified. The reactions (Schemes 16a-c) are shown overleaf.



(R = OH or C_6H_5)

Scheme 16a

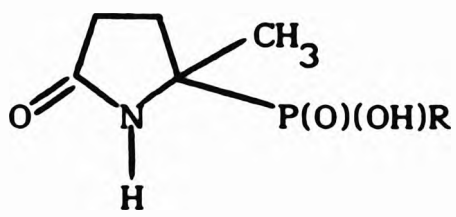


$(HO)_2P(O)C(CH_3)(NH_2)CH_2CH_2CO_2C_2H_5$

Scheme 16b

$(HO)_2P(O)C(CH_3)(NH_2)CH_2CH_2CO_2H$ (34) $\xrightarrow{R\text{-}OH}$

$(HO)_2P(O)C(CH_3)(NH_2)CH_2CH_2CO_2C_2H_5$ +



Scheme 16c

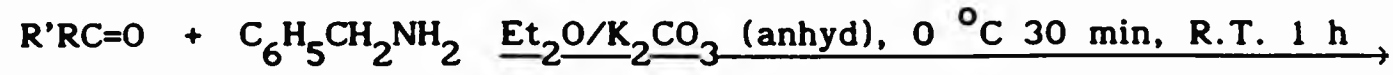
A variety of 1-aminoalkanephosphonic acids were prepared in the present work using some of the methods highlighted earlier. The results of these experiments will be discussed in the following section.

1.2. THE SYNTHESIS OF 1-AMINOALKANEPHOSPHONIC ACIDS FROM *O,O*-DIALKYL 1-BENZYLAMINOALKANEPHOSPHONATES

1.2.1. THE SYNTHESIS OF *N*-ALKYLIDENEBENZYLAMINES & N-BENZYLIDENEBENZYLAMINES (SCHIFF'S BASES)

Crude *N*-alkylidenebenzylamines derived from the addition of aliphatic aldehydes or ketones to benzylamine at 0 ^{o}C, were fractionated by vacuum distillation (15 mmHg), to afford the compounds as clear, free-flowing liquids. When to left to stand at room temperature for a few days, these liquids darkened considerably in colour, indicating that some form of decomposition was taking place. This observation was clearly demonstrated by *N*-propylidenebenzylamine, whose relatively simple ^{1}H N.M.R. spectrum immediately following distillation, became unintelligible a few days after.

With a view to synthesising 1-aminofluoroalkanephosphonic acids, numerous attempts were made to form imines by the reaction of benzylamine with various hydrated perfluoroaldehydes (said to contain varying amounts of their ethyl hemiacetals, as specified by the manufacturers, Lancaster Synthesis). What were expected to be crude *N*-2,2,2-trifluoroethylidenebenzylamine (35), *N*-2,2,3,3,3-pentafluoropropylidenebenzylamine (36), and *N*-(hexafluoroisopropylidene)benzylamine (37), formed on the basis of the general reaction (Scheme 17), were distilled under vacuum to afford clear free-flowing liquids.



$R'RC{=}NHCH_2C_6H_5$

[R' = CF_3, R = H (35); R' = C_2F_5, R = H (36); R'= R = CF_3 (37)]

Scheme 17

When these products were examined immediately after distillation by ^1H N.M.R (60 MHz), it appeared from the movement of the benzyl CH_2 group to lower field (δ 5.50), and disappearance of the amino group originally resonating at δ 2.00, that the desired compounds may have been formed. However upon standing at room temperature for a few days, the products had become pleasant-smelling, green, viscous liquids, whose ^1H and ^{13}C N.M.R. spectra were very complicated, suggesting that significant decomposition had occurred.

In contrast, *N*-benzylidenebenzylamines derived in the present work from the reactions of benzylamine with aromatic aldehydes, were isolated as stable, pleasant-smelling, yellow solids, in a high state of purity. Although on one occasion *N*-2'-hydroxybenzylidenebenzylamine was distilled under high vacuum (b.p. 130 - 134 °C at 0.10 mmHg), elemental and spectroscopic analysis showed that further purification of the aromatic derivatives was not necessary. Even after standing at room temperature for several months, these compounds still maintained their integrity. Interestingly, *N*-pentafluorobenzylidenebenzylamine was prepared as an orange solid in a high state of purity. It is thought

that the extended conjugation provided by the aromatic ring in the benzylidenebenzylamine compounds, appears to confer significantly greater stability than is the case with the aliphatic derivatives. A summary of the *N*-alkylidenebenzylamines and *N*-benzylidenebenzylamines prepared is given in Table 3.

TABLE 3. *N*-ALKYLIDENEBENZYLAMINES & *N*-BENZYLIDENEBENZYLAMINES

$R'RC{=}NCH_2C_6H_5$ [25]

R'	R	MOLECULAR FORMULA	YIELD %	B.P. (°C/ mmHg)
CH_3CH_2	H	$C_{10}H_{13}N$	45	94 - 96/10
CH_3	CH_3	$C_{10}H_{13}N$	40	113 - 116/15
n-BuCH(Et)CH*	H	$C_{15}H_{23}N$	60	98 - 102/0.2
2-HOC_6H_4	H	$C_{14}H_{12}NO$	100	130 - 134/0.1
4-$CH_3OC_6H_4$	H	$C_{15}H_{15}NO$	100	~
C_6H_5	H	$C_{14}H_{13}N$	100	~
C_6F_5*	H	$C_{14}F_5H_8N$	100	~

~ not distilled, * new compound

(Although some of these compounds have been used elsewhere to synthesise the corresponding aminophosphonic acids, until the present work, they have not been characterised in any great detail).

1.2.2. THE SYNTHESIS OF *O,O*-DIALKYL 1-BENZYLAMINOALKANE-PHOSPHONATES

Nearly all the *O,O*-dialkyl 1-benzylaminoalkanephosphonates (38) prepared by the nucleophilic addition of dialkyl phosphites to *N*-alkylidenebenzylamines and *N*-benzylidenebenzylamines, were isolated as pure compounds, in very good yield. These phosphonates remained stable, showing no sign of decomposition, even after standing at room temperature for several months. The compounds with aliphatic substituents in the α-position, were isolated as reddish-orange, viscous oils, whilst those with aromatic substituents were bright yellow or orange solids. The general equation for the reaction (Scheme 18) is given below.

$$R'RC{=}NCH_2C_6H_5 + (R''O)_2P(O)H \longrightarrow (R''O)_2P(O)CR(NHCH_2C_6H_5)R' \quad (38)$$

(R = H or alkyl; R' = alkyl or aryl; R'' = CH_3 or CH_3CH_2)

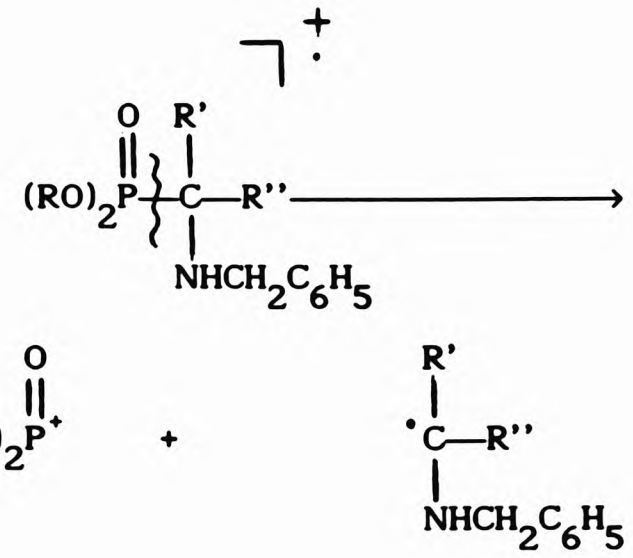
Scheme 18

Most of the compounds gave excellent elemental analyses and very good ^{1}H, ^{13}C and ^{31}P N.M.R. spectra, from which the structures of the compounds were authenticated. Although the fluoroalkylidenebenzylamines referred to in the previous section had not been clearly identified [compounds: (35), (36) and (37)], reaction of the products with dialkyl phosphite was attempted. Also hexafluoroacetone trihydrate, benzylamine

and dimethyl phosphite, were mixed together in methanol, in the hope that the corresponding phosphonate would be formed by rapid reaction of the phosphite with the imine before the latter had time to decompose. The products showed complex spectra and were not identifiable. Elemental analyses for these products were poor, suggesting that the fluoroalkylphosphonates had not been formed.

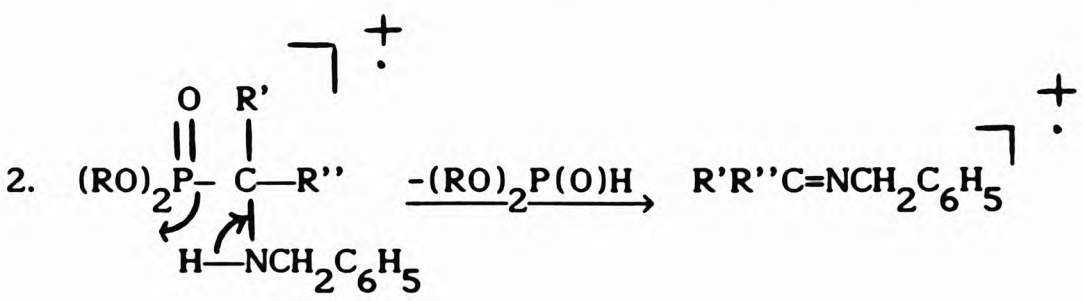
When attempts were made to further analyse *O,O*-dimethyl 1-benzylaminopropanephosphonate, *O,O*-diethyl 1-benzylaminopropane-phosphonate, *O,O*-dimethyl 1-benzylamino-2'-hydroxybenzylphosphonate and *O,O*-dimethyl 1-benzylamino-2-ethylhexanephosphonate by electron impact mass spectrometry, it was observed that the parent ion was present in only 0.7 % relative abundance in the *O,O*-dimethyl and *O,O*-diethylpropanephosphonate derivatives, and not at all in the other two cases. The significant signals that were readily observed corresponded to cleavage of the P-C bond and loss of neutral dialkyl phosphite or dialkoxy phosphinyl ion. In the two propane derivatives and in the 2'-hydroxybenzyl and 2-ethylhexyl derivatives, relative abundances of the dialkoxy phosphinyl ions were: 83 %, 98 %, 16.3 % and 100 % respectively. In the same order, the fragments caused by loss of neutral dialkyl phosphite were: 14 %, 14.1 %, 55 % and 36 % abundant. These compounds were also characterised by the appearance of the benzyl ion in 100 % relative abundance, corresponding to cleavage of the N-C bond, in the 1-benzylamino moiety. A general representation of these fragmentation patterns (Scheme 19) is given overleaf.

1.



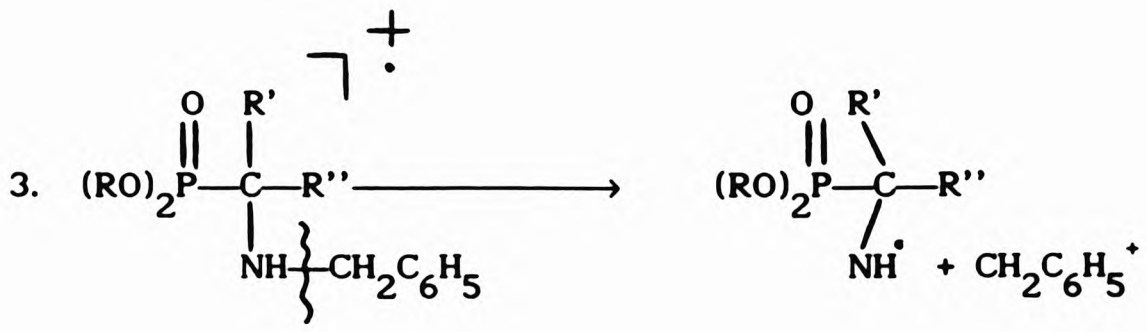
(R = Me or Et; R' = H or alkyl; R'' = alkyl or aryl)

2.



(R = Me or Et; R' = H or alkyl; R'' = alkyl or aryl)

3.



(R = Me or Et; R' = H or alkyl; R'' = alkyl or aryl)

Scheme 19

A summary of the *O,O*-dialkyl 1-benzylaminoalkanephosphonates prepared is given in Table 4.

TABLE 4. ELEMENTAL ANALYSES OF *O,O*-DIALKYL 1-BENZYLAMINO-ALKANEPHOSPHONATES $(R''O)_2P(O)CR(NHCH_2C_6H_5)R'$[25]

				FOUND (%)		
R'	R''	R	YIELD (%)	C	H	N
1. CH_2CH_3	CH_3	H	90	56.11	7.89	6.06
2. CH_2CH_3	CH_3CH_2	H	98	59.36	8.68	4.87
3. CH_3	CH_3	CH_3	100	55.97	7.93	5.61
4. CH_3	CH_3CH_2	CH_3	83	58.76	8.33	4.88
5. C_6H_5	CH_3	H	100	63.11	6.71	4.93
6. 2-HOC_6H_4	CH_3	H	100	59.67	6.37	4.42
7. 4-$CH_3OC_6H_4$	CH_3	H	100	59.10	6.72	4.08
8. n-BuCH(Et)CH*	CH_3	H	90	62.42	9.36	4.22
9. n-BuCH(Et)CH*	CH_3CH_2	H	94	64.28	9.50	4.01
10. C_6F_5*	CH_3	H	95	48.22	3.65	3.46

		REQUIRES (%)		
COMPOUND	FORMULA	C	H	N
1.	$C_{12}H_{20}NO_3P$	56.03	7.78	5.45
2.	$C_{14}H_{24}NO_3P$	58.95	8.42	4.91
3.	$C_{12}H_{20}NO_3P$	56.03	7.78	5.45
4.	$C_{14}H_{24}NO_3P$	58.95	8.42	4.91
5.	$C_{16}H_{20}NO_3P$	62.95	6.56	4.59
6.	$C_{16}H_{20}NO_4P$	59.81	6.23	4.36

COMPOUND	FORMULA	C	H	N
7.	$C_{17}H_{22}NO_3P$	60.90	6.57	4.18
8.	$C_{17}H_{30}NO_3P$	62.39	9.17	4.28
9.	$C_{19}H_{34}NO_3P$	64.23	9.58	3.94
10.	$C_{16}F_5H_{15}NO_3P$	48.61	3.80	3.54

* = new compound

(All compounds were fully characterised for the first time).

O,O-Dimethyl 1-benzylamino-1-methylethanephosphonate was subjected to catalytic hydrogenolysis over moist palladium on carbon (5 %), under 250 p.s.i. of hydrogen at 90 ^{o}C, for 6 h in glacial acetic acid as the solvent for the reaction.[40] Debenzylation generated the crude *O,O*-dimethyl 1-amino-1-methylethanephosphonate derivative in quantitative yield, and was characterised by ^{1}H N.M.R. (60 MHz). Acid hydrolysis of the phosphonate followed by treatment with propene oxide, afforded 1 amino-1-methylethanephosphonic acid in 77 % yield from 0.02 mol of the *N*-benzylamino precursor, as a fluffy, white, crystalline material.

The above method of synthesising 1-aminophosphonic acids, does not lend itself to the use of relatively large amounts of substrate. As in the similar case of the *O,O*-dialkyl 1-hydroxyiminoalkane-phosphonates,[41] an increase in the concentration of benzylaminoalkane-phosphonate being hydrogenated (0.10 mol and above in 200 cm^3 of

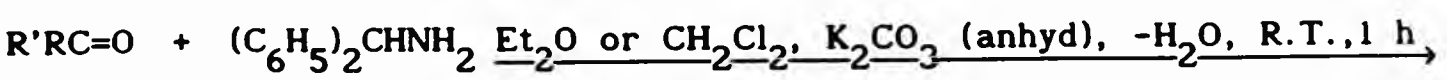
solvent), sees a concomitant drop in the yield of the corresponding aminoalkane derivative. Less laborious methods of synthesising 1-aminoalkanephosphonic acids will be discussed later.

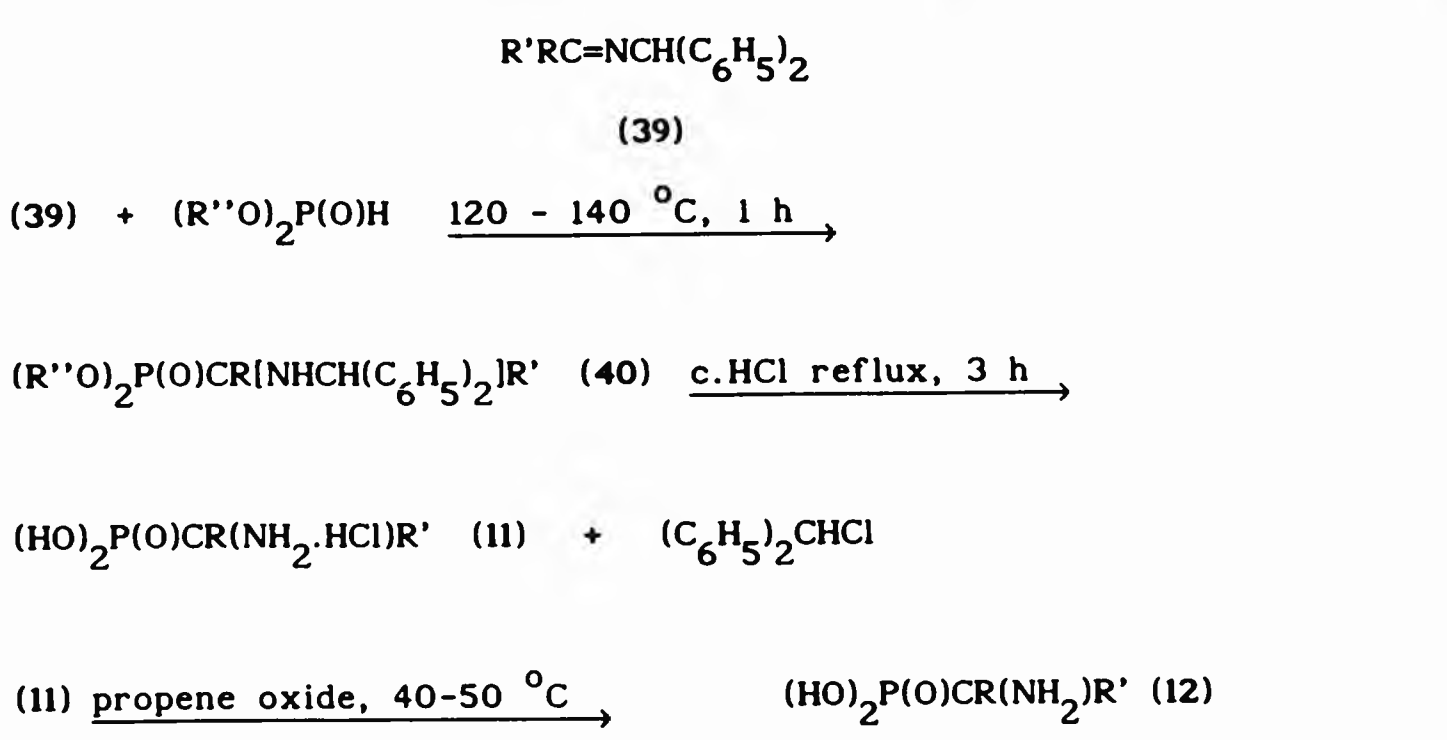
1.3. THE SYNTHESIS OF 1-AMINOALKANEPHOSPHONIC ACIDS VIA *O,O*-DIALKYL 1-DIPHENYLMETHYLAMINOALKANEPHOSPHONATES

1.3.1. THE SYNTHESIS OF *N*-ALKYLIDENEDIPHENYLMETHYLAMINES & *N*-BENZYLIDENEDIPHENYLMETHYLAMINES

The '1-pot' synthesis of 1-aminoalkanephosphonic acids via imines, readily synthesised by addition of aldehyde or ketone to 1,1-disubstituted benzylamines, is a useful reaction that avoids having to use a hydrogenation step to liberate the aminophosphonate derivative from its protected precursor (J.Lukszo & R.Tyka).[27]

A similar approach has been used successfully during the course of the present work, where novel Schiff's bases (39) derived from aliphatic or aromatic aldehydes and diphenylmethylamine have been subjected to nucleophilic addition by dimethyl or diethyl phosphite at elevated temperature. The *O,O*-dialkyl 1-diphenylmethylaminoalkane-phosphonates (40) which are formed, may be acid-hydrolysed to afford the corresponding 1-aminoalkanephosphonic acids after treatment with propene oxide.[32] The reactions (Scheme 20) are given overleaf.





(R = H or alkyl; R' = alkyl or aryl; R'' = Me or Et)

Scheme 20

The *N*-alkylidenediphenylmethylamines are formed in quantitative yields as viscous orange-yellow liquids. Although they may be distilled under high vacuum, elemental and N.M.R. analysis revealed that further purification was not necessary. The *N*-benzylidenediphenylmethylamines are also formed in quantitative yields, but as bright orange-yellow low melting point solids. These compounds are very useful substrates for conversion to their corresponding 1-aminoalkyl- or 1-aminoaryl- phosphonic acids. A significant number of these Schiff's bases were used conveniently to synthesise 1-aminophosphonic acids which

were not possible to obtain by other routes. A summary of these novel Schiff's bases is given in Table 5.

Attempts were also made to prepare *N*-2,2,2-trifluoroethylidene-diphenylmethylamine (41) and *N*-hexafluoroisopropylidenediphenyl-methylamine (42).

$CF_3CH{=}NCH(C_6H_5)_2$ (41) $(CF_3)_2C{=}NCH(C_6H_5)_2$ (42)

The results of the elemental analyses of the condensation products of trifluoroacetaldehyde monohydrate (said to contain varying amounts of the ethyl hemiacetal, according to the manufacturers, Lancaster Synthesis), and hexafluoroacetone trihydrate, with diphenyl-methylamine, clearly showed that the desired product in each instance had not been formed.

TABLE 5. *N*-ALKYLIDENEDIPHENYLMETHYLAMINES & *N*-BENZYLIDENEDIPHENYL-METHYLAMINES SYNTHESISED DURING CURRENT WORK $RCH{=}NCH(C_6H_5)_2$

R	FOUND (%)			REQUIRES (%)		
	C	H	N	C	H	N
$4\text{-}CH_3OC_6H_4$	83.74	6.37	4.49	83.72	6.31	4.65
$2\text{-}HOC_6H_4$	83.62	5.92	4.88	83.62	5.92	4.88
$4\text{-}HOC_6H_4$	83.56	5.87	4.87	83.62	5.92	4.88
$2\text{-}CH_3CH_2OC_6H_4$	83.77	6.63	4.40	83.81	6.67	4.44
$4\text{-}CH_3C_6H_4$	88.28	6.72	4.85	88.42	6.67	4.91

$3\text{-}C_5H_5N$	83.74	5.66	10.31	83.82	5.88	10.29
$4\text{-}(CH_3)_2CHC_6H_4$	87.96	7.40	4.49	88.18	7.35	4.47
C_6H_5	88.43	6.30	4.79	88.56	6.27	5.17
$3,4,5\text{-}(CH_3O)_3C_6H_2$	76.54	6.41	3.73	76.45	6.37	3.88
$4\text{-}(CH_3)_2NC_6H_4$	83.97	14.00	8.95	84.08	7.01	8.92
$3\text{-}CH_3O\text{-}4\text{-}HOC_6H_3$	83.67	6.37	4.57	83.72	6.31	4.65
$2\text{-}NO_2C_6H_4$	76.03	5.00	8.84	75.95	5.06	8.86
$4\text{-}NO_2C_6H_4$	76.02	4.97	8.96	75.95	5.06	8.86
$2\text{-}FC_6H_4$	83.01	5.53	4.86	83.05	5.54	4.84
$4\text{-}FC_6H_4$	82.91	5.60	4.89	83.05	5.54	4.84
$4\text{-}CF_3C_6H_4$	74.30	4.82	4.07	74.34	4.72	4.13
$3\text{-}CF_3OC_6H_4$	70.89	4.54	3.84	70.99	4.51	3.94
C_6F_5	66.67	3.39	3.91	66.48	3.32	3.38
n-BuCH(Et)CH	86.16	9.37	4.83	86.01	9.22	4.78
CH_2=CH	86.95	6.90	6.38	86.88	6.79	6.34
$3\text{-}(3\text{-}CF_3C_6H_4O)C_6H_4$	78.02	4.80	3.37	78.07	4.82	3.37

The structures of the diphenylmethylamine derivatives were authenticated using ^{1}H & ^{13}C N.M.R. Very useful information was also obtained using low resolution electron impact mass spectrometry. All the compounds analysed by mass spectrometry, produced a molecular ion. For the most part, this ion was generated with between 40 % & nearly 80 % relative abundance. *N*-2'-Nitrobenzylidenediphenylmethylamine and *N*-2-ethylhexylidenediphenylmethylamine, produced their molecular ions

with 5 % and 11 % relative abundance respectively, however they too were able to generate fragmentation patterns that were highly characteristic of compounds of this type. In all examples the benzhydryl cation $(C_6H_5)_2CH^+$, usually the base peak, was generated by the loss of the R-CH=N moiety from the molecular ion. A constant feature observed, was the fragment associated with the loss of the phenyl group, C_6H_5. Other fragmentations associated with this part of the molecule were also observed. Depending upon the substituent carried on the alkylidene or benzylidene portion of the structure, definitive fragmentations associated with these functional groups were also observed. For example in the case of some of the fluorinated diphenylmethylamine derivatives, a fragment associated with the loss of fluorine, $[M-F]^+$, was observed: from *N*-[3-(3-trifluoromethyl)phenoxybenzylidene]diphenylmethylamine, *N*-2'-fluorobenzylidenediphenylmethylamine, *N*-4'-trifluoromethyldiphenylmethylamine and *N*-pentafluorobenzylidenediphenylmethylamine with relative abundances of 3.5 %, 5 %, 25.2 % and 7.6 % respectively. A summary of some major fragments generated for these compounds is given in Table 6.

TABLE 6. m/z AND RELATIVE ABUNDANCES (%) OF IMPORTANT FRAGMENTS OF R-CH=NCH(C_6H_5)$_2$-

R	M^+	$(C_6H_5)_2CH^+$	$M^+ - C_6H_5$
4-$CH_3OC_6H_4$	301, 72.0	167, 89.8	224, 50.6
2-HOC_6H_4	287, 74.7	167 100.0	210, 4.8
4-HOC_6H_4	287, 77.5	167, 100.0	210, 30.7
2-$CH_3CH_2OC_6H_4$	315, 46.1	167, 100.0	238, 10.0
4-$CH_3C_6H_4$	285, 61.1	167, 93.8	208, 41.2
4-$CH_3CH_2C_6H_4$	299, 41.8	167, 100.0	222, 13.4
3-C_5H_5N	272, 54.1	167, 100.0	195, 9.4
4-$(CH_3)_2CHC_6H_4$	313, 72.2	167, 100.0	236, 13.1
C_6H_5	271, 43.9	167, 100.0	194, 11.7
3,4,5-$(CH_3O)_3C_6H_2$	361, 43.4	167, 100.0	284, 1.8
4-$(CH_3)_2NC_6H_4$	314, 57.2	167, 91.3	237, 23.0
3-CH_3O-4-HOC_6H_3	317, 61.5	167, 69.8	240, 50.3
2-$NO_2C_6H_4$	316, 5.0	167, 100.0	239, 5.3
4-$NO_2C_6H_4$	316, 59.3	167, 76.7	239, 37.8
2-FC_6H_4	289, 49.8	167, 100.0	212, 25.9
4-FC_6H_4	289, 61.0	167, 100.0	212, 13.5
4-$CF_3C_6H_4$	339, 54.8	167, 100.0	262, 29.4
3-$CF_3OC_6H_4$	355, 57.8	167, 94.6	278, 41.5
C_6F_5	361, 34.2	167, 100.0	284, 31.7

3-(3-$CF_3C_6H_4O$)C_6H_4	431, 58.6	167, 100.0	354, 3.8
n-BuCH(Et)CH	293, 11.0	167, 100.0	216, 2.6
CH_2=CH-	221, 34.0	167, 90.9	-

Exact mass measurements run on *N*-4-dimethylaminobenzylidene-diphenylmethylamine and *N*-pentafluorobenzylidenediphenylmethylamine gave confirmation that many fragments observed in the mass spectra of this general class of compounds were authentic. All the diphenylmethylamine derivatives that were analysed by low resolution electron impact mass spectrometry, gave rise to satellite peaks in accordance with the natural abundance of ^{13}C, responsible for peaks such as $[M + 1]^+$.

1.3.2 THE ADDITION OF DIALKYL PHOSPHITE TO *N*-ALKYLIDENEDIPHENYLMETHYLAMINES AND *N*-BENZYLIDENEDIPHENYLMETHYLAMINES

Several *N*-benzylidenediphenylmethylamines were treated with dialkyl phosphite at elevated temperature (Scheme 20). The *O,O*-dialkyl 1-diphenylmethylaminobenzylphosphonates formed as intermediates (but not characterised), gave rise to the corresponding 1-aminophosphonic acids by acid hydrolysis and treatment with propene oxide. A summary of the 1-aminophosphonic acids synthesised this way is given in Table 7.

TABLE 7. 1-AMINOBENZYLPHOSPHONIC ACIDS SYNTHESISED BY ACID HYDROLYSIS OF THE CORRESPONDING *O,O*-DIALKYL 1-DIPHENYL-METHYLAMINOBENZYLPHOSPHONATES $(HO)_2P(O)CH(NH_2)R$

R	YIELD (%)	M.P/°C	REQUIRED (%)			FOUND (%)		
			C	H	N	C	H	N
4-$CH_3OC_6H_4$ [116]	35	285-8	44.24	5.53	6.45	44.18	5.52	6.00
2-HOC_6H_4	17	310-3	41.38	4.93	6.90	41.24	4.92	6.37
4-$CH_3C_6H_4$ [34]	4	275-8	47.76	5.97	6.97	45.32	5.91	6.01
4-$CH_3CH_2C_6H_4$	42	284-6	50.23	6.51	6.51	50.15	6.48	6.50
4-$(CH_3)_2CHC_6H_4$	27	286-8	52.40	6.99	6.11	52.46	6.98	5.75
C_6H_5 [34]	42	286-9	44.92	5.35	7.49	45.10	5.29	7.25
3-CH_3O-4-HOC_6H_3 *	1	290-4	41.20	5.15	6.01	37.88	6.18	3.76
4-$NO_2C_6H_4$ [27]	48	230-4	36.21	3.88	12.07	36.25	3.82	11.94
2-FC_6H_4 *	28	270-3	40.98	4.39	6.83	41.05	4.41	6.61
4-$CF_3C_6H_4$ *	46	287-9	37.65	3.53	5.49	37.50	3.55	5.40
3-$CF_3OC_6H_4$ *	43	277-80	35.42	3.32	5.17	36.62	3.54	5.40
C_6F_5 *	18	268-70	31.15	2.03	5.69	31.04	2.15	5.38
4-FC_6H_4 *	55	278-82	40.98	4.39	6.83	40.98	4.48	6.80

* = new compound

All the 1-aminophosphonic acids listed in Table 7 gave excellent infrared, ^{1}H, ^{13}C, and ^{31}P N.M.R. spectra, and in the case of the fluorinated derivatives, ^{19}F N.M.R. spectra. In addition, some of these compounds were submitted for FAB mass spectrometry, giving intense ions at $[M+H]^{+}$ (normally the base peak) in the positive ion spectrum and other highly characteristic fragmentation patterns. An appraisal of this information will be given in a later section.

1.4. THE '1-POT' SYNTHESIS OF 1-AMINOALKANEPHOSPHONIC ACIDS

1-Aminoalkanephosphonic acids were synthesised using the '1-pot' approach of Oleksyszyn and Tyka.[34] It has been well documented that the reaction involves condensation of ethyl or benzyl carbamate, aldehyde or ketone and triphenyl phosphite, in glacial acetic acid, and it has been suggested that the reaction may involve nucleophilic attack by triphenyl phosphite on the Schiff's base (43) formed between the carbonyl compound and the carbamate. Acid hydrolysis of the crude unisolated condensation intermediates (44), followed by propene oxide treatment affords the desired product in fair yields. The reaction (Scheme 21) is shown below.

$$R'RC{=}O + H_2NOCOR'' \xrightarrow{H^+} R'RC(HO)NH_2{}^{+}OCOR'' \xrightarrow{-H^+,-H_2O^+}$$

$$R'RC{=}NOCOR'' \quad (43)$$

(43) + $(C_6H_5O)_3P$: $\xrightarrow{HOAc}$

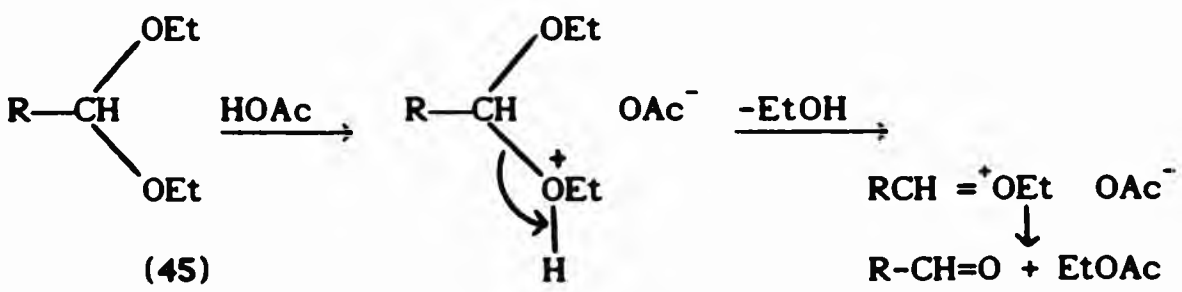
$(C_6H_5O)_2P(O)CR(NHOCOR'')R'$ **(44)**

(44) $\xrightarrow{\text{(i) c.HCl, (ii) propene oxide}}$ $(HO)_2P(O)CR(NH_2)R'$ + $2C_6H_5OH$

(R = H or alkyl; R' = alkyl or aryl; R'' = Et or Bz)

Scheme 21

To investigate the possible use of acetals in place of free aldehydes in this type of reaction, propionaldehyde diethyl acetal was heated with ethyl carbamate and triphenyl phosphite in glacial acetic acid at 100 ^{o}C for an extended period and was found to give rise to 1-aminopropanephosphonic acid in 25 % yield after acid hydrolysis of the condensation intermediate and isolation as described earlier. It is thought that a Schiff's base intermediate may be formed as above, as the acetal **(45)** becomes converted into the free aldehyde *in situ* possibly as follows (Scheme 22).



Scheme 22

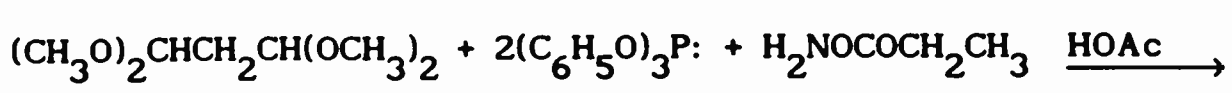
This result was particularly interesting in that it was envisaged that trifluoroacetaldehyde monohydrate, pentafluoropropanal monohydrate (both said to contain varying amounts of their ethyl hemiacetals, as specified by the manufacturers Lancaster Synthesis) and hexafluoroacetone trihydrate, might be similarly used in the '1-pot' reaction to synthesise the corresponding 1-aminofluoroalkanephosphonic acids. The preparation and use of fluoroaldehydes and ketones is particularly difficult because of their high volatility.[42-46] The boiling points of free trifluoroacetaldehyde, pentafluoropropanal and hexafluoroacetone have been recorded as -19 to -18 ^{o}C (746 mmHg),[42-44] 2 ^{o}C (746 mmHg),[44,45] and -26 ^{o}C[46] respectively.

A number of attempts were initially made to liberate trifluoroacetaldehyde from trifluoroacetaldehyde monohydrate, by gently warming the hydrated aldehyde over concentrated sulphuric acid and collecting the volatilising material thought to be the desired aldehyde, in a Cardice-acetone cooled trap, as a colourless liquid.[45,47] After removing the coolant, the trap returned to room temperature and its contents were allowed to distil into a cooled (ice-salt) mixture of ethyl carbamate and triphenyl phosphite in glacial acetic acid. The reaction was allowed to proceed in the usual way, but after work-up, no 1-aminofluoroalkanephosphonic acid could be isolated. Prior to the hydrolysis stage Cardice-acetone cooled condensers were fitted to the reaction flask while the reagents were slowly heated to 100 ^{o}C in an oil bath. It may be that this technique was not sufficient to contain the

volatile aldehyde under the elevated temperature conditions required for the reaction.

In view of the success of using propionaldehyde diethyl acetal to synthesise 1-aminopropanephosphonic acid, trifluoroacetaldehyde monohydrate, pentafluoropropanal monohydrate and hexafluoroacetone trihydrate were used in an analogous way. In each case however the corresponding 1-aminofluoroalkanephosphonic acid was not formed. The likelihood that the presence of water associated with the hydrated aldehyde or ketone might be interfering with the reaction, was investigated by carrying out the '1-pot' procedure of condensing propanal, ethyl carbamate and triphenyl phosphite in glacial acetic acid with either one or three molecular equivalents of water added to the mixture. In each case no product was isolated possibly because the presence of water caused hydrolysis of triphenyl phosphite, before it could react with the carbonyl compound and carbamate as desired.

The precedent established by using propionaldehyde diethyl acetal to generate the corresponding 1-aminoalkanephosphonic acid, led to an investigation of the use of 1,1,3,3-tetramethoxypropane in the hope that 1,3-diaminopropane-1,3-bisphosphonic acid (46) might be synthesised in a similar way. The proposed reaction (Scheme 23) is shown overleaf.



$$(HO)_2P(O)CH(NH_2)CH_2(NH_2)CHP(O)(OH)_2 \quad (46)$$

Scheme 23

The reaction was repeated on a number of occasions where the amount of time allowed for the reagents to mix together before acid hydrolysis, was varied considerably. Unfortunately no aminophosphonic product could be isolated. Elemental analysis of the creamy-white crystalline material obtained revealed that there was no carbon present, but the nitrogen content and the very high melting point (greater than 350 ^{o}C) suggested that it may have been an inorganic ammonium salt.

Although 1-aminobenzylphosphonic acid has been synthesised by the '1-pot' procedure[34], (Scheme 21, R = H and R' = C_6H_5), the corresponding 1-aminophosphonic acids could not be obtained from 2'-hydroxybenzaldehyde (salicylaldehyde), 4'-methoxybenzaldehyde (*p*-anisaldehyde), 4'-hydroxybenzaldehyde, 3'-methoxy-4'-hydroxy-benzaldehyde (vanillin) and 3'-hydroxy-4'-methoxybenzaldehyde (iso-vanillin). Glycolaldehyde and DL-glyceraldehyde also failed to give the corresponding 1-aminophosphonic acids. The material obtained at the end of each reaction, after work-up, was a viscous oily residue which when examined by 60 MHz ^{1}H N.M.R. displayed no aminophosphonic acid character. The spectrum was a complicated distribution of broad signals

indicating that the product was little more than an intractable residue. The implication is that the '1-pot' procedure mainly gives favourable results when aliphatic aldehydes or ketones, without accompanying groups are used. A complication may also arise if the aldehyde contains hydroxy groups which may displace C_6H_5O from $(C_6H_5O)_3P$ before the required reaction can take place. A summary of the 1-aminoalkanephosphonic acids synthesised by the '1-pot' procedure is given in Table 8.

TABLE 8. 1-AMINOALKANEPHOSHONIC ACIDS SYNTHESISED BY THE '1-POT' ROUTE $(HO)_2P(O)CR(NH_2)R'$

R	R	YIELD (%)	M.P./°C	REQUIRES (%)			FOUND (%)		
				C	H	N	C	H	N
CH_2CH_3 [34]	H	30	263-5	25.90	7.19	10.07	26.09	7.33	9.87
$CH_2CH_2CH_3$ [34]	H	20	271-4	31.37	7.84	9.15	32.23	8.10	9.16
CH_3 [125]	CH_3	30	250-3	25.90	7.19	10.07	25.30	7.84	9.65
$CH_2CH(CH_3)_2$ [126]	H	60	263-4	35.93	8.38	8.38	36.03	8.60	8.35
n-BuCH(Et)CH*	H	20	240-3*	45.93	9.57	6.69	45.45	9.67	6.86

* = new compound

1.5. THE STRUCTURAL CHARACTERISATION OF 1-AMINOPHOSPHONIC ACIDS

Apart from 1-amino-4'-nitrobenzylphosphonic acid which was isolated as a bright yellow crystalline material, the other 1-aminophosphonic acids were white, crystalline, high-melting point, water-soluble solids. The compounds gave highly characteristic infra-red, ^{1}H, ^{13}C, ^{31}P and where appropriate ^{19}F spectra, as well as definitive FAB ms data.

Preliminary examination of the aminophosphonic acids by infra-red spectroscopy, in all cases showed strong absorptions associated with the stretching vibrations of the major distinguishing features of the molecule. υ_{max} (KBr) / cm^{-1} for the compounds were generally in the regions: 1040 - 1080 (P-O-C) and 1180 - 1250 (P=O). Other stretching vibrations were present, depending upon the structural attributes of the molecule in question. It was possible quickly to establish the presence of the 1-aminophosphonic acids in this way before embarking upon the detailed confirmatory use of N.M.R. spectroscopy and FAB mass spectrometry.

The ^{1}H N.M.R. spectra of the 1-aminoalkanephosphonic acids frequently gave highly complex multiplicities by virtue of the coupling between the hydrogen atom attached to the chiral carbon atom in the α-position, and the adjacent non-equivalent methylene protons in the alkyl chain ($^{3}J_{HCCH}$). The additional coupling from the phosphorus atom to this methine hydrogen atom ($^{2}J_{PCH}$) and the non-equivalent methylene

protons ($^3J_{PCCH}$) as in the case of 1-aminopropanephosphonic acid, PNL 62, explains why the spectra of such compounds are so complex. The ^1H N.M.R of PNL 62 is shown in Fig. 1 (see appendix).

The situation is simplified considerably when the α-carbon is attached to two identical alkyl groups. For example in the case of 1-amino-1-methylethanephosphonic acid, a structural analogue of 1-amino-propanephosphonic acid, one observes only a neat doublet for the pair of methyl groups resonating at approximately δ 1.30 - 1.31, with $^3J_{PCCH}$ 12.20 Hz. The 1-aminobenzylphosphonic acids, give much less complex ^1H N.M.R. spectra. The hydrogen atom residing on the chiral α-carbon atom, resonates as a doublet by virtue of its coupling with the phosphorus atom of the phosphonic acid moiety. $^2J_{PCH}$ is in the region of 15.0 - 20.0 Hz, with chemical shift varying slightly, depending upon the nature of the substituents attached to the aromatic ring.

A comparison of the ^1H N.M.R. chemical shifts, and where possible $^2J_{PCH}$ is given in Table 9, for the methine hydrogen in the α-position of the 1-aminophosphonic acids prepared during the course of the present work. The solvent referred to as NaOD, was NaOH dissolved in D_2O which readily dissolved the aminophosphonic acids more efficiently than D_2O was able to on its own. It should be noted that chemical shifts and coupling constants for phosphonic acids are pH dependent and the data given here are those for the anionic form, $^{=}O_2P(O)CH(NH_2)R$ when excess of NaOD is present.

TABLE 9

^{1}H N.M.R. DATA FOR THE HYDROGEN ATOM IN THE α-POSITION IN 1-AMINOPHOSPHONIC ACIDS $(HO)_2P(O)CH(NH_2)R$

R	SOLVENT	δ_H/ppm	MULTIPLICITY	$^2J_{PCH}$/Hz
CH_2CH_3	D_2O	3.11 - 3.23	ddd	13.20
$CH_2CH_2CH_3$	NaOD	2.48 - 2.58	ddd	-
$CH_2CH(CH_3)_2$	NaOD	2.99 - 3.09	ddd	-
n-BuCH(Et)CH	NaOD	2.65 - 2.72	dd	14.22
4-$CH_3OC_6H_4$	NaOD	3.79	d	18.52
2-HOC_6H_4	NaOD	4.32	d	14.35
4-$CH_3C_6H_4$	NaOD	3.77	d	15.28
4-$CH_3CH_2C_6H_4$	NaOD	3.78	d	15.31
4-$(CH_3)_2CHC_6H_4$	NaOD	3.79	d	15.30
C_6H_5	NaOD	4.24	d	14.84
3-CH_3O-4-HOC_6H_3	NaOD	3.64	d	14.36
4-$NO_2C_6H_4$	NaOD	4.01	d	17.29
2-FC_6H_4	D_2O	4.75	d	16.55
,,	NaOD	4.14	d	16.10
4-FC_6H_4	NaOD	3.86	d	15.36
4-$CF_3C_6H_4$	NaOD	3.95	d	16.41
3-$CF_3OC_6H_4$	NaOD	3.87	d	16.24
C_6F_5	NaOD	4.20	d	17.53

The broad band decoupled ^{13}C N.M.R. spectra of the 1-aminophosphonic acids gave useful information as to the identity of these molecules. It was observed in the aliphatically substituted derivatives, that while $^{1}J_{PC}$ and $^{3}J_{PCCC}$ could be observed, the methylene carbon resonated as a singlet, indicating that there was negligible or no $^{2}J_{PCC}$ coupling, when a field strength of 62.896 MHz was used. In the case of the aromatically substituted derivatives, $^{1}J_{PC}$, $^{2}J_{PCC}$ and $^{3}J_{PCCC}$ could be observed in almost every instance. The multiplicities of these signals become complex in the case of the 1-aminofluorobenzyl derivatives, where coupling from the fluorine atom to the aromatic ring is present. A summary of these data is given in Table 10.

The ^{1}H decoupled ^{31}P N.M.R. spectra of the 1-aminophosphonic acids usually gave sharp singlets resonating in the region of approximately 15 to 20 ppm. In the examples of the fluorinated derivatives, where a single fluorine atom was bonded directly to the aromatic ring, the phosphorus signal was observed as a sharp doublet. In the case of 1-aminopentafluorobenzylphosphonic acid the signal was observed as a poorly resolved multiplet, consistent with the contribution that one would have expected from each of the fluorine atoms attached to the ring, coupling to phosphorus, namely $2x^{4}J_{FP}$, $2x^{5}J_{FP}$ and $1x^{6}J_{FP}$. By contrast the ^{31}P N.M.R. spectra of 1-amino-3'-trifluoromethoxybenzylphosphonic acid and 1-amino-4'-trifluoromethylbenzylphosphonic acid were observed as singlets, where intervening bonds separate the fluorine moiety from the aromatic ring,

abolishing the long-range F-P coupling.

TABLE 10. SUMMARY OF ^{13}C N.M.R. DATA OF 1-AMINOPHOSPHONIC ACIDS $(HO)_2P(O)CR(NH_2)R'$, SYNTHESISED DURING PRESENT WORK

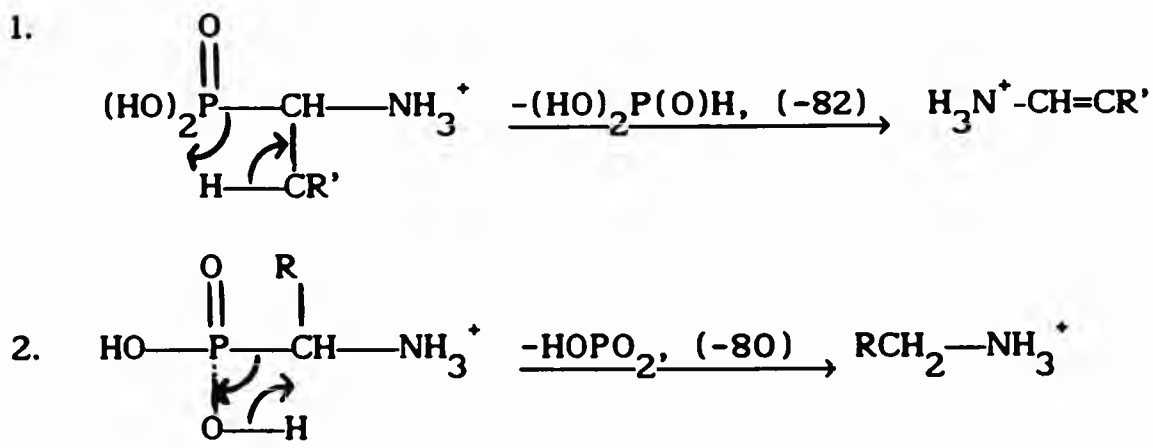
R'	R	SOLVENT	$^1J_{PC}$/Hz	$^2J_{PCC}$/Hz	$^3J_{PCCC}$/Hz
CH_2CH_3	H	NaOD	134.86	0	10.67
,,		D_2O	142.87	0	9.52
CH_3	CH_3	NaOD	139.16	0	-
,,		D_2O	148.00	0	-
$CH_2CH_2CH_3$	H	NaOD	138.57	0	12.64
$CH_2CH(CH_3)_2$	H	NaOD	134.59	0	10.40
n-BuCH(Et)CH	H	NaOD	137.28	0	11.85
4-$CH_3OC_6H_4$	H	NaOD	132.65	2.01	5.22
2-HOC_6H_4	H	NaOD	137.55	0	3.40
,,					7.49
4-$CH_3C_6H_4$	H	NaOD	131.52	2.64	1.57
4-$CH_3CH_2C_6H_4$	H	NaOD	131.83	0	4.78
4-$(CH_3)_2CHC_6H_4$	H	NaOD	131.08	2.45	4.91
C_6H_5	H	NaOD	127.30	4.65	1.57
3-CH_3O-4-HOC_6H_3	H	NaOD	135.16	0	4.91
4-$NO_2C_6H_4$	H	NaOD	126.36	2.45	4.28
2-FC_6H_4	H	NaOD	132.20	1.89	2.39

$4\text{-}FC_6H_4$	H	NaOD	131.08	0	5.06
$4\text{-}CF_3C_6H_4$	H	NaOD	128.06	0	4.65
$3\text{-}CF_3OC_6H_4$	H	NaOD	128.06	0	4.53
,,					4.72
C_6F_5	H	NaOD	130.89	m	m

The solvent referred to as NaOD, was NaOH dissolved in D_2O, which was found to dissolve the aminophosphonic acids with little difficulty, for the purposes of N.M.R. analysis. In these cases the data refer to the anionic form, $^{=}O_2P(O)C(NH_2)RR'$.

1.6. FAB MASS SPECTROMETRY OF 1-AMINOALKANE- & 1-AMINO-BENZYL- PHOSPHONIC ACIDS

Aminophosphonic acids, due to their zwitterionic nature, are not ordinarily amenable to electron impact mass spectrometry. When subjected to fast atom bombardment ionisation, however, they give the abundant ion corresponding to $[M+H]^+$ (usually the base peak), and characteristic fragments associated with cleavage of the P-C bond, with proton transfer, to yield the ions $[M+H - H_3PO_3]^+$ and the relatively less abundant $[M+H - HPO_3]^+$.[48,49,50] These typical fragmentations (Scheme 24) are shown overleaf, e.g.



Scheme 24

Adduct ions such as $[2M+H]^+$ and $[M+H+MATRIX]^+$, with fragmentations thereof, were also observed.[51] A summary of the compounds analysed by FAB ms in the present studies is given in Table 11.

TABLE 11. RELATIVE ABUNDANCIES (%) OF FRAGMENTS IN THE FAB ms OF 1-AMINOPHOSPHONIC ACIDS $(HO)_2P(O)CH(NH_2)R$

R	MATRIX	M+H	2M+H	M+H-H_3PO_3	M+H-HPO_3	M+H+X
CH_2CH_3	G	75.0	15.8	100.0	12.5	35.8
$CH_2CH_2CO_2H$	G	100.0	21.5	85.4	7.5	13.9
$CH_2CH_2CO_2CH_3$	G	95.9	28.1	100.0	17.3	2.4
$CH_2CH(CH_3)_2$	G	18.5	16.8	100.0	1.5	-
n-BuCH(Et)CH	N	10.0	-	-	-	8.8
4-$NO_2C_6H_4$	N	47.5	24.0	100.0	27.1	15.8

$4\text{-}CF_3C_6H_4$	T	52.5	20.83	100.0	12.08	-
$3\text{-}CF_3OC_6H_4$	3-NOBA	24.6	-	6.3	-	-
C_6F_5	T	74.6	40.42	100.0	2.92	2.92

(X = matrix; G = glycerol, T = thioglycerol, 3-NOBA = 3-nitrobenzyl alcohol)

The relatively new *caesium ion* source LSIMS, which has been used to characterise protected phosphonopeptides derived from ω-amino-α-hydroxyiminoalkanephosphonates (**47**),[52] as shown below:

$$(RO)_2P(O)\text{-}(C{=}N\text{-}OH)CHR'(CH_2)_n\text{-}NH_2$$

(47)

(R' = H or CH_3; n = 0, 1, 2)

was applied to 1-aminopropanephosphonic acid and 1-amino-4'-trifluoro-methylbenzylphosphonic acid. The ion source is said to be more sensitive than conventional FAB ms, and gives rise to fewer fragments in the postive ion spectrum. Both compounds characteristically gave rise to the: $[M+H]^+$ ion, $[2M+H]^+$ ion, and the fragment due to loss of H_3PO_3 from the protonated ion, as well as other less abundant species. In the case of 1-aminopropanephosphonic acid, the fragmentation pattern observed was: 418 (3M+H, 10.7), 371 (2M+H+G, 3.6), 279 (2M+H, 68.9),

232 (M+H+G, 31.4), 197 (2M+H - H_3PO_3, 6.4) and 140 (M+H, 100). In the case of 1-amino 4'-trifluoromethylbenzylphosphonic acid, the fragmentation pattern observed was: 511 (2M+H, 22.9), 348 (M+H+G, 7.1), 256 (M+H, 31.8), 176 (M+H - HPO_3, 3.6) and 174 (M+H - H_3PO_3, 100). In both examples very few background peaks were observed, giving the spectra a marked clarity and ease of interpretation.

1.7. THE SYNTHESIS OF 1-AMINOPHOSPHONOUS ACIDS

A range of 1-aminophosphonous acids, including new examples, were prepared as described[4] via the condensation of aldehyde, hypophosphorous acid and diphenylmethylamine hydrochloride, at elevated temperature to form first a 1-diphenylmethylaminoalkyl- or 1-diphenylmethylaminobenzyl- phosphonous acid (**48**), as an isolable intermediate. The intermediate in each instance was hydrolysed by refluxing in 18 % hydrochloric acid, and after work-up and treatment with propene oxide, gave rise to desired 1-aminoalkyl or 1-aminobenzyl-phosphonous acid (**49**).[4] The reactions (Scheme 25) are given below.

$$RCHO + H_3PO_2 + (C_6H_5)_2CHNH_2.HCl \xrightarrow{\text{heat, 2 h}}$$

$$H(HO)P(O)CH[NHCH(C_6H_5)_2]R \quad (48)$$

$$(47) + \text{(i) reflux in 18 \% c.HCl, 4 h; (ii) propene oxide} \longrightarrow$$

$$H(HO)P(O)CH(NH_2)R \quad (49)$$

(R = alkyl or aryl)

Scheme 25

In an analogous fashion earlier work by Schmidt[31] demonstrated that hypophosphorous acid could be added to alkylidenebenzylamine or substituted benzylidenebenzylamine derivatives to give the 1-benzylaminoalkyl or 1-benzylaminobenzyl-phosphonous acids (50) readily. However, all attempts to liberate the free 1-aminophosphonous acid by catalytic hydrogenolysis failed because of catalyst poisoning. Also when more forceful conditions were tried, P-C cleavage occurred, with loss of substrate.[31] The reactions (Scheme 26) are shown below.

$$RCH{=}NCH_2C_6H_5 \;+\; H_3PO_2 \longrightarrow H(HO)P(O)CH(NHCH_2C_6H_5)R \quad (50)$$

(49) + $\underline{H_2/cat.}\longrightarrow$ no product formed

[R = C_6H_5 or $(CH_3)_2CH$]

Scheme 26

Tyka and Hägele[53] have shown that aminobenzylphosphonous acids (53) may be obtained by amidoalkylation of hypophosphorous acid with *N,N'*-arylidene bisamides (51). In so doing, the use of a Schiff's base is avoided. The *N,N'*-arylidene bisamides are easily accessible precursors. The reactions (Scheme 27) are shown below.

$$RCH(NHCOCH_3)NHCOCH_3 \;(51) + \underline{H_3PO_2/AcOH}\longrightarrow$$

$H(HO)P(O)CH(NHCOCH_3)R$ (52) $\xrightarrow{\text{(i) } H^+,\ \text{(ii) propene oxide}}$ (unisolated)

$H(HO)P(O)CH(NH_2)R$ (53)

(R = aryl)

Scheme 27

It should be stressed, however, that only bisamides prepared from aromatic aldehydes are able to undergo the above reaction; bisamides derived from aliphatic aldehydes are unreactive. This method of preparation although restricted to 1-aminobenzylphosphonous acids could be attractive, as attempts to synthesise 1-amino-2'-ethoxy-benzylphosphonous acid and 1-amino-3',4',5'-trimethoxybenzylphosphonous acid in the present work, by condensation of the corresponding aldehydes with diphenylmethylamine hydrochloride and hypophosphorous acid failed to produce the desired product. However other 1-aminobenzylphosphonous acids were synthesised by the diphenylmethylamine hydrochloride-hypophosphorous acid route during the course of the present work, showing the utility of this condensation approach.

The 1-aminophosphonous acids synthesised were afforded as white microcrystalline, high-melting point, water soluble solids. The compounds gave very good elemental analyses, and excellent infrared, ^{1}H, ^{13}C and ^{31}P N.M.R. spectra. This class of compound is of particular interest as they have been described as having attractive antimicrobial

activities, plant growth inhibiting properties and other very useful biological activities.[4] The compounds may also provide a useful route to the corresponding 1-aminophosphonic acids in high yield and purity, by oxidation of the precursor molecule.[4] A summary of the 1-diphenylmethylaminoalkane- and 1-diphenylmethylaminobenzyl-phosphonous acids and 1-aminoalkane- and 1-aminobenzyl-phosphonous acids synthesised during the present work, is given in Table 12 and Table 13.

TABLE 12. SUMMARY OF 1-DIPHENYLMETHYLAMINOALKANE-PHOSPHONOUS ACIDS & 1-DIPHENYLMETHYLAMINOBENZYL-PHOSPHONOUS ACIDS $H(HO)P(O)CH[NHCH(C_6H_5)_2]R$

R	REQUIRED			OBSERVED		
	C	H	N	C	H	N
CH_3[4]	65.46	6.55	5.09	65.49	6.62	5.02
CH_2CH_3[113]	66.44	6.92	4.84	66.04	7.01	5.00
$CH_2CH(CH_3)_2$[4]	68.14	7.57	4.42	67.59	7.58	4.19
$2\text{-}HOC_6H_4$*	67.99	5.67	3.97	68.24	6.00	4.21
$4\text{-}CH_2CH_3C_6H_4$*	72.33	6.58	3.84	72.26	6.78	3.56
$4\text{-}FC_6H_4$*	67.61	5.35	3.94	67.04	5.33	3.96
n-BuCH(Et)CH*	70.20	8.36	3.90	70.10	8.42	3.62

* = new compound

TABLE 13. SUMMARY OF 1-AMINOALKANE- & 1-AMINOBENZYL-PHOSPHONOUS ACIDS $H(HO)P(O)CH(NH_2)R$

R	REQUIRED			OBSERVED		
	C	H	N	C	H	N
CH_3 [4]	22.02	7.34	12.84	22.34	7.42	12.89
CH_2CH_3 [113]	29.27	8.13	11.38	30.21	8.41	11.40
$CH_2CH(CH_3)_2$ [4]	39.74	9.27	9.27	39.81	9.06	9.31
2-HOC_6H_4 *	44.92	5.35	7.49	43.69	5.03	6.84
4-$CH_3CH_2C_6H_4$ *	54.27	7.04	7.04	54.66	7.07	6.52
4-FC_6H_4 *	44.44	4.76	7.41	45.22	5.10	6.32

* = new compound

1.8. STRUCTURAL CHARACTERISATION AND IDENTIFICATION OF THE 1-AMINOALKANE- & 1-AMINOBENZYL-PHOSPHONOUS ACIDS

Initial examination of the 1-aminoalkane- and 1-aminobenzyl-phosphonous acids by infrared spectroscopy, gave absorptions similar to those observed in the corresponding 1-aminoalkane- and 1-aminobenzyl-phosphonic acids but with additional P-H absorption. υ_{max} (KBr) / cm^{-1} for the compounds were generally in the region 2300 - 2400 (P-H); 1150 - 1200 (P=O); and 1000 - 1100 (P-O). Associated stretching vibrations were also present depending upon the nature of the moieties present. Infrared spectroscopy was used initially to establish the presence of

the phosphonous acids.

As in the case of the aminophosphonic acids above, N.M.R. spectra were run for solutions in NaOD (NaOH dissolved in D_2O, for ease of dissolution). The ^1H N.M.R. spectra were very similar to those of the corresponding phosphonic acids. The AB type multiplicities observed in the aliphatically substituted phosphonic acids were also present in the phosphonous acids in addition to the extra contribution of a low field doublet, with coupling constant of 500 - 520 Hz for $^1J_{PH}$. In some cases further coupling to the methine proton split the signal further to give a doublet of doublets, with $^3J_{HCPH}$ of 1.00 - 1.40 Hz. The methine proton attached to the chiral α-carbon atom in the benzylphosphonous acids resonated as a neat doublet. No coupling to the P-H proton was observed, even when the latter was a doublet of doublets. The chemical shift of the methine proton was similar to that observed in the corresponding phosphonic acids, with $^2J_{PCH}$ around 13.0 Hz. A summary of the ^{1}N.M.R. data is given in Table 14.

TABLE 14. COUPLING CONSTANTS (Hz) IN THE ^{1}H N.M.R. SPECTRA OF 1-AMINOALKANE- & 1-AMINOBENZYL-PHOSPHONOUS ACIDS $H(HO)P(O)CH(NH_2)R$ (IN NaOD)

R	$^{1}J_{PH}$	$^{2}J_{PCH}$	$^{3}J_{HCPH}$
CH_3	520.9	m	0.00
CH_2CH_3	513.3	m	1.42
$CH_2CH(CH_3)_2$	501.5	m	1.30
$2\text{-}HOC_6H_4$	513.0	12.5	0.00
$4\text{-}CH_2CH_3C_6H_4$	514.3	13.5	1.17
$4\text{-}FC_6H_4$	515.0	13.2	1.09

The broad-band decoupled ^{13}C N.M.R. data for the 1-aminoalkane- and 1-aminobenzyl-phosphonous acids also gave interesting results. As in the case of the phosphonic acids, one-bond and three-bond phosphorus-carbon coupling was observed, but no two-bond coupling was present in the 1-aminoalkanephosphonous acids. As in the case of the corresponding 1-aminobenzylphosphonic acids, no two bond phosphorus-carbon coupling to the aromatic ring was observed in the 1-aminobenzylphosphonous acids. A summary of these data is given in Table 15.

TABLE 15. PHOSPHORUS-CARBON COUPLING CONSTANTS (Hz) IN THE ^{13}C N.M.R. SPECTRA OF 1-AMINOALKANE- & 1-AMINOBENZYL-PHOSPHONOUS ACIDS $H(HO)P(O)CH(NH_2)R$

R	SOLVENT	$^1J_{PC}$	$^2J_{PCC}$	$^3J_{PCCC}$
CH_3	NaOD	95.22	0.00	-
CH_2CH_3	D_2O	92.77	0.00	9.16
,,	NaOD	97.09	0.00	10.69
$CH_2CH(CH_3)_2$	NaOD	99.43	0.00	12.05
2-HOC_6H_4	NaOD	96.29	0.00	5.66
				5.47
4-$CH_3CH_2C_6H_4$	NaOD	94.22	0.00	5.28
4-FC_6H_4	NaOD	93.97	0.00	5.22

For these compounds one observes that $^3J_{PCCC}$ is comparable to the values obtained for the corresponding aminophosphonic acids. Interestingly though, $^1J_{PC}$, in the region of approximately 94 - 100 Hz, is an average of 30 % lower than the values obtained for the corresponding phosphonic derivatives. This diminution might be explained by the replacement of O⁻ (in NaOD) by the H- atom, so that electron density at the phosphorus atom is increased, thereby reducing the amount of phosphorus coupling that is experienced by the α-carbon.

The chemical shift of the 1-aminoalkane- and 1-aminobenzyl-phosphonous acids in ^{31}P N.M.R. with respect to 85 % H_3PO_4, was generally at considerably lower field (higher frequency), than for the corresponding 1-aminophosphonic acids, corresponding to relatively lower shielding of P in the case of the phosphonous acids. A comparison of these results is given in Table 16.

TABLE 16. COMPARISON OF CHEMICAL SHIFT (ppm) IN THE ^{31}P N.M.R SPECTRA OF CORRESPONDING PHOSPHONOUS & PHOSPHONIC ACIDS (vs 85 % H_3PO_4)

R	SOLVENT	$H(HO)P(O)CH(NH_2)R$	$(HO)_2P(O)CH(NH_2)R$
CH_2CH_3	D_2O	20.27	14.21
,,	NaOD	28.02	14.47
$CH_2CH(CH_3)_2$	NaOD	25.44	14.19
2-HOC_6H_4	NaOD	30.33	20.82
4-$CH_3CH_2C_6H_4$	NaOD	29.97	18.42
4-FC_6H_4	NaOD	29.51	17.03

As stated earlier, in themselves 1-aminoalkane- and 1-amino-benzyl-phosphonous acids have been shown to demonstrate important biological activity. In addition, because of their chemical reactivity,

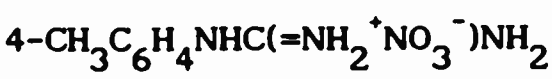
they may also function as key intermediates for further synthetic transformations.

1.9. THE SYNTHESIS OF 1-GUANIDINOALKANEPHOSPHONIC ACIDS

1.9.1. INTRODUCTION

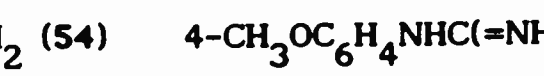
The breadth of biological activity exhibited by substituted guanidines has long been recognised; and due to the marked anti-bacterial and antifungal activity of derivatives such as 1-dodecyl guanidinium acetate, these compounds have acquired economic importance in the treatment, control and eradication of various fungal pathogens.

Following initial results King and Tonkin (1946), synthesised a large number of aliphatic and aromatic guanidine derivatives and demonstrated that some of these compounds acted antiplasmodially, inhibiting a sporozite-induced infection of *Plasmodium Gallinaceum* in chicks with varying degrees of success.[54] One compound in particular, *p*-tolylguanidinium nitrate (54), was shown to have useful inhibitory activity, but another derivative in the series, *p*-anisylguanidinium nitrate (55), was found to possess superior activity.



4-$CH_3C_6H_4NHC(=NH_2^+NO_3^-)NH_2$ (54)

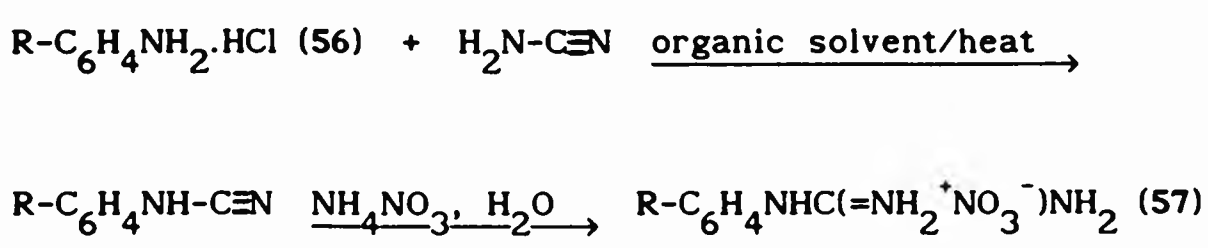
p-tolylguanidinium nitrate



4-$CH_3OC_6H_4NHC(=NH_2^+NO_3^-)NH_2$ (55)

p-anisylguanidinium nitrate

Preparation of these compounds and other derivatives, involved heating the corresponding amine hydrochloride (56) with cyanamide under reflux in an organic solvent, concentrating the crude material, and recrystallising the residue from water after treatment with an inorganic salt. The product (57) was isolated as a crystalline solid. The reaction (Scheme 28) is shown below.



Scheme 28

Y. Kishi *et al.*, found that in their stereospecific total synthesis of dl-tetrodotoxin, great difficulty was experienced when attempts were made to convert the *N*-acetylethylisothiourea or the corresponding ethylisothiourea, into a guanidine derivative by treatment with ammonia or ammonium salts.[55] One of the major reasons, was that the lactone group as well as the acetyl group in the substrate were exceptionally labile to bases. To overcome this difficulty, the *N*-acetylethylisothiourea derivative was heated with acetamide to give a diacetyl guanidine, which was stable enough to be subjected to acid hydrolysis. Given these difficulties, the requirement for a mild procedure to convert free amino groups into guanidino groups, prompted

interest in the synthetic procedure developed by Marynoff *et al.*, (1986). They developed a convenient and cost effective synthesis of guanidines from thioureas and amines, the key transformation involving activation of the sulphur in the thiourea through S-oxidation, followed by displacement of the activated sulphur group by amine nucleophiles, as shown (Scheme 29).[56]

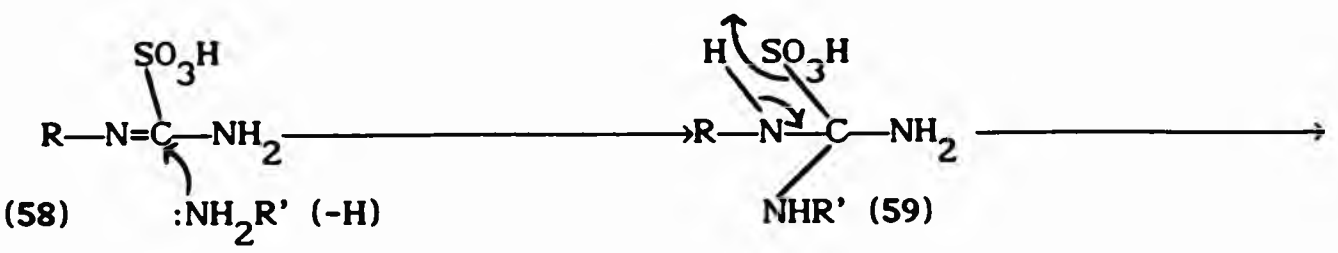
$$RHNC(S)NH_2 \xrightarrow{H_2O_2} RN{=}C(SO_xH)NH_2 \xrightarrow{R'NH_2} RN{=}C(NHR')NH_2$$

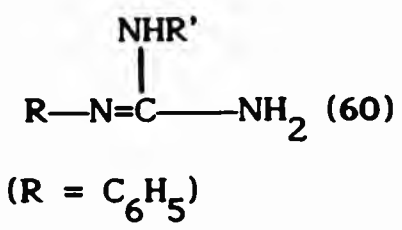
(x = 2 or 3; R = C_3H_7 or C_6H_5)

Scheme 29

Their preliminary experiments showed that *N*-phenylthiourea could be conveniently oxidised to the corresponding sulphonic acid using sodium molybdate reagent, in high yield and high state of purity. When the product, *N*-phenylaminoiminomethanesulphonic acid, was added to an acetonitrile solution of an amine, and was stirred at ambient temperature, displacement of the sulphur by amine nucleophile was achieved in less than 1 h. The reaction mixture was basified, extracted into organic solvent and concentrated to afford the guanidine derivatives as fine bases, in good to excellent yields. The reaction is thought to involve an addition/elimination mechanism, involving addition of the amine nucleophile to an aminoiminomethanesulphonic acid (58) to form a tetrahedral intermediate (59) that collapses to product (60), as

shown (Scheme 30).



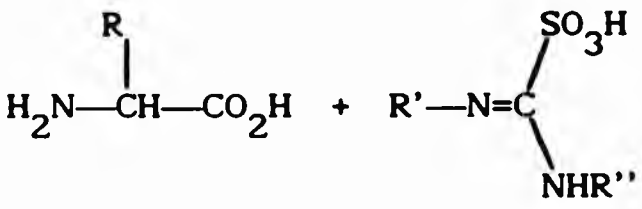


Scheme 30

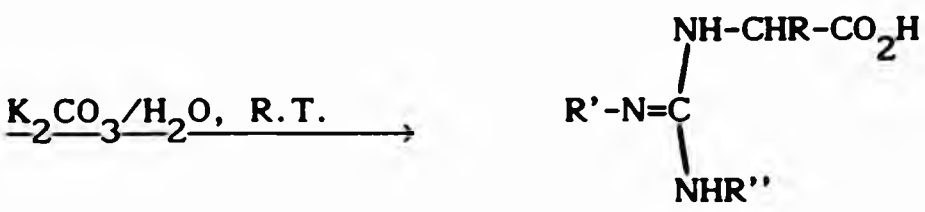
The fact that the method is facile, produces no noxious odours, and gives rise to stable, pure product, in very quick reaction times, made it attractive in application to other primary amines.[57]

A.E.Miller and J.J.Bischoff (1986) demonstrated that amino-iminomethanesulphonic acid (61) *N*-phenylaminoiminomethanesulphonic acid (62), and *N,N'*-diphenylaminoiminomethanesulphonic acid (63) could be used to guanidate a range of amino acids.[58] The reactions required only one equivalent of potassium carbonate, and occurred at ambient temperature in a few minutes for the unsubstituted derivative and a few days for the *N,N'*-diphenyl substituted derivative. Isolation and purification of the products were generally very simple, as the products precipitated from the reaction mixture before being purified by recrystallisation. The reactions involved dissolving a mixture of potassium carbonate and the amino acid (1:1 equivalents) in water,

followed by addition of the sulphonic acid with vigourous swirling during a period of about 10 minutes. After the mixture had been left to stand uncovered for 24 h at ambient temperature, the white solid was filtered off, washed, air dried and subsequently characterised. If the filtrate was left to stand at room temperature for a few days, further crops of the guanidated amino acid could be collected. The reaction (Scheme 31) is shown below.



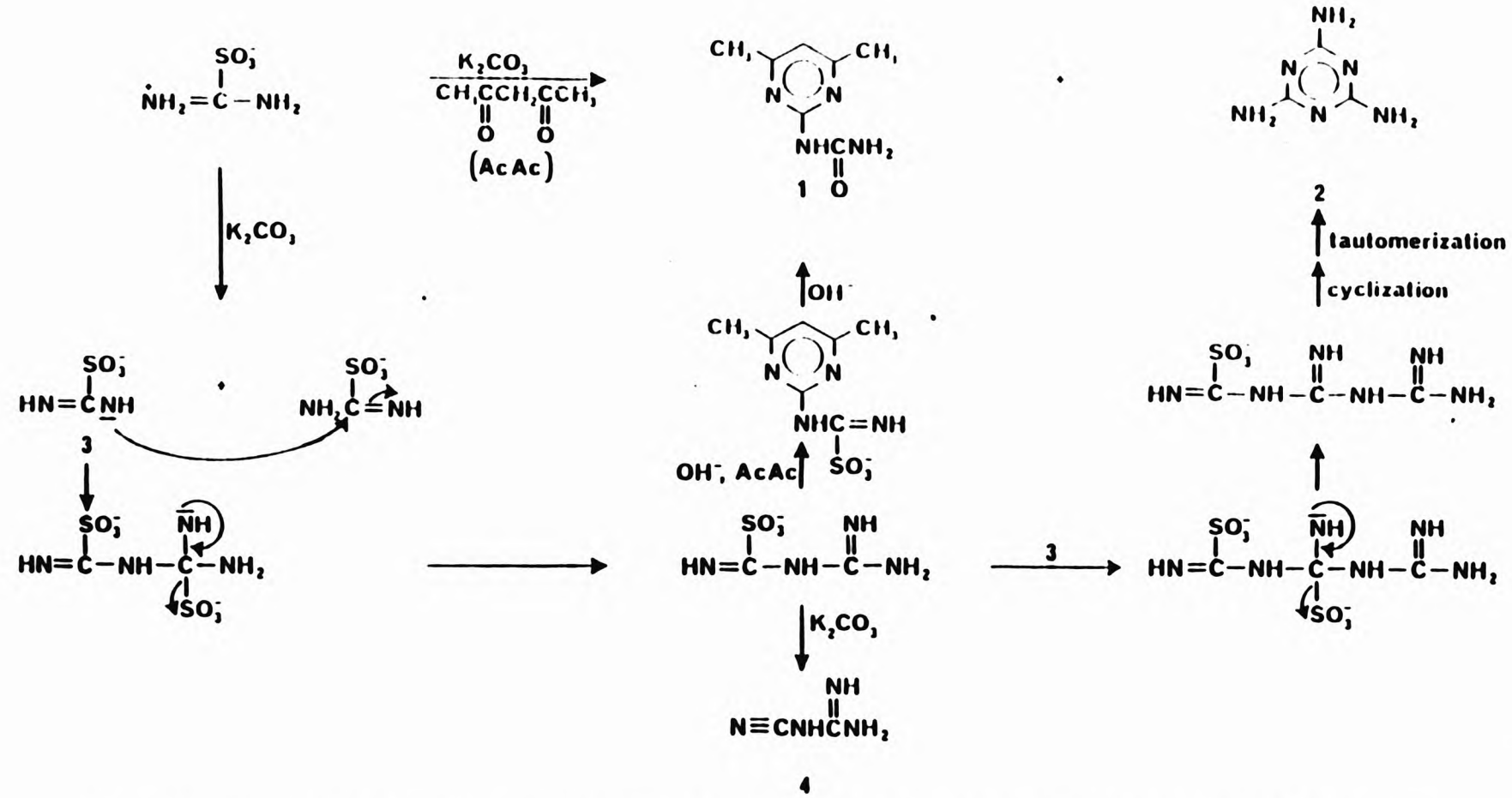
(61), (62), (63)



Scheme 31

The three aminoiminomethanesulphonic acid derivatives: (61), where R' = R'' = H; (62), where R' = H, R'' = C_6H_5; (63), where R' = R'' = C_6H_5, were used to guanidate a number of amino acids. (61) produced 13 guanidino acids from reactions with amino acids, in up to 80 % yield; (62) similarly produced three guanidino acids in up to 85 % yield, and (63) produced three guanidino acids in up to 35 % yield.

Miller and Bischoff also examined the differences in the relative rates of reaction of the three aminoiminomethanesulphonic acids, by carrying out reactions between them and one molecular equivalent of potassium carbonate.[59] *N*-Phenylaminoiminomethanesulphonic acid reacted to give an 85 % yield of phenylurea, while *N,N'*-diphenylaminoiminomethanesulphonic acid gave 33 % of the corresponding potassium salt and a mixture of diphenylthiourea and diphenylcarbodiimide. Even when the amount was lowered to 0.010 mol in the case of aminoiminomethanesulphonic acid, melamine and cyanoguanidine were produced in 50 % and 7 % yield respectively. In the above example an intermediate was trapped, when aminoiminomethanesulphonic acid, potassium carbonate and 2,4-pentanedione were reacted in solution in equimolar quantities. This product, 2-ureido-4,6-dimethylpyrimidine, was afforded in 50 % yield, as well as melamine in 20 % yield. The hypothesis for these differences in reactivity was based on the fact that the electronic effect of the phenyl groups should be to strengthen the electrophilicity of the carbon undergoing nucleophilic attack. As in the case of *N,N'*-diphenylaminoiminomethanesulphonic acid the lesser reactivity of the molecule is primarily governed by the steric effect of the phenyl groups which are not present in the case of aminoiminomethanesulphonic acid, and readily accessible electrophilic centre. A theoretical pathway for the reaction of aminoiminomethanesulphonic acid plus potassium carbonate is given in Scheme 32.



Scheme 32 Possible Reaction Pathways for AIBSO Plus Potassium Carbonate and Trapping with 2,4-Pentanedione

The synthesis of guanidinophosphonic acids is particularly desirable, as a number of examples exist which are analogues of creatine and other neuroactive molecules. In addition, a number of these compounds have demonstrated useful antifungal activity.[50] A number of methods were investigated during the course of the present studies for the synthesis of guanidinophosphonic acids.

1.9.2. THE SYNTHESIS OF 1-GUANIDINOPROPANEPHOSPHONIC ACID

1-Guanidinopropanephosphonic acid (68) was synthesised via the initial condensation of propanal, triphenyl phosphite and thiourea.[60] The reaction produced a mixture of *O,O*-diphenyl 1-thioureidoalkane-phosphonate intermediate (64) and corresponding diphosphonate (65). Treatment of this crude mixture with water and acetonitrile gave rise to the crude 1-thioureidopropanephosphonic acid (66). When this material was refluxed in the presence of methyl iodide the *S*-methylated iodide derivative was readily formed (67). This compound (67) was treated with ammonia gas to give rise to the corresponding crude 1-guanidinopropanephosphonic acid (68), with evolution of methanethiol gas. After the compound, isolated as a crystalline precipitate, was dissolved in methanol/water, treated with glacial acetic acid and concentrated under reduced pressure on a rotary evaporator, the thick oily residue that formed was left to stand in a fridge at 4 ^{o}C for several months before crystallisation ensued. The product (68) was

filtered off, washed with methanol and dry ether, before being dried in a vacuum oven for 2 h at 70 °C. On one occasion, when a creamy-white crystalline material was obtained, the product, 1-guanidinopropanephosphonic acid, was isolated as an acetate salt. This was confirmed by ^{1}H and ^{13}C N.M.R. spectroscopy. On subsequent occasions however, the product was isolated as a white, crystalline, high-melting point, water-soluble material and found by elemental and N.M.R. analysis to be the required unadulterated product. The reactions (Scheme 33) are shown below.

$$R\text{-}CHO + H_2N\text{-}C(S)\text{-}NH_2 + (C_6H_5O)_3P \xrightarrow{HOAc,\ heat} (64) + (65)$$

$$(C_6H_5O)_2P(O)CH[NHC(=S)NH_2]R \quad (64) +$$

$$(C_6H_5O)_2P(O)\text{-}CHR\text{-}NHC(=S)\text{-}NHCHR\text{-}P(O)(OC_6H_5)_2 \quad (65)$$

$$(64) + (65) \xrightarrow{H_2O,\ CH_3CN} (HO)_2P(O)CH[NH\text{-}C(=S)\text{-}NH_2]R \quad (66)$$

$$(66) + CH_3I \longrightarrow (HO)_2P(O)CH[NH\text{-}C(=NH_2^+)S\text{-}CH_3]R.\ I^- \quad (67)$$

$$(67) \xrightarrow{(i)\ NH_3(g),\ [-MeSH\ (g)];\ (ii)\ AcOH} (68) + NH_4I$$

$$(HO)_2P(O)CH[NHC(=NH)NH_2]R \quad (68)\ (R = ethyl)$$

Scheme 33

This method was found to be inconvenient, due to the inordinately long time it took for the guanidinophosphonic acid to crystallise from viscous solution.

Several attempts were made to guanidate 1-aminopropane-phosphonic acid directly, using *S*-methylisothiouronium chloride and *O*-methylisouronium chloride, in analogous fashion to the method used to guanidate *N*-(ω-aminoalkyl)aminomethanephosphonic acids.[50] The intended reactions (Scheme 34) are shown below.

$$H_2N\text{-}C(=NH_2^+)\text{-}X\text{-}CH_3\ Cl^- + (HO)_2P(O)CH(NH_2)R$$

$$\xrightarrow{\text{water/base, 60-90 }^{o}\text{C, 4 h, -MeXH}}$$

$$(HO)_2P(O)CHNH[C(=NH)NH_2HCl]R\ (69) \xrightarrow{\text{(i) } H^+\text{, (ii) propene oxide}} (HO)_2P(O)CH[NHC(=NH)NH_2]R\ (68)$$

(X = O or S; R = Et)

Scheme 34

No reaction occurred, even though the addition of base was thought to generate the free amino group in the aminophosphonic acid (bearing in mind that the compound is zwitterionic), and so make it more amenable to conversion. This methodology was also applied to the attempted preparation of 1-aminopropanephosphonous acid, in the hope

that the guanidinophosphonous acid (72), would be a useful intermediate for mild oxidation to the corresponding guanidinophosphonic acid. The proposed reactions (Scheme 35) are similar to the above.

$$H(HO)P(O)CH(NH_2)R + H_2N\text{-}C(=NH_2^+)\text{-}XCH_3\ Cl^- + 3KOH \xrightarrow{-2KCl,\ -3H_2O}$$

$$H(KO)P(O)CH(NH_2)R\ (70) + H_2N\text{-}C(=NH)\text{-}XCH_3 \xrightarrow{-MeXH}$$

$$H(KO)P(O)CH[NHC(=NH)NH_2]R\ (71) \xrightarrow{\text{(i) c.HCl, (ii) propene oxide}}$$

$$H(HO)P(O)CH[NHC(=NH)NH_2]R\ (72) + KCl$$

(X = O or S; R = Et)

Scheme 35

Here too, no guanidated product was obtained, as the substrate was recovered with minimal losses. It is thought that steric hindrance of the 1-amino group in the α-position of the phosphonic and phosphonous acids may have been responsible for the ineffectiveness of the reaction. To test this hypothesis, 2-aminoethanephosphonic acid[117] (5) was prepared by alkylation of *N*-(2-bromoethyl)phthalimide with triethyl phosphite, followed by hydrolysis of the unisolable *O,O*-diethyl *N*-ethylphthalimidophosphonate intermediate (73), and work up with propylene oxide[61] and was treated with *S*-methylisothiouronium chloride. 2-Guanidinoethanephosphonic acid (77) was isolated at the

first attempt, as a white crystalline, high-melting point, water-soluble solid. The product gave excellent microanalytical, ^{1}H, ^{13}C and ^{31}P N.M.R. data, and good FAB ms data. The reactions (Scheme 36) are shown below.

$(CH_3CH_2O)_3P$: + $BrCH_2CH_2N$-Pht $\xrightarrow{\text{reflux, 4 h}}$

$(CH_3CH_2O)_2P(O)CH_2CH_2N$-Pht **(73)** + CH_3CH_2Br

(71) $\xrightarrow{\text{(i) } H^+\text{, 8 h; (ii) propene oxide}}$

$(HO)_2P(O)CH_2CH_2NH_2$ **(5)** + 2-$C_6H_4(CO_2H)_2$

$(HO)_2P(O)CH_2CH_2NH_2$ + 2 H_2N-$C(=NH_2^+)$-S-CH_3 Cl^- + 4KOH $\longrightarrow$

$(KO)_2P(O)CH_2CH_2NH_2$ **(74)** + 2 H_2N-$C(=NH_2)$-S-CH_3 + 2 KCl + 4 H_2O

$\xrightarrow{-CH_3SH}$

$(KO)_2P(O)CH_2CH_2NHC(=NH)NH_2$ **(75)** + $\xrightarrow{\text{c.HCl}}$

$(HO)_2P(O)CH_2CH_2NHC(=NH)NH_2HCl$ **(76)** $\xrightarrow{\text{propene oxide}}$

$(HO)_2P(O)CH_2CH_2NHC(=NH)NH_2$ **(77)**

(Pht-N = phthalimido group)

Scheme 36

Several attempts were made in the present work to guanidate 1-aminopropanephosphonic acid and 1-aminopropanephosphonous acid, using aminoiminomethanesulphonic acid (61), prepared by the peracetic acid oxidation of aminoiminomethanesulphinic acid.[62]

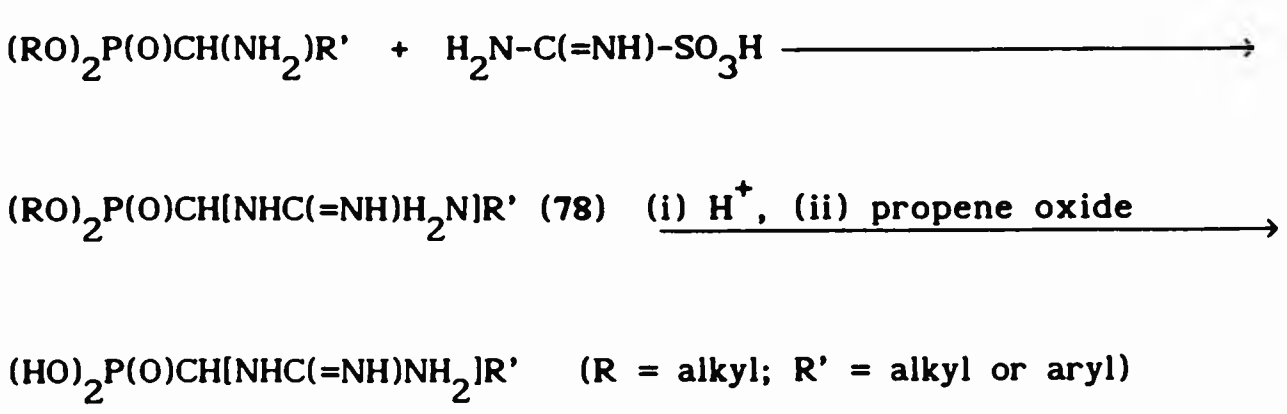
$$H_2N\text{-}C(=NH)\text{-}SO_2H \quad + \quad CH_3CO_3H \longrightarrow H_2N\text{-}C(=NH)\text{-}SO_3H \quad (61)$$

In analogous fashion to the method used to guanidate several amino acids,[59] a number of experiments were carried out, in which 1-aminopropanephosphonic acid and 1-aminopropanephosphonous acid were treated with 2 and 3 molecular equivalents of sodium hydroxide, in water, before being treated with 1 molecular equivalent of the guanidating reagent. The clear mixtures were left to stir at ambient temperature for varying periods, ranging from 1 h to 12 h. In each instance the solution was treated with hydrochloric acid, sodium chloride was removed, by filtration, and the filtrate was concentrated under reduced pressure to afford a thick oily residue. After dissolving this material in methanol and treating it with propene oxide, a white crystalline material was isolated which was filtered off, washed and dried under vacuum. Microanalysis, infrared, ^{1}H, ^{13}C and ^{31}P N.M.R. spectroscopy, showed by comparison with the original substrate that in every instance, unchanged 1-aminopropanephosphonic acid and 1-aminopropanephosphonous acid were recovered, with minimal losses.

An experiment was performed in which 1-aminopropanephosphonic acid was treated with 1 molecular equivalent of potassium carbonate in water, before 1 molecular equivalent of aminoiminomethanesulphonic acid was added to the mixture, with vigourous stirring. The clear solution was left to stand at ambient temperature for 48 h, during which time a clear, shiny, highly crystalline precipitate had formed. This material was filtered off, and the filtrate was concentrated under reduced pressure and worked up in the normal way, to afford a white crystalline substance. Microanalysis and ^{13}C N.M.R. spectroscopy showed that neither of the products isolated possessed any guanidino- character.

In their method of converting an amino sugar into its guanidino derivative, using aminoiminomethanesulphonic acid, Kim *et al.*, used absolute methanol as the solvent for the reaction, without the addition of any other component, and simply stirred the substrate and reagent together at ambient temperature for 24 h.[62] Using this protocol as a guide, *O,O*-diethyl 1-aminopropanephosphonate and *O,O*-diethyl 1-amino-butanephosphonate, both synthesised during the course of the present work, were each treated with 1 molecular equivalent of aminoimino-methanesulphonic acid in methanol, and stirred at ambient temperature for 24 h. After removal of the solvent in each case, no attempt was made to purify further the oily white viscous residue. From the ^{1}H and ^{13}C N.M.R. spectra of these materials, it was very difficult to give a positive identification of the intended guanidinophosphonates (78). The ^{31}P N.M.R. spectra were also very complex, indicating that the reactions

had not gone simply to the expected product. Microanalysis also showed that the material isolated was other than that expected. Had these guanidinophosphonates been synthesised, the intention would have been to hydrolyse these intermediates in order to liberate the corresponding phosphonic acids. The proposed reactions (Scheme 37) are shown.



Scheme 37

It would appear from the outcome of these experiments that direct guanidation of 1-aminoalkanephosphonic acids and 1-aminoalkane-phosphonous acids with the appropriate reagent is difficult to effect. As demonstrated by the synthesis of 2-guanidinoethanephosphonic acid, using *S*-methylisothiouronium chloride, if the amino group is readily accessible to attack from the guanidating reagent, the transformation is more likely to occur than if it is sterically hindered, as in the case of the 1-amino derivatives. Although the '1-pot' condensation of aldehyde, triphenyl phosphite and thiourea is a laborious method of synthesising 1-guanidinophosphonic acids, the product is nevertheless

obtained in moderate yield and high state of purity.

1.10. THE STRUCTURAL CHARACTERISATION AND IDENTIFICATION OF 1-GUANIDINOPROPANEPHOSPHONIC ACID

The infrared spectrum of 1-guandinopropanephosphonic acid (66) was used as a qualitative means of establishing the presence of the molecule. In the case where this phosphonic acid derivative possessed a molecule of crystallisation of acetic acid, this fact was highlighted by the characteristically strong absorption at υ_{max} 1690 cm^{-1} for C=O in CO_2H. The absorptions characteristic of phosphonic acids were present, as well as those associated with -NH and $-NH_2$, from the guanidino moiety.

The ^1H N.M.R. spectrum in D_2O highlighted the magnetic non-equivalence of the methylene hydrogens adjacent to the methine hydrogen attached to the chiral α-carbon atom. The ABX type multiplicity that was observed, was typical of the resonance displayed by its precursor, 1-aminopropanephosphonic acid. The complex resonances of the hydrogen in the α-position, and the adjacent methylene hydrogens were clearly displayed as shown in Fig 2. No other contributions were observed for the hydrogens in the guanidino group, as these are exchangeable in the solvent system used.

The broad-band proton decoupled ^{13}C N.M.R. spectrum was clear, giving doublets for one bond and three bond phosphorus-carbon coupling.

Expanded ^{1}H N.M.R. spectrum of 1-guanidinopropanephosphonic acid (in NaOD)

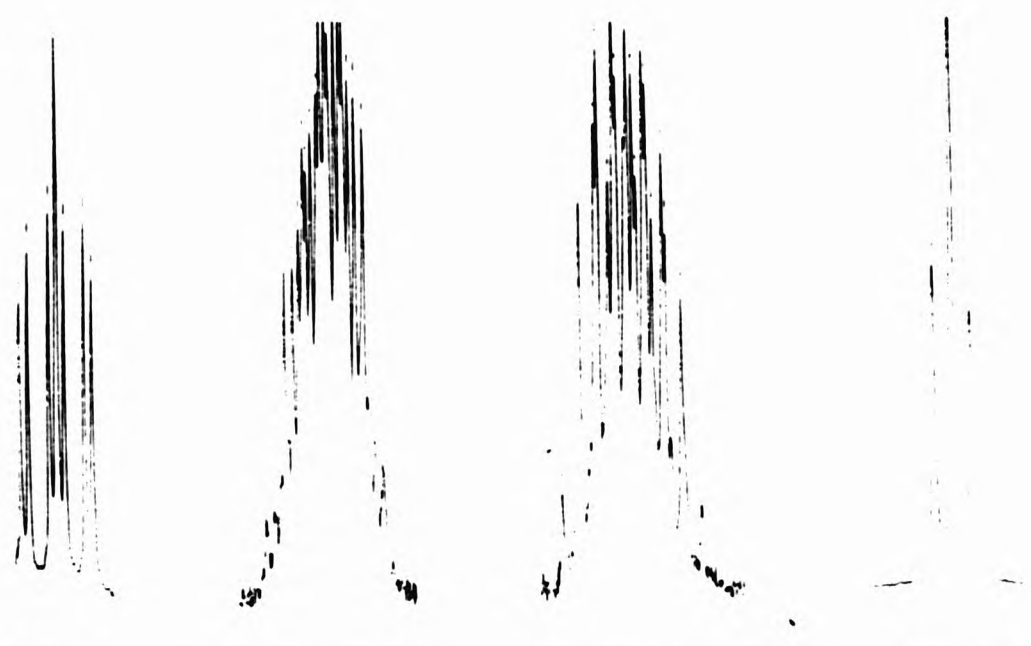


Fig 2

The methylene carbon was observed as a singlet, and was characteristic of compounds of this type. The carbon associated with the guanidino group had a chemical shift of 160.18 ppm and $^{3}J_{PCNC}$ 3.59 Hz (saturated in D_2O). The chemical shift of the phosphorus atom in the ^{31}P N.M.R. spectrum was 17.5 ppm (saturated in D_2O) and comparable to the values obtained for 1-aminopropanephosphonic acid. A comparison of $^{1}J_{PC}$, $^{3}J_{PCCC}$ and δ ^{31}P, between 1-aminopropanephosphonic acid, 1-aminopropanephosphonous acid and 1-guanidinopropanephosphonic acid is given in Table 17.

TABLE 17

COMPARISON OF $^{1}J_{PC}$, $^{3}J_{PCCC}$ & δ ^{31}P IN 1-AMINOPROPANEPHOSPHONIC ACID 1-AMINOPROPANEPHOSPHONOUS ACID & 1-GUANIDINOPROPANEPHOSPHONIC

COMPOUND	SOLVENT	$^{1}J_{PC}$/Hz	$^{3}J_{PCCC}$/Hz	δ ^{31}P/ppm
$(HO)_2P(O)CH(NH_2)R$	D_2O	142.87	9.52	14.21
	NaOD	134.86	10.67	14.47
$H(HO)P(O)CH(NH_2)R$	D_2O	92.77	9.16	20.27
	NaOD	97.09	10.69	28.02
$(HO)_2P(O)CH[NHC(=NH)NH_2]R$	D_2O	149.06	12.96	17.50

Elemental analysis revealed that 2-guanidinoethanephosphonic acid (77) had been isolated as a dihydrate, consistent with the findings

in the synthesis of *N*-(ω-guanidinoalkyl)aminoalkanephosphonic acids by the same approach, where the products were also obtained as crystalline dihydrates.[50] Once again, infrared spectroscopy was used qualitatively, to ascertain whether guanidation had been successfully achieved. Strong bands in the region of υ_{max}(KBr)/cm^{-1} 1600-1700 cm^{-1} for guanidino NH and NH_2 stretching frequencies, were quite different from those observed in the aminophosphonic acid precursor, indicating that the transformation had taken place.

The ^{1}H N.M.R. spectrum was similar to that of the precursor, in which the methylene groups resonated as a pair of multiplets. In the broad band proton decoupled ^{13}C N.M.R. spectrum, apart from the presence of the singlet of the guanidino carbon at 159.39 ppm, the resonance profile of the molecule was similar to that of its aminophosphonic precursor. The chemical shift of the phosphorus atom in ^{31}P N.M.R. was also of comparable value to that observed for the precursor molecule. A summary of these results is given in Table 18.

TABLE 18

COMPARISON OF ^{13}C & ^{31}P N.M.R. DATA FOR 2-AMINO & GUANIDINOETHANEPHOSPHONIC ACID $(HO)_2P(O)CH_2CH_2NH\text{-}X$

COMPOUND, X	SOLVENT	$^1J_{PC}$/Hz	$^2J_{PCC}$/Hz	$\delta\ ^{31}P$/ppm
H	D_2O	126.53	0.00	-
	NaOD	126.74	1.64	18.84
$C(=NH)NH_2$	D_2O	131.58	0.00	20.88

The guanidinoalkanephosphonic acids represent a very interesting class of compounds, being biologically active in their own right, and being potentially useful intermediates for the possible synthesis of novel phosphonic acid derivatives, e.g. pyrimidines.[63]

CHAPTER 2

2.1. THE SYNTHESIS OF *O,O*-DIALKYL 1-OXOALKANE- & *O,O*-DIALKYL 1-OXOARYL-PHOSPHONATES

1-Aminoalkanephosphonic acids may also be prepared via the conversion of *O,O*-dialkyl 1-oxoalkanephosphonates (79) to the corresponding *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates (80), followed by reduction to the *O,O*-dialkyl 1-aminoalkanephosphonates (81), and acid hydrolysis of these intermediates to liberate the 1-aminophosphonic acids. The reactions (Scheme 38) are shown below.

$(RO)_3P:$ + R'COCl $\xrightarrow{0\ ^{o}C\ \text{to R.T.}}$ $(RO)_2P(O)C(O)R'$ (79) + RCl

(79) + $H_2NOH.HCl/C_5H_5N$, MeOH, - 10 ^{o}C to R.T. $\longrightarrow$ (80)

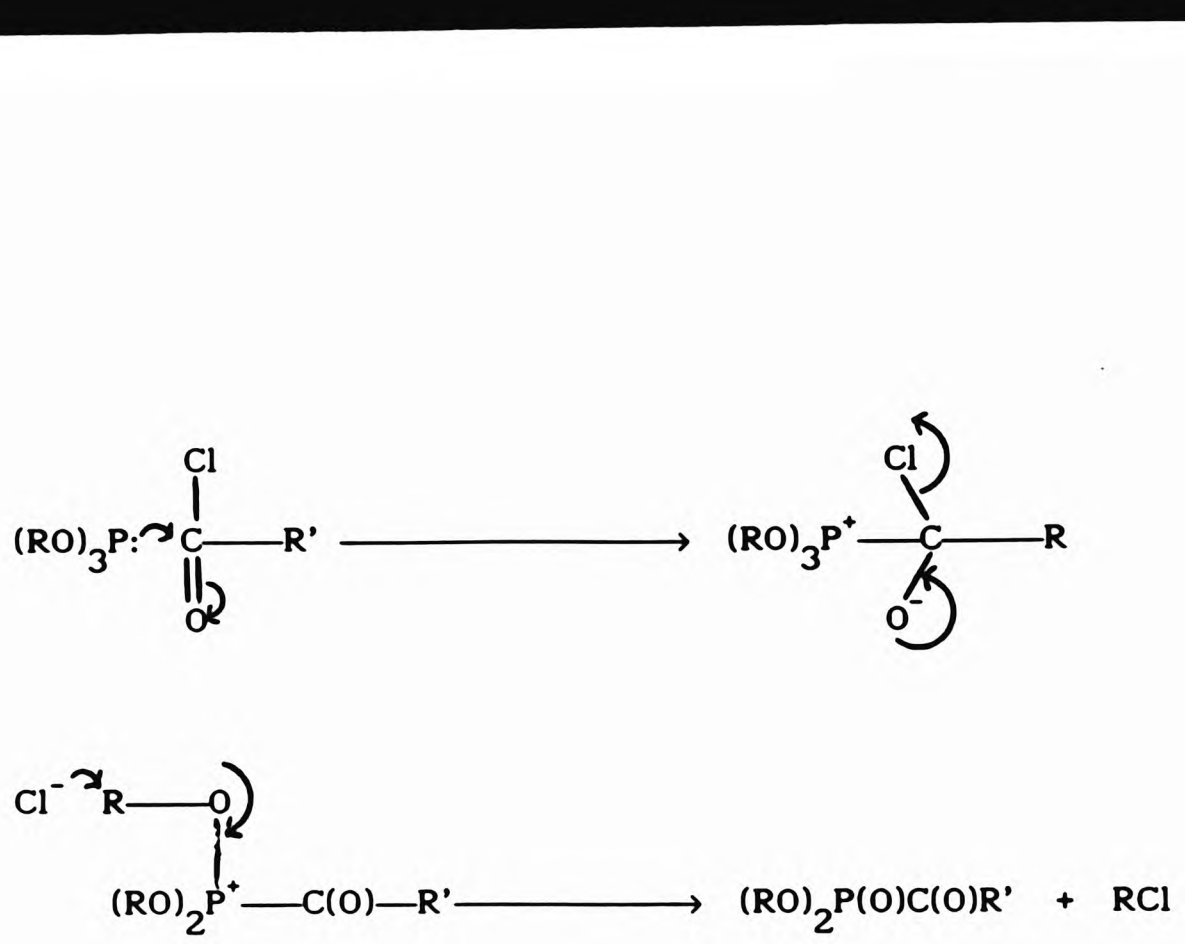
$(RO)_2P(O)C(=N\text{-}OH)R'$ (80) $\xrightarrow{H_2/\text{cat., 250 p.s.i., 60-90 }^{o}C}$ (81)

$(RO)_2P(O)CH(NH_2)R'$ (81) $\xrightarrow{\text{(i) c.HCl, (ii) propene oxide}}$ $(HO)_2P(O)CH(NH_2)R'$

Scheme 38

The *O,O*-dialkyl 1-oxoalkanephosphonates or α-ketophosphonates as they are otherwise known, may be synthesised by the classically re nowned, Michaelis - Arbuzov reaction.[64,65,66]

When trialkyl phosphite is allowed to react with an excess of acyl chloride under dry nitrogen, at 0 to 10 ^{o}C, followed by stirring at room temperature, the corresponding α-ketophosphonate is formed smoothly, and in high yield. Care must be taken to ensure that the addition does not take place too quickly, as the reaction can be extremely exothermic. Removal of volatile alkyl chloride and excess of acyl chloride under reduced pressure, followed by distillation under high vacuum of the bulk material affords the desired compound as a colourless, odourless free-flowing liquid, which in certain instances is irritating to the skin. The *O,O*-dialkyl 1-oxoalkane- and *O,O*-dialkyl 1-oxoaryl- phosphonates prepared in the present studies gave excellent microanalytical and infra-red spectral data, as well as extremely good ^{1}H, ^{13}C and ^{31}P N.M.R. data, indicating that the compounds were formed in an analytically pure state. The reaction involves the formation of an alkoxyphosphonium type tetrahedral intermediate, followed by nucleophilic S_N2 displacement of an alkyl group by the displaced chloride ion to generate the phosphonate. The mechanism (Scheme 39) is shown overleaf.



(R = alkyl; R' = aryl)

Scheme 39

A summary of the *O,O*-dialkyl 1-oxoalkane- and *O,O*-dialkyl 1-oxoaryl-phosphonates prepared during the current studies is given in Table 19.

TABLE 19

***O,O*-DIALKYL 1-OXOALKANE- & *O,O*-DIALKYL 1-OXOARYL-PHOSPHONATES PREPARED DURING CURRENT STUDIES $(RO)_2P(O)C(O)R'$**

R	R'	B.P./°C (mmHg)	YIELD (%)	REQUIRES (%) C	REQUIRES (%) H	FOUND (%) C	FOUND (%) H
CH_3	CH_3 [79]	61-64/0.05	83	31.58	5.92	31.59	6.06
CH_3	CH_2CH_3 [76]	90-91/0.10	67	36.14	6.63	36.35	6.75
CH_3	$(CH_2)_2CO_2CH_2CH_3$ *	84-87/0.05	65	40.00	7.23	39.54	7.36
CH_3	cyclo-C_3H_5 *	86-88/0.60	87	40.34	6.30	40.80	6.44
CH_3	C_6H_5 [79]	116-20/0.10	91	50.47	5.14	50.53	5.28
C_2H_5	CH_3 [120]	80-82/0.15	84	40.00	7.22	39.66	7.52
C_2H_5	C_2H_5 [120]	81-83/0.10	63	43.30	7.73	43.21	7.79
C_2H_5	n-C_3H_7 [120]	120/0.10	83	46.15	8.17	45.51	8.23
C_2H_5	$(CH_2)_2CO_2CH_3$ *	180-2/0.10	75	42.86	6.75	42.96	6.80
C_2H_5	$(CH_2)_2CO_2CH_2CH_3$ [81]	134-8/0.10	43	45.11	7.14	44.83	7.39
C_2H_5	cyclo-C_3H_5 *	87-90/0.05	92	46.60	7.28	46.83	7.44
C_2H_5	C_6H_5 [71]	118-22/0.10	79	54.55	6.20	54.63	6.23
n-C_3H_7	C_2H_5 *	76/0.04	27	48.65	8.56	49.02	8.73
n-C_3H_7	n-C_3H_7 *	68-72/0.04	28	50.85	8.90	51.16	9.07
i-C_3H_7	CH_3 [100]	73-74/0.10	75	46.15	8.17	46.21	8.24
i-C_3H_7	C_2H_5 [100]	106-7/0.04	66	48.65	8.56	48.82	8.85
i-C_3H_7	n-C_3H_7 *	76-80/0.05	61	50.85	8.90	50.40	9.05
i-C_3H_7	$(CH_2)_2CO_2CH_3$ *	178-82/0.10	67	47.14	7.50	47.21	7.56

$i\text{-}C_3H_7$	$(CH_2)_2CO_2CH_2CH_3$*	102-5/0.10	48	48.98	7.82	48.72	7.77
$i\text{-}C_3H_7$	C_6H_5*	120-4/0.20	67	57.78	7.04	57.27	7.22
$n\text{-}C_4H_9$	CH_3*	104-8/0.10	52	50.85	8.90	50.87	9.02
$n\text{-}C_4H_9$	C_3H_7*	118-20/0.20	54	54.55	9.47	53.11	9.42
$n\text{-}C_4H_9$	$(CH_2)_2CO_2CH_2CH_3$*	137/0.08	56	52.17	8.39	52.46	8.53
$i\text{-}C_4H_9$	C_2H_5*	84-88/0.05	48	52.80	9.20	52.85	9.21
$CH_2C_6H_5(CH_2)_2CO_2CH_2CH_3$*		~	~	61.54	5.90	59.33	8.01

~ = was not distilled, * = new compound.

To extend the range of *O,O*-dialkyl 1-oxoalkanephosphonates prepared, a number of attempts were made to synthesise: *O,O*-dimethyl 1-oxo-2-methoxyethanephosphonate (**82**) and *O,O*-dimethyl 1-oxo-2-phenoxy-ethanephosphonate (**83**). Methoxyacetyl chloride and phenoxyacetyl chloride were added in excess, in separate reactions, to trimethyl phosphite under the same reaction conditions described earlier. The intended reactions (Scheme 40) are given below.

$$(CH_3O)_3P: + CH_3OCH_2COCl \longrightarrow (CH_3O)_2P(O)C(O)CH_2OCH_3 \quad (82)$$

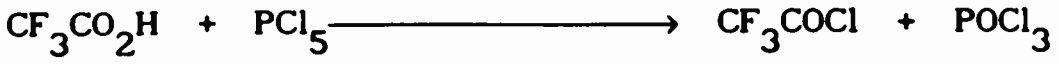
$$(CH_3O)_3P: + C_6H_5OCH_2OCOCl \longrightarrow (CH_3O)_2P(O)C(O)CH_2OC_6H_5 \quad (83)$$

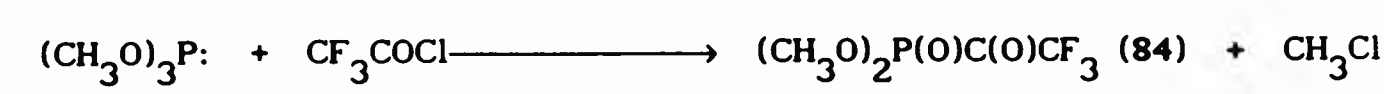
Scheme 40

The crude products, after removal of volatile materials under vacuum, appeared to be the expected compounds on the basis of elemental analysis. However attempts at purification by vacuum distillation or column chromatography (through silica gel, 80 - 200 mesh, using dichloromethane as the eluting solvent), caused considerable decomposition as evidenced by the complex ^{1}H, ^{13}C and ^{31}P N.M.R. spectra that were obtained of the fractions isolated by both these methods.

An attempt was made to oximinate what was thought to be crude *O,O*-dimethyl 1-oxo-2-methoxyethanephosphonate on the basis of elemental analysis. However the reaction did not give rise to the corresponding 1-hydroxyiminophosphonate derivative, as evidenced by the absence of the characteristic low field, broad, hydroxyl peak in the ^{1}H N.M.R. spectrum (60 & 250 MHz), indicative of the presence of this functional group; and the highly complex nature of the other higher field signals in the region where one expected to observe a simple doublet and associated singlet for the three methoxy groups of the molecule.

A number of attempts were also made to synthesise *O,O*-dimethyl 1-oxo-2,2,2-trifluoroethanephosphonate (84). Trifluoroacetyl chloride (b.p. - 27 ^{o}C),[67] prepared by the careful addition of trifluoroacetic acid to phosphorus pentachloride, and collected in a Cardice/acetone cooled trap, was allowed to volatilise and bubble into a stirred solution of trimethyl phosphite, cooled in Cardice. The expected reactions (Scheme 41) are shown overleaf.





Scheme 41

Crude material was afforded as a faint yellow, viscous liquid and when distilled under high vacuum, fractionated to a colourless, free-flowing, pleasant-smelling liquid. However the ^{1}H, ^{13}C and ^{31}P N.M.R. spectra of the distilled product were extremely complex, and the microanalytical data were not consistent with the expected structure. The ^{31}P N.M.R. spectrum was particularly interesting, as there were two major multiplets observed in the regions, - 1.79 to + 1.73 ppm and + 7.81 to + 11.79 ppm, indicating the possible presence of both phosphate and phosphonate structures.

This type of situation has been reported previously in the study of the reaction of fluorinated alkanoic acid chlorides with trialkyl phosphites by Ishihara *et al.* (1987). They also studied carefully the reaction of trimethyl phosphite and trifluoroacetyl chloride. They were unable to detect any trace of the expected fluoroalkylphosphonate derivative in spite of the amount of phosphite, the mode of addition, and the reaction temperature being varied.[68] They managed to isolate exclusively what they referred to as a (Z)-1-(dialkyoxyphosphinyl)-oxy-F-1-alkene phosphonate

$(CH_3O)_2P(O)$-O-$C(=CF_2)$-$P(O)(OCH_3)_2$ (85), regardless of the type of trialkyl phosphite they used.

In an analogous fashion, Pudovik and Gazizov (1969) had earlier demonstrated that reactions of trialkyl phosphites with chlorine-substituted acetyl chlorides (including trichloroacetyl chloride) lead to the formation of dialkyl 1-(dialkoxyphosphinyl)vinyl phosphates and derivatives with chlorine in the 2-position of the vinyl group.[69] This confirmed the results of the detailed studies done by Soborovskii *et al.* (1960) in similar investigations of the above reaction.[70]

The results in this area of the present work seemed to be consistent with those obtained in other similar studies and appear to indicate the reactions (Scheme 42) shown below.

$CF_3COCl + (CH_3O)_3P: \longrightarrow$

$(CH_3O)_2P(O)C(O)CF_3$ or $^-Cl\ (CH_3O)_3P^+$-C(O)-CF_3 $\xrightarrow{(CH_3O)_3P:}$

$(CH_3O)_3P^+$-O-$C^-(CF_3)P(O)(OCH_3)_2$ $\xrightarrow{-20\ ^oC\ to\ R.T.}$

$(CH_3O)_3PF$-$OC(=CF_2)$-$P(O)(OCH_3)_2$ $\xrightarrow{distillation}$

$(CH_3O)_2P(O)$-O-$C(=CF_2)$-$P(O)(OCH_3)_2$

(85)

Scheme 42

The two distinct multiplets observed in the ^{31}P N.M.R. spectrum may correspond to the phosphonate and phosphate parts of the postulated Perkow type product (85). A summary of the microanalytical results of the attempts to synthesise *O,O*-dimethyl 1-oxo-2,2,2-trifluoroethane-phosphonate is given in Table 20.

TABLE 20

SUMMARY OF MICROANALYTICAL RESULTS OF THE PRODUCT FORMED VIA THE REACTION OF TRIMETHYL PHOSPHITE WITH TRIFLUOROACETYL CHLORIDE

	B.P/°C (mmHg)	DISTILLED YIELD (%)	CALC. FOR (%)		FOUND (%)	
			C	H	C	H
(i)	114-6/0.10	46	24.00	4.00	21.44	3.89
(ii)	122-6/0.08	40	24.00	4.00	23.07	3.99
(iii)	114-8/0.15	42	24.00	4.00	22.96	4.02

[The calculations were based on the possible formation of the product $(CH_3O)_2P(O)-O-C(=CF_2)-P(O)(OCH_3)_2$ (85)].

2.2 THE SYNTHESIS OF *O,O*-DIALKYL 1-HYDROXYIMINOPHOSPHONATES

A wide range of *O,O*-dialkyl 1-hydroxyiminophosphonates, many of which are new compounds, was prepared by oximination of the 1-oxophosphonate precursors. The α-ketophosphonates as they are otherwise known, were reacted with equimolar amounts of hydroxylamine hydrochloride, in the presence of a slight excess of pyridine, using methanol as the solvent for the reaction. After allowing the reaction to run for 2 h at 0 °C to 10 °C, the mixture was left to stir for 12 h at R.T., before being worked up. In most cases, the hydroximinophosphonates (80) were afforded as clear-yellow, viscous, oily products.[71,118] The reaction (Scheme 43) is given below.

$$(RO)_2P(O)C(O)R' \xrightarrow[\text{(i) 0 - 10 °C, 2 h; (ii) R.T., 12 h}]{H_2NOH.HCl,\ C_5H_5N,\ CH_3OH} (RO)_2P(O)C(=N\text{-}OH)R' \quad \textbf{(80)}$$

(R = alkyl, R' = alkyl or aryl)

Scheme 43

The compounds were generally isolated in quantitative yields and carried a faint smell of pyridine, even after prolonged shaking under high vacuum. In themselves the 1-hydroxyiminophosphonates are very useful intermediates for conversion to other phosphonate

derivatives.[72,73,74] This type of compound has been found to exert biological activity, by virtue of their bidentate nature, producing metal binding properties, that can make them good candidates for inhibitors of metalloenzymes.[52] Taneja and Roy (1988) claimed to have found that 1-oxoacylphosphonates and their 1-hydroxyiminophosphonates, particularly those derived from chloroacetyl chlorides, show interesting fungitoxicity against 5 pathogenic fungi; namely: *Pyricularia oryzae, Rhizoctonia bataticola, Helminthosporium oryzae, Alternaria alternata* and *Pithiam aphanidermatum*.[75,76] Some doubt has been expressed as to the validity of these results, as it has been found to be impossible to synthesise *O,O*-dimethyl 1-hydroxyimino-2,2,2-trichloroethanephosphonate (87) by the method described[75,76] in this laboratory.[77] The 1-oxophosphonate precursor (86) was found to undergo spontaneous methanolysis with P-C cleavage under the conditions normally used for the production of the oxime. This is particularly interesting in the light of the fact that these workers reported that (86) and (87) had shown activity; especially (86) whose activity was found to be particularly good against *Pyricularia oryzae* and *Helminthosporium oryzae*.

$(CH_3O)_2P(O)C(O)CCl_3$ (86) $(CH_3O)_2P(O)C(=N\text{-}OH)CCl_3$ (87)

A summary of the *O,O*-dialkyl 1-hydroxyiminophosphonates synthesised during the present work is given in Table 21.

TABLE 21

SUMMARY OF THE *O,O*-DIALKYL 1-HYDROXYIMINOPHOSPHONATES

$(RO)_2P(O)C(=N-OH)R'$

R	R'	MOLECULAR FORMULA	REQUIRED (%) C	H	N	FOUND (%) C	H	N
CH_3	CH_3 [79]	$C_4H_{10}NO_4P$	28.74	5.99	8.38	29.85	6.11	8.12
CH_3	C_2H_5 [76]	$C_5H_{12}NO_4P$	33.14	6.63	7.74	33.60	6.61	7.82
CH_3	n-C_3H_7 [75]	$C_6H_{14}NO_4P$	36.92	7.18	7.18	36.01	7.10	7.07
CH_3	$(CH_2)_2CO_2C_2H_5$ *	$C_8H_{16}NO_6P$	37.94	6.32	5.53	38.12	6.26	5.60
CH_3	cyclo-C_3H_5 *	$C_6H_{12}NO_4P$	37.31	6.22	7.25	36.92	6.25	5.37
CH_3	C_6H_5 [79]	$C_9H_{12}NO_4P$	47.16	5.24	6.11	47.00	5.26	6.03
C_2H_5	CH_3 [120]	$C_6H_{14}NO_4P$	36.92	7.18	7.18	39.16	7.54	7.76
C_2H_5	C_2H_5 [120]	$C_7H_{16}NO_4P$	40.19	7.66	6.70	39.58	7.59	6.07
C_2H_5	n-C_3H_7 [120]	$C_8H_{18}NO_4P$	40.05	8.28	6.27	40.56	8.06	5.40
C_2H_5	$(CH_2)_2CO_2CH_3$ *	$C_9H_{18}NO_6P$	40.45	6.74	5.24	40.62	6.80	5.20
C_2H_5	$(CH_2)_2CO_2C_2H_5$ [81]	$C_{10}H_{20}NO_6P$	45.11	7.52	5.26	41.37	7.04	4.92
C_2H_5	cyclo-C_3H_5 *	$C_8H_{16}NO_4P$	43.44	7.24	6.34	43.33	7.44	6.58
C_2H_5	C_6H_5 [121]	$C_{11}H_{16}NO_4P$	51.36	6.23	5.45	51.19	6.20	5.37
n-C_3H_7	C_2H_5 *	$C_9H_{20}NO_4P$	45.57	8.44	5.91	47.36	9.06	4.69
n-C_3H_7	n-C_3H_7 *	$C_{10}H_{22}NO_4P$	47.81	8.77	5.58	45.80	8.76	5.63
i-C_3H_7	CH_3 [100]	$C_8H_{18}NO_4P$	43.05	8.07	6.28	43.06	8.13	6.33
i-C_3H_7	C_2H_5 [100]	$C_9H_{20}NO_4P$	45.57	8.44	5.91	46.03	8.70	5.93

i-C_3H_7 n-C_3H_7	$C_{10}H_{22}NO_4P$	47.81	8.77	5.58	48.12	9.07	5.69
i-C_3H_7 $(CH_2)_2CO_2CH_3$	$C_{11}H_{22}NO_6P$	44.75	7.46	4.75	44.76	7.46	4.94
i-C_3H_7 $(CH_2)_2CO_2C_2H_5$	$C_{12}H_{24}NO_6P$	46.60	7.77	4.53	47.90	7.51	3.33
i-C_3H_7 C_6H_5	$C_{13}H_{20}NO_4P$	54.74	7.02	4.91	54.72	7.13	4.96
n-C_4H_9 CH_3	$C_{10}H_{22}NO_4P$	47.81	8.77	5.78	47.99	8.91	5.52
n-C_4H_9 n-C_3H_7	$C_{12}H_{26}NO_4P$	51.61	9.32	5.02	49.34	9.16	4.86
n-C_4H_9 $(CH_2)_2CO_2C_2H_5$	$C_{14}H_{28}NO_4P$	55.08	9.18	4.59	55.40	9.36	4.66
i-C_4H_9 C_2H_5	$C_{11}H_{24}NO_4P$	49.81	9.06	5.28	52.70	9.56	2.76
C_7H_7 $(CH_2)_2CO_2C_2H_5$	$C_{20}H_{22}NO_6P$	59.26	5.93	3.96	58.07	5.11	2.98

(C_7H_7 is $C_6H_5CH_2$)

(Elemental analyses were carried out on all products without further purification).

2.3. THE STRUCTURAL CHARACTERISATION AND IDENTIFICATION OF *O,O*-DIALKYL 1-OXO- & 1-HYDROXYIMINO- PHOSPHONATES

Infrared spectroscopy was used as a qualitative tool to establish the presence of the 1-oxo- and 1-hydroxyimino- phosphonates. The more characteristic absorption maxima of the stretching vibrations were observed at frequencies of: 1030 - 1050 (P-O-C), 1260 - 1290 (P=O), and 1680 - 1710 (C=O), cm^{-1} in the case of the 1-oxophosphonates. Corresponding values for the hydroxyimino derivatives, were observed at the frequencies of 1040 - 1070 (P-O-C), 1240 - 1260 (P=O) and 3100 -

3200 (N-OH), cm^{-1}. The absence of the highly characteristic C=O stretching vibration, in the latter compounds, confirmed that conversion had taken place. A stretching vibration observed with a frequency of 1600 - 1640 cm^{-1} (corresponding to C=N in the oxime moiety) was additional confirmation that the compound had been successfully synthesised.[78,79]

The ^{1}H N.M.R. spectra of the *O,O*-dialkyl 1-oxoalkane-phosphonates, where the molecule contains two or more carbon atoms in the α-alkane chain, exhibits three-bond phosphorus-hydrogen coupling ($^{3}J_{PCCH}$) of the order of 1.00 to 2.00 Hz (observable under high resolution conditions). In the corresponding 1-hydroxyimino derivatives, this value is in the region of 14.00 Hz and therefore much easier to observe under normal conditions. In the *O,O*-dimethyl derivatives the $^{3}J_{POCH}$ coupling constant is generally in the region of 10.50 to 11.50 Hz, for both classes of compound. As the number of carbon atoms in the *O,O*-dialkyl moiety increases, this $^{3}J_{POCH}$ coupling becomes difficult to evaluate without adopting high resolution techniques. The 1-hydroximinophosphonates were further characterised by the presence of a low field (high frequency) broad singlet in the region of 11.0 to 12.0 ppm for the imino hydroxyl group. The presence of this functionality was further confirmed by its absence after a D_2O shake, illustrating the acidity of this proton which is readily exchangeable.

The ^{13}C N.M.R. signal of the α-carbon atom resonates as a doublet in the region of 210 - 212 ppm, with a one-bond phosphorus-

carbon coupling constant of approximately 160.0 Hz in the case of the 1-oxophosphonates. For the corresponding carbon atom in the 1-hydroxy-iminophosphonates, the chemical shift moves upfield to between 154.0 and 156.0 ppm, with the one-bond phosphorus-carbon coupling constant generally in excess of 200 Hz. Variations in $^{2}J_{PCC}$ and $^{3}J_{PCCC}$ within the alkane chain also occur. In the case of the 1-oxo derivatives, the values range between 52.00 to 58.00 Hz for $^{2}J_{PCC}$ and 2.00 to 5.00 Hz for $^{3}J_{PCCC}$. The $^{2}J_{PCC}$ values drop by more than 50 %, to 15.00 - 20.00 Hz and the $^{3}J_{PCCC}$ values similarly to 1.00 - 2.00 Hz, in the case of the 1-hydroxyiminophosphonates. These changes are assumed to reflect the lower electronegativity of N compared to O. Very little variation appears to occur in the $^{2}J_{POC}$ and $^{3}J_{POCC}$ values for both class of compounds, for which the coupling constants generally reside in the region of 7.00 to 7.50 Hz for the former case and 5.50 to 6.00 Hz for the latter.

Differences were also observed in the ^{31}P N.M.R of both classes of compound. The phosphorus chemical shifts of the α-ketophosphonates were in the region of - 0.50 to - 5.00 ppm, while those of the corresponding oximes were in the region of + 9.00 to + 15.00 ppm; relative to 85 % phosphoric acid used as a external reference.

The presence of what was a residual amount of pyridine in the *O,O*-dialkyl 1-hydroxyiminophosphonates had negligible effect on their elemental analyses. Where differences did occur between the calculated and observed values, N.M.R. examination showed that the compound in

question was clearly present. The α-ketophosphonates and the corresponding oximes remain stable for several months and are important intermediates for use in the synthesis of related 1-aminophosphonic acid derivatives. A summary of the comparison of the ^{13}C and ^{31}P N.M.R. data of these phosphonates is given in Table 22.

TABLE 22

SUMMARY OF THE ^{13}C & ^{31}P N.M.R. DATA FOR THE *O,O*-DIALKYL 1-OXO- & 1-HYDROXYIMINO- PHOSPHONATES SYNTHESISED DURING THE PRESENT WORK

R	R'	$(RO)_2P(O)C(O)R'$			
		δ, α-C(ppm)	$^1J_{PC}$/Hz	$^2J_{PCC}$/Hz	δ ^{31}P(ppm)
CH_3	CH_3	208.38	170.00	59.81	- 0.55
CH_3	C_2H_5	210.85	165.79	56.48	- 0.75
CH_3	n-C_3H_7	210.57	164.66	61.84	- 0.97
CH_3	$(CH_2)_2CO_2C_2H_5$	209.18	171.51	57.37	- 1.52
CH_3	cyclo-C_3H_5	210.30	174.35	73.15	- 0.29
CH_3	C_6H_5	198.37	174.54	64.97	+ 0.58
C_2H_5	CH_3	208.83	170.95	59.31	- 2.42
C_2H_5	C_2H_5	211.37	166.04	56.92	- 2.72
C_2H_5	n-C_3H_7	210.98	165.42	53.78	- 2.79
C_2H_5	$(CH_2)_2CO_2CH_3$	209.33	172.40	57.30	- 3.25
C_2H_5	$(CH_2)_2CO_2C_2H_5$	210.30	172.06	58.02	- 2.65
C_2H_5	cyclo-C_3H_5	210.70	175.42	72.90	- 3.04

C_2H_5	C_6H_5	199.04	175.23	63.65	- 1.43
n-C_3H_7	C_2H_5	211.29	166.86	56.42	- 2.61
n-C_3H_7	n-C_3H_7	210.89	165.67	54.28	- 2.99
i-C_3H_7	CH_3	209.14	173.53	59.37	- 4.80
i-C_3H_7	C_2H_5	211.86	168.75	56.15	- 3.63
i-C_3H_7	n-C_3H_7	211.61	167.62	53.51	- 3.77
i-C_3H_7	$(CH_2)_2CO_2C_2H_5$	209.82	174.10	57.17	- 4.95
i-C_3H_7	$(CH_2)_2CO_2CH_3$	209.85	174.79	57.05	- 4.77
i-C_3H_7	C_6H_5	199.60	177.12	63.52	- 2.98
n-C_4H_9	CH_3	208.89	171.39	59.19	- 3.01
n-C_4H_9	n-C_3H_7	211.22	165.48	55.96	- 2.67
n-C_4H_9	$(CH_2)_2CO_2C_2H_5$	210.12	171.12	57.90	- 3.08
i-C_4H_9	C_2H_5	211.36	167.05	56.10	- 2.95
C_7H_7	$(CH_2)_2CO_2C_2H_5$	210.67	173.66	58.66	- 1.37

(C_7H_7 = $C_6H_5CH_2$)

R	R'	$(RO)_2P(O)C(=N-OH)R'$			
		δ α-C(ppm)	$^1J_{PC}$ /Hz	$^2J_{PCC}$/Hz	δ ^{31}P(ppm)
CH_3	CH_3	149.20	219.38	16.73	14.23
CH_3	C_2H_5	154.11	213.59	16.60	13.68
CH_3	n-C_3H_7	153.61	212.84	15.92	13.92
CH_3	$(CH_2)_2CO_2C_2H_5$	151.31	217.29	17.08	10.52

CH_3	cyclo-C_3H_5	154.01	215.92	18.40	12.26
CH_3	C_6H_5	150.00	220.07	19.60	11.64
C_2H_5	CH_3	149.84	218.56	17.11	11.56
C_2H_5	C_2H_5	154.61	213.59	17.04	13.68
C_2H_5	n-C_3H_7	153.63	213.66	16.73	11.12
C_2H_5	$(CH_2)_2CO_2CH_3$	151.80	216.87	16.92	10.06
C_2H_5	$(CH_2)_2CO_2C_2H_5$	152.10	217.05	16.98	10.27
C_2H_5	cyclo-C_3H_5	154.12	215.42	18.43	9.03
C_2H_5	C_6H_5	151.12	217.81	20.00	8.87
n-C_3H_7	C_2H_5	154.72	213.66	15.22	11.61
n-C_3H_7	n-C_3H_7	154.31	211.90	16.10	11.70
i-C_3H_7	CH_3	151.14	217.87	16.50	8.87
i-C_3H_7	C_2H_5	155.44	214.54	16.73	9.00
i-C_3H_7	n-C_3H_7	154.87	213.78	16.04	9.55
i-C_3H_7	$(CH_2)_2CO_2C_2H_5$	152.38	216.79	17.09	10.93
i-C_3H_7	$(CH_2)_2CO_2CH_3$	152.85	218.25	16.67	8.05
i-C_3H_7	C_6H_5	151.43	219.32	18.30	7.05
n-C_4H_9	n-C_3H_7	153.84	211.39	16.10	11.12
n-C_4H_9	$(CH_2)_2CO_2C_2H_5$	151.83	217.05	17.11	11.62
i-C_4H_9	C_2H_5	155.47	212.40	15.72	10.67
C_7H_7	$(CH_2)_2CO_2C_2H_5$	152.79	216.90	17.12	9.06

(C_7H_7 = $C_6H_5CH_2$)

O,O-Dimethyl 1-oxopropanephosphonate, *O,O*-diethyl 1-oxo-3-carbomethoxypropanephosphonate and *O,O*-di-isopropyl 1-oxo-3-carbomethoxypropanephosphonate were further analysed by electron impact mass spectrometry. All three phosphonates gave rise to their molecular ions, and abundant fragments associated with cleavage of the P-C bond.[80] In the case of the 3-carbomethoxypropanephosphonates, a 3-carbomethoxypropionyl ion, $C(=O)(CH_2)_2CO_2CH_3^+$, was generated at m/z 115. Dialkyl phosphite ion, $(RO)_2P(O)H^+$ and dialkoxy phosphinyl ion, $(RO)_2P(O)^+$ were also formed by hydrogen transfer with notable abundance. A peak associated with the loss of the carbomethoxy moiety, $[M - CO_2CH_3]^+$, was also produced in 10.2 and 52.1 % relative abundance respectively (this fragment has not been tabulated). In a similar fashion, P-C cleavage also occurred in *O,O*-dimethyl 1-oxopropanephosphonate, with generation of an acylium ion $C(=O)CH_2CH_3^+$, at m/z 57, in 67.8 % relative abundance. Dimethyl phosphite ion, m/z 110, and the dimethoxy phosphinyl ion, m/z 109, were produced in 49.3 and 45.1 % relative abundance respectively. A summary of these results is given in Table 23.

TABLE 23. (m/z) DATA OF SOME *O,O*-DIALKYL 1-OXOALKANE-PHOSPHONATES, $(RO)_2P(O)C(O)R'$

R	R'	$[M]^+$	(%)	$[RC(=O)]^+$	(%)	$[(RO)_2P(O)]^+$	(%)	$[(RO)_2P(O)H]^+$	(%)
CH_3	CH_2CH_3	166,	4.7	57,	67.8	109,	45.1	110,	49.3
C_2H_5	$(CH_2)_2CO_2CH_3$	252,	15.8	115,	100.0	137,	39.4	138,	47.1
i-C_3H_7	$(CH_2)_2CO_2CH_3$	280,	22.1	115,	100.0	165,	65.7	166,	56.4

O,O-Di-isopropyl 1-hydroxyimino-3-carboethoxypropanephosphonate was similarly subjected to electron impact mass spectrometry. The only identifiable peak observed was the fragment associated with the loss of the carboethoxy moiety, $[M - CO_2C_2H_5]^+$, at m/z 236 in 7.3 % relative abundance. No fragments were observed for the molecular ion, or peaks due to P-C cleavage, as in the case of the 1-oxoalkanephosphonates. The implication here was that the 1-hydroximinophosphonates were probably not volatile enough to be analysed by electron impact mass spectrometry. *O,O*-Dimethyl 1-hydroxyiminopropanephosphonate, and *O,O*-dimethyl 1-hydroxyimino-3-carboethoxypropanephosphonate were subjected to FAB ms analysis, using thioglycerol as the matrix in the first example, and direct bombardment of the phosphonate in the second example. Both compounds gave the characteristic $[M+H]^+$ signal and other associated species in very simple fragmentation profiles. A base peak at m/z 94 and 127 respectively was also observed in these phosphonates. A summary

of these results is given in Table 24.

TABLE 24

FAB MASS SPECTROMETRIC DATA OF *O,O*-DIALKYL 1-HYDROXYIMINO-ALKANEPHOSPHONATES $(RO)_2P(O)C(=N\text{-}OH)R'$

R	R	$[M+H]^+$ (%)	$[2M+H]^+$ (%)	$[(RO)_2P(O)]^+$ (%)	BASE PEAK(%)
CH_3	C_2H_5	182, 64.4	363, 5.0	109, 25.0	94, 100.0
CH_3	$(CH_2)_2CO_2C_2H_5$	254, 72.5	507, 2.1	109, 52.9	127, 100.0

O,O-Dimethyl 1-hydroxyiminopropanephosphonate was also analysed by caesium ion FAB ms, to give rise to a much simpler fragmentation pattern. The peaks $[M+H]^+$ and $[2M+H]^+$, were 100 % and 12.5 % abundant respectively. A fragment associated with P-C cleavage, and the liberation of the dimethoxy phosphinyl ion, was 20 % abundant. The application of FAB ms in the analysis of 1-hydroxyiminophosphonates is a relatively new undertaking.

2.4. THE REDUCTION OF *O,O*-DIALKYL 1-HYDROXYIMINOALKANE-PHOSPHONATES

2.4.1 THE SYNTHESIS OF 1-AMINO-3-CARBOXYPROPANEPHOSPHONIC ACID

Given that the 1-hydroxyiminoalkanephosphonates could be synthesised in very good yields, an investigation was carried out to adapt and develop a method of reduction that would afford the corresponding 1-aminophosphonates in comparable yields.

A number of ways of reducing oximes have been reported in the literature.[83] During the course of the present studies *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates were reduced by using one of the following methods: (a) catalytic hydrogenation over 5 % palladium on carbon, with trace amounts of water, with methanol or acetic acid as solvent;[84] (b) catalytic hydrogenation over Raney nickel, using methanol or liquid ammonia as solvent;[85,86] (c) reduction over aluminium amalgam in anhydrous ether;[87,88,89,90] (d) reduction over activated zinc dust in formic acid;[91] and (e) chemical reduction with lithium borohydride and trimethylsilyl chloride, using dry THF as the solvent for the reaction.[92]

During the initial studies a number of *O,O*-dialkyl 1-hydroxyimino-3-carboethoxypropanephosphonates [(88), where R = CH_3, C_2H_5, n-C_4H_9 and $C_6H_5CH_2$] were reduced using the methods: (a), (b) and (d) to give the 1-amino derivatives (89) which were acid-hydrolysed *in-situ* and

treated with propene oxide in methanol as described,[24] in the hope of isolating the corresponding ω-carboxyphosphonic acid which was particularly desirable (see chapter 1). Interestingly, 1-amino-3-carbomethoxypropanephosphonic acid (91) rather than the free carboxy acid (90) was obtained, and the structure was confirmed by infrared, ^{1}H, ^{13}C and ^{31}P N.M.R spectroscopy; and later FAB mass spectrometry in one example. The reactions (Scheme 44) are shown below.

$(RO)_2P(O)C(=N\text{-}OH)(CH_2)_2CO_2C_2H_5$ (88) $\xrightarrow{\text{reduced by methods: (a), (b), (d)}}$

$(RO)_2P(O)CH(NH_2)(CH_2)_2CO_2C_2H_5$ (89) $\xrightarrow{\text{(i) c.HCl, (ii) propene oxide}}$

$(HO)_2P(O)CH(NH_2)(CH_2)_2CO_2H$ (90) + $\xrightarrow{CH_3OH\ (40\text{-}50\ ^{o}C)}$

$(HO)_2P(O)CH(NH_2)(CH_2)_2CO_2CH_3$ (91)

Scheme 44

When the work-up procedure was modified by treating the acid-hydrolysed products with propene oxide in water, 1-amino-3-carboxypropanephosphonic was isolated in 15 to 20 % crude yield. The desired product was purified by recrystallisation from ethanol and water and was authenticated by N.M.R. spectroscopy and FAB mass spectrometry. A summary of the results is given in Table 25. It

appears that the free acid, undergoes ready esterification of the carboxyl group in methanolic solution and isolation of the free carboxylic acid from this solvent is not possible (Scheme 45). An attempt to reduce the dimethyl ester with aluminium amalgam [method (c)] failed, although this approach has been used to reduce other oximes.[87-90]

TABLE 25

SUMMARY OF HYDROLYSIS PRODUCTS AFTER CATALYTIC HYDROGENATION VARIOUS *O,O*-DIALKYL 1-HYDROXYIMINO-3-CARBOETHOXYPROPANEPHOSPHONATE

$(RO)_2P(O)C(=N\text{-}OH)(CH_2)_2CO_2C_2H_5 \longrightarrow (HO)_2P(O)CH(NH_2)(CH_2)_2CO_2R'$

SUBSTRATE/R	METHOD	TIME/h	TEMP/°C	PRESS./p.s.i.	HYDROLYSED PRODUCT/R'	(YIELDS/%)
CH_3	A	3	80	400	CH_3	42
CH_3	B	4	114	400	CH_3	10
CH_3	C	15	80	250	CH_3	32
C_2H_5	B	4	40	450	CH_3	67
C_2H_5	C	6	70	300	CH_3	44
C_2H_5	C	6	76	350	H	22
$n\text{-}C_4H_9$	B	5	75-6	500	CH_3	49

$n\text{-}C_4H_9$	C	6	80	300	*	0
$C_6H_5CH_2$	C	16	86	300	*	0
$C_6H_5CH_2$	D	6	40	100	*	0

Where A = 5 %, Pd/C in MeOH or liq. NH_3

B = Ni in MeOH

C = 5 %, Pd/C in HOAc (+ 2.5 cm^3 H_2O)

D = 5 %, Pd/C in HOAc

* = no product isolated

2.4.2 THE SYNTHESIS OF *O,O*-DIALKYL 1-AMINOALKANEPHOSPHONATES

Crude *O,O*-dimethyl 1-aminopropanephosphonate (92) and crude *O,O*-dimethyl 1-aminobutanephosphonate (93) were isolated following the catalytic hydrogenation of their 1-hydroxyimino precursors using: (i) nickel and (ii) 5 % palladium on carbon respectively, with glacial acetic acid as the solvent in both examples. The general reaction (Scheme 45) is shown below.

$(RO)_2P(O)C(=N\text{-}OH)R' \xrightarrow{\text{catalytic hydrogenation}} (RO)_2P(O)CH(NH_2)R'$ (92, 93)

[(92) R = CH_3, R' = C_2H_5; (93) R = CH_3, R' = $n\text{-}C_3H_7$]

Scheme 45

After the spent catalyst had been filtered off the filtrates were concentrated under reduced pressure to remove as much glacial acetic acid as possible, and an attempt was made to purify the oily residues by distillation under high vacuum. In both cases, only a few drops of distillate, predominantly acetic acid, could be collected before the bulk material polymerised and upon cooling became a hard intractable residue. ^{1}H N.M.R (60 MHz) examination revealed that none of the expected 1-aminoalkanephosphonate was present in either instance. However, when the *O,O*-dimethyl 1-aminobutanephosphonate residue was acid-hydrolysed and worked-up in the normal way with propene oxide in methanol, 1-aminobutanephosphonic acid was isolated in 20 - 30 % overall yield. The catalytic hydrogenations of the 1-hydroxyiminophosphonates that were carried out produced fair yields of the 1-aminophosphonic acids, after hydrolysis of the 1-amino intermediates, when 0.01 to 0.04 mol of the starting material was reduced in this way in 70 cm^3 of solvent.

J. Volckman (1988)[41] had observed that when catalytic hydrogenation was carried out at higher concentrations e.g. on *O,O*-dimethyl 1-hydroxyiminobutanephosphonate (0.10 mol in 100 cm^3 of solvent) with 5 % palladium on carbon and *O,O*-diethyl 1-hydroxyiminopropanephosphonate (0.10 mol) with nickel, the amount of crude ester obtained in each case, dropped considerably.[41] Similarly when these phosphonates (0.10 mol in 70 cm^3 of solvent) were hydrogenated in the present work using 5 % palladium on carbon in

glacial acetic acid, the amount of crude ester isolated was also poor. The observations seemed to favour the use of catalytic hydrogenation on lower concentrations of substrate.

A number of attempts were made in the present work to obtain the corresponding 1-aminophosphonates from the 1-hydroxyimino precursors $(RO)_2P(O)C(=N\text{-}OH)R'$ [0.10 mol, where (i) R = R' = CH_3; (ii) R = CH_3, R' = CH_2CH_3; (iii) R = R' = CH_2CH_3 and (iv) R = CH_2CH_3, R' = n-C_3H_7], by chemical reduction using zinc powder and formic acid.[91] The reactions (Scheme 46) involved formation of the *N*-formyl derivative (94) of the required amino compound, cleavage of the *N*-formyl derivative with HCl gas, and treatment of the hydrochloride with ammonia gas in dry ether to liberate the desired product in crude form. The compounds were then distilled under high vacuum, when they were afforded as clear high-boiling liquids. The reactions (Scheme 46) are shown below.

$$(RO)_2P(O)C(=N\text{-}OH)R' \xrightarrow{Zn\ /\ HCO_2H} (RO)_2P(O)CH(NHCHO)R' \quad (94)$$

$$(94) + HCl(g)/CH_3OH \longrightarrow (RO)_2P(O)CH(NH_3^+.Cl^-)R' \quad (95)$$

$$(95) + NH_3(g) \text{ in dry } Et_2O \longrightarrow (RO)_2P(O)CH(NH_2)R' + NH_4Cl$$

Scheme 46

At best the crude yield of the 1-aminophosphonate $(RO)_2P(O)CH(NH_2)R'$, was 35 %, when R = R' = C_2H_5, even after the zinc powder had been activated by the method of Reformatsky.[94] When the above crude phosphonate, and the case where R = C_2H_5, R' = n-C_3H_7; were distilled under high vacuum, the pure compounds were afforded in 26 % and 8 % yield respectively (from approximately 0.10 mol of starting material). Contrasting results were obtained in the cases where R = R' = CH_3; and R = CH_3, R' = C_2H_5. In these instances no product was isolated from the starting material (0.10 mol, in both examples). A summary of these preparations is given in Table 26.

TABLE 26

PREPARATION OF *O,O*-DIALKYL 1-AMINOALKANEPHOSPHONATES USING Zn/HCO_2H METHOD $(RO)_2P(O)CH(NH_2)R'$

R	R'	AMOUNT OF SUBSTRATE/mol	YIELD (%) CRUDE	YIELD (%) DISTILLED	B.P °C/mmHg
CH_3	CH_3	0.10	-	-	-
CH_3	C_2H_5	0.12	-	-	-
C_2H_5	C_2H_5[122]	0.09	12.00	9.50	76/0.075
C_2H_5	C_2H_5[122]	0.09	18.60	5.24	92-5/0.10
C_2H_5	C_2H_5[122]	0.088	35.00	26.00	80-2/0.05
C_2H_5	n-C_3H_7	0.10	35.60	7.75	124-8/0.05

It is suggested that the poor yields of the distilled dialkyl 1-aminophosphonates might be accounted for by polymerisation of the product. After distillation, it was noticeable that a light brown intractable residue always remained in the distillation flask and was presumed to be a polymeric product from the bulk material.

The synthesis of *O,O*-dialkyl 1-aminoalkanephosphonates was dramatically improved when lithium borohydride/trimethylsilyl chloride was used as the reducing agent with various 1-hydroxyiminophosphonate precursors, in dry THF at room temperature. A mixture of lithium borohydride and trimethylsilyl chloride has recently been shown to reduce a variety of substrates such as amino acids, carboxylic acids, amides, nitriles, nitroalkanes and sulphoxides in very high yield.[92] It was suggested that the reagent exerts its effect by forming a borane-THF complex, which acts as a reducing agent, as illustrated by Scheme 47 below.

$$LiBH_4 + (CH_3)_3SiCl \xrightarrow{THF} (CH_3)_3SiH + BH_3.THF + LiCl$$

Scheme 47

The addition of trimethylsilyl chloride makes it possible to carry out chemical reductions with $LiBH_4$ which are either very slow or do not occur in its absence. It appears that this reagent has not previously been applied to the reduction of oximes, but was investigated in the

present work for the reduction of *O,O*-dialkyl 1-hydroxyiminoalkane-phosphonates.

When *O,O*-diethyl 1-hydroxyiminopropanephosphonate and *O,O*-di-isopropyl 1-hydroxyiminopropanephosphonate (both 0.10 mol) were reduced using this approach, the crude yields of the 1-amino derivatives were roughly 70 % and 90 % respectively. Distillation under high vacuum, in both instances, afforded the products as colourless, odourless, free-flowing liquids. Results were a little less encouraging when *O,O*-dimethyl 1-hydroxyiminopropanephosphonate (0.02 mol and 0.04 mol) and *O,O*-dimethyl 1-hydroxyiminobutanephosphonate (0.02 mol) were reduced by this method. The crude yields of the corresponding 1-aminophosphonates were 30 % and 11 % respectively. However, distillation under high vacuum, as in the case of the other derivatives, afforded the compounds in a very high state of purity. As in the case of the zinc/formic acid method, when an attempt was made to reduce *O,O*-dimethyl 1-hydroxyiminoethanephosphonate with $LiBH_4/(CH_3)_3SiCl$, no product could be isolated. By contrast the *O,O*-diethyl phosphonate derivative (0.021 mol) when reduced gave the crude product in 44 % yield. Distillation of this material under high vacuum gave the diethyl aminophosphonate ester as a colourless, odourless free-flowing liquid, in a high state of purity.

The fact that $LiBH_4/(CH_3)_3SiCl$ reductions of 1-hydroxyimino-phosphonates take place at room temperature and normal pressure in the inert solvent THF, ensures that a large proportion of the substrate is

reduced with a minimum of decomposition whilst they are being converted into the desired 1-aminophosphonates. It is known that *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates are unstable at elevated temperature and in some cases decompose violently if any attempts are made to purify them by distillation.[95] Under the conditions required to carry out catalytic hydrogenations of 1-hydroxyiminophosphonates, prolonged heating of these substrates, particularly under high pressure, may result in decomposition.

During the synthesis of *O,O*-dialkyl 1-hydroxyiminophosphonates it is recommended that an alcohol with the same functional group as the substituent in the *O,O*-dialkyl moiety should be used as the solvent of the reaction, to negate the effects of transesterification.[71] For example if one is preparing a dimethyl phosphonate then the solvent recommended would be methanol; for the diethyl phosphonate, the solvent recommended would be ethanol, and so on. It is a possibility that transesterification may have been taken place whilst solvents with functional groups other than those in the dialkyl moiety were being used (as in the cases of glacial acetic acid and methanol), in the catalytic hydrogenations of several of the substrates that were treated in this way. More importantly Katzhendler *et al.*, (1989) found that *O,O*-dimethyl 1-hydroxyiminobenzylphosphonate underwent fragmentation in alcohols to benzonitrile and a phosphodiester via a concerted, dissociative bond cleavage mechanism. They showed that the rate of *O,O*-dialkyl cleavage was similar through the series : Bu^tOH, Pr^iOH,

EtOH, MeOH, proceeding by a dissociative mechanism either involving monomeric metaphosphate anion as a reactive intermediate, or through an open transition state dissociative structure, resembling monomeric metaphosphate.[96] These findings could be used to explain why the catalytic hydrogenations were relatively poor. It was difficult to characterise accurately the material obtained after these catalytic hydrogenations by ^{1}H N.M.R. (60 MHz), where at best one observed that there were a number of components present. In the $LiBH_4/(CH_3)_3SiCl$ procedure this system does not give rise to such difficulties, as even the crude products only show resonances for the required product and no other component.

Although the 1-aminophosphonates derived from $LiBH_4/(CH_3)_3SiCl$ reductions readily distilled under high vacuum to give very pure products, it was noticeable that in every case one could observe a light-brown intractable residue, similar to that observed in the zinc/formic acid experiments, after the distillations had finished. One attempt was made to characterise the residue left after distillation of *O,O*-diethyl 1-aminopropanephosphonate, by high field ^{1}H N.M.R. (250 MHz) but it was clear that the extremely complex nature of the spectrum was probably representative of a degradation product. The hypothesis that some form of inter- or intra- molecular reaction may have been taken place between the amino group and one of the alkoxy groups might be a reason to explain the nature of this observation. Interestingly, even in the use of $LiBH_4/(CH_3)_3SiCl$, the *O,O*-dimethyl 1-hydroxyimino-

phosphonates appear not to respond well to reductions, be they catalytic or otherwise. The possiblity that the ester function (*O,O*-dimethyl groups) may be undergoing cleavage during the reaction would account for the poor yield of the corresponding 1-aminophosphonate using this method.

A summary of the $LiBH_4/(CH_3)_3SiCl$ and Zn/HCO_2H reductions is given in Tables 27 and 28.

TABLE 27

PREPARATION OF *O,O*-DIALKYL 1-AMINOALKANEPHOSPHONATES USING $LiBH_4/(CH_3)_3SiCl$ $(RO)_2P(O)CH(NH_2)R'$

R	R'	AMOUNT OF SUBSTRATE/mol	YIELD (%) CRUDE	YIELD (%) DISTILLED	B.P ^oC/mmHg
CH_3	CH_3	0.10	-	-	
CH_3	C_2H_5	0.02	14.40	-	
CH_3	C_2H_5	0.04	30.40	5	84/2.0
CH_3	$n\text{-}C_3H_7$	0.02	11.00	2	82/0.2
C_2H_5	CH_3	0.021	44.00	24	84-5/0.3
C_2H_5	C_2H_5[122]	0.019	61.00	36	86-9/0.1
C_2H_5	C_2H_5[122]	0.099	69.00	27	95/0.1
C_2H_5	C_2H_5[122]	0.057	65.30	26	92-3/0.1
C_2H_5	C_2H_5[122]	0.083	69.00	29	91-1/0.1
$i\text{-}C_3H_7$	C_2H_5	0.100	87.10	14	87-90/0.1

TABLE 28

***O,O*-DIALKYL 1-AMINOALKANEPHOSPHONATES SYNTHESISED DURING STUDIES $(RO)_2P(O)CH(NH_2)R'$**

METHOD	R	R'	B.P. (^oC/mmHg)	YIELD(%) DIST.	CALC. FOR (%) C	H	N	FOUND (%) C	H	N
A	CH_3	C_2H_5	84/2.0	5	35.93	8.38	8.38	35.62	8.32	8.38
A	CH_3	n-C_3H_7	82/0.2	2	39.78	8.84	7.74	40.00	8.31	7.69
A	C_2H_5	CH_3	85/0.3	24	39.78	8.84	7.74	39.50	8.92	7.41
A	C_2H_5	C_2H_5	95/0.01	36*	43.08	9.23	7.18	43.08	9.14	7.56
B	C_2H_5	C_2H_5	82/0.05	26	43.08	9.23	7.18	43.15	9.42	6.52
B	C_2H_5	n-C_3H_7	128/0.05	8	45.93	9.57	7.18	45.90	9.81	6.80
A	i-C_3H_7	C_2H_5	90/0.1	14	48.43	9.87	6.28	48.43	9.99	6.34

* (This was the maximum yield from a number of distillations of the crude material)

A = reduction by $LiBH_4/(CH_3)_3SiCl$

B = reduction by Zn/HCO_2H

Sodium borohydride/trimethylsilyl chloride has also been shown to be an effective reducing agent for numerous organic substrates.[92] However no product could be isolated when an attempt was made to reduce *O,O*-diethyl 1-hydroxyiminopropanephosphonate (0.10 mol) under the conditions specified for the reaction. The implication is that

$LiBH_4/(CH_3)_3SiCl$ is the more suitable reagent for the reduction of *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates, particularly as no external heat is required to effect the reaction. The use of $NaBH_4/(CH_3)_3SiCl$ requires that the substrate be heated under reflux with the reagent in THF for 12 h beneath an inert atmosphere. Such reaction conditions do not appear to be suitable for the reductions of 1-hydroxyiminophosphonates, which are unstable at elevated temperature.

2.5. THE STRUCTURAL CHARACTERISATION OF *O,O*-DIALKYL 1-AMINOALKANEPHOSPHONATES BY N.M.R.

The *O,O*-dialkyl 1-aminoalkanephosphonates possess a chiral α-carbon atom, and show complex multiplicities in the ^1H N.M.R. spectra that arise out of coupling between the methine hydrogen atom attached to this carbon, the adjacent magnetically non-equivalent methylene hydrogen atoms and the phosphorus atom in the phosphonate moiety which contributes $^2J_{PCH}$ and $^3J_{PCCH}$ coupling to this region of the spectrum. Magnetic non-equivalence was also observed in the *O,O*-methylene groups of the *O,O*-diethyl 1-aminophosphonates, where these species resonated as a pair of highly complex multiplets. Magnetic non-equivalence of the alkoxy groups was easier to observe in the cases of *O,O*-dimethyl 1-aminopropanephosphonate and *O,O*-dimethyl 1-aminobutanephosphonate, for which the *O,O*-dimethyl groups were clearly observed as a pair of doublets resonating at approximately 3.60 to 3.80 ppm. When

the high-field ^{1}H N.M.R. spectrum of *O,O*-diethyl 1-aminoethane-phosphonate was observed 2-dimensionally, one was more able to observe the asymmetry that was present in the *O*-methylene region of the molecule. This N.M.R. spectrum is shown overleaf (Fig. 3).

The application of broad-band proton decoupled ^{13}C N.M.R. spectroscopy, further exemplified the magnetic non-equivalence of the alkoxy groups in these 1-aminophosphonates. In most cases the *O*-methyl or *O*-methylene moiety resonated as a pair of doublets. A summary of the ^{13}C and ^{31}P N.M.R. data of the *O,O*-dialkyl 1-amino-alkanephosphonates is given in Table 29.

TABLE 29

^{13}C & ^{31}P N.M.R. SUMMARY OF THE *O,O*-DIALKYL 1-AMINOALKANE-PHOSPHONATES SYNTHESISED DURING THE CURRENT WORK

$(RO)_2P(O)CH(NH_2)R'$

R	R'	δ α-C/ppm	$^{1}J_{PC}$/Hz	$^{2}J_{PCC}$/Hz	$^{3}J_{PCCC}$/Hz	δ ^{31}P/ppm
CH_3	C_2H_5	50.01	148.94	0.00	13.02	31.36
CH_3	n-C_3H_7	48.18	149.15	0.00	12.93	31.61
C_2H_5	CH_3	44.08	150.42	0.00	-	28.87
C_2H_5	C_2H_5	50.36	148.49	0.00	13.13	29.12
C_2H_5	n-C_3H_7	48.53	148.70	0.00	12.49	28.81
i-C_3H_7	C_2H_5	50.84	148.98	0.00	13.09	26.99

2-Dimensional ^{1}H N.M.R. spectrum of *O,O*-methylene groups in *O,O*-diethyl 1-aminoethanephosphonate

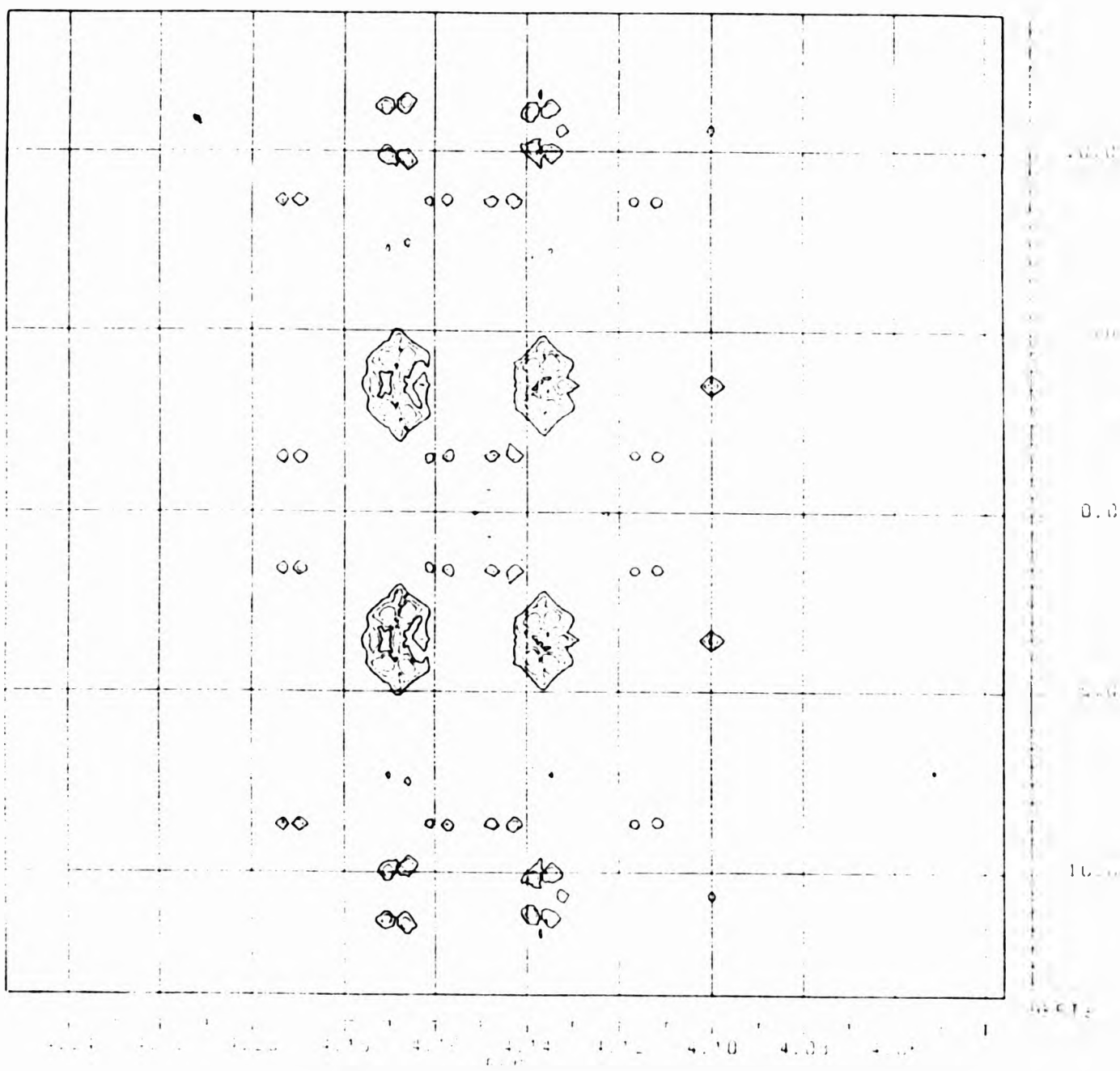


Fig 3

2.6. THE SYNTHESIS OF *O,O*-DIALKYL 1-NITROALKANEPHOSPHONATES & THEIR DERIVATIVES

Oximes (not including *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates) may be generally oxidized using: (a) peroxy trifluoroacetic acid,[97] or (b) in a three stage procedure, involving chlorination of the oxime to the chloronitroso derivative (96) followed by oxidation with ozone to the nitro compound (97) and catalytic hydrogenation to afford the desired nitro derivative (98).[98] The reactions (Scheme 52) are given below.

$$R\text{-}C(=N\text{-}OH)R' \xrightarrow{\text{(i) } Cl_2/CH_2Cl_2} R\text{-}CCl(N=O)R' \quad (96)$$

$$(96) + \text{(ii) } O_3/CH_2Cl_2 \longrightarrow (97)$$

$$R\text{-}CCl(NO_2)R' \ (97) + NaOH,\ H_2/H_2O,\ Pd/C \longrightarrow (98)$$

$$R\text{-}CH(NO_2)R' \quad (98)$$

Scheme 48

In a similar fashion, oximes may be rapidly transformed to the 1-chloronitrosoderivatives (96) by aqueous hypochlorous acid at 25 ^{o}C. The intermediate may be smoothly oxidized to the 1-chloronitro derivative with tetra-n-butylammonium hypochlorite. A number of

reagents may be used to effect hydrodechlorination of the 1-chloronitro compound to the secondary nitro derivative.[99] The reactions (Scheme 49) are given below.

$$R\text{-}C(=N\text{-}OH)R' \quad + \text{(i) } HOCl \longrightarrow \textbf{(96)}$$

$$\textbf{(96)} \quad + \quad \text{(ii) } (C_4H_9)_4N^+OCl^- \longrightarrow \textbf{(97)}$$

$$\textbf{(97)} \quad + \quad \text{reductive chlorination} \longrightarrow R\text{-}CH(NO_2)R' \ \textbf{(98)}$$

Scheme 49

O,O-Dialkyl 1-nitroalkanephosphonates may be synthesised by oxidative nitration of 2-alkoxyalkanephosphonates; by oxidation of *O,O*-dialkyl 1-aminoalkanephosphonates; by nitration of phosphono-carbanions and by phosphorylation of halonitroalkanes.[100]

During the course of the present work, several *O,O*-dialkyl 1-nitroalkane- and *O,O*-dialkyl 1-nitrobenzylphosphonates (99) were prepared via the easy oxidation of their 1-hydroxyiminophosphonate precursors, using *m*-chloroperbenzoic acid in dichloromethane, in good yields.[100] The reaction (Scheme 50) is shown overleaf.

$$(RO)_2P(O)C(=N\text{-}OH)R' + 3\text{-}ClC_6H_4CO_3H \xrightarrow{\text{1 week R.T. in } CH_2Cl_2} (RO)_2P(O)CH(NO_2)R' \quad (99)$$

(99)

Scheme 50

The advantages of using this method were that the work-up procedure was easy, reagent costs were low, scale-up was easy to operate and virtually no by-products were formed. The compounds were generally obtained in 75 to 95 % crude yield as viscous, yellow or orange, pleasant-smelling oils. Although a few of these compounds were distilled under high vacuum, ^{1}H, ^{13}C and ^{31}P N.M.R. spectroscopy as well as C, H, N analysis, showed that further purification was not necessary. The fact that these compounds were readily accessible was advantageous as it had been reported that these compounds display some unspecified biological activity.[100]

The *O,O*-dialkyl 1-nitroalkanephosphonates have the potential to be used as substrates for the synthesis of highly branched novel 1-aminoalkanephosphonic acids. If suitable methods are used to abstract the acidic methine α-hydrogen from the nitrophosphonate, the resultant carbanion may be available for nucleophilic addition to a variety of appropriate species thereby producing a tertiary α-carbon atom, with the introduction of useful functionality to the molecule. Reduction of the nitro group to the amino group, would give rise to the possiblity of producing interesting branched (e.g. α-fluoroalkyl) 1-aminophosphonic

acids.

It was also observed that when an attempt was made to oxidise *O,O*-dimethyl 1-hydroxyiminoethanephosphonate (0.10 mol) using the above reagent, no product could be isolated. Also when *O,O*-dimethyl 1-hydroxyiminopropanephosphonate and *O,O*-dimethyl 1-hydroxyiminobutane-phosphonate (both 0.03 mol) were oxidised in this way, the crude yields of the corresponding nitro derivatives were 33 % and 45 % respectively; the propane compound being a gelatinous, pleasant-smelling, orange-yellow residue, while the butane compound was a viscous, orange pleasant smelling oil. Despite the comparatively low yield of these particular nitrophosphonates, ^{1}H, ^{13}C and ^{31}P N.M.R. spectroscopy confirmed that these compounds had clearly been formed, and were reasonably pure. Low yields of products appear therefore to be obtained both in reduction and the oxidation of dimethyl 1-hydroxyiminophosphonates. The reason is not clear but may be related to easier *O,O*-dealkylation in the case of the methyl esters. A summary of the 1-nitrophosphonates synthesised during the course of the present work is given in Table 30.

As indicated in the Table overleaf a few of these nitro-phosphonates were distilled under high vacuum to purify them further. *O,O*-Dimethyl 1-nitro-3-ethoxycarbonylpropanephosphonate appeared to undergo considerable decomposition as indicated by the microanalytical and N.M.R. spectral data obtained for the fractionated product. During one attempt to distil a crude sample of *O,O*-diethyl 1-nitrobenzyl-

phosphonate, the bulk material violently decomposed soon after commencement of the experiment. Although a small amount of distillate was collected, elemental analysis and N.M.R. spectroscopy showed that this product was considerably contaminated by degradation products.

O,O-Diethyl 1-nitropropanephosphonate, *O,O*-diethyl 1-nitro-3-ethoxycarbonylpropanephosphonate, *O,O*-di-isopropyl 1-nitroethane-phosphonate and *O,O*-di-isopropyl 1-nitropropanephosphonate, however, were successfully distilled under high vacuum, to afford clear, free-flowing distillates. Although these 1-nitrophosphonates were distillable, the yields were moderate and always accompanied by the formation of an intractable residue as the bulk material was being heated.

TABLE 30

SUMMARY OF *O,O*-DIALKYL 1-NITROPHOSPHONATES SYNTHESISED DURING THE CURRENT WORK $(RO)_2P(O)CH(NO_2)R'$

R	R'	YIELD(%) (CRUDE)	CALCULATED(%) C	H	N	FOUND (%) C	H	N
CH_3	CH_3 [101]	0	26.23	5.47	7.65			
CH_3	C_2H_5 [101]	33	30.46	6.09	7.11	32.02	6.04	6.17
CH_3	$n\text{-}C_3H_7$ [101]	45	34.12	6.64	6.64	34.03	6.76	6.46
CH_3	$(CH_2)_2CO_2C_2H_5$ *	60^	35.69	5.95	5.20	36.56	6.12	4.22
CH_3	C_6H_5 *	55	44.08	4.90	5.71	45.64	5.11	5.94

C_2H_5	CH_3[101]	41	34.12	6.64	6.64	33.95	6.66	6.55
C_2H_5	C_2H_5[101]	75^	37.33	7.11	6.22	37.51	7.17	5.90
C_2H_5	n-C_3H_7[101]	80	40.17	7.53	5.86	40.33	7.48	6.28
C_2H_5	$(CH_2)_2CO_2CH_3$*	100	38.16	6.36	4.95	38.21	6.35	5.03
C_2H_5	$(CH_2)_2CO_2C_2H_5$*	76^	40.40	6.73	4.71	41.35	6.96	4.00
C_2H_5	C_6H_5*	71^	48.35	5.86	5.13	49.64	5.89	4.85
i-C_3H_7	CH_3[100]	75	40.17	7.53	5.86	40.99	7.70	4.99
i-C_3H_7	C_2H_5[100]	90^	42.69	7.91	5.53	42.51	8.12	5.52
i-C_3H_7	n-C_3H_7[119]	85	44.94	8.24	5.24	44.96	8.18	5.33
i-C_3H_7	$(CH_2)_2CO_2CH_3$*	100	42.44	7.07	4.50	42.31	7.07	4.67
i-C_3H_7	C_6H_5*	85	51.83	6.65	4.65	52.49	6.57	4.14
n-C_4H_9	n-C_3H_7[119]	85	48.81	8.81	4.75	48.98	8.74	4.74
i-C_4H_9	C_2H_5*	96	46.98	8.54	4.98	47.28	8.96	4.17
$(CH_3)_3Si$	C_2H_5	25^	34.51	7.67	4.47	34.29	7.79	4.28

* = new compound, ^ = distilled under reduced pressure.

(When some of the products were analysed as crude materials, some discrepancy did occur between the observed and calculated microanalytical data for a few examples. However the structures of these compounds were authenticated by N.M.R. spectroscopic analysis).

2.7. STRUCTURAL CHARACTERISATION OF 1-NITROPHOSPHONATES

Preliminary investigation of the 1-nitrophosphonates was carried out using infrared spectroscopy. The compounds were characterised by the presence of a particularly strong stretching vibration at υ_{max} 1550 - 1560 cm^{-1}, associated with N-O stretching in the NO_2 group of the molecule. Other absorptions associated with the phosphonate moiety of these molecules were also observed.[101]

As with the *O,O*-dialkyl 1-aminoalkanephosphonates, the 1-nitro compounds possess a chiral α-carbon atom. In the ^1H N.M.R. spectra, 1-nitroalkanephosphonates display the complex multiplicities that arise out of coupling between the methine hydrogen atom attached to the α-carbon atom, the adjacent magnetically non-equivalent methylene hydrogens and the $^2J_{PCH}$ and $^3J_{PCCH}$ contribution from the phosphorus atom in the phosphonate moiety. These compounds were further characterised by the presence of a sharply resolved multiplet for the methine hydrogen, similar to that seen for the 1-aminophosphonates but resonating at lower field (5.00 to 5.50 ppm), shown in the ^1H N.M.R. spectrum of *O,O*-dimethyl 1-nitropropanephosphonate (Fig 4). In the case of the aromatically substituted nitrophosphonates, the methine hydrogen resonated as a slightly lower field doublet with a chemical shift of approximately 6.00 ppm. The phosphorus-hydrogen interaction, $^2J_{PCH}$ was in the region of 17.00 Hz. The *O*-methylene hydrogens of *O,O*-dialkyl groups possessing two or more carbon atoms in this position, were also

^{1}H N.M.R. spectrum of *O,O*-dimethyl 1-nitropropanephosphonate

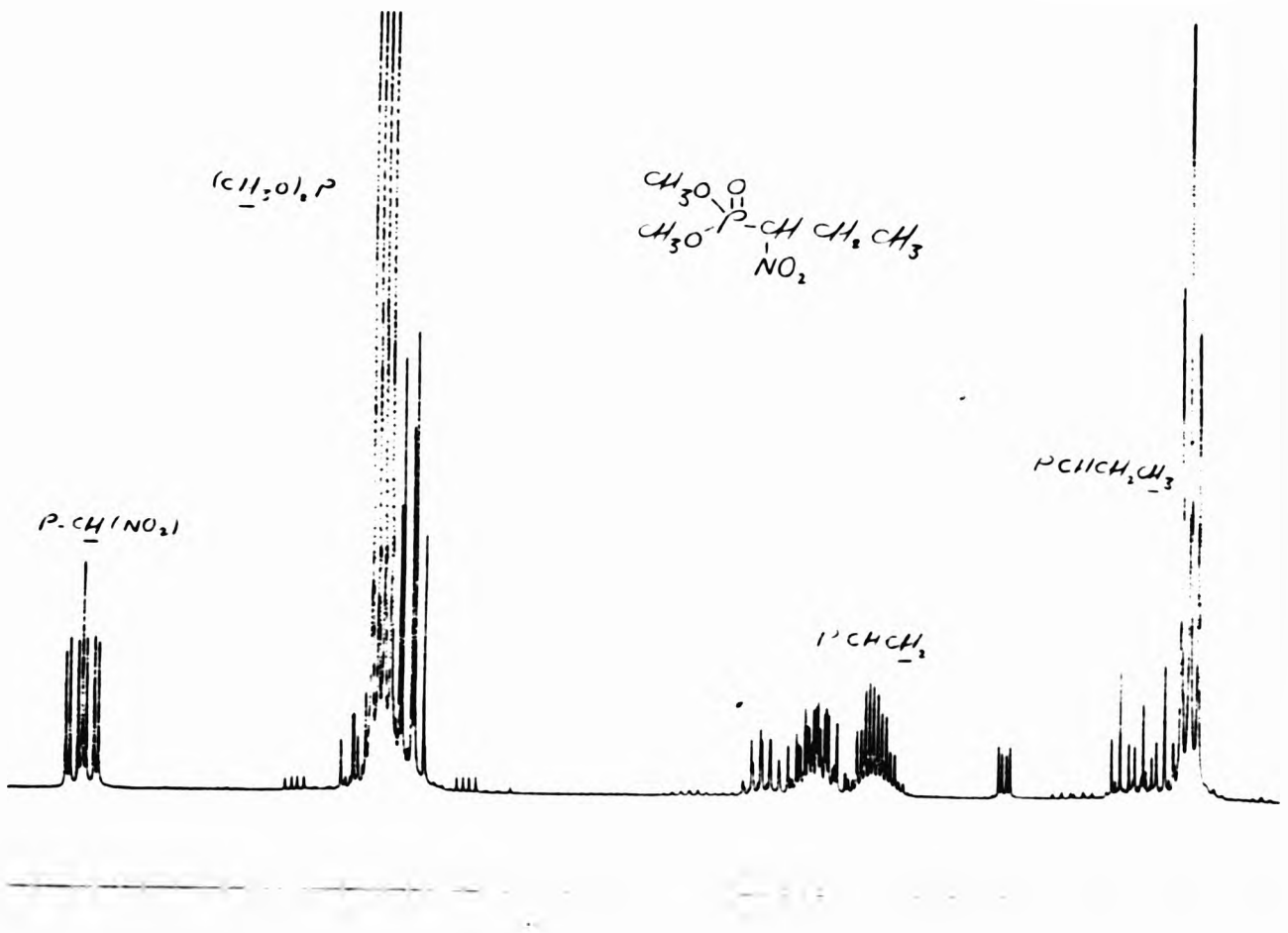


Fig 4

found to exhibit very complex multiplicities, resulting from magnetic non-equivalence of the methylene protons and further that the alkyl groups were also magnetically non-equivalent. The latter effect was clearly demonstrated by the *O,O*-dimethyl 1-nitrophosphonates for which the methyl protons resonated as a nicely resolved pair of doublets.

^{13}C N.M.R. studies showed that the α-carbon atom in these compounds resonated as a doublet with a chemical shift of 80.0 to 85.0 ppm and $^{1}J_{PC}$ 140 - 145 Hz. Interestingly, whilst two-bond phosphorus-carbon coupling was not observed in the 1-amino-phosphonates, $^{2}J_{PCC}$ for the 1-nitroalkyl derivatives was found to be in the region of 2.00 to 3.00 Hz. As in the case of the 1-amino-phosphonates, the 1-nitrophosphonates displayed $^{3}J_{PCCC}$ values in the region of 11.00 to 13.00 Hz. The chemical shift of the phosphorus atom in the ^{31}P N.M.R. spectra of these compounds was comparable to that of the 1-hydroxyiminophosphonate precursors, resonating in the region of roughly 10.00 to 15.00 ppm. A summary of the ^{13}C and ^{31}P N.M.R. data of the 1-nitrophosphonates is given in Table 31.

TABLE 31. SUMMARY OF ^{13}C & ^{31}P N.M.R. DATA OF 1-NITROPHOSPHONATES $(RO)_2P(O)CH(NO_2)R'$

R	R'	δ α-C/ppm	$^1J_{PC}$/Hz	$^2J_{PCC}$/Hz	$^3J_{PCCC}$/Hz	δ ^{31}P/ppm
CH_3	C_2H_5	86.13	143.84	2.70	13.33	15.83
CH_3	n-C_3H_7	84.45	143.97	2.83	12.64	16.08
CH_3	$(CH_2)_2CO_2C_2H_5$	83.11	143.91	1.82	11.82	15.53
CH_3	C_6H_5	87.25	151.14	58.56	-	12.89
C_2H_5	CH_3	74.49	144.28	3.77	-	11.45
C_2H_5	C_2H_5	86.69	142.96	2.77	13.33	13.32
C_2H_5	n-C_3H_7	84.97	142.91	2.79	12.66	13.56
C_2H_5	$(CH_2)_2CO_2CH_3$	83.59	142.59	1.70	11.95	12.22
C_2H_5	$(CH_2)_2CO_2C_2H_5$	83.72	142.65	1.82	12.20	12.85
C_2H_5	C_6H_5	87.98	149.44	63.78	1.64	10.27
i-C_3H_7	CH_3	80.11	144.98	3.85	-	11.37
i-C_3H_7	C_2H_5	87.33	143.92	2.68	13.47	10.55
i-C_3H_7	n-C_3H_7	85.63	143.84	2.79	13.24	11.22
i-C_3H_7	$(CH_2)_2CO_2CH_3$	84.29	143.28	1.76	12.01	10.09
i-C_3H_7	C_6H_5	88.60	149.82	63.78	3.77	8.54
n-C_4H_9	n-C_3H_7	84.84	142.64	2.69	12.82	13.49
i-C_4H_9	C_2H_5	86.44	142.59	2.64	13.27	12.01

2.8. ATTEMPTED SYNTHESIS OF 1-NITROPROPANEPHOSPHONIC ACID

In view of its close structural resemblance to 1-aminopropanephosphonic acid (PNL 62) attempts were made in the present work to synthesise 1-nitropropanephosphonic acid (101) as an example of a new type of derivative which might have biological activity. The only previous reference to an α-nitrophosphonic acid apprears to be in the case of 1-nitro-1-methylethanephosphonic acid, formed by potassium permanganate oxidation of the corresponding aminophosphonate precursor, and isolated only as the phenylamine salt.[102]

In the present investigations *O,O*-diethyl 1-nitropropane-phosphonate was heated under reflux in the presence of concentrated hydrochloric acid, during an 8 h period, in order to effect hydrolysis. Microanalysis, ^{1}H, ^{13}C and ^{31}P N.M.R. spectral analysis of the clear-orange, viscous, oily residue that was isolated after work-up, clearly showed however that the 1-nitrophosphonic acid had not been formed. A possible explanation may be that the strongly electron attracting NO_2 group promotes hydrolytic cleavage of the P-C bond, or carbanion formation at the α-carbon, then further reaction to give other products. ^{31}P N.M.R. spectroscopy revealed a multitude of phosphorus-containing species consistent with the presence of degradation products.

To avoid using such vigorous conditions, *O,O*-diethyl 1-nitropropanephosphonate was silylated with trimethylsilyl bromide, and the product, *O,O*-bis-trimethylsilyl 1-nitropropanephosphonate (100), was hydrolysed by stirring with water at room temperature. Although this method has been used to dealkylate a range of dialkyl phosphonates,[103] it is believed that this is a new application of the reagent to *O,O*-dialkyl 1-nitroalkanephosphonates. The intended reactions (Scheme 51) are shown below.

$$(CH_3CH_2O)_2P(O)CH(NO_2)CH_2CH_3 + 2(CH_3)_3SiBr \longrightarrow (100)$$

$$[(CH_3)_3SiO]_2P(O)CH(NO_2)CH_2CH_3\ (100) + 2CH_3CH_2Br$$

$$(100) + H_2O\ /\ R.T. \longrightarrow (101) + (102)$$

$$(HO)_2P(O)CH(NO_2)CH_2CH_3\ (101) + (CH_3)_3SiOSi(CH_3)_3\ (102)$$

Scheme 51

Water and hexamethyldisiloxane (102) were removed by vigorous shaking under high vacuum. ^1H N.M.R. (60 MHz) spectroscopy of the clear-orange, viscous oily residue showed that the characteristic multiplet of the α-methine hydrogen resonating at approximately 5.00 ppm was still present. Although the adjacent magnetically non-equivalent

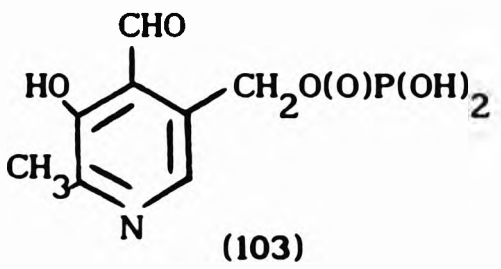
methylene hydrogens were poorly resolved, one could observe these too. The presence of a well defined triplet corresponding to the terminal methyl group in the α-alkane chain, and the absence of the *O,O*-methylene groups of the substrate, indicated that the desired compound had been present. However, the presence of a number of high-field signals (δ 0.50 ppm), thought to be associated with trimethylsilyl by-products, indicated that purification was necessary. Further treatment of the residue with water however caused decomposition.

In a subsequent experiment, *O,O*-di-isopropyl 1-nitropropane-phosphonate was treated with trimethylsilyl bromide and the subsequently formed bis-trimethylsilyl α-nitropropanephosphonate (100) was distilled and characterised. Reaction of this ester with water at room temperature did not however give the desired 1-nitropropanephosphonic acid. The ^{13}C N.M.R. spectrum was complex and the characteristic $^{1}J_{PC}$ and $^{3}J_{PCCC}$ couplings were absent.

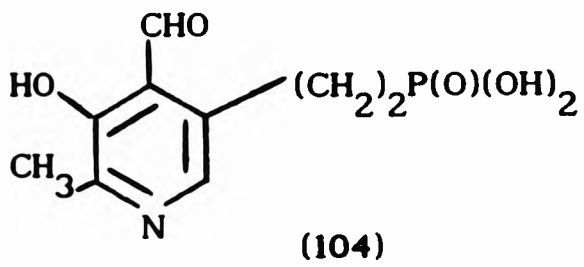
CHAPTER 3

3.1. THE SYNTHESIS OF PYRIDYLETHYLPHOSPHONIC ACIDS & THEIR DERIVATIVES

There are relatively few examples of phosphonic acids and their esters, in which the phosphonic group or dialkyl phosphono group is attached directly to a heterocyclic ring or its side chain. Phosphonic acids (104), which are analogous to biologically important phosphate monoesters such as pyridoxal phosphate (103), contain a methylene group in place of the ester oxygen.



(103)



(104)

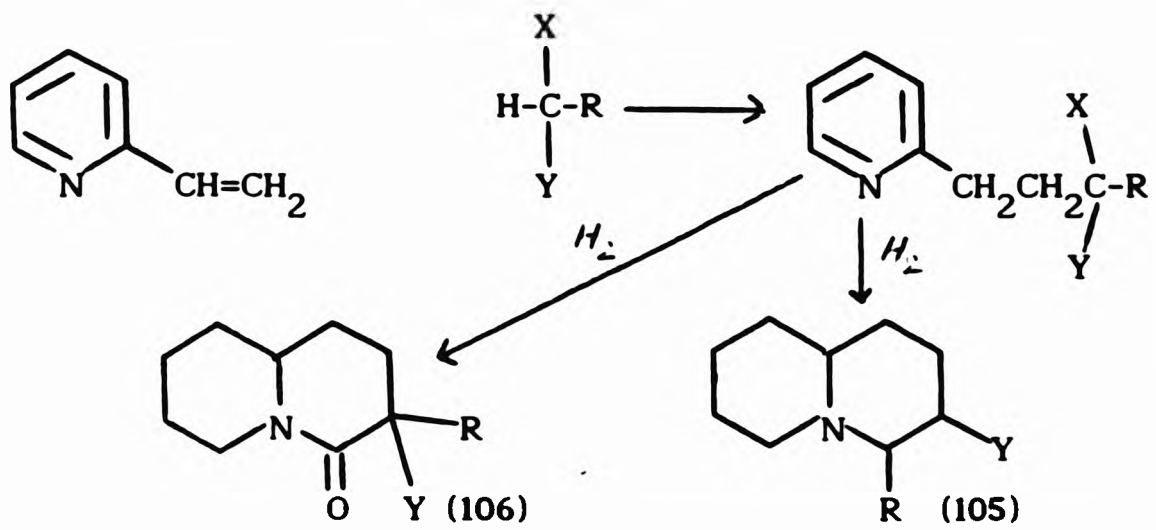
These phosphonic acid analogues have an important role to play in biochemical studies, as they inhibit important biological functions,[104] enabling these reactions to be studied analytically.

In the light of the results obtained by Redmore (1973) who demomnstrated that substituted *N*-alkyl 2-pyridylethylphosphonic acids function as very useful biocides, such as bacteriocides, corrosion inhibitors and chelating agents,[113] a number of such derivatives were

prepared in the present work to examine whether they would display any useful fungitoxicity.

The 2- and 4-vinyl pyridines have been shown to be important substrates, as the pyridyl group activates the conjugated double bond (in the 2- or 4- position) to attack by nucleophilic reagents in the same way as the carbonyl, carboxyl, carbalkoxy, cyano, nitro and sulphonyl groups among others, behave in other compounds. This arises out of the fact that the electronegative nitrogen inhibits substitution by electrophilic reagents, facilitates reaction with nucleophilic reagents and extends electron deficiency to the double bond conjugated in the 2- or 4- positions.[105]

Reagents which react with substrates to form carbon-carbon bonds, carbon-nitrogen bonds and carbon-oxygen bonds have been used to synthesise a variety of 2- and 4-vinyl pyridine derivatives by nucleophilic addition to the vinyl double bond.[106] Interestingly when nucleophilic additions of diethyl malonate, diethyl orthoformate, ethyl acetoacetate and acetylacetone to 2-vinyl pyridine were followed by reductive cyclizations, substituted quinolizidines (105) or 4-keto-quinolizidines (106) were isolated in good yield, highlighting that the vinyl pyridines are excellent substrates for the synthesis of interesting biannular derivatives (Scheme 52).



(X = $CO_2C_2H_5$, $CO_3C_2H_5$, $COCH_3$, Y = $CO_2C_2H_5$, $COCH_3$, R = H, C_2H_5)

Scheme 52

In the present work, 2-[2'-(diethoxyphosphinyl)ethyl]-pyridine **(107)** and 4-[2'-(diethoxyphosphinyl)ethyl]pyridine **(108)** were prepared in very good yields by the catalysed nucleophilic addition of diethyl phosphite to 2- and 4-vinyl pyridine.[109,110,111] The addition of diethyl phosphite to 2-vinyl pyridine required brief heating, while the addition of diethyl phosphite to 4-vinyl pyridine took place at room temperature, being briefly exothermic. The reactions (Scheme 53) are shown below.

CH_2=CH-2-C_5H_4N + $(C_2H_5O)_2P(O)H/Na^+$ $^-OC_2H_5$ ⟶

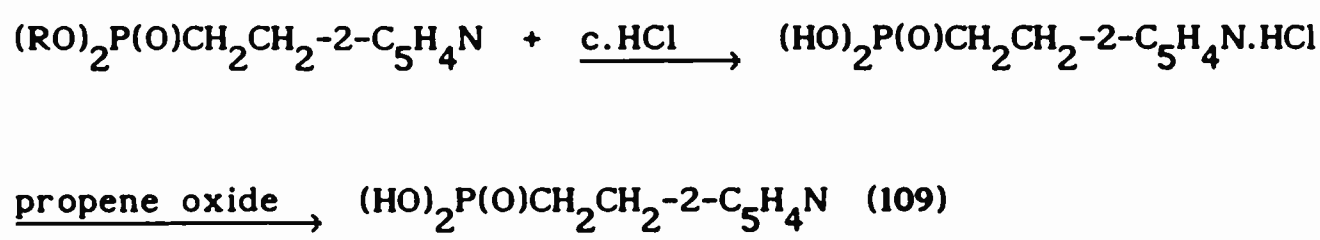
$(C_2H_5O)_2P(O)CH_2CH_2$-2-C_5H_4N **(107)**

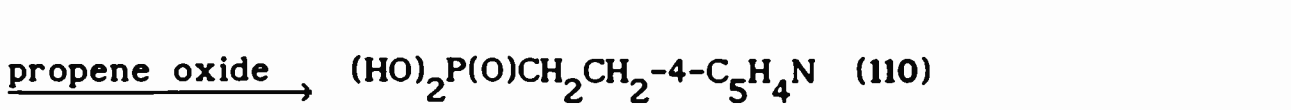
$(C_2H_5O)_2P(O)CH_2CH_2$-4-C_5H_4N (108)

Scheme 53

The phosphonates were obtained in 90 % crude yield (on 0.2 mol scale), and when distilled under reduced pressure the compounds were afforded as clear, free-flowing liquids. Upon standing for a prolonged period at room temperature, the 4-pyridyl compound (108) turned deep red in colour. This however was not symptomatic of extensive decomposition as evidenced by detailed N.M.R. spectroscopy and elemental analysis.

When the pyridyl esters were hydrolysed by heating under reflux in the presence of concentrated hydrochloric acid for 5 h, the corresponding 2-(2'-pyridyl)ethylphosphonic acid (109) and 4-(2'-pyridyl)ethylphosphonic acid (110) were formed and isolated as white, crystalline, high-melting point, water-soluble solids. The reactions (Scheme 54) are shown below.



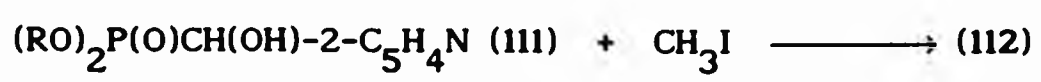


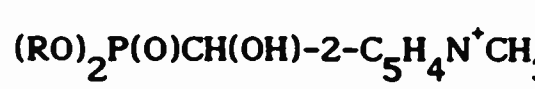
Scheme 54

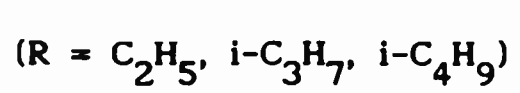
The pyridyl phosphonates and the corresponding phosphonic acids gave excellent elemental analysis, infrared, ^{1}H, ^{13}C and ^{31}P N.M.R. spectroscopic data and the phosphonic acids gave very good FAB ms data.

3.2. THE SYNTHESIS OF QUATERNARY AMMONIUM SALTS OF PYRIDYLETHYLPHOSPHONIC ACIDS & THEIR DERIVATIVES

Quaternary ammonium salts (112) have been obtained by the addition of methyl iodide to 2-[dialkoxyphosphinyl(hydroxy)methyl]-pyridines (111) as shown in the reaction (Scheme 55) below:[112]







Scheme 55

In a similar fashion, in the present work, 2-[2'-(diethoxyphosphinyl)ethyl]pyridine (107) and 4-[2'-(diethoxyphosphinyl)-ethyl]pyridine (108) were quaternised with a range of alkyl iodides. The reactions (Scheme 56) are shown below.

$(RO)_2P(O)(CH_2)_2$-2-C_5H_4N (107) + R'I ⟶ (113)

$(RO)_2P(O)(CH_2)_2$-2-$C_5H_4N^+R'\ I^-$ (113)

$(RO)_2P(O)(CH_2)_2$-4-C_5H_4N (108) + R'I ⟶ (114)

$(RO)_2P(O)(CH_2)_2$-4-$C_5H_4N^+R'\ I^-$ (114)

(R = C_2H_5; R' = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, n-C_4H_9)

Scheme 56

In the cases of the pyridinium iodides (113) and (114) where R' = CH_3 and C_2H_5, these compounds were afforded as viscous dark brown residues, at room temperature. In the cases of (113) and (114), where R' = n-C_3H_7, i-C_3H_7 and n-C_4H_9, the pyridinium iodides were formed by heating the phosphonates at elevated temperature in the presence of 1 molecular equivalent of the corresponding alkyl iodide. Upon cooling, the products were afforded as very hard intractable residues, and no

attempt was made to characterise them. Compounds (113) and (114) where R' = CH_3, C_2H_5 were characterised by elemental analysis in accompaniment with ^1H, ^{13}C and ^{31}P N.M.R. spectroscopy.

The *N*-alkyl-2- or 4- [2'-(dialkoxyphosphinyl)ethyl]pyridinium iodides prepared, were hydrolysed to give the corresponding phosphonic acids (115) & (116), by heating them under reflux in the presence of concentrated hydrochloric acid for 12 h. The reactions (Scheme 57) are shown below.

$(RO)_2P(O)(CH_2)_2$-2-$C_5H_4N^+R'$ I^- (113) + (i) c.HCl, (ii) propene oxide →

$^-O(HO)P(O)(CH_2)_2$-2-$C_5H_4N^+R'$ (115)

$(RO)_2P(O)(CH_2)_2$-4-$C_5H_4N^+R'$ I^- (114) + (i) c.HCl, (ii) propene oxide →

$^-O(HO)P(O)(CH_2)_2$-4-$C_5H_4N^+R'$ (116)

(R' = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, n-C_4H_9)

Scheme 57

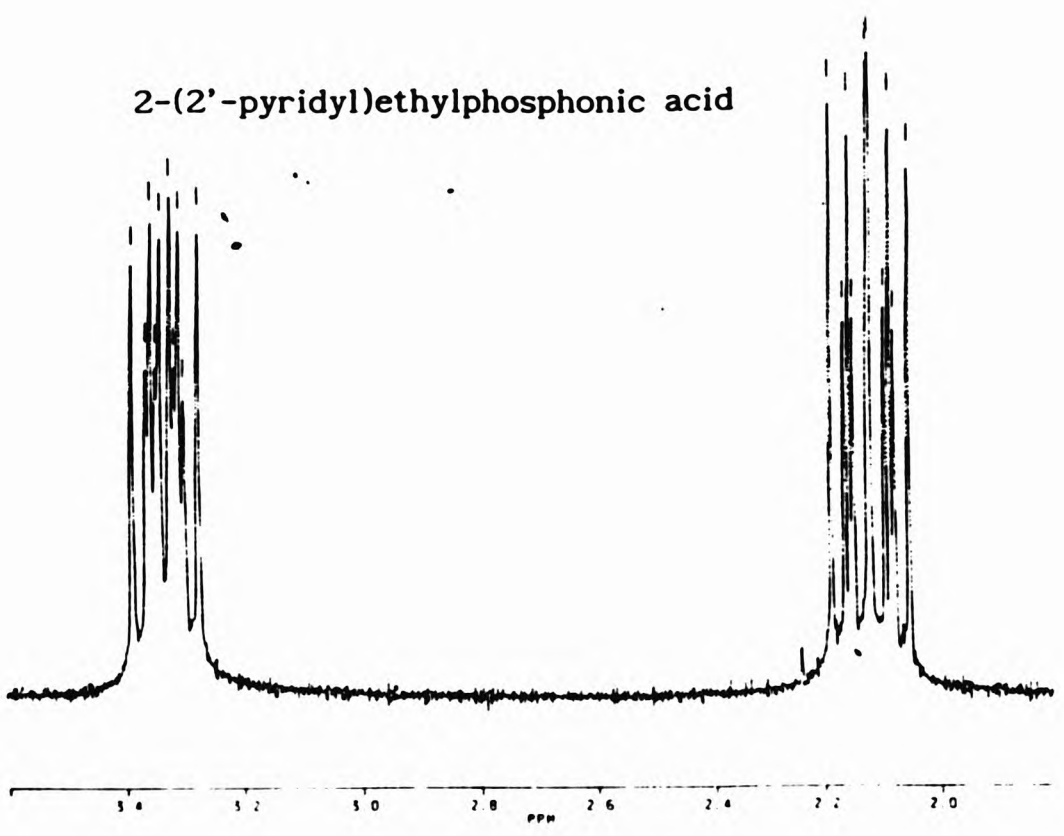
After concentrating the hydrolysates under reduced pressure to remove aqueous HCl, dissolving them in water, extracting with diethyl ether or toluene to remove organic by-products and re-concentrating them under reduced pressure, the *N*-alkylated pyridylethylphosphonic acids were afforded in good yield. Only the *N*-methyl derivative of 2-(2'-pyridyl)ethylphosphonic acid was isolated as an off-white crystalline solid. The other *N*-alkylated pyridylphosphonic acids were obtained as dark-brown viscous sticky residues, even after prolonged and vigorous shaking under high vacuum to remove as much water as possible. All of these phosphonic acid derivatives were highly water-soluble, giving excellent ^{1}H, ^{13}C and ^{31}P N.M.R. spectroscopic data as well as very good FAB mass spectrometric data. Elemental analysis of most of these compounds showed by depression of their observed C, H, N, values in comparison to the values expected on the basis of their putative structures, that they contained a significant amount of water that was difficult to remove, even after vigorous shaking under high vacuum for a prolonged period. Elemental analysis of the *N*-methyl derivative of 2-(2'-pyridyl)ethylphosphonic acid revealed that the crystalline compound had been isolated as a monohydrate.

3.3. THE STRUCTURAL CHARACTERISATION & IDENTIFICATION OF PYRIDYLPHOSPHONATES & THEIR PHOSPHONIC ACID DERIVATIVES

Preliminary investigation of 2-(2'-pyridyl)ethylphosphonic acid, 4-(2'-pyridyl)ethylphosphonic acid and the *N*-methyl derivative of 2-(2'-pyridyl)ethylphosphonic acid by infrared spectroscopy showed that these compounds possessed stretching vibrations characteristic of P=O, P-O-C and the pyridine ring. Analysis by ^{1}H, ^{13}C and ^{31}P N.M.R. spectroscopy as well as FAB mass spectrometry added to the complete authentication of these compounds.

The ^{1}H N.M.R. spectra of the pyridylphosphonates, pyridylphosphonic acids, *N*-alkyl-2- or 4- [2'-(dialkoxyphosphinyl)ethyl]-pyridinium iodides and *N*-alkyl substituted pyridylphosphonic acids, were complex. In all instances, the methylene groups in the alkane chain attached to the pyridine ring resonated as a pair of very complex 2nd order multiplets. The CH_2CH_2-P protons resonated with a chemical shift of 1.90-2.10 ppm; while the CH_2CH_2-P protons resonated at a relatively higher frequency and chemical shift of 3.10-3.40 ppm. The additional coupling these protons experience from the phosphorus atom, namely $^{2}J_{PCH}$ and $^{3}J_{PCCH}$ serves to make this region of the spectrum very complex. The high-field regions in the ^{1}H N.M.R. spectra of 2-(2'-pyridyl)ethylphosphonic acid and 4-(2'-pyridyl)ethylphosphonic acid are shown in Fig. 5.

2-(2'-pyridyl)ethylphosphonic acid



4-(2'-pyridyl)ethylphosphonic acid

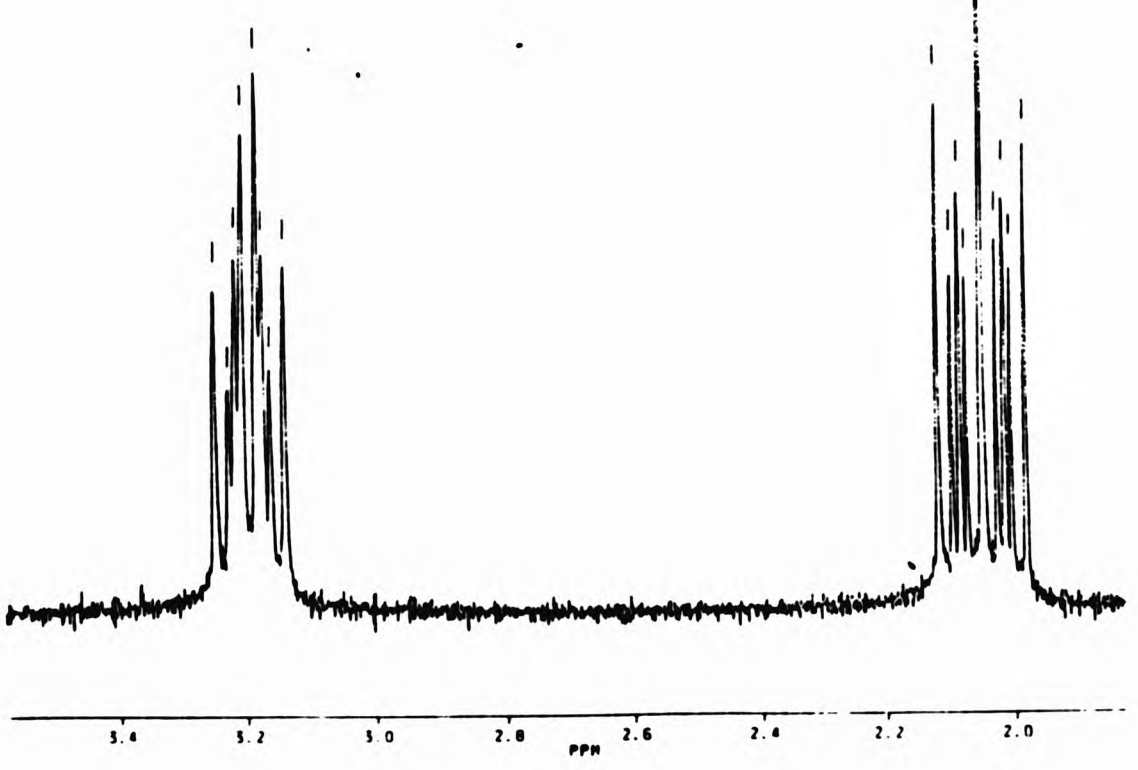


Fig 5

The ^{13}C and ^{31}P spectra further added to the detailed authentication of the structures of these molecules. In the ^{13}C N.M.R. spectra one could clearly observe a doublet for $^{1}J_{PC}$ in $CH_2\underline{C}H_2$-P with a coupling constant in the region of 130.0 to 143.0 Hz. All the pyridine compounds were also characterised by coupling to the pyridine ring, $^{3}J_{PCCC'}$ with coupling constants in the region of 14.0-17.0 Hz. $^{2}J_{PCC}$ in $\underline{C}H_2CH_2$-P was in the region of 2.5- 5.0 Hz, although in a few examples this coupling could not be observed. The ^{31}P N.M.R. spectra of these compounds were characterised by a peak resonating between 20.0 and 30.0 ppm. A summary of the ^{13}C and ^{31}P N.M.R. data is given in Table 32.

TABLE 32

N.M.R. SUMMARY OF THE PYRIDYLPHOSPHONATES & THEIR PYRIDYLPHOSPHONIC ACID DERIVATIVES[109,113]

(A) $(RO)_2P(O)(CH_2)_2$-2-$C_5H_4N^+R'$ (B) $(RO)_2P(O)(CH_2)_2$-4-$C_5H_4N^+R'$

CMPD.	R	R'	δ P-C/ppm	$^{1}J_{PC}$/Hz	$^{2}J_{PCC}$/Hz	$^{3}J_{PCCC}$/Hz	δ ^{31}P/ppm
A	C_2H_5	-	24.90	141.26	4.21	16.29	30.76
B	C_2H_5	-	26.19	141.33	4.40	16.98	29.04
A	H	H	29.72	133.72	5.47	15.10	21.52
B	H	H	30.79	133.21	3.02	16.54	22.38
A	C_2H_5	CH_3	23.74	142.59	3.84	14.34	27.35

B	C_2H_5	CH_3	25.10	142.71	4.21	15.22	28.55
A	H	CH_3	28.46	133.28	0.00	17.61	21.95
B	H	CH_3	30.47	133.15	2.83	16.16	22.25
A	C_2H_5	C_2H_5	24.52	142.40	3.71	14.21	27.56
B	C_2H_5	C_2H_5	25.03	142.33	4.15	15.10	28.44
A	H	C_2H_5	32.76	133.47	2.58	17.61	20.86
B	H	C_2H_5	30.40	133.53	0.00	15.85	-
A	H	n-C_3H_7	30.29	129.69	0.00	18.18	19.30
B	H	n-C_3H_7	28.24	136.23	3.52	15.91	28.08
A	H	i-C_3H_7*	28.57	134.72	2.58	17.61	23.22
B	H	i-C_3H_7*	28.43	136.67	0.00	15.22	31.27
A	H	n-C_4H_9*	29.35	133.40	0.00	17.80	20.50
B	H	n-C_4H_9*	30.39	133.97	3.08	16.23	23.22

* = new compound

3.4. FAB ms ANALYSIS OF PYRIDYLPHOSPHONIC ACIDS & *N*-ALKYLATED PYRIDYLPHOSPHONIC ACIDS

In the FAB mass spectra of the pyridylethylphosphonic acids and the *N*-alkylated pyridylethylphosphonic acids, an intense $[M+H]^+$ ion was observed, usually the base peak, together with a fragment due to cleavage of the P-C bond and loss of phosphorous acid, $[M+H-H_3PO_3]^+$, and to a lesser extent a fragment associated with the loss of metaphosphonic acid, $[M+H-HPO_3]^+$. Occasionally the aggregrate $[2M+H]^+$ was observed, but this was a much less abundant species. The results were consistent with the similar type of fragmentation patterns observed earlier with the 1-aminoalkanephosphonic acids, and demonstrate the utility of FAB mass spectrometry for the identification of zwitterionic compounds of this type. A summary of these results is given in Table 33.

TABLE 33

RELATIVE INTENSITIES (%) OF FRAGMENTS IN THE FAB ms OF PYRIDYLPHOSPHONIC ACIDS & *N*-ALKYL PYRIDYLPHOSPHONIC ACIDS (A) $^{-}O(HO)P(O)(CH_2)_2$-2-$C_5H_4N^{+}R$ & (B) $^{-}O(HO)P(O)(CH_2)_2$-4-$C_5H_4N^{+}R$

CMPD.	MATRIX	R	M+H	2M+H	M+H - HPO_3	M+H - H_3PO_3
A	N	H	100.0	19.4	-	15.0
B	N	H	39.8	-	-	86.3
A	G	CH_3	100.0	4.6	5.0	12.7
B	T	CH_3	82.9	-	8.8	100.0
A	G	C_2H_5	100.0	16.5	7.9	27.5
A	N	n-C_3H_7	100.0	26.7	6.7	45.0
B	T	n-C_3H_7	100.0	-	18.8	92.7
A	N	i-C_3H_7	50.0	2.9	3.8	7.5
B	T	i-C_3H_7	74.6	-	16.3	47.3
A	T	n-C_4H_9	100.0	3.8	19.6	36.9
B	G	n-C_4H_9	100.0	18.1	2.9	78.5

where G = glycerol

T = thioglycerol

N = 3-nitrobenzylalcohol

CHAPTER 4

EXPERIMENTAL

4.1. STARTING MATERIALS AND SUPPLIER

Acetic anhydride	Aldrich
Acetaldehyde	BDH
Acetic acid	BDH
Acetone	BDH
Acetyl chloride	Aldrich
Aminoiminomethanesulphinic acid	Lancaster Synthesis
Ammonia gas	B.O.C.
Ammonium chloride	BDH
Barium chloride	BDH
Benzaldehyde	Aldrich
Benzyl alcohol	BDH
Benzylamine	Aldrich
Benzyl carbamate	Aldrich
Benzoyl chloride	BDH
Boron trifluoride etherate (45 % w/v)	Aldrich
N-(2-Bromoethyl)phthalimide	Aldrich
n-Butyl iodide	Aldrich
Butyryl chloride	BDH
Carbomethoxypropionyl chloride	Aldrich

m-Chloroperbenzoic acid	Lancaster Synthesis
Cyclopropylcarbonyl chloride	Lancaster Synthesis
1,2-Dibromomethane	BDH
Dichloromethane	BDH
Diethyl ether	BDH
Diethyl phosphite	Aldrich
Dimethylaminobenzaldehyde	Aldrich
Dimethyl phosphite	Aldrich
Diphenylmethylamine	Aldrich
Diphenylmethylamine hydrochloride	Aldrich
Ethanol	BDH
2-Ethoxybenzaldehyde	Aldrich
4-Ethylbenzaldehyde	Aldrich
Ethyl carbamate	Aldrich
2-Ethylhexanal	Aldrich
Ethyl iodide	Aldrich
Ethyl succinyl chloride	Lancaster Synthesis
2-Fluorobenzaldehyde	Aldrich
4-Fluorobenzaldehyde	Aldrich
Formic acid	Aldrich
DL-Glyceraldehyde	Aldrich
Hydrochloric acid	BDH
Hydroquinone	Aldrich
Hydroxylamine hydrochloride	Lancaster

Hypophosphorus acid	BDH
Hexafluoroacetone trihydrate	Aldrich
4-Isopropylbenzaldehyde	Aldrich
Isopropyl iodide	Aldrich
Isovaleraldehyde	Aldrich
Lithium borohydride	Aldrich
Magnesium sulphate	BDH
Methanol	BDH
4-Methylbenzaldehyde	BDH
Methyl iodide	BDH
S-Methylisothiouronium sulphate	BDH
4-Methoxybenzaldehyde	BDH
3-Methoxy-4-hydroxybenzaldehyde	Aldrich
2-Nitrobenzaldehyde	Aldrich
4-Nitrobenzaldehyde	Aldrich
Palladium on Carbon (5 %)	Aldrich
Pentafluorobenzaldehyde	Aldrich
Pentafluoropropanal monohydrate	Lancaster Synthesis
Phosphorus pentachloride	Aldrich
Phosphorus trichloride	Aldrich
Potassium carbonate	BDH
Potassium hydroxide	BDH
Propanal	Aldrich
Propan-2-ol	BDH

Propionaldehyde diethyl acetal	Aldrich
Propionyl chloride	Aldrich
Pyridine	Aldrich
Pyridine-3-carboxaldehyde	Aldrich
Propene oxide	Aldrich
n-Propyl iodide	BDH
Raney nickel	Aldrich
Salicylaldehyde	Aldrich
Silica gel (60-200 mesh)	BDH
Sodium chloride	BDH
Sodium hydrogen carbonate	BDH
Sodium metal	BDH
Sodium sulphate	BDH
Sodium sulphite	BDH
Sulphuric acid	BDH
Tetrahydrofuran	BDH
Tri-n-butyl phosphite	Kodak
Triethyl phosphite	Aldrich
Trifluoroacetaldehyde monohydrate	Lancaster Synthesis
Trifluoroacetic acid	Aldrich
4-Trifluoromethylbenzaldehyde	Aldrich
3-Trifluoromethoxybenzaldehyde	Aldrich
3-[3-(Trifluoromethyl)phenoxy]benzaldehyde	Aldrich
Tri-isobutyl phosphite	Kodak

Tri-isopropyl phosphite	Aldrich
3,4,5,-Trimethoxybenzaldehyde	Aldrich
1,1,3,3-Trimethoxypropane	Lancaster Synthesis
Trimethylsilyl bromide	Aldrich
Trimethylsilyl chloride	Aldrich
Toluene	BDH
Tri-n-propyl phosphite	Kodak
2-Vinylpyridine	Aldrich
4-Vinylpyridine	Aldrich
Zinc powder	Aldrich

4.2 INSTRUMENTAL ANALYSIS

Melting points were determined on a Reichert stage-mounted melting-point apparatus and are uncorrected. Elemental analyses were performed using a Carlo Erba 1106 Microanalyser. Infrared spectra were obtained using a Perkin Elmer P.E. 781 double beam infrared spectrophotometer.

^{1}H N.M.R. spectra were obtained using a Perkin Elmer R 12B continuous-wave spectrometer operating at 60 MHz and Bruker-Spectrospin AM 250 Fourier transform N.M.R. spectrometer operating at 250.13 MHz. ^{13}C N.M.R. spectra were obtained on a Bruker WP 80 Fourier transform spectrometer operating at 20.12 MHz and Bruker-Spectrospin AM 250 Fourier transform N.M.R. spectrometer operating at 62.90 MHz. Samples were dissolved in D_2O, or NaOH dissolved in D_2O (referenced to internal TSP-d_4) or $CDCl_3$ (referenced to internal TMS). ^{31}P N.M.R. spectra were obtained on a WP 80 Fourier transform N.M.R. spectrometer operating at 32.39 MHz with 85 % H_3PO_4 as an external reference. ^{19}F N.M.R. spectra were obtained on a Varian VXR 400 Fourier transform spectrometer operating at 376 MHz with $CFCl_3$ as an external reference. Chemical shifts were recorded in ppm (downfield positive) and coupling constants in Hz.

Low resolution electron impact mass spectra were obtained on a Kratos 'Profile' HV3 spectrometer operating at 70 eV ionizing energy. FAB mass spectra were obtained with a Vacuum Generator (VG) Analytical ZAB-E mass spectrometer, with a primary beam of xenon atoms generated in

an ion gun operating at 8 kV. Samples were inserted immediately after mixing with the matrix. LSIMS mass spectra were obtained using a Vacuum Generator (VG) Kratos 'Profile' Double Focussing mass spectrometer, equipped with a Cs fast ion gun operating at 10 kV. Samples were inserted immediately after mixing with the matrix. The intensities of the ions in all three cases were expressed in percent relative to the intensity of the most abundant peak.

Hydrogenations were carried out in a 600 cm^3 Parr Minireactor (Autoclave), model 4563, fitted with a pressure gauge, a magnetic stirrer drive system, a water cooling channel, a temperature controller and a thermocouple.

4.3. PREPARATION OF INTERMEDIATES AND REAGENTS

PREPARATION OF S-METHYLISOTHIOURONIUM CHLORIDE

Barium chloride dihydrate (26.50 g, 0.11 mol) and S-methylisothiouronium sulphate (30.30 g, 0.11 mol) were each dissolved in water (150 cm^3). The solutions were combined with stirring, and heated at 80-90 ^oC for 15 min. The sticky, insoluble barium sulphate was filtered off, and the clear filtrate was concentrated under reduced pressure on a rotary evaporator. The white solid residue, was recrystallised from water/acetone, washed with acetone (3 x 50 cm^3), and dried in a vacuum oven for 2 h at 60 ^oC, to afford S-methylisothiouronium chloride as a fine white crystalline solid (21.63 g, 91.4 %); m.p. 119-121 ^oC (lit.[11] 121-123 ^oC).

PREPARATION OF AMINOIMINOMETHANESULPHONIC ACID

Peracetic acid (8 cm^3, 35 % in dilute acetic acid) was added dropwise and with stirring to a suspension of aminoiminomethanesulphinic acid (3.24 g, 0.03 mol) in glacial acetic acid (10 cm^3) at 0 ^oC. After the addition was completed, the suspension was stirred for a further 2.5 h at room temperature. During the reaction, the fine white crystals of the sulphinic acid substrate were converted to larger crystals of the corresponding sulphonic acid. These were removed by filtration, washed

thoroughly with absolute ethanol and dried in a vacuum oven for 2 h, to afford aminoiminomethanesulphonic acid as a white crystalline solid (3.10 g, 83 %); m.p. 126.5-128 ^{o}C (lit.[62] 125-126 ^{o}C); (Found: C, 9.71; H, 3.24; N, 22.75. Calc. for $CH_4N_2SO_3$: C, 9.68; H, 3.23; N, 22.58 %); $^{13}C(D_2O)$ δ 168.83 (s, $\underline{C}(=NH)NH_2$).

PREPARATION OF TRIFLUOROACETYL CHLORIDE[67]

Trifluoroacetic acid (48 g, 0.42 mol) was added in 5 cm^3 portions under dry nitrogen to phosphorus pentachloride (65 g, 0.33 mol) contained in a flask fitted with a Cardice/acetone - cooled Hopkin's condenser, and an outlet to a Cardice/acetone cooled trap. Trifluoroacetyl chloride generated rapidly as a cloudy gas, and as much as possible was collected in the cooled trap. When all the gas had evolved, further portions of trifluoroacetic acid were added with extreme caution throughout a period of 6 h. 10 min was allowed to elapse between each addition of the acid to ensure complete reaction of the reagents had taken place. When all the acid had been added the flask's contents were warmed to 50 ^{o}C to force out residual traces of the acid chloride. Under these conditions, trifluoroacetyl chloride was afforded as a straw coloured liquid.

PREPARATION OF TRIBENZYL PHOSPHITE

Phosphorus trichloride (4.67 g, 0.034 mol) in dry ether (20 cm^3) was added dropwise and with stirring to a mixture of benzyl alcohol (10.75 g, 0.10 mol) and pyridine (8.36 g, 0.105 mol) during a period of 15 minutes. The mixture was then vigorously shaken and after 1 h, the phosphite was separated by filtration from the white precipitate that formed during the course of the reaction. The filtrate was concentrated under reduced pressure on a rotary evaporator and the yellow phosphite residue formed was distilled under high vacuum. Tribenzyl phosphite was afforded as a viscous yellow oil before prolonged heating caused the bulk material to polymerise (6.22 g, 52 %); b.p. 155-160 ^{o}C at 0.05 mmHg (lit.[123] 160-175 ^{o}C at 0.08 mmHg).

4.4 PREPARATIONS

4.4.1 PREPARATION OF 1-AMINOALKANEPHOSPHONIC ACIDS VIA THE 1-POT PROCEDURE

PREPARATION OF 1-AMINOPROPANEPHOSPHONIC ACID " PNL 62 "

A mixture of triphenyl phosphite (29.7 g, 0.096 mol), propanal (8.1 g, 0.14 mol) and ethyl carbamate (9.2 g, 0.10 mol) was heated in the presence of glacial acetic acid (20 cm^3), in an oil bath, set at 100 - 110 ^oC, for 1 h. Concentrated hydrochloric acid (100 cm^3) was added and the dark brown reaction mixture was refluxed (6 h). After cooling, the mixture was extracted with dry toluene (3 x 20 cm^3) to remove phenol. The aqueous layer was concentrated under reduced pressure on a rotary evaporator, to afford a thick, viscous, yellow oil. The oil was dissolved in methanol (20 cm^3) and treated with propylene oxide at 40 - 50 ^oC, in a water bath, producing fine white crystals of the crude aminoalkanephosphonic acid. This material was recrystallised from ethanol/water, filtered off and dried in a vacuum oven at 60 ^oC for 2 h to give 1-aminopropanephosphonic acid (4.2 g, 31 %); m.p. 263-265 ^oC (lit.[34] 264-266 ^oC); (Found: C, 26.09; H, 7.33; N, 9.87. Calc. for $C_3H_{10}NO_3P$: C, 25.90; H, 7.19; N, 10.07 %); ^1H (D_2O) δ 1.04-1.11 (3H, t, $CH_2\underline{CH_3}$, $^3J_{HCCH}$ 7.00 Hz), 1.68-2.04 (2H, m, $CH\underline{CH_2}$), 3.10-3.24 (1H, ddd, $\underline{CH}CH_2$); $^{13}C(D_2O)$ δ 13.15 (d, $CH_2\underline{CH_3}$, $^3J_{PCCC}$ 9.52 Hz), 24.76 (s, $\underline{CH_2}CH_3$), 53.71 (d, P-$\underline{C}HCH_2$, $^1J_{PC}$ 142.87 Hz); $^{31}P(D_2O)$ δ 14.21 (s); LSIMS ms (glycerol): m/z(%) 836 (0.35), 696 (5M+H, 0.65), 557 (4M+H,

2.90), 418 (3M+H, 10), 371 (2M+H+G, 7.1), 324 (M+H+2G, 13.9), 279 (2M+H, 68.6), 232 (M+H+G, 56.4), 197 (2M+H - H_3PO_3, 2.1), 140 (M+H, 100); FAB ms (glycerol): m/z(%) 324 (M+H+2G, 7.92), 279 (2M+H, 15.83), 232 (M+H+G, 35.83), 140 (M+H, 75), 60 (M+H - HPO_3, 12.5), 58 (M+H - H_3PO_3, 100).

PREPARATION OF 1-AMINOPROPANEPHOSPHONIC ACID USING PROPIONALDEHYDE DIETHYL ACETAL

A mixture of triphenyl phosphite (15.5 g, 0.05 mol) propionaldehyde diethyl acetal (9.9 g, 0.075 mol) and ethyl carbamate (5.25 g, 0.059 mol) was heated in the presence of glacial acetic acid (25 cm^3), in an oil bath at 95-100 ^oC for 12 h. Concentrated hydrochloric acid (100 cm^3) was carefully added dropwise to the stirring dark brown reaction mixture, and the solution was heated under reflux for 6 h. After cooling, the solution was extracted with toluene (3x40 cm^3) and the yellow aqueous layer was concentrated under reduced pressure on a rotary evaporator. The thick viscous, yellow, oily, residue that formed, was dissolved in methanol (20 cm^3) and treated with propylene oxide at 40-50 ^oC. The white crystalline solid that formed, was filtered off, washed with acetone and dry ether, and dried in a vacuum oven for 2 h. The product, 1-aminopropanephosphonic acid was afforded as a white crystalline material (1.75 g, 25 %); m.p. 259-261 ^oC (lit.[34] 264-266 ^oC); ^1H(NaOD) δ 1.05 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^3J_{HCCH}$

7.49 Hz), 1.48-2.00 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 2.77-2.87 (ddd, 1H, P-C$\underline{H}$); ^{13}C (NaOD) δ 13.76 (d, P-CHCH$_2$C$\underline{H}_3$, $^3J_{PCCC}$ 10.67 Hz), 25.82 (s, P-CH$\underline{C}$H$_2$), 55.18 (d, P-$\underline{C}$H, $^1J_{PC}$ 134.86 Hz); ^{31}P(NaOD) δ 14.47 (s).

PREPARATION OF 1-AMINO-1-METHYLETHANEPHOSPHONIC ACID

A mixture of triphenyl phosphite (31.0 g, 0.10 mol), acetone (8.7 g, 0.15 mol) and ethyl carbamate (9.2 g, 0.10 mol) was heated in the presence of glacial acetic (20 cm^3), in an oil bath at 95-100 ^{o}C for 12 h. Concentrated hydrochloric acid (100 cm^3) was carefully added dropwise to the stirring dark brown reaction mixture, and the solution was heated under reflux for 6 h. After cooling, the solution was extracted with dry toluene (3x50 cm^3) and the straw coloured aqueous layer was concentrated under reduced pressure on a rotary evaporator. The thick viscous, yellow, oily residue that formed was dissolved in methanol (30 cm^3) and treated with propylene oxide (40-50 ^{o}C). The white crystalline solid that formed, was filtered off, recrystallised from ethanol/water, washed with dry ether, and dried in a vacuum oven for 2 h at 60 ^{o}C. The product, 1-amino-1-methylethanephosphonic acid was obtained as a white fluffy crystalline material (4.2 g, 30 %); m.p. 250-253 ^{o}C (lit.[125] 256-257 ^{o}C); (Found: C, 25.30; H, 7.84; N, 9.65. Calc. for $C_3H_{10}NO_3P$: C, 25.90; H, 7.19; N, 10.07 %); ^{1}H(NaOD) δ 1.31 (d, 6H, P-C(C$\underline{H}_3$)C$\underline{H}_3$, $^3J_{PCCH}$ 12.20 Hz); ^{13}C(NaOD) δ 26.53 (s, P-C($\underline{C}$H$_3$)$\underline{C}$H$_3$), 53.87 (d, P-$\underline{C}$, $^1J_{PC}$ 139.16 Hz); ^{31}P(NaOD) δ 19.85 (s).

PREPARATION OF 1-AMINO-3-METHYLBUTANEPHOSPHONIC ACID

A mixture of triphenyl phosphite (26.7 g, 0.086 mol), benzyl carbamate (13.0 g, 0.086 mol) and isovaleraldehyde (7.4 g, 0.086 mol) was dissolved in dry toluene (80 cm^3). Boron trifluoride etherate (2.5 cm^3, 45 % w/v) in dry toluene (50 cm^3) was added dropwise with rapid stirring, at room temperature, during a period of 15-20 min. The mixture was refluxed in an oil bath (90-100 ^oC) for 5 h. Toluene was removed from the mixture under vacuum on a rotary evaporator to afford a reddish viscous residue. Concentrated hydrochoric acid was added (100 cm^3) and the resultant mixture was refluxed for 6 h (100-110 ^oC). After cooling, the mixture was extracted with toluene (3x30 cm^3) to remove phenol. The aqueous layer was concentrated under reduced pressure on a rotary evaporator. The yellow oil produced, was dissolved in methanol (20 cm^3) and treated with propylene oxide at 40-50 ^oC, to produce fine white powdery crystals of the crude aminoalkanephosphonic acid. The crystals were filtered off, washed with ethanol and ether, and dried in a vacuum oven at 60 ^oC for 2 h to give 1-amino-3-methylbutanephosphonic acid (9.01 g, 62 %); m.p. 263-264 ^oC (lit.[126] 279 ^oC, 288-90 ^oC); (Found: C, 36.03; H, 8.60; N, 8.35. Calc. for $C_5H_{14}NO_3P$: C, 35.93; H, 8.38; N, 8.38 %); ^1H(NaOD) δ 0.92 (d, 3H, P-CHCH$_2$CH(CH$_3$)C$\underline{H}_3$, $^3J_{HCCH}$ 6.17 Hz), 0.97 (d, 3H, P-CHCH$_2$CH(C$\underline{H}_3$)CH$_3$, $^3J_{HCCH}$ 6.19 Hz), 1.52-1.61 (m, 3H, P-CHC$\underline{H}_2$C$\underline{H}$(CH$_3$)CH$_3$), 2.99-3.09 (ddd, 1H, P-C$\underline{H}$); ^{13}C(NaOD) δ 23.11 (s, P-CHCH$_2$CH(CH$_3$)C$\underline{H}_3$), 25.72 (s,

P-CHCH$_2$CH(C$\underline{H}_3$)CH$_3$), 26.98 (d, P-CHCH$_2$C$\underline{H}$(CH$_3$)CH$_3$, $^3J_{PCCC}$ 10.40 Hz), 41.24 (s, P-CH$\underline{C}$H$_2$), 51.24 (d, P-$\underline{C}$H, $^1J_{PC}$ 134.59 Hz); ^{31}P (NaOD) 14.19 (s); FAB ms (glycerol): m/z(%) 502 (3M+H, 1.5); 335 (2M+H, 16.8); 168 (M+H, 18.5); 86 (M+H - H_3PO_3, 100).

PREPARATION OF 1-AMINO-2-ETHYLHEXANEPHOSPHONIC ACID

A mixture of triphenyl phosphite (31.0 g, 0.10 mol), 2-ethylhexanal (16.7 g, 0.13 mol), and ethyl carbamate (8.9 g, 0.10 mol) was heated in the presence of glacial acetic acid (30 cm^3), in an oil bath, set at 100-110 ^{o}C for 2 h. Concentrated hydrochloric acid (60 cm^3) was added to the deep yellow reaction mixture which was refluxed for 6 h. After cooling, the mixture was extracted with dry toluene (3x40 cm^3) to remove phenol. The aqueous layer was concentrated under reduced pressure on a rotary evaporator, to afford a thick, viscous, yellow oil. The oil was dissolved in methanol (30 cm^3) and treated with propene oxide at 40-50 ^{o}C, in a water-bath, producing fine white crystals of the crude aminoalkanephosphonic acid. This material was recrystallised from ethanol/water filtered off, and dried in a vacuum oven at 60 ^{o}C for 2 h to give *1-amino-2-ethylhexanephosphonic acid* (4.10 g, 20 %); m.p. 240-243 ^{o}C; (Found: C, 45.45; H, 9.67; N, 6.86. $C_8H_{20}NO_3P$ requires: C, 45.93; H, 9.57; N, 6.69 %); ^{1}H(NaOD) δ 0.89 (t, 6H, (CH$_2$)$_3$C$\underline{H}_3$ overlapping with CHCH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 6.92 Hz), 1.02-1.37 (m, 7H, C$\underline{H}$(C$\underline{H}_2$)$_3$), 1.61-1.81 (m, 2H, CHC$\underline{H}_2$CH$_3$), 2.65-2.72 (dd, 1H, P-C$\underline{H}$, $^2J_{PCH}$ 14.22 Hz);

^{13}C(NaOD) δ 14.18 (s, $(CH_2)_3\underline{C}H_3$), 16.26 (s, $CH(CH_2\underline{C}H_3)$), 24.10 (s, $CHCH_2CH_2\underline{C}H_2$), 25.13 (s, $CHCH_2\underline{C}H_2CH_2$), 31.99 (s, $CH(\underline{C}H_2CH_3)$), 32.46 (d, $CHCH\underline{C}H_2$, $^3J_{PCCC}$ 11.85 Hz), 42.73 (s, $CH\underline{C}H$), 54.24 (d, P-$\underline{C}$H, $^1J_{PC}$ 137.28 Hz); ^{31}P(NaOD) δ 22.03 (s); FAB ms (3-NOBA): m/z(%) 363 (M+H+N, 8.8), 210 (M+H, 10), 156 (100).

ATTEMPT TO PREPARE 1-AMINO-2-HYDROXYETHANEPHOSPHONIC ACID

A mixture of triphenyl phosphite (1.55 g, 0.005 mol), glycolaldehyde (0.5 g, 0.0083 mol) and ethyl carbamate (0.46 g, 0.005 mol), was heated in the presence of glacial acetic acid (20 cm^3), in an oil bath, at 95-100 ^oC for 1 h. Concentrated hydrochloric acid (50 cm^3) was added to the yellow reaction mixture, and heated under reflux for 6 h. After cooling, the deep blue reaction mixture was extracted with toluene (3x20 cm^3) and the deep yellow aqueous layer was concentrated under reduced pressure on a rotary evaporator, to produce a sticky brown residue. This material was dissolved in methanol (10 cm^3), and treated with propylene oxide (40-50 ^oC). No precipitation occurred, so the solution was left to stand at 4 ^oC for 1 month. However even after this period no sign of precipitation of the desired aminoalkanephosphonic acid could be observed.

ATTEMPT TO PREPARE 1-AMINO-2,3-DIHYDROXYPROPANEPHOSPHONIC ACID

A mixture of triphenyl phosphite (1.55 g, 0.005 mol), DL-glyceraldehyde (0.50 g, 0.0056 mol) and ethyl carbamate (0.46 g, 0.005 mol) was heated in the presence of glacial acetic acid (20 cm^3), in an oil bath, at 95-100 ^oC for 1 h. Concentrated hydrochloric acid was added to the yellow reaction mixture, and heated under reflux for 6 h. After cooling, the reddish brown reaction mixture was extracted with toluene, and the aqueous layer was concentrated under reduced pressure on a rotary evaporator, to afford a sticky brown residue. This material was dissolved in methanol and treated with propylene oxide (40-50 ^oC). No obvious signs of precipitation occurred, so the solution was concentrated under reduced pressure on a rotary evaporator and the oily residue was treated with ethanol at 0 ^oC. A granular material formed which was left to stand in solution for 12 h at 4 ^oC. When an attempt was made to filter this product, an extremely sticky substance was isolated. As much of this material as possible was dissolved in the minimum of cold water, treated with ethanol, and left to stand for a month at 4 ^oC. However, even after this period, no sign of precipitation of the desired aminophosphonic acid could be observed.

ATTEMPT TO PREPARE 1,3-DIAMINOPROPANE-1,3-BISPHOSPHONIC ACID

A mixture of triphenyl phosphite (62.0 g, 0.20 mol), 1,1,3,3-tetramethoxypropane (16.4 g, 0.10 mol) and ethyl carbamate (17.8 g, 0.20 mol) was heated in the presence of glacial acetic (50 cm^3), in an oil bath, set at 100 ^oC, for 12 h. Concentrated hydrochloric acid (100 cm^3) was added and the dark brown reaction mixture was refluxed (6 h). After cooling, the mixture was extracted with dry toluene (3x50 cm^3) to remove phenol. The aqueous layer was concentrated under reduced pressure on a rotary evaporator, to afford a thick, viscous, orange oil. The oil was dissolved in methanol (40 cm^3) and treated with propylene oxide at 50 ^oC, in a water bath. A creamy white crystalline material was produced which was filtered off, washed with dry ether, and dried in a vacuum oven for 2 h at 60 ^oC. Elemental analysis and infrared spectroscopy showed that this material did not show any aminophosphonic acid character.

ATTEMPT TO PREPARE 1-AMINOTRIFLUOROETHANEPHOSPHONIC ACID

Trifluoroacetaldehyde monohydrate (5.00 g, 0.043 mol), said to contain varying amounts of the ethyl hemiacetal, as specified by the manufacturers (Lancaster Synthesis), was poured onto concentrated sulphuric acid (20 cm^3) heated to 100 ^oC in an oil bath. The liberated trifluoroacetaldehyde was collected in a Cardice/acetone cooled trap, as

a colourless liquid. When the trap had come to room temperature, trifluoroacetaldehyde (2.27 g, 0.023 mol), volatilised into a mixture of triphenyl phosphite (6.21 g, 0.020 mol), ethyl carbamate (1.78 g, 0.020 mol), and glacial acetic acid, at 0 ^{o}C. When all the aldehyde passed into the reaction mixture, the solution was heated under reflux for 1 h at 100 ^{o}C. Concentrated hydrochloric acid (50 cm^{3}) was then added, and the resultant mixture was heated under reflux for 4 h. Upon cooling, the solution was extracted with toluene (3x20 cm^{3}) and the yellow aqueous layer was concentrated under reduced pressure on a rotary evaporator to afford a granular-like residue. This material was dissolved in methanol (20 cm^{3}), and treated with a large excess of propylene oxide (40 - 50 ^{o}C). No precipitation occurred, so the mixture was left to stir at room temperature for 12 h, under dry nitrogen. The solution was concentrated under reduced pressure on a rotary evaporator, and the viscous oily residue was treated with ethanol at 0 ^{o}C. The solution was left to stand at 4 ^{o}C for 1 month, but no precipitation of the desired aminophosphonic acid derivative was observed.

4.4.2. PREPARATION OF 1-AMINOALKANEPHOSPHONIC ACIDS VIA HYDROGENATION

PREPARATION OF 1-AMINO-1-METHYLETHANEPHOSPHONIC ACID

O,O-Dimethyl 1-benzylamino-1-methylethanephosphonate (3.20 g, 0.02 mol), formed from the addition of dimethyl phosphite to *N*-methylethylidenebenzylamine, was debenzylated by hydrogen in the presence of 5 % Pd/C catalyst (0.75 g), glacial acetic acid (65 cm^3) and water (3 cm^3), under a pressure of 250 p.s.i., for 6 h at 65 ^oC. After the autoclave had been cooled and depressurized, the crude material was washed out with glacial acetic acid and filtered to remove spent catalyst. The filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O*-dimethyl 1-amino-1-methylethane-phosphonate as a clear reddish viscous oily residue. No attempt was made to isolate the intermediate in pure form; although ^1H N.M.R. (60 MHz) showed the compound had been formed. The crude phosphonate was refluxed in the presence of concentrated hydrochloric acid for 12 h. The cool mixture was extracted with toluene to remove any organic by-products, and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The reddish-brown, viscous oily residue formed, was dissolved in methanol (20 cm^3), and treated with propylene oxide at 40-50 ^oC in a water bath. 1-Amino-1-methylethanephosphonic acid was afforded in a fluffy white

crystalline form. The material was filtered off, washed with dry ether and dried in a vacuum oven for 2 h at 60 ^{o}C (2.1 g, 77 %); m.p. 278-281 ^{o}C (lit.[125] 256-257 ^{o}C); (Found: C, 26.05; H, 7.85; N, 9.73. Calc. for $C_3H_{10}NO_3P$: C, 25.90; H, 7.19; N, 10.07 %); ^{1}H(D_2O/KOH) δ (d, 6H, P-C($\underline{C}H_3$)$\underline{C}H_3$, $^{3}J_{PCCH}$ 13.10 Hz), ^{13}C(D_2O/KOH) δ 32.34 (s, P-C($\underline{C}H_3$)$\underline{C}H_3$), 57.20 (d, P-$\underline{C}$, 148.00 Hz); ^{31}P (D_2O/KOH) δ 25.29 (s).

PREPARATION OF 1-AMINOBUTANEPHOSPHONIC ACID

Crude *O,O*-diethyl 1-aminobutanephosphonate (19.6 g, 0.094 mol), obtained from catalytic hydrogenation of *O,O*-diethyl-1-hydroxyiminobutanephosphonate (22.3 g, 0.10 mol), over 5 % Pd/C (1 g in 250 cm^3 glacial acetic acid) at 85 ^{o}C, for 7 h, at 300 p.s.i., was refluxed in the presence of concentrated hydrochloric acid (100 cm^3) for 12 h. After cooling, the mixture was extracted with toluene (3x30 cm^3) to remove any organic by-products. The aqueous layer was concentrated under vacuum on a rotary evaporator to produce a viscous oily residue. The material was dissolved in methanol (20 cm^3) and treated with propylene oxide, to afford fine white crystals of crude 1-aminobutanephosphonic acid. The product was recrystallised from ethanol/water, filtered, washed with dry ether and allowed to dry in a vacuum oven at 60 ^{o}C for 2 h, to afford 1-aminobutanephosphonic acid (2.16 g, 15 %) m.p. 271-274 ^{o}C (lit.[34] 262-264 ^{o}C, 276 ^{o}C); (Found: C, 32.23; H, 8.10; N, 9.16. Calc. for $C_4H_{12}NO_3P$: C, 31.37; H, 7.84; N,

9.15 %); $^{1}H(D_2O)$ δ 0.91 (3H, t, $CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.05 Hz), 1.28-1.39 (m, 2H, $C\underline{H}_2CH_3$), 1.48-1.71 (m, 2H, $C\underline{H}_2CH_2$), 2.48-2.58 (ddd, 1H, $C\underline{H}CH_2$); ^{13}C (D_2O) δ 16.16 (s, $CH_2\underline{CH}_3$) 22.43 (d, $\underline{C}H_2CH_3$, $^{3}J_{PCCC}$ 12.64 Hz), 36.65 (s, $\underline{C}H_2CH_2$), 52.40 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 138.57 Hz); ^{31}P (D_2O) δ 22.16 (s).

PREPARATION OF 1-AMINO-3-METHOXYCARBONYLPROPANEPHOSPHONIC ACID

O,O-Dimethyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (5.05 g, 0.020 mol) was hydrogenated in the presence of 5 % Pd/C catalyst (5.00 g), liquid ammonia (30 cm^3) and freshly distilled methanol (100 cm^3) under a pressure of 400 p.s.i., for 3.0 h, at 80 °C. After the autoclave had been cooled and depressurised, the crude material was washed out with methanol and filtered to remove spent catalyst. The filtrate was concentrated under reduced pressure on a rotary evaporator to afford crude *O,O*-dimethyl-1-amino-3-ethoxycarbonylpropanephosphonate. No attempt was made to isolate the intermediate in pure form. The thick reddish-orange viscous oily residue was refluxed in the presence of concentrated hydrochloric acid for 12 h. The cool mixture was extracted with toluene to remove any organic by-products, and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The reddish-orange oily residue was dissolved in methanol (10 cm^3) and treated with propylene oxide at 40-50 °C, in a water bath. *1-Amino-3-methoxycarbonylpropanephosphonic acid* was afforded as a creamy

coloured powdery material after being filtered off and allowed to dry in a vacuum oven for 2 h at 60 °C (1.66 g, 42.1 %); m.p. 154-156 °C; (Found: C, 29.39; H, 6.16; N, 7.02. $C_5H_{12}NO_5P$ requires: C, 30.46; H, 6.09; N, 7.11 %); $^1H(D_2O)$ δ 2.28 (m, 2H, $C\underline{H}_2CH_2CO_2CH_3$), 3.36 (m, 2H, $CH_2CH_2CO_2CH_3$), 4.06 (ddd, 1H, $C\underline{H}CH_2$), 4.45 (s, 3H, $CO_2C\underline{H}_3$); $^{13}C(D_2O)$ δ 26.55 (s, $\underline{C}H_2CH_2CO_2CH_3$), 33.28 (d, $CH_2\underline{C}H_2CO_2CH_3$, $^3J_{PCCC}$ 8.55 Hz), 51.23 (d, P-$\underline{C}$H, $^1J_{PC}$ 142.21 Hz), 55.18 (s, $CO_2\underline{C}H_3$), 178.29 (s, $\underline{C}O_2CH_3$); $^{31}P(D_2O)$ δ 12.58 (s); FAB ms (glycerol): m/z(%) 592 (3M+H, 2.9), 395 (2M+H, 28.1), 290 (M+H+G, 2.4), 198 (M+H, 95.9), 118 (M+H - HPO_3, 17.3) 116 (M+H - H_3PO_3, 100), 100 (13.5), 84 (24.3).

FURTHER PREPARATIONS OF 1-AMINO-3-CARBOXYPROPANE-PHOSPHONIC ACID

(i) The reaction was repeated when *O,O*-dimethyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (5.00 g, 0.020 mol), was hydrogenated over Ni (4 cm^3 liquid slurry) in methanol (100 cm^3) for 4 h at 114 °C and 400 p.s.i. The crude 1-aminophosphonate was isolated and hydrolysed as described above and after work-up, *1-amino-3-carbomethoxypropane-phosphonic acid* was afforded as an off-white powder (0.37 g, 10 %); m.p. 165 - 168 °C.

(ii) The reaction was repeated when *O,O*-dimethyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (5.00 g, 0.020 mol), was hydrogenated over Pd/C (0.75 g) in acetic acid (60 cm^3) and water (2.5 cm^3) for 15 h at 80 ^oC and 250 p.s.i. The crude 1-aminophosphonate was isolated and hydrolysed as described above and after work-up, *1-amino-3-carbomethoxypropanephosphonic acid* was afforded as a white powder (1.26 g, 32 %); m.p. 154 - 156 ^oC.

(iii) The reaction was repeated when *O,O*-diethyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (2.69 g, 0.010 mol), was hydrogenated over Ni (2 cm^3 liquid slurry) in methanol (50 cm^3) for 4 h at 40 ^oC and 450 p.s.i. The crude 1-aminophosphonate was isolated and hydrolysed as described above and after work-up, *1-amino-3-carbomethoxypropanephosphonic acid* was afforded as an off-white powder (1.31 g, 67 %); m.p. 156 - 157 ^oC.

(iv) The reaction was repeated when *O,O*-diethyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (3.97 g, 0.014 mol), was hydrogenated over Pd/C (0.75 g), acetic acid (60 cm^3) and water (2.5 cm^3) for 6 h at 70 ^oC and 300 p.s.i. The crude 1-aminophosphonate was isolated and hydrolysed as described earlier and after work-up, *1-amino-3-carbomethoxypropanephosphonic acid* was afforded as a white powder (1.20 g, 44 %); m.p. 156 - 159 ^oC.

(v) The reaction was repeated when *O,O*-di-n-butyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (4.81 g, 0.014 mol), was hydrogenated over Ni (3 cm^3 liquid slurry) in methanol (50 cm^3) for 5 h at 75-76 ^oC and 500 p.s.i. The crude 1-aminophosphonate was isolated and hydrolysed as described earlier and after work-up, *1-amino-3-carbomethoxypropane-phosphonic acid* was afforded as a white crystalline powder (1.36 g, 49 %); m.p. 150 - 151 ^oC.

(vi) The reaction was repeated when *O,O*-di-n-butyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (5.00 g, 0.015 mol), was hydrogenated over Pd/C (0.75 g) in acetic acid (70 cm^3) and water (2.5 cm^3) for 6 h at 80 ^oC and 300 p.s.i. When the material expected to be the crude 1-aminophosphonate was hydrolysed and worked-up as described earlier, the corresponding aminophosphonic acid could not be isolated.

(vii) The reaction was repeated when *O,O*-dibenzyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (1.30 g, 0.0032 mol), was hydrogenated over Pd/C (0.50 g) in acetic acid (50 cm^3) and water (2.5 cm^3) for 16 h at 86 ^oC and 300 p.s.i. When the material expected to be the crude 1-aminophosphonate was hydrolysed and worked-up as described earlier, the corresponding aminophosphonic acid could not be isolated.

(viii) The reaction was repeated when *O,O*-dibenzyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (10 g, 0.025 mol), was hydrogenated over Pd/C (0.75 g) in acetic acid (100 cm^3) for 6 h at 40 ^oC and 100 p.s.i. When the material expected to be the crude 1-aminophosphonate was hydrolysed and worked-up as described earlier, the corresponding aminophosphonic acid could not be isolated.

PREPARATION OF 1-AMINO-3-CARBOXYPROPANEPHOSPHONIC ACID

O,O-Diethyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (5.0 g, 0.018 mol) was hydrogenated in the presence of Ni catalyst (0.75 g), and methanol (70 cm^3) ,under a pressure of 350 p.s.i., for 6 h at 76 ^oC. After the autoclave had been cooled and depressurized, the crude material was washed out with glacial acetic acid and filtered to remove spent catalyst. The filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O*-dimethyl 1-amino-3-ethoxycarbonylpropanephosphonate as a reddish-orange viscous oily residue. The crude phosphonate was refluxed in the presence of concentrated hydrochloric acid for 12 h. The cool mixture was extracted with toluene to remove any organic by-products, and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The pale-yellow, viscous oily residue, was dissolved in the minimum of water, and treated with propylene oxide at 40-50 ^oC in a water bath. A creamy suspension formed, which was concentrated under

reduced pressure on a rotary evaporator, dissolved in the minimum of water, cooled in ice and treated dropwise with propan-2-ol. When the solution had become turbid, it was left to stand at 4 ^{o}C in a fridge overnight, where crystallisation took place. The fine powdery off-white crystals were filtered off, washed with acetone and dry ether, and dried in a vacuum oven for 2 h at 60 ^{o}C to afford 1-amino-3-carboxypropanephosphonic acid (0.72 g, 22 %); m.p. 170 ^{o}C (lit.[81] 166-167 ^{o}C, 167-169 ^{o}C, 174-175 ^{o}C); (Found: C, 26.17; H, 5.79; N, 7.35. Calc. for $C_4H_{10}NO_5P$: C, 25.95; H, 5.41; N, 7.57 %); ^{1}H(D_2O) δ 1.93-2.32 (m, 2H, $C\underline{H}_2CH_2$), 2.63-2.71 (t, 2H, $CH_2C\underline{H}_2$, $^{3}J_{HCCH}$ 7.47 Hz), 3.26-3.40 (ddd, 1H, P-C$\underline{H}$); ^{13}C(D_2O) δ 26.72 (d, $\underline{C}H_2CH_2$, $^{2}J_{PCC}$ 1.61 Hz), 33.56 (d, $CH_2\underline{C}H_2$, $^{3}J_{PCCC}$ 8.06 Hz), 51.32 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 142.63 Hz) 179.90 (s, $\underline{C}O_2H$); ^{31}P(D_2O) δ 13.39 (s); FAB ms (glycerol): m/z(%) 550 (3M+H, 3.4), 367 (2M+H, 21.5), 276 (M+H+G, 13.9), 184 (M+H, 100), 104 (M+H - HPO_3, 7.5),102 (M+H-H_3PO_3, 85.4), 84 (29.1).

4.4.3. PREPARATION OF 2-AMINOETHANEPHOSPHONIC ACID

Triethyl phosphite (16.7 g, 0.10 mol) and *N*-(2-bromoethyl)phthalimide (24.7 g, 0.097 mol), were mixed and heated under reflux at 170-180 ^{o}C for 4 h. No attempt was made to collect the evolving ethyl bromide. Concentrated hydrochloric acid (150 cm^3) was added to the adduct, and heated under reflux for 8 h. The cooled solution was filtered to remove the precipitated phthalic acid, and the

filtrate was concentrated under reduced pressure on a rotary evaporator. The resulting yellow viscous residue was dissolved in methanol (30 cm^3) and treated with propylene oxide (40-50 ^oC), producing a creamy coloured crystalline solid. This material was filtered, washed with methanol and recrystallised from cold ethanol and water. The fine white crystalline solid produced, 2-aminoethanephosphonic acid was filtered off, washed with methanol, and dried in a vacuum oven for 2 h at 60 ^oC (9.2 g, 75.9 %); m.p. 285-288 ^oC (lit.[117] 277-280 ^oC) (Found: C, 19.31; H, 6.38; N, 11.10. Calc. for $C_2H_8NO_3P$: C, 19.20; H, 6.40; N, 11.20 %); ^1H(NaOD) δ 1.56-1.69 (m, 2H, CH_2CH_2), 2.85-2.88 (m, 2H, CH_2CH_2, $^3J_{HCCH}$ 7.15 Hz); ^{13}C(NaOD) δ 34.35 (d, CH_2CH_2, $^1J_{PC}$ 126.74 Hz), 39.71 (d, CH_2CH_2, $^2J_{PCC}$ 1.64 Hz); ^{31}P(NaOD) δ 18.84 (s).

4.4.4. PREPARATION OF GUANIDINOALKANEPHOSPHONIC ACIDS

PREPARATION OF THE ACETATE DERIVATIVE OF 1-GUANIDINOPROPANE-PHOSPHONIC ACID

Propanal (11.62 g, 0.20 mol) was added dropwise and with stirring during the course of 30 mins to a refluxing mixture of thiourea (15.20 g, 0.20 mol), triphenyl phosphite (62.00 g, 0.20 mol), glacial acetic acid (2 cm^3) and toluene (40 cm^3). When the addition was completed, the mixture was refluxed for a further 15 min, after which water (15 cm^3) and acetonitrile (20 cm^3) were added. After the reaction mixture had been heated under reflux for 2 h, water (50 cm^3) was added and the solution was left to cool. The organic layer was separated, and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The yellow oily residue that formed was dissolved in methanol (50 cm^3), mixed with methyl iodide (12.5 cm^3) and heated under reflux for 6 h. Methanol (50 cm^3) was added to the cooled solution, and ammonia gas was bubbled through with stirring for 4 h at 0 ^oC. The creamy yellow crystalline precipitate that formed was filtered off, washed off, dissolved in water (100 cm^3) and methanol (30 cm^3), before being acidified with glacial acetic acid. The solution was concentrated under reduced pressure on a rotary evaporator to a volume of approximately 40 cm^3. The oily residue was stored for 3 months. The crystalline material that formed was filtered off, washed with methanol

repeatedly, and dried in a vacuum oven at 60 °C, for 2 h, to afford the acetate derivative of 1-guanidinopropanephosphonic, as a creamy-white crystalline solid. No attempt was made to convert the compound to the free phosphonic acid (2.0 g, 4.2 %); m.p. 278-280 °C (lit.[11] 289 °C); (Found: C, 29.34; H, 6.15; N, 16.82. Calc. for $C_6H_{16}N_3O_5P$: C, 29.88; H, 6.64; N, 17.34 %); ^{1}H(D_2O-saturated) δ 0.99 (t, 3H, $CH_2\underline{CH}_3$, $^3J_{HCCH}$ 7.35 Hz), 1.54-2.06 (m, 2H, $\underline{CH}_2CH_3$), 2.07 (s, 3H, $\underline{CH}_3CO_2^-$), 3.44 (ddd, 1H, P-$\underline{CH}$); ^{13}C(D_2O-saturated) δ 13.24 (d, $CH_2\underline{CH}_3$, $^3J_{PCCC}$ 12.89 Hz), 23.56 (s, $\underline{CH}_3CO_2^-$), 25.96 (s, $\underline{CH}_2CH_3$), 55.96 (d, P-$\underline{CH}$, $^1J_{PC}$ 148.94 Hz), 160.15 (s, $\underline{C}(=NH)NH_2$), 179.98 (s, $CH_3\underline{CO}_2^-$); ^{31}P(D_2O-saturated) δ 17.44 (s).

PREPARATION OF 1-GUANIDINOPROPANEPHOSPHONIC ACID

Propanal (11.62 g, 0.20 mol) was added dropwise and with stirring during the course of 30 min, to a refluxing mixture of thiourea (15.20 g, 0.20 mol, triphenyl phosphite (62.00 g, 0.20 mol), glacial acetic acid (2 cm^3) and toluene (40 cm^3). When the addition was completed, the mixture was refluxed for a further 15 min, after which water (15 cm^3) and acetonitrile (20 cm^3) were added. After the reaction mixture had been heated under reflux for 2 h, water (50 cm^3) was added and the solution was left to cool. The organic layer was separated, and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The yellow residue that formed was dissolved in methanol

(50 cm^3), mixed with methyl iodide (12.5 cm^3) and heated under reflux for 6 h. This solution was left to stand for 1 month at room temperature. Methanol (50 cm^3) was added to the cooled solution, and ammonia gas bubbled through with stirring for 4 h at 0 ^oC. The creamy yellow crystalline precipitate that formed, was filtered off, dissolved in water (100 cm^3) and methanol (30 cm^3), before being acidified with glacial acetic acid. The solution so formed was concentrated under reduced pressure on a rotary evaporator to afford a viscous, oily, yellow residue. This was stored in a fridge for 6 months at 4 ^oC, during which time the material was checked periodically for signs of precipitation. The crystalline material that formed was filtered off, washed with methanol and dry ether repeatedly, and dried in a vacuum oven for 2 h at 60 ^oC, to afford 1-guanidinopropanephosphonic acid as a white crystalline material (3.52 g 19.5 %); m.p. 294-297 ^oC (lit.[60] 296-298 ^oC); (Found: C, 26.55; H, 6.64; N, 23.09. Calc. for $C_4H_{12}N_3O_3P$: C, 26.52; H, 6.63; N, 23.20 %); ^1H(NaOD) δ 0.96 (t, 3H, $CH_2\underline{CH}_3$, $^3J_{HCCH}$ 7.38 Hz), 1.49-2.02 (m, 2H, $\underline{CH}_2CH_3$), 3.13-3.24 (ddd, 1H, P-$\underline{CH}$); ^{13}C(NaOD) δ 13.67 (d, $CH_2\underline{CH}_3$, $^3J_{PCCC}$ 11.89 Hz), 26.76 (s, $\underline{CH}_2CH_3$), 56.92 (d, P-$\underline{CH}$, $^1J_{PC}$ 141.39 Hz), 161.34 (d, $\underline{C}(=NH)NH_2$, $^3J_{PCNC}$ 4.65 Hz); ^{31}P(NaOD) δ 18.87 (s); FAB ms (3-NOBA): m/z(%) 324 (22.1), 213 (24.2), 182 (M+H, 10.8), 171 (100), 154 (15.4), 136 (41.3), 100 (M+H - H_3PO_3, 5.0).

ATTEMPT TO PREPARE 1-GUANIDINOPROPANEPHOSPHONIC ACID USING AMINOIMINOMETHANESULPHONIC ACID

1-Aminopropanephosphonic acid (0.695 g, 0.005 mol) was added in portions to a stirring suspension of aminoiminomethanesulphonic acid (0.620 g, 0.005 mol) in water (10 cm^3) at room temperature. After 3 h, the clear solution that formed was concentrated under reduced pressure on a rotary evaporator to afford a white crystalline residue. This material was dissolved in water and recrystallised by the addition of ethanol at 0 ^oC. The white crystalline solid produced was filtered off, washed with dry ether and dried in a vacuum oven for 2 h at 70 ^oC. Analyses showed that the substrate had not been guanidated: (0.635 g, 91.4 % recovery of 1-aminopropanephosphonic acid); m.p. 276-279 ^oC, mixed melting point with 1-aminopropanephosphonic acid supplied by KenoGard AB, 270-273 ^oC, indicating that the product of the above reaction was unchanged 1-aminopropanephosphonic acid; (lit.[60] 1-guanidinopropanephosphonic acid: 296-298 ^oC); (Found: C, 25.69; H, 7.19, N, 10.29. Calc. for $C_4H_{12}N_3O_3P$: C, 26.52; H, 6.63; N, 23.20 %; Calc. for $C_3H_{10}NO_3P$: C, 25.90; H, 7.19; N, 10.07 %); $^{13}C(D_2O)$ δ 13.19 (d,$CH_2\underline{C}H_3$, $^3J_{PCCC}$ 9.56 Hz), 24.83 (s, $\underline{C}H_2CH_3$), 53.93 (d, P-$\underline{C}$H, $^1J_{PC}$ 141.26 Hz).

ATTEMPT TO PREPARE 1-GUANIDINOPROPANEPHOSPHONIC ACID USING AMINOIMINOMETHANESULPHONIC ACID IN THE PRESENCE OF SODIUM HYDROXIDE

1-Aminopropanephosphonic acid (0.35 g, 0.0025 mol) and sodium hydroxide (0.30 g, 0.0075 mol) dissolved in water (10 cm^3) were added dropwise to a stirring suspension of aminoiminomethanesulphonic acid (0.31 g, 0.0025 mol) in water (10 cm^3). The mixture was left to stir under nitrogen for 48 h at room temperature. The clear solution was acidified with concentrated hydrochloric acid, before water was removed under reduced pressure on a rotary evaporator. The white gelatinous residue was dissolved in methanol (20 cm^3), and filtered to remove sodium chloride. Propylene oxide was added to the filtrate at 40-50 ^{o}C generating a white crystalline solid. This material was filtered off, dissolved in the minimum of cold water, and treated with acetone until a faint cloudiness appeared. This solution was allowed to stand at 4 ^{o}C for 48 h, during which time a white crystalline solid had precipitated. The material was filtered off, washed with acetone and dried in a vacuum oven for 2 h at 60 ^{o}C. Analysis showed that the aminophosphonic acid had not been guanidated (0.27 g, 77 % recovery of 1-aminopropanephosphonic acid); m.p. 278-281 ^{o}C (lit.[60] 1-guanidino-propanephosphonic acid 296-298 ^{o}C); (Found: C, 23.93; H, 6.66; N, 12.05. Calc. for $C_4H_{12}N_3O_3P$: C, 26.52; H, 6.63; N, 23.20 %; Calc. for $C_3H_{10}NO_3P$: C, 25.90; H, 7.19; N, 10.07 %).

PREPARATION OF 2-GUANIDINOETHANEPHOSPHONIC ACID

2-Aminoethanephosphonic acid (2.50 g, 0.02 mol) and *S*-methylisothiouronium chloride (8.7 g, 0.04 mol) were dissolved in water (100 cm^3) in the presence of potassium hydroxide (5.61 g, 0.10 mol). The solution was heated at 60-90 ^oC (5 h), cooled, and then acidified to pH 1.0 (HCl), before being concentrated under reduced pressure on a rotary evaporator. Methanol (100 cm^3) was added to the yellow oily residue, and potassium chloride was removed by filtration. The filtrate was treated with propylene oxide (40-50 ^oC), producing a white crystalline solid. This material was dissolved in the minimum of cold water and acetone was added until a faint cloudiness appeared. A little water was added to clear the solution, which was then stored at 4 ^oC for several days, during which time crystallisation ensued. The product, 2-guanidinoethanephosphonic acid,[116] was filtered off, washed with acetone and dried in a vacuum oven for 3 h at 60 ^oC to give the crystalline dihydrate as a white solid (0.67 g, 20 %); m.p. 230-233 ^oC; (Found: C, 18.15; H, 7.26; N, 21.75. Calc. for $C_3H_{14}N_3O_5P$: C, 17.73; H, 6.90; N, 20.69 %); $^1H(D_2O)$ δ 1.92 (m, 2H, P-C$\underline{H}_2$$CH_2$), 3.41 (m, 2H, P-$CH_2C\underline{H}_2$); $^{13}C(D_2O)$ δ 30.27 (d, P-$\underline{C}H_2CH_2$, $^1J_{PC}$ 131.58 Hz), 39.65 (s, P-$CH_2\underline{C}H_2$), 159.39 (s, $\underline{C}$(=NH)NH_2); $^{31}P(D_2O)$ δ 20.88 (s); FAB ms (3-NOBA): m/z(%) 335 (2M+H, 7.5), 321 (M+H+N, 6.5), 279 (M+H+N - H_2NCN, 2.9), 168 (M+H, 76.7), 103 (100), 226 (55.8).

4.4.5. PREPARATION OF *O,O*-DIALKYL 1-OXOALKANEPHOSPHONATES AND *O,O*-DIALKYL 1-OXOBENZYLPHOSPHONATES

PREPARATION OF *O,O*-DIMETHYL 1-OXOETHANEPHOSPHONATE

Acetyl chloride (19.63 g, 0.25 mol) was slowly added dropwise to a stirring solution of trimethyl phosphite (31.03 g, 0.25 mol) at 0 - 2 ^{o}C, under dry nitrogen, during a period of 30 min. When the addition was completed the mixture was left to stir overnight at room temperature. The following day, any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material remaining was distilled under high vacuum to afford colourless free flowing fractions of *O,O*-dimethyl 1-oxoethanephosphonate (25.97 g, 68 %); b.p. 64-66.5 ^{o}C at 0.15-0.50 mmHg; (lit.[79] 71.5-72.0 ^{o}C at 4.5 mmHg); (Found: C, 31.59; H, 6.06. Calc. for $C_4H_9O_4P$: C, 31.58, H, 5.92 %); $^{1}H(CDCl_3)$ δ 2.50 (d, 3H, P-C-$\underline{C}H_3$, $^{3}J_{PCCH}$ 5.38 Hz), 3.88 (d, 6H, 2x$\underline{C}H_3O$-, $^{3}J_{POCH}$ 10.64 Hz); $^{13}C(CDCl_3)$ δ 30.80 (d, P-C-$\underline{C}H_3$, $^{2}J_{PCC}$ 59.81 Hz), 54.00 (d, 2x$\underline{C}H_3O$-, $^{2}J_{POC}$ 7.48 Hz), 208.38 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 170.00 Hz); $^{31}P(CDCl_3)$ δ - 0.55 (s).

PREPARATION OF *O,O*-DIETHYL 1-OXOETHANEPHOSPHONATE

Acetyl chloride (19.63 g, 0.25 mol) was slowly added dropwise to a stirring solution of triethyl phosphite (41.54 g, 0.25 mol) at 0-2 ^{o}C, under dry nitrogen, during a period of 30 min. When the addition was completed the mixture was left to stir overnight at room temperature. The following day, any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material remaining was distilled under high vacuum to afford colourless free flowing fractions of *O,O*-diethyl 1-oxoethanephosphonate (37.02 g, 84 %); b.p. 77-82 ^{o}C at 0.15-0.20 mmHg (lit.[76] 80 ^{o}C at 1.20 mmHg); (Found: C, 40.00; H, 7.82. Calc. for $C_6H_{13}O_4P$: C, 40.00; H, 7.22 %); $^{1}H(CDCl_3)$ δ 1.39 (t, 6H, 2xCH_3CH_2O-, $^{3}J_{HCCH}$ 7.04 Hz), 2.49 (d, 3H, P-C-CH_3, $^{3}J_{PCCH}$ 5.05 Hz), 4.24 (dq overlapping, 4H, 2xCH_3CH_2O-, $^{3}J_{POCH}$ 10.60 Hz); $^{13}C(CDCl_3)$ δ 16.45 (d, 2xCH_3CH_2O-, $^{3}J_{POCC}$ 5.47 Hz), 31.04 (d, P-C-CH_3, $^{2}J_{PCC}$ 59.31 Hz), 63.78 (d, 2xCH_3CH_2O-, $^{2}J_{POC}$ 7.11 Hz), 208.83 (d, P-C=O, $^{1}J_{PC}$ 170.95 Hz); $^{31}P(CDCl_3)$ δ - 2.42 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-OXOETHANEPHOSPHONATE

Acetyl chloride (12.56 g, 0.16 mol) was slowly added dropwise to a stirring solution of tri-isopropyl phosphite (27.50 g, 0.13 mol) at 0-2 ^{o}C, during a period of 20 min. When the addition was completed the mixture was left to stir overnight at room temperature. The following

day, any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material left remaining was distilled under high vacuum to afford colourless free-flowing fractions of *O,O*-di-isopropyl 1-oxoethanephosphonate[100] (19.40 g, 71.8 %); b.p. 73-74 ^{o}C at 0.10 mmHg; (Found: C, 46.00; H, 8.14. $C_8H_{17}O_4P$ requires: C, 46.15; H, 8.17 %); $^{1}H(CDCl_3)$ δ 1.38 (d, 12H, 2x$(C\underline{H}_3)_2$CHO-, $^{3}J_{HCCH}$ 6.22 Hz), 2.46 (d, 3H, P-C-C$\underline{H}_3$, $^{3}J_{PCCH}$ 4.94 Hz), 4.70-4.85 (m, 2H, 2x$(CH_3)_2C\underline{H}$O-); $^{13}C(CDCl_3)$ δ 23.86 (dd, 2x$(\underline{C}H_3)_2$CHO-, $^{3}J_{POCC}$ 4.76 Hz), 30.29 (d, P-C-$\underline{C}H_3$, $^{2}J_{PCC}$ 59.37 Hz), 72.81 (d, 2x$(CH_3)_2\underline{C}$HO-, $^{2}J_{POC}$ 7.55 Hz), 209.14 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 173.53 Hz); $^{31}P(CDCl_3)$ δ - 4.80 (s).

PREPARATION OF *O,O*-DI-n-BUTYL 1-OXOETHANEPHOSPHONATE

Acetyl chloride (28.30 g, 0.36 mol) was slowly added dropwise to a stirring solution of tri-n-butyl phosphite (63.80 g, 0.26 mol) at 0 - 2 ^{o}C, under dry nitrogen, during a period of 20 min. When the addition was completed the mixture was left to stir overnight at room temperature. The following day, any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material was distilled under high vacuum to afford colourless fractions of *O,O-di-n-butyl 1-oxoethanephosphonate* (30.11 g, 50.06 %); b.p. 104-108 ^{o}C at 0.050-0.100 mmHg; (Found: C, 50.87; H, 9.02. $C_{10}H_{21}O_4P$ requires: C, 50.85; H, 8.90 %); $^{1}H(CDCl_3)$ δ 0.95 (t, 6H, 2x$\underline{CH}_3CH_2CH_2CH_2$O-, $^{3}J_{HCCH}$ 7.35 Hz), 1.36-1.51 (m, 4H, 2x$CH_3\underline{CH}_2CH_2CH_2$O-),

1.64-1.76 (m, 4H, 2x$CH_3CH_2\underline{CH}_2CH_2O$-), 2.48 (d, 3H, P-C-$\underline{CH}_3$, $^3J_{PCCH}$ 5.08 Hz), 4.16(dt overlapping, 4H, 2x$CH_3CH_2CH_2\underline{CH}_2O$-, $^3J_{HCCH}$ 6.81 Hz); $^{13}C(CDCl_3)$ δ 13.56 (s, 2x$\underline{CH}_3CH_2CH_2CH_2O$-), 18.70 (s, 2x$CH_3\underline{CH}_2CH_2CH_2O$-), 30.69 (d, P-C-$\underline{CH}_3$, $^2J_{PCC}$ 59.15 Hz), 32.52 (d, 2x$CH_3CH_2\underline{CH}_2CH_2O$-, $^3J_{POCC}$ 5.72 Hz), 67.39 (dd, 2x$CH_3CH_2CH_2\underline{CH}_2O$-, $^2J_{POC}$ 7.01 Hz), 208.90 (d, P-$\underline{C}$=O, $^1J_{PC}$ 171.39 Hz); $^{31}P(CDCl_3)$ δ - 3.01 (s).

PREPARATION OF *O,O*-DIMETHYL 1-OXOPROPANEPHOSPHONATE

Propionyl chloride (55 g, 0.60 mol) was slowly added dropwise to a stirring solution of trimethyl phosphite (62 g, 0.50 mol) at 0 - 2 °C under dry nitrogen, during a period of 1 h. When the addition was completed the mixture was left to stir at room temperature. The following day, any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material was distilled under high vacuum to afford several fractions of colourless free-flowing *O,O*-dimethyl 1-oxopropanephosphonate (55.85 g, 67 %); b.p. 90-91 °C at 0.10-0.20 mmHg; (lit.[76] 65 °C at 0.10 mmHg); (Found: C, 36.14; H, 6.55. Calc. for $C_5H_{11}O_4P$: C, 36.14; H, 6.63 %); $^1H(CDCl_3)$ δ 1.11 (t, 3H, P-C-$CH_2\underline{CH}_3$, $^3J_{HCCH}$ 7.45 Hz), 2.87 (dq overlapping, 2H, P-C-$\underline{CH}_2CH_3$, $^3J_{PCCH}$ 1.18 Hz, $^3J_{HCCH}$ 7.20 Hz), 3.88 (d, 6H, 2x$\underline{CH}_3O$-, $^3J_{POCH}$ 10.73 Hz); $^{13}C(CDCl_3)$ δ 6.34 (d, P-C-$CH_2\underline{CH}_3$, $^3J_{PCCC}$ 4.40 Hz), 37.19 (d, P-C-$\underline{CH}_2CH_3$, $^2J_{PCC}$ 56.48 Hz), 54.00 (d, 2x$\underline{CH}_3O$-, $^2J_{POC}$ 6.73 Hz), 210.85 (d, P-$\underline{C}$=O, $^1J_{PC}$ 165.79 Hz); $^{31}P(CDCl_3)$ δ - 0.75 (s).

PREPARATION OF *O,O*-DIETHYL 1-OXOPROPANEPHOSPHONATE

Propionyl chloride (46.25 g, 0.5 mol) was slowly added dropwise to a stirring solution of triethyl phosphite (83.00 g, 0.5 mol) at 0 - 2 ^{o}C, under dry nitrogen, during a period of 1 h. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day, any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk solution was distilled under high vacuum to afford several fractions of colourless free-flowing *O,O*-diethyl 1-oxopropanephosphonate (71.07 g, 73.30 %); b.p. 92.0 ^{o}C at 0.20 mm Hg; (lit.[120] 85 ^{o}C at 1.0 mmHg); (Found: C, 43.21; H, 7.90. Calc. for $C_7H_{15}O_4P$: C, 43.30; H, 7.73 %); $^{1}H(CDCl_3)$ δ 1.08 (t, 3H, P-C-$CH_2\underline{C}H_3$, $^{3}J_{HCCH}$ 7.28 Hz), 1.37 (t, 6H, 2x$\underline{C}H_3CH_2O$-, $^{3}J_{HCCH}$ 7.07 Hz), 2.86 (dq overlapping, 2H, P-C-$CH_2\underline{C}H_3$, $^{3}J_{PCCH}$ 1.04 Hz, $^{3}J_{HCCH}$ 7.08 Hz), 4.22 (dq overlapping, 4H, 2x$CH_3\underline{C}H_2O$-, $^{3}J_{POCH}$ 10.69 Hz, $^{3}J_{HCCH}$ 7.10 Hz); $^{13}C(CDCl_3)$ δ 6.48 (d, P-C-$CH_2\underline{C}H_3$, $^{3}J_{PCCC}$ 3.90 Hz), 16.51 (d, 2x$\underline{C}H_3CH_2O$-, $^{3}J_{POCC}$, 5.66 Hz), 36.89 (d, P-C-$\underline{C}H_2CH_3$, $^{2}J_{PCC}$ 56.92 Hz), 63.75 (d, 2x$CH_3\underline{C}H_2O$-, $^{2}J_{POC}$ 5.35 Hz), 211.37 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 166.04 Hz); $^{31}P(CDCl_3)$ δ - 2.72 (s).

PREPARATION OF *O,O*-DI-n-PROPYL 1-OXOPROPANEPHOSPHONATE

Propionyl chloride (10.20 g, 0.11 mol), was slowly added dropwise to a stirring solution of tri-n-propyl phosphite (23.40 g, 0.11 mol), at 0 - 2 ^{o}C under dry nitrogen, during a period of 20 min. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford colourless free-flowing fractions of *O,O-di-n-propyl 1-oxopropane-phosphonate* (6.2 g, 25 %); b.p. 76 ^{o}C at 0.040 mmHg; (Found: C, 49.16; H, 8.96. $C_9H_{19}O_4P$ requires: C, 48.65; H, 8.56 %); $^{1}H(CDCl_3)$ δ 0.99 (t, 6H, 2x$\underline{CH}_3CH_2CH_2O$-, $^{3}J_{HCCH}$ 7.37 Hz), 1.10 (t, 3H, P-C-$CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.12 Hz), 1.73 (m, 4H, 2x$CH_3\underline{CH}_2CH_2O$-), 2.87 (q, 2H, P-C-$\underline{CH}_2CH_3$, $^{3}J_{HCCH}$ 7.15 Hz), 4.12 (dt overlapping 4H, 2x$CH_3CH_2\underline{CH}_2O$-, $^{3}J_{HCCH}$ 6.82 Hz); $^{13}C(CDCl_3)$ δ 6.46 (d, P-C-$CH_2\underline{CH}_3$, $^{3}J_{PCCC}$ 4.03 Hz), 10.07 (s, 2x$\underline{CH}_3CH_2CH_2O$-), 24.05 (d, 2x$CH_3\underline{CH}_2CH_2O$-, $^{3}J_{POCC}$ 5.66 Hz), 36.99 (d, P-C-$\underline{CH}_2CH_3$, $^{2}J_{PCC}$ 56.42 Hz), 69.13 (d, 2x$CH_3CH_2\underline{CH}_2O$-, $^{2}J_{POC}$ 7.61 Hz), 211.29 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 166.86 Hz); $^{31}P(CDCl_3)$ δ - 2.61 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-OXOPROPANEPHOSPHONATE

Propionyl chloride (46.27 g, 0.50 mol) was slowly added dropwise to a stirring solution of tri-isopropyl phosphite (101.13 g, 0.49 mol) at 0 - 2 ^{o}C under dry nitrogen, during a period of 1 h. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford several fractions of *O,O*-di-isopropyl 1-oxopropanephosphonate[100] (71.12 g, 66 %); b.p. 104-107 ^{o}C at 0.40-0.60 mmHg; (Found: C, 48.65; H, 8.85. Calc. for $C_9H_{19}O_4P$: C, 48.65; H, 8.56 %); $^{1}H(CDCl_3)$ δ 1.54 (t, 3H, P-C-$CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.20 Hz), 1.82 (d, 12H, 2x$(\underline{CH}_3)_2$CHO-, $^{3}J_{HCCH}$ 6.70 Hz), 4.28 (dq overlapping, 2H, P-C-$\underline{CH}_2CH_3$, $^{3}J_{HCCH}$ 7.21 Hz, $^{3}J_{PCCH}$ 1.29 Hz), 5.24 (m, 2H, 2x$(CH_3)_2\underline{CH}$O-); $^{13}C(CDCl_3)$ δ 6.48 (d, P-C-$CH_2\underline{CH}_3$, $^{3}J_{PCCC}$ 4.53 Hz), 23.99 (dd, 2x$(\underline{CH}_3)_2$CHO-, $^{3}J_{POCC}$ 4.20 Hz), 36.54 (d, P-C-$\underline{CH}_2CH_3$, $^{2}J_{PCC}$ 56.15 Hz), 72.79 (d, 2x$(CH_3)_2\underline{CH}$O-, $^{2}J_{POC}$ 7.45 Hz), 211.86 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 168.75 Hz); $^{31}P(CDCl_3)$ δ - 4.16 (s).

PREPARATION OF *O,O*-DI-ISOBUTYL 1-OXOPROPANEPHOSPHONATE

Propionyl chloride (18.51 g, 0.20 mol) was slowly added dropwise to a stirring solution of tri-isobutyl phosphite (29.26 g, 0.12 mol), at 0-2 ^{o}C under dry nitrogen, during a period of 30 min.

When the addition was complete the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford colourless free-flowing fractions of *0,0-di-isobutyl 1-oxopropanephosphonate* (13.96 g, 46.53 %); b.p. 84-88 ^{o}C at 0.05-0.10 mmHg; (Found: C, 52.80; H, 9.25. $C_{11}H_{23}O_4P$ requires: C, 52.80; H, 9.20 %) $^{1}H(CDCl_3)$ δ 0.97 (d, 12H, 2x$(C\underline{H}_3)_2CHCH_2O$-, $^{3}J_{HCCH}$ 6.81 Hz), 1.11 (t, 3H, P-C-$CH_2C\underline{H}_3$, $^{3}J_{HCCH}$ 7.13 Hz), 1.97 (m, 2H, 2x$(CH_3)C\underline{H}CH_2O$-), 2.87 (dq overlapping, 2H, P-C-$C\underline{H}_2CH_3$, $^{3}J_{HCCH}$ 7.23 Hz, $^{3}J_{PCCH}$ 1.18 Hz), 3.93 (t, 4H, 2x$(CH_3)CHC\underline{H}_2O$-, $^{3}J_{HCCH}$ 6.65 Hz); $^{13}C(CDCl_3)$ δ 6.39 (d, P-C-$CH_2\underline{C}H_3$, $^{3}J_{PCCC}$ 3.96 Hz), 18.63 (s, 2x$(\underline{C}H_3)_2CHCH_2O$-), 29.29 (d, 2x$(CH_3)_2\underline{C}HCH_2O$-, $^{3}J_{POCC}$ 5.85 Hz), 37.02 (d, P-C-$\underline{C}H_2CH_3$, $^{2}J_{PCC}$ 56.10 Hz), 73.34 (d, 2x$(CH_3)CH\underline{C}H_2O$-, $^{2}J_{POC}$ 7.74 Hz), 211.36 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 167.05 Hz); $^{31}P(CDCl_3)$ δ - 2.95 (s).

PREPARATION OF *0,0*-DIMETHYL 1-OXOBUTANEPHOSPHONATE

Butyryl chloride (63.93 g, 0.60 mol) was slowly added dropwise to a stirring solution of trimethyl phosphite (62.04 g, 0.50 mol), at 0 - 2 ^{o}C, under dry nitrogen, during a period of 1 h. When the addition was complete the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material was distilled under

high vacuum to afford several fractions of colourless, free-flowing *O,O*-dimethyl 1-oxobutanephosphonate (58.75 g, 65 %); b.p. 84-87 ^{o}C at 0.025-0.050 mmHg; (lit.[76] 70 ^{o}C at 0.10 mmHg);(Found: C, 39.54; H, 7.36. Calc. for $C_6H_{13}O_4P$: C, 40.00; H, 7.23 %); $^{1}H(CDCl_3)$ δ 0.95 (t, 3H, P-C-$CH_2CH_2\underline{C}H_3$, $^{3}J_{HCCH}$ 7.60 Hz), 1.67 (m, 2H, P-C-$CH_2\underline{C}H_2CH_3$, $^{3}J_{HCCH}$ 7.30 Hz), 2.82 (t, 2H, P-C-$\underline{C}H_2CH_2CH_3$, $^{3}J_{HCCH}$ 7.10 Hz), 3.87 (d, 6H, 2x$\underline{C}H_3O$-, $^{3}J_{POCH}$ 10.70 Hz), $^{13}C(CDCl_3)$ δ 13.47 (s, P-C-$CH_2CH_2\underline{C}H_3$), 16.00 (d, P-C-$CH_2\underline{C}H_2CH_3$, $^{3}J_{PCCC}$ 2.77 Hz), 45.55 (d, P-C-$\underline{C}H_2CH_2CH_3$, $^{2}J_{PCC}$ 61.84 Hz), 53.94 (d, 2x$\underline{C}H_3O$-, $^{2}J_{POC}$ 7.42 Hz), 210.57 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 164.66 Hz); $^{31}P(CDCl_3)$ δ - 0.97 (s).

PREPARATION OF *O,O*-DIETHYL 1-OXOBUTANEPHOSPHONATE

Butyryl chloride (34.40 g, 0.32 mol) was slowly added dropwise to a stirring solution of triethyl phosphite (49.80 g, 0.30 mol), at 0 - 2 ^{o}C, under dry nitrogen, during a period of 45 min. When the addition was complete the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford several fractions of colourless, free-flowing *O,O*-diethyl 1-oxobutanephosphonate (51.85 g, 83 %); b.p. 120 ^{o}C at 0.10 mmHg; (lit.[120] 80 ^{o}C at 0.50 mmHg); (Found: C, 45.66; H, 8.23. Calc. for $C_8H_{17}O_4P$: C, 46.15; H, 8.17 %); $^{1}H(CDCl_3)$ δ 0.95 (t, 3H, P-C-$CH_2CH_2\underline{C}H_3$, $^{3}J_{HCCH}$ 7.00 Hz), 1.35 (t, 6H, 2x$\underline{C}H_3CH_2O$-, $^{3}J_{HCCH}$

7.00 Hz), 1.75 (m, 2H, P-C-$CH_2\underline{C}H_2CH_3$), 2.80 (t, 2H, P-C-$\underline{C}H_2CH_2CH_3$, $^3J_{HCCH}$ 7.00 Hz), 4.23 (dq overlapping, 4H, 2x$CH_3\underline{C}H_2O$-, $^3J_{HCCH}$ 7.10 Hz); $^{13}C(CDCl_3)$ δ 13.59 (s, P-C-$CH_2CH_2\underline{C}H_3$) 16.10 (d, 2x$\underline{C}H_3CH_2O$-, $^3J_{POCC}$ 6.67 Hz), 16.37 (d, P-C-$CH_2\underline{C}H_2CH_3$, $^3J_{PCCC}$ 3.77 Hz), 45.26 (d, P-C-$\underline{C}H_2CH_2CH_3$, $^2J_{PCC}$ 53.78 Hz), 63.71 (d, 2x$CH_3\underline{C}H_2O$-, $^2J_{POC}$ 7.48 Hz), 210.98 (d, P-$\underline{C}$=O, $^1J_{PC}$ 165.42 Hz); $^{31}P(CDCl_3)$ δ - 2.79 (s).

PREPARATION OF *O,O*-DI-n-PROPYL 1-OXOBUTANEPHOSPHONATE

Butyryl chloride (12.8 g, 0.12 mol) was slowly added dropwise to a stirring solution of tri-n-propyl phosphite (24.0 g, 0.12 mol), at 0-2 ^oC, under dry nitrogen, during the course of 30 min. When the addition was complete the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford colourless, free-flowing fractions of *O,O-di-n-propyl 1-oxobutanephosphonate* (6.7 g, 24 %); b.p. 69-72 ^oC at 0.025-0.040 mmHg; (Found: C, 50.67; H, 8.82. $C_{10}H_{21}O_4P$ requires: C, 50.85; H, 8.90 %); $^1H(CDCl_3)$ δ 0.91-1.02 (2xt overlapping, 9H, P-C-$CH_2CH_2\underline{C}H_3$ & 2x$\underline{C}H_3CH_2CH_2O$-, $^3J_{HCCH}$ 7.00 Hz), 1.59-1.81 (m, 6H, P-C-$CH_2\underline{C}H_2CH_3$ & 2x$CH_3\underline{C}H_2CH_2O$-), 2.81 (t, 2H, P-C-$\underline{C}H_2CH_2CH_3$, $^3J_{HCCH}$ 7.10 Hz), 4.13 (dt overlapping, 4H, 2x$CH_3CH_2\underline{C}H_2O$-, $^3J_{HCCH}$ 6.86 Hz); $^{13}C(CDCl_3)$ 10.07 (s, P-C-$CH_2CH_2\underline{C}H_3$), 10.16 (s, 2x$\underline{C}H_3CH_2CH_2O$-), 16.15 (d, P-C-$CH_2\underline{C}H_2CH_3$, $^3J_{PCCC}$ 3.77 Hz), 24.06 (d, 2x$CH_3\underline{C}H_2CH_2O$-, $^3J_{POCC}$

5.54 Hz), 45.40 (d, P-C-$\underline{C}H_2CH_2CH_3$, $^2J_{PCC}$ 54.28 Hz), 69.16 (d, 2x$CH_3CH_2\underline{C}H_2O$-, $^2J_{POC}$ 7.49 Hz), 210.89 (d, P-$\underline{C}$=O, $^1J_{PC}$ 165.67 Hz); $^{31}P(CDCl_3)$ δ - 2.98 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-OXOBUTANEPHOSPHONATE

Butyryl chloride (39.0 g, 0.37 mol) was slowly added dropwise to a stirring solution of tri-isopropyl phosphite (76.21 g, 0.37 mol) at 0-2 °C, under dry nitrogen during the course of 1 h. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford several fractions of colourless free-flowing *O,O-di-isopropyl 1-oxobutanephosphonate* (31 g, 35 %); b.p. 74-76 °C at 0.050 mmHg; (Found: C, 50.40; H, 9.05. $C_{10}H_{21}O_4P$ requires: C, 50.85; H, 8.90 %); $^1H(CDCl_3)$ δ 0.95 (t, 3H, P-C-$CH_2CH_2\underline{C}H_3$, $^3J_{HCCH}$ 7.36 Hz), 1.38 (d, 12H, 2x$(\underline{C}H_3)_2CHO$, $^3J_{HCCH}$ 6.19 Hz), 1.66 (m, 2H, P-C-$CH_2\underline{C}H_2CH_3$), 2.82 (t, 2H, P-C-$\underline{C}H_2CH_2CH_3$, $^3J_{HCCH}$ 7.13 Hz), 4.80 (m, 2H, 2x$(CH_3)_2\underline{C}HO$-); $^{13}C(CDCl_3)$ δ 13.50 (s, P-C-$CH_2CH_2\underline{C}H_3$), 16.06 (d, P-C-$CH_2\underline{C}H_2CH_3$, $^3J_{PCCC}$ 3.76 Hz), 24.00 (d, 2x$(\underline{C}H_3)_2CHO$-, $^3J_{POCC}$ 4.30 Hz), 44.99 (d, P-C-$\underline{C}H_2CH_2CH_3$, $^2J_{PCC}$ 53.51 Hz), 72.75 (d, 2x$(CH_3)\underline{C}HO$-, $^2J_{POC}$ 7.59 Hz), 211.61 (d, P-$\underline{C}$=O, $^1J_{PC}$ 167.62 Hz); $^{31}P(CDCl_3)$ δ - 3.80 (s).

PREPARATION OF *O,O*-DI-n-BUTYL 1-OXOBUTANEPHOSPHONATE

Butyryl chloride (60 0 g, 0.57 mol) was slowly added dropwise to a stirring solution of tri-n-butyl phosphite (106 g, 0.42 mol) at 0 - 2 ^{o}C, under dry nitrogen during a period of 1 h. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford several fractions of colourless, free-flowing *O,O-di-n-butyl 1-oxobutanephosphonate* (60.4 g, 53.9 %); b.p. 118-120.5 ^{o}C at 0.20-0.25 mmHg; (Found: C, 53.14; H, 9.42. $C_{12}H_{25}O_4P$ requires: C, 54.55; H, 9.47 %); $^{1}H(CDCl_3)$ δ 0.95 (t, 9H, P-C-$CH_2CH_2\underline{CH}_3$ & 2x$\underline{CH}_3CH_2CH_2CH_2O$-, $^{3}J_{HCCH}$ 7.30 Hz), 1.35-1.50 (m, 4H, 2x$CH_3\underline{CH}_2CH_2CH_2O$-, $^{3}J_{HCCH'}$ 7.40 Hz), 1.60-1.76 (m, 6H, P-C-$CH_2\underline{CH}_2CH_3$ & 2x$CH_3CH_2\underline{CH}_2CH_2O$-), 2.82 (t, 2H, P-C-$\underline{CH}_2CH_2CH_3$, $^{3}J_{HCCH}$ 7.20 Hz), 4.16 (dt overlapping, 4H, 2x$CH_3CH_2CH_2\underline{CH}_2O$-, $^{3}J_{HCCH}$ 6.80 Hz); $^{13}C(CDCl_3)$ δ 13.51 (s, P-C-$CH_2CH_2\underline{CH}_3$), 13.56 (s, 2x$\underline{CH}_3CH_2CH_2CH_2O$-), 16.03 (d, P-C-$CH_2\underline{CH}_2CH_3$, $^{3}J_{PCCC}$ 3.76 Hz), 18.70 (s, 2x$CH_3\underline{CH}_2CH_2CH_2O$-), 32.54 (d, 2x$CH_3CH_2\underline{CH}_2CH_2O$-, $^{3}J_{POCC}$ 5.67 Hz), 45.37 (d, P-C-$\underline{CH}_2CH_2CH_3$, $^{2}J_{PCC}$ 55.96 Hz), 67.34 (d, 2x$CH_3CH_2CH_2\underline{CH}_2O$-, $^{2}J_{POC}$ 7.61 Hz), 211.22 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 165.48 Hz); $^{31}P(CDCl_3)$ δ - 2.67 (s).

PREPARATION OF *O,O*-DIMETHYL 1-OXOCYCLOPROPYLMETHANEPHOSPHONATE

Cyclopropanecarbonyl chloride (10.45 g, 0.10 mol) was slowly added dropwise to a stirring solution of trimethyl phosphite (12.41 g, 0.10 mol) at 0-2 ^{o}C, under dry nitrogen, during a period of 20 min. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford clear fractions of the colourless, free-flowing *O,O-dimethyl 1-oxocyclopropylmethanephosphonate* (4.75 g, 57 %); b.p. 86-88 ^{o}C at 0.60 mmHg; (Found: C, 40.04; H, 6.13. $C_6H_{11}O_4P$ requires: C, 40.45; H, 6.18 %); $^{1}H(CDCl_3)$ δ 1.22 (m, 4H, C$\underline{H}_2$'s of the cyclopropane ring), 2.63 (m, 1H, C$\underline{H}$ of cyclopropane ring), 3.86 (d, 6H, 2xC$\underline{H}_3$O-, $^{3}J_{POCH}$ 10.87 Hz); $^{13}C(CDCl_3)$ δ 13.89 (s, $\underline{C}H_2$'s of cyclopropane ring), 22.65 (d, P-C-$\underline{C}$H, $^{2}J_{PCC}$ 73.15 Hz), 53.99 (d, 2x$\underline{C}H_3$O-, $^{2}J_{POC}$ 7.36 Hz); 210.30 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 174.35 Hz); $^{31}P(CDCl_3)$ δ - 0.29 (s).

PREPARATION OF *O,O*-DIETHYL 1-OXOCYCLOPROPYLMETHANEPHOSPHONATE

Cyclopropanecarbonyl chloride (13.75 g, 0.13 mol), was slowly added dropwise to a stirring solution of triethyl phosphite (18.26 g, 0.11 mol), at 0-2 ^{o}C under dry nitrogen, during a period of 20 min. When the addition had been completed the mixture was left to stir

overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford clear fractions of colourless, free-flowing *O,O-diethyl 1-oxocyclopropyl-methanephosphonate* (21.24 g, 92 %); b.p. 84-90 ^{o}C at 0.05-0.10 mmHg; (Found: C, 46.65; H, 7.31. $C_8H_{15}O_4P$ requires: C, 46.60; H, 7.28 %); $^{1}H(CDCl_3)$ δ 1.13-1.35 (m, 4H, C$\underline{H}_2$'s of cyclopropane ring), 1.39 (t, 6H, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{HCCH}$ 7.02 Hz), 2.61-2.71 (m, 1H, C$\underline{H}$ of cyclopropane ring), 4.23 (dq overlapping, 4H, 2xCH$_3$C$\underline{H}_2$O-, $^{3}J_{HCCH}$ 7.13 Hz); $^{13}C(CDCl_3)$ δ 13.81 (s, C$\underline{H}_2$'s of cyclopropane ring), 16.47 (d, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{POCC}$ 5.60 Hz), 22.27 (d, C$\underline{H}$ of cyclopropane ring, $^{2}J_{PCC}$ 72.90 Hz), 63.75 (d, 2xCH$_3$C$\underline{H}_2$O-, $^{2}J_{POC}$ 7.30 Hz), 210.70 (d, P-C$\underline{=}$O, $^{1}J_{PC}$ 175.42 Hz); $^{31}P(CDCl_3)$ δ - 3.04 (s).

PREPARATION OF *O,O*-DIMETHYL 1-OXOBENZYLPHOSPHONATE

Benzoyl chloride (84.34 g, 0.60 mol) was slowly added dropwise to a stirring solution of trimethyl phosphite (62.04 g, 0.50 mol), at 0-2 ^{o}C, under dry nitrogen, during a period of 1 h. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure. The remaining bulk material was distilled under high vacuum to afford several fractions of clear free-flowing *O,O*-dimethyl 1-oxobenzylphosphonate (97.41 g, 91 %); b.p. 116-120 ^{o}C at

0.075-0.100 mmHg; (lit.[79] 146 °C at 2.5 mmHg); (Found: C, 50.34; H, 5.15. Calc. for $C_9H_{11}O_4P$: C, 50.47; H, 5.14 %); $^1H(CDCl_3)$ δ 3.92 (d, 6H, 2x$\underline{C}H_3O$-, $^3J_{POCH}$ 10.82 Hz), 7.47-7.54 (m, 2H, $\underline{H}_3$ & $\underline{H}_4$ of aromatic ring), 7.61-7.68 (m, 1H, $\underline{H}_4$ of aromatic ring), 8.23-8.28 (m, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring); $^{13}C(CDCl_3)$ δ 54.15 (d, 2x$\underline{C}H_3O$-, $^2J_{POC}$ 7.55 Hz), 128.98 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 129.76 (s, $\underline{C}_4$ of aromatic ring), 135.01 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 136.04 (d, P-C-$\underline{C}_1$ of aromatic ring, $^2J_{PCC}$ 64.97 Hz), 198.37 (d, P-$\underline{C}$=O, $^1J_{PC}$ 174.54 Hz); $^{31}P(CDCl_3)$ δ +0.58 (s).

PREPARATION OF *O,O*-DIETHYL 1-OXOBENZYLPHOSPHONATE

Benzoyl chloride (42.17 g, 0.30 mol) was slowly added dropwise to a stirring solution of triethyl phosphite (41.54 g, 0.25 mol), at 0 - 2 °C under dry nitrogen, during a period of 45 min. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on rotary evaporator. The remaining bulk material was distilled under high vacuum to afford several fractions of clear free flowing *O,O*-diethyl 1-oxobenzylphosphonate (47.61 g, 78.70 %); b.p. 120-124 °C at 0.10 mmHg; (lit.[71] 136-137 °C at 1.4-1.5 mmHg); (Found: C, 54.63; H, 6.23. Calc. for $C_{11}H_{15}O_4P$: C, 54.55; H, 6.20 %); $^1H(CDCl_3)$ δ 1.39 (t, 6H, 2x$\underline{C}H_3CH_2O$-, $^3J_{HCCH}$ 7.13 Hz), 4.29 (dq overlapping, 4H, 2x$CH_3\underline{C}H_2O$-, $^3J_{HCCH}$ 7.13 Hz), 7.48-7.55 (m, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic

ring), 7.61-7.68 (m, 1H, $\underline{H}_4$ of aromatic ring), 8.26-8.31 (m, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring); $^{13}C(CDCl_3)$ δ 16.38 (d, 2x$\underline{C}H_3CH_2O$-, $^3J_{POCC}$ 5.27 Hz), 64.01 (d, 2x$CH_3\underline{C}H_2O$-, $^2J_{POC}$ 7.30 Hz), 128.89 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 129.82 (s, $\underline{C}_4$ of aromatic ring), 134.78 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 135.68 (d, P-C-$\underline{C}_1$ of aromatic ring, $^2J_{PCC}$ 63.65 Hz), 199.04 (d, P-$\underline{C}$=O, $^1J_{PC}$ 175.23 Hz); $^{31}P(CDCl_3)$ δ - 1.43 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-OXOBENZYLPHOSPHONATE

Benzoyl chloride (42.17 g, 0.30 mol) was slowly added dropwise to a stirring solution of tri-isopropyl phosphite (52.06 g, 0.25 mol), at 0-2 °C under dry nitrogen, during a period of 45 min. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The remaining bulk material was distilled under high vacuum to afford several fractions of clear free-flowing *O,O-di-isopropyl 1-oxobenzylphosphonate* (45.33 g, 67.20 %); b.p. 138-142 °C at 0.15 mmHg; (Found: C, 57.12; H, 7.25. $C_{13}H_{19}O_4P$ requires: C, 57.78; H, 7.04 %); $^1H(CDCl_3)$ δ 1.39 (dd, 12H, 2x$(C\underline{H}_3)_2$CHO-, $^3J_{HCCH}$ 6.20 Hz), 4.85 (m, 2H, 2x$(CH_3)_2\underline{C}$HO-, $^3J_{HCCH}$ 6.21 Hz), 7.47-7.59 (m, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic ring), 7.62-7.66 (m, 1H, $\underline{H}_4$ of aromatic ring), 8.27-8.31 (m, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring); $^{13}C(CDCl_3)$ δ 23.97 (dd, 2x$(\underline{C}H_3)_2$CHO-, $^3J_{POCC}$ 3.71 Hz), 73.13 (d, 2x$(CH_3)_2\underline{C}$HO-, $^2J_{POC}$ 7.55 Hz), 128.77 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring),

129.88 (s, $\underline{C}_4$ of aromatic ring), 134.51 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 135.76 (d, P-C-$\underline{C}_1$ of aromatic ring, $^2J_{PCC}$ 63.52 Hz), 199.60 (d, P-$\underline{C}$=O, $^1J_{PC}$ 177.12 Hz); $^{31}P(CDCl_3)$ δ - 2.98 (s).

PREPARATION OF *O,O*-DIETHYL 1-OXO-3-METHOXYCARBONYLPROPANE-PHOSPHONATE

Carboxymethoxypropionyl chloride (12 g, 0.088 mol) was slowly added dropwise to a stirring solution of triethyl phosphite (12.46 g, 0.075 mol), at 0-2 ^oC, under dry nitrogen, during a period of 20 min. When the addition was completed the mixture was left to stir overnight at room temperature and then left to stand for 3 weeks. Any volatile material was removed under reduced pressure on a rotary evaporator and the bulk material remaining was distilled under reduced pressure to afford clear, free-flowing fractions of *O,O-diethyl 1-oxo-3-methoxycarbonylpropanephosphonate* (10.18 g, 53.90 %), b.p. 120-123 ^oC at 0.050-0.100 mm Hg; (Found: C, 42.96; H, 6.80. $C_9H_{17}O_6$ requires: C, 42.86; H, 6.75 %); $^1H(CDCl_3)$ δ 1.39 (t, 6H, 2x$\underline{CH}_3CH_2O$-, $^3J_{HCCH}$ 7.06 Hz), 2.65 (dt overlapping, 2H, P-C-$CH_2\underline{CH}_2$, $^3J_{HCCH}$ 6.22 Hz), 3.18 (dt overlapping, 2H, P-C-$\underline{CH}_2CH_2$, $^3J_{HCCH}$ 6.43 Hz); 3.69 (s, 3H, $CO_2\underline{CH}_3$), 4.27 (dq, overlapping, 4H, 2x$CH_3\underline{CH}_2O$-, $^3J_{HCCH}$ 7.10 Hz); $^{13}C(CDCl_3)$ δ 16.39 (d, 2x$\underline{CH}_3CH_2O$-, $^3J_{POCC}$ 5.66 Hz), 26.60 (d, P-C-$CH_2\underline{CH}_2$, $^3J_{PCCC}$ 4.91 Hz), 31.16 (d, P-C-$\underline{CH}_2CH_2$, $^2J_{PCC}$ 57.30 Hz), 51.99 (s, $CO_2\underline{CH}_3$), 64.09 (d, 2x$CH_3\underline{CH}_2O$-, $^2J_{POC}$ 6.92 Hz), 172.37 (s, $\underline{C}O_2CH_3$), 209.33 (d, P-$\underline{C}$=O, $^1J_{PC}$

172.40 Hz); $^{31}P(CDCl_3)$ δ - 3.25 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-OXO-3-METHOXYCARBONYLPROPANE-PHOSPHONATE

Carbomethoxypropionyl chloride (13 g, 0.095 mol) was slowly added dropwise to a stirring solution of tri-isopropyl phosphite (17.70 g, 0.085 mol), at 0-2 °C, under dry nitrogen, during a period of 20 min When the addition was completed the mixture was left to stir overnight at room temperature and then left to stand for 3 weeks. Any volatile material was removed under reduced pressure on a rotary evaporator and the bulk material remaining was distilled under high vacuum to afford clear free flowing fractions of *O,O-di-isopropyl 1-oxo-3-methoxycarbonylpropanephosphonate* (10.53 g, 44.24 %); b.p. 130-133 °C at 0.050-0.100 mmHg; (Found: C, 47.21; H, 7.56. $C_{11}H_{21}O_6P$ requires: C, 47.14; H, 7.50 %); $^{1}H(CDCl_3)$ δ 1.38 (d, 12H, 2x$(C\underline{H}_3)_2$CHO-, $^{3}J_{HCCH}$ 6.21 Hz), 2.63 (t, 2H, P-C-$CH_2\underline{CH}_2$, $^{3}J_{HCCH}$ 6.46 Hz), 3.18 (dt overlapping, 2H, P-C-$\underline{CH}_2CH_2$, $^{3}J_{HCCH}$ 6.50 Hz), 3.69 (s, 3H, $CO_2\underline{CH}_3$), 4.73 - 4.86 (m, 2H, 2x$(CH_3)_2\underline{CH}$O-); $^{13}C(CDCl_3)$ δ 23.97 (dd, 2x$(\underline{CH}_3)_2$CHO-, $^{3}J_{POCC}$ 4.09 Hz), 26.61 (d, P-C-$CH_2\underline{CH}_2$, $^{3}J_{PCCC}$ 4.91 Hz), 38.01 (d, P-C-$\underline{CH}_2CH_2$, $^{2}J_{PCC}$ 57.05 Hz), 51.94 (s, $CO_2\underline{CH}_3$), 73.19 (d, 2x$(CH_3)_2\underline{CH}$O-, $^{2}J_{POC}$ 7.42 Hz), 172.79 (s, $\underline{CO}_2CH_3$), 209.85 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 174.79 Hz); $^{31}P(CDCl_3)$ δ - 4.77 (s).

PREPARATION OF *O,O*-DIMETHYL 1-OXO-3-ETHOXYCARBONYLPROPANE-PHOSPHONATE

Ethyl succinyl chloride (51.26 g, 0.31 mol) was slowly added dropwise to a stirring solution of trimethyl phosphite (34.20 g, 0.28 mol), at 0-2 ^{o}C, under dry nitrogen, during a period of 30-45 min. When the addition was complete the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material left remaining, was distilled under reduced pressure, to afford colourless free flowing fractions of *O,O-dimethyl 1-oxo-3-ethoxycarbonyl propane-phosphonate* (43.08 g, 66 %); b.p. 136-140 ^{o}C at 0.10 mmHg; (Found: C, 39.79; H, 5.73. $C_8H_{15}O_6P$ requires: C, 40.34; H, 6.30 %); $^{1}H(CDCl_3)$ δ 1.24 (t, 3H, $CO_2CH_2C\underline{H}_3$, $^{3}J_{HCCH}$ 7.32 Hz), 2.70 (m, 2H, P-C-$CH_2C\underline{H}_2$), 3.17 (m, 2H, P-C-$C\underline{H}_2CH_2$), 3.90 (d, 6H, 2x$C\underline{H}_3O$-, $^{3}J_{POCH}$ 10.70 Hz, 4.18 (q, 2H, $CO_2C\underline{H}_2CH_3$, $^{3}J_{HCCH}$ 7.34 Hz); $^{13}C(CDCl_3)$ δ 14.23 (s, $CO_2CH_2\underline{C}H_3$), 26.97 (d, P-C-$CH_2\underline{C}H_2$, $^{3}J_{PCCC}$ 4.89 Hz), 38.62 (d, P-C-$\underline{C}H_2CH_2$, $^{2}J_{PCC}$ 57.36 Hz), 54.10 (d, 2x$\underline{C}H_3O$-, $^{2}J_{POC}$ 6.72 Hz), 60.85 (s, $CO_2\underline{C}H_2CH_3$), 171.88 (s, $\underline{C}O_2CH_2CH_3$), 209.18 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 171.51 Hz); $^{31}P(CDCl_3)$ δ - 1.52 (s).

PREPARATION OF *O,O*-DIETHYL 1-OXO-3-ETHOXYCARBONYLPROPANE-PHOSPHONATE

Ethyl succinyl chloride (19.75 g, 0.12 mol), was slowly added dropwise to a stirring solution of triethyl phosphite (16.60 g, 0.10 mol), at 0-2 ^{o}C, under dry nitrogen, during a period of 30-45 min. When the addition had been completed the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material left remaining, was distilled under high vacuum, to afford colourless free flowing fractions of *O,O*-diethyl 1-oxo-3-ethoxy-carbonylpropanephosphonate[81] (11.32 g, 43 %); b.p. 134-138 ^{o}C at 0.050-0.075 mmHg; (Found: C, 44.86; H, 7.35. Calc. for $C_{10}H_{19}O_6P$: C, 45.11; H, 7.14 %); $^{1}H(CDCl_3)$ δ 1.26 (t, 3H, $CO_2CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.60 Hz), 1.40 (t, 6H, 2x$\underline{CH}_3CH_2O$-, $^{3}J_{HCCH}$ 7.50 Hz), 2.63 (t, 2H, P-C-$CH_2\underline{CH}_2$, $^{3}J_{HCCH}$ 7.20 Hz), 3.15 (m, 2H, P-C-$\underline{CH}_2CH_2$, $^{3}J_{HCCH}$ 7.30 Hz), 4.00-4.43 (dq overlapping, 6H, $CO_2\underline{CH}_2CH_3$ and 2x$CH_3\underline{CH}_2O$-, $^{3}J_{HCCH}$ 7.00 Hz, $^{3}J_{POCH}$ 10.70 Hz); $^{13}C(CDCl_3)$ δ 14.40 (s, $CO_2CH_2\underline{CH}_3$), 16.64 (d, 2x$\underline{CH}_3CH_2O$-, $^{3}J_{POCC}$ 5.50 Hz), 27.28 (d, P-C-$CH_2\underline{CH}_2$, $^{3}J_{PCCC}$ 4.43 Hz), 39.06 (d, P-C-$\underline{CH}_2CH_2$, $^{2}J_{PCC}$ 58.02 Hz), 54.61 (d, 2x$CH_3\underline{CH}_2O$-, $^{2}J_{POC}$ 6.67 Hz), 61.25 (s, $CO_2\underline{CH}_2CH_3$), 172.33 (s, $\underline{CO}_2CH_2CH_3$) 210.60 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 172.06 Hz); $^{31}P(CDCl_3)$ δ - 2.65 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-OXO-3-ETHOXYCARBONYLPROPANE-PHOSPHONATE

Ethyl succinyl chloride (25.05 g, 0.15 mol) was slowly added dropwise to a stirring solution of tri-isopropyl phosphite (20.82 g, 0.10 mol), at 0-2 ^{o}C, under dry nitrogen, during a period of 30 min. When the addition was completed the mixture was left to stir overnight at room temperature. The following day, any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material remaining was distilled under reduced pressure to afford colourless free flowing fractions of *O,O-di-isopropyl 1-oxo-3-ethoxycarbonylpropanephosphonate* (11.14 g, 47.90 %); b.p. 120-122 ^{o}C at 0.050-0.100 mmHg; (Found: C, 48.72; H, 7.77. $C_{12}H_{23}O_6P$ requires: C, 48.98; H, 7.82 %); $^{1}H(CDCl_3)$ δ 1.25 (t, 3H, $CO_2CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.12 Hz), 1.32 (d, 12H, $2x(\underline{CH}_3)_2CHO$-, $^{3}J_{HCCH}$ 6.40 Hz), 2.68 (t, 2H, P-C-$CH_2\underline{CH}_2$, $^{3}J_{HCCH}$ 6.53 Hz), 3.23 (t, 2H, P-C-$\underline{CH}_2CH_2$, $^{3}J_{HCCH}$ 6.51 Hz), 4.15 (q, 2H, $CO_2\underline{CH}_2CH_3$, $^{3}J_{HCCH}$ 6.90 Hz), 4.60 - 4.86 (m, 2H, $2x(CH_3)_2\underline{CH}O$-); $^{13}C(CDCl_3)$ δ 14.17 (s, $CO_2CH_2\underline{CH}_3$), 23.66 (s, $2x(\underline{CH}_3)_2CHO$-), 28.79 (d, P-C-$CH_2\underline{CH}_2$, $^{3}J_{PCCC}$ 4.63 Hz), 38.10 (d, P-C-$\underline{CH}_2CH_2$, $^{2}J_{PCC}$ 57.17 Hz), 61.12 (s, $CO_2\underline{CH}_2CH_3$), 73.22 (d, $2x(CH_3)_2\underline{CH}O$, $^{2}J_{POC}$ 7.49 Hz), 170.03 (s, $\underline{CO}_2CH_2CH_3$), 209.82 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 174.10 Hz); $^{31}P(CDCl_3)$ δ - 4.95 (s)

PREPARATION OF *O,O*-DI-n-BUTYL 1-OXO-3-ETHOXYCARBONYLPROPANE-PHOSPHONATE

Ethyl succinyl chloride (19.75 g, 0.12 mol) was slowly added dropwise to a stirring solution of tri-n-butyl phosphite (25.0 g, 0.10 mol), at 0-2 ^{o}C under dry nitrogen, during a period of 30-40 min. When the addition was complete, the mixture was left to stir overnight at room temperature. The following day, any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material remaining was distilled under reduced pressure to afford colourless free flowing fractions of *O,O-di-n-butyl 1-oxo-3-ethoxy-carbonylpropanephosphonate* (10.90 g, 34 %); b.p. 137 ^{o}C at 0.075 mmHg; (Found: C, 51.64; H, 8.02. $C_{14}H_{27}O_6P$ requires: C, 52.17; H, 8.39 %); $^{1}H(CDCl_3)$ δ 0.95 (t, 6H, 2x$CH_3CH_2CH_2CH_2O$-, $^{3}J_{HCCH}$ 7.20 Hz), 1.25 (t, 3H, $CO_2CH_2CH_3$, $^{3}J_{HCCH}$ 7.30 Hz), 1.35-1.90 (m, 8H, 2x$CH_3CH_2CH_2CH_2O$-), 2.61 (t, 2H, P-C-CH_2CH_2, $^{3}J_{HCCH'}$ 7.00 Hz), 3.06-3.26 (m, 2H, P-C-CH_2CH_2, $^{3}J_{HCCH}$ 7.10 Hz), 4.00-4.30 (m, 6H, 2x$CH_3CH_2CH_2CH_2O$- & $CO_2CH_2CH_3$); $^{13}C(CDCl_3)$ δ 14.30 (s, $CO_2CH_2CH_3$), 16.70 (s, 2x$CH_3CH_2CH_2CH_2O$-), 19.15 (s, 2x$CH_3CH_2CH_2CH_2O$-), 28.32 (d, P-C-CH_2CH_2, $^{3}J_{PCCC}$ 4.26 Hz), 33.60 (d, 2x$CH_3CH_2CH_2CH_2O$-, $^{3}J_{POCC}$ 5.54 Hz), 39.22 (d, P-C-CH_2CH_2, $^{2}J_{PCC}$ 57.90 Hz), 58.90 (d, 2x$CH_3CH_2CH_2CH_2O$-, $^{2}J_{POC}$ 7.03 Hz), 61.60 (s, $CO_2CH_2CH_3$), 173.22 (s, $CO_2CH_2CH_3$), 210.12 (d, P-C=O, $^{1}J_{PC}$ 171.12 Hz); $^{31}P(CDCl_3)$ δ - 3.08 (s).

PREPARATION OF *O,O*-DIBENZYL 1-OXO-3-ETHOXYCARBONYLPROPANE-PHOSPHONATE

Ethyl succinyl chloride (8.38 g, 0.051 mol) was slowly added dropwise to a stirring solution of tribenzyl phosphite (17.37 g, 0.049 mol, prepared by the method of Gerrard[123]), at 0-2 ^{o}C, under dry nitrogen, during a period of 10 min. When the addition was complete, the mixture was left to stir overnight at room temperature. The following day any volatile material was removed under reduced pressure on a rotary evaporator. The bulk material was immersed in a water bath set at 80 ^{o}C and vigourously shaken under high vacuum (0.05 mmHg), for 1 h. No attempt was made to distil *O,O-dibenzyl 1-oxo-3-ethoxy-carbonylpropanephosphonate* under reduced pressure, which was afforded as a reddish-brown, viscous oily residue. (3.39 g, 54 %); (Found: C, 61.62; H, 6.02. $C_{20}H_{21}O_6P$ requires: C, 61.86; H, 5.41 %); $^{1}H(CDCl_3)$ δ 1.24 (t, 3H, $CO_2CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.40 Hz), 2.64 (m, 2H, P-C-$CH_2\underline{CH}_2$), 3.20 (m, 2H, P-C-$\underline{CH}_2CH_2$, $^{3}J_{HCCH}$, 6.75 Hz, 4.16 (q, 2H, $CO_2\underline{CH}_2CH_3$, $^{3}J_{HCCH}$ 7.01 Hz), 5.07 (d, 4H, 2x$C_6H_5\underline{CH}_2O$-, $^{3}J_{POCH}$ 11.25 Hz), 7.35 (m, 10H, 2x$C_6\underline{H}_5CH_2O$-); $^{13}C(CDCl_3)$ δ 14.13 (s, $CO_2CH_2CH_3$), 28.89 (d, P-C-$CH_2\underline{CH}_2$, $^{3}J_{PCCC}$ 4.72 Hz), 41.58 (d, P-C-$\underline{CH}_2CH_2$, $^{2}J_{PCC}$ 58.66 Hz), 60.76 (s, $CO_2\underline{CH}_2CH_3$), 66.60 (d, 2x$C_6H_5\underline{CH}_2O$-, $^{2}J_{POC}$ 7.05 Hz), 127.54 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 130.66 (s, $\underline{C}_4$ of aromatic ring), 134.12 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 136.22 (d, $\underline{C}_1$ of aromatic ring, $^{3}J_{POCC}$ 2.66 Hz), 172.21 (s, $\underline{C}O_2CH_2CH_3$), 210.67 (d, P-$\underline{C}$=O, $^{1}J_{PC}$ 173.66 Hz); $^{31}P(CDCl_3)$ δ

- 1.37 (s), (the compound was found to be 60 % pure on the basis of ^{31}P integrations).

PREPARATION OF *O,O*-DIETHYL-2-BROMOETHANEPHOSPHONATE

Triethyl phosphite (33.20 g, 0.20 mol) was added dropwise and with stirring to 1,2-dibromoethane (150 g, 0.80 mol). The mixture was heated under reflux, with stirring at 160 ^{o}C for 4 h. No attempt was made to collect the evolving ethyl bromide formed as a by-product of the reaction. The cooled solution was concentrated under reduced pressure on a rotary evaporator, to afford a viscous yellow oil. This material was distilled under high vacuum, producing *O,O*-diethyl 2-bromoethanephosphonate as a colourless free-flowing liquid. (20.10 g, 41 %); b.p. 85-87.5 ^{o}C at 0.05-0.10 mmHg (lit.[22] 75 ^{o}C at 1.0 mmHg; (Found: C, 30.01; H, 5.87. Calc. for $C_6H_{14}O_3PBr$: C, 29.39; H, 5.71 %); $^{1}H(CDCl_3)$ δ 1.36 (t, 6H, 2xCH_3CH_2O-, $^{3}J_{HCCH}$ 7.22 Hz), 2.08-2.66 (m, 2H, P-CH_2CH_2Br), 3.30-3.71 (m, 2H, P-CH_2CH_2Br), 4.11 (dq overlapping, 4H, 2xCH_3CH_2O-, $^{3}J_{HCCH}$ 7.36 Hz); $^{13}C(CDCl_3)$ δ 16.47 (d, 2xCH_3CH_2O-, $^{3}J_{POCC}$ 5.94 Hz), 24.03 (s, P-CH_2CH_2Br), 30.75 (d, P-CH_2CH_2Br, $^{1}J_{PC}$ 134.58 Hz), 61.90 (d, 2xCH_3CH_2O-, $^{2}J_{POC}$ 6.55 Hz); $^{31}P(CDCl_3)$ δ 24.95 (s).

ATTEMPTED PREPARATION OF *O,O*-DIMETHYL 1-OXOTRIFLUOROETHANE-PHOSPHONATE

Trifluoroacetyl chloride (18.79 g, 0.14 mol) condensed in a Cardice/acetone trap, was allowed to come to room temperature and volatilise into a flask containing trimethyl phosphite (17.37 g, 0.14 mol), immersed in a Cardice bath. When all the acid chloride had passed into the flask with stirring, the solution was stirred for 1 h, before the ice bath was removed. As the reaction mixture approached room temperature, considerable effervescence occurred. As this activity subsided, the clear solution was left to stir at room temperature for 12 h. Any volatile material was removed under reduced pressure on a rotary evaporator, and the clear oily residue that remained was distilled under high vacuum, to afford colourless free-flowing fractions of a fluorophosphonate derivative. Analysis showed that this material was not the desired product (12.78 g); b.p. 114-116 ^{o}C at 0.050-0.100 mmHg; (Found: C, 23.07; H, 3.99. Calc. for $C_4F_3H_6O_4P$: C, 23.30; H, 2.91 %. Calc. for (Z)-1-(dialkyoxyphosphinyl)-oxy-F-1-alkene phosphonate[68], $C_6F_2H_{12}O_7P_2$: C, 24.32; H, 4.05 %); $^{1}H(CDCl_3)$ extremely complex; $^{13}C(CDCl_3)$ extremely complex; $^{31}P(CDCl_3)$ extremely complex; $^{19}F(CDCl_3)$ extremely complex.

4.4.6 PREPARATION OF *O,O*-DIALKYL 1-HYDROXYIMINOALKANEPHOSPHONATE AND *O,O*-DIALKYL 1-HYDROXYIMINOBENZYLPHOSPHONATES

PREPARATION OF *O,O*-DIMETHYL 1-HYDROXYIMINOETHANEPHOSPHONATE

O,O-Dimethyl 1-oxoethanephosphonate (43.63 g, 0.29 mol), was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (20.50 g, 0.30 mol) and pyridine (23.73 g, 0.30 mol), dissolved in methanol (100 cm^3), in an ice-salt bath at -10 ^oC to 2 ^oC, under dry nitrogen, during a period of 1 h. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3) and extracted with dichloromethane (10 %, 50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and filtrate concentrated under reduced pressure on a rotary evaporator, to afford *O,O*-dimethyl 1-hydroxyiminoethanephosphonate[79] as a clear-yellow, viscous oily residue. When left to stand, the compound became a white, waxy solid (21.00 g, 44 %); (Found: C, 29.85; H, 6.11; N, 8.12. Calc. for $C_4H_{10}NO_4P$: C, 28.74; H, 5.99; N, 8.38 %); $^1H(CDCl_3)$ δ 2.01 (d, 3H,

P-C-C$\underline{H}_3$, $^3J_{PCCH}$ 11.41 Hz), 3.80 (d, 6H 2xC$\underline{H}_3$O-, $^3J_{POCH}$ 10.95 Hz), 11.78 (s, 1H, P-$\underline{C}$=N-OH, confirmed by absence after D_2O shake), $^{13}C(CDCl_3)$ δ 11.76 (d, P-C-$\underline{C}H_3$, $^2J_{PCC}$ 16.73 Hz), 53.55 (d, 2xC$\underline{H}_3$O-, $^2J_{POC}$ 6.35 Hz), 149.20 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 219.38 Hz); $^{31}P(CDCl_3)$ δ 14.23 (s).

PREPARATION OF *O,O*-DIETHYL 1-HYDROXYIMINOETHANEPHOSPHONATE

O,O-Diethyl 1-oxoethanephosphonate (70.61 g, 0.39 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (28.49 g, 0.41 mol) and pyridine (33.22 g, 0.42 mol), dissolved in methanol (150 cm^3), in an ice-salt bath at -10 °C to 2 °C under dry nitrogen, during a period of 1 h. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3) and extracted with dichloromethane (3x80 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x70 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure to afford *O,O*-diethyl 1-hydroxyiminoethane-phosphonate[120] as a clear-yellow, oily residue (69.97 g, 91.5 %); (Found: C, 36.16; H, 7.54; N, 7.76. Calc. for $C_6H_{14}NO_4P$: C, 36.92; H,

7.18; N, 7.18 %); $^{1}H(CDCl_3)$ δ 1.34 (t, 6H, 2x$\underline{CH_3}CH_2O$-, $^{3}J_{HCCH}$ 7.24 Hz), 2.03 (d, 3H, P-C-$\underline{CH_3}$, $^{3}J_{PCCH}$ 11.18 Hz), 4.17 (dq overlapping, 4H, 2x$CH_3\underline{CH_2}O$-, $^{3}J_{HCCH}$ 7.22 Hz), 11.67 (s, 1H, P-C=N-$\underline{OH}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 11.66 (d, P-C-$\underline{CH_3}$, $^{2}J_{PCC}$ 17.11 Hz), 16.18 (d, 2x$\underline{CH_3}CH_2O$-, $^{3}J_{POCC}$ 5.96 Hz), 63.11 (d, 2x$CH_3\underline{CH_2}O$-, $^{2}J_{POC}$ 5.85 Hz), 149.84 (d, P-$\underline{C}$=N-OH, $^{1}J_{PC}$ 218.56 Hz); $^{31}P(CDCl_3)$ δ 11.56 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-HYDROXYIMINOETHANEPHOSPHONATE

O,O-Di-isopropyl 1-oxoethanephosphonate (18.54 g, 0.089 mol), was added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (6.95 mol, 0.010 mol), and pyridine (11.87 g, 0.015 mol) dissolved in methanol (50 cm^3), in an ice-salt bath at -10 °C to 2 °C, under nitrogen, during a period of 20 min. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 30 cm^3) and extracted with dichloromethane (3x30 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3), and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent and the filtrate was concentrated

under reduced pressure on a rotary evaporator, to afford *O,O*-di-isopropyl 1-hydroxyiminoethanephosphonate[100] as a clear-yellow, viscous oily residue. Upon standing, the product became a waxy off-white solid (15.82 g, 79.6 %); (Found: C, 43.06; H, 8.13; N, 6.33. Calc. for $C_8H_{18}NO_4P$: C, 43.05; H, 8.07; N, 6.28 %); $^1H(CDCl_3)$ δ 1.34 (d, 12H, $2x(C\underline{H}_3)_2CHO$-, $^3J_{HCCH}$ 7.00 Hz), 2.02 (d, 3H, P-C-C$\underline{H}_3$, $^3J_{PCCH}$ 10.98 Hz), 4.60-4.83 (m, 2H, $2x(CH_3)_2C\underline{H}O$-), 11.12 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 11.78 (d, P-C-$\underline{C}H_3$, $^2J_{PCC}$ 16.54 Hz), 23.94 (d, $2x(\underline{C}H_3)_2CHO$-, $^3J_{POCC}$ 5.72 Hz), 71.63 (d, $2x(CH_3)_2\underline{C}HO$-, $^2J_{POC}$ 5.85 Hz), 151.14 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 211.14 Hz); $^{31}P(CDCl_3)$ δ 8.87 (s).

PREPARATION OF *O,O*-DI-n-BUTYL 1-HYDROXYIMINOETHANEPHOSPHONATE

O,O-Di-n-butyl 1-oxoethanephosphonate (27.43 g, 0.12 mol) was added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (10.42 g, 0.15 mol) and pyridine (15.82 g, 0.20 mol), dissolved in methanol (100 cm^3), in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 30 min. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 40 cm^3)

and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O-di-n-butyl 1-hydroxyiminoethanephosphonate* as a clear-yellow, viscous, oily residue. (24.10 g, 80 %); (Found C, 47.99; H, 8.91; N, 5.52. $C_{10}H_{22}NO_4P$ requires: C, 47.18; H, 8.77; N, 5.58 %); $^1H(CDCl_3)$ δ 0.93 (t, 6H, 2x$CH_3$$CH_2CH_2CH_2O$-, $^3J_{HCCH}$ 7.34 Hz), 1.35-1.48 (m, 4H, 2x$CH_3CH_2$$CH_2CH_2O$-), 1.61-1.72 (m, 4H, $CH_3CH_2CH_2$$CH_2O$-), 2.03 (d, 3H, P-C-$CH_3$, $^3J_{PCCH}$ 11.14 Hz), 4.02-4.15 (m, 4H, $CH_3CH_2CH_2$$CH_2O$-), 11.27 (s, sharp, 1H, P-C=N-OH, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 11.80 (d, P-C-CH_3, $^2J_{PCC}$ 16.42 Hz), 13.60 (s, 2x$CH_3CH_2CH_2CH_2O$-), 18.71 (s, 2x$CH_3$$CH_2CH_2CH_2O$-), 32.41 (d, $CH_3CH_2$$CH_2CH_2O$-, $^3J_{POCC}$ 6.35 Hz), 66.70 (d, 2x$CH_3CH_2CH_2$$CH_2O$-, $^2J_{POC}$ 6.29 Hz), 150.25 (d, P-C=N-OH, $^1J_{PC}$ 218.00 Hz); $^{31}P(CDCl_3)$ δ 10.68 (s).

PREPARATION OF *O,O*-DIMETHYL 1-HYDROXYIMINOPROPANEPHOSPHONATE

O,O-Dimethyl 1-oxopropanephosphonate (57.01 g, 0.29 mol), was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (21.54 g, 0.31 mol) and pyridine (26.10 g, 0.33 mol) dissolved in methanol (100 cm^3), in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 1 h. When the addition had been

completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day, volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3) and extracted with dichloromethane (3x70 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x60 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O*-dimethyl 1-hydroxyiminopropane-phosphonate[76] as a clear-yellow, viscous, oily residue. Upon standing the compound became an off-white, waxy solid (41.9 g, 80 %); (Found: C, 33.60; H, 6.61; N, 7.82. Calc. for $C_5H_{12}NO_4P$: C, 33.14; H, 6.63; N, 7.74 %) $^1H(CDCl_3)$ δ 1.12 (t, 3H, P-C-$CH_2\underline{C}H_3$, $^3J_{HCCH}$ 7.50 Hz), 2.50 (dq overlapping, 2H, P-C-$\underline{C}H_2CH_3$, $^3J_{HCCH}$ 7.74 Hz), 3.79 (d, 6H, 2x$\underline{C}H_3O$-, $^3J_{POCH}$ 11.14 Hz), 11.80 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 10.19 (d, P-C-$CH_2\underline{C}H_3$, $^3J_{PCCC}$ 1.82 Hz), 19.89 (d, P-C-$\underline{C}H_2CH_3$, $^2J_{PCC}$ 16.60 Hz), 53.45 (d, 2x$\underline{C}H_3O$-, $^2J_{POC}$ 5.72 Hz), 154.11 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 213.59 Hz); $^{31}P(CDCl_3)$ δ 13.68 (s); FAB ms (glycerol): m/z (%) 363 (2M+H, 4.58), 182 (M+H, 64.20), 109 (25), 94 (100).

PREPARATION OF *O,O*-DIETHYL 1-HYDROXYIMINOPROPANEPHOSPHONATE

O,O-Diethyl 1-oxopropanephosphonate (57.01 g, 0.29 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (21.54 g, 0.31 mol) and pyridine (26.10 g, 0.33 mol), dissolved in methanol (100 cm^3), in an ice-salt bath at -10 ^oC to 2 ^oC, under dry nitrogen, during a period of 1 h. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3), and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O*-diethyl 1-hydroxyiminopropanephosphonate[120] as a clear-yellow, viscous, oily residue. (55.27 g, 90 %); (Found: C, 39.58; H, 7.59; N, 6.07. Calc. for $C_7H_{16}NO_4P$: C, 40.19; H, 7.66; N, 6.70 %); $^1H(CDCl_3)$ δ 1.14 (t, 3H, P-C-$CH_2\underline{CH_3}$, $^3J_{HCCH}$ 7.63 Hz), 1.34 (t, 6H, 2x$\underline{CH_3}CH_2O$-, $^3J_{HCCH}$ 7.37 Hz), 2.53 (dq overlapping, 2H, P-C-$\underline{CH_2}CH_3$, $^3J_{HCCH}$ 7.37 Hz), 4.17 (dq overlapping, 4H, 2x$CH_3\underline{CH_2}O$-, $^3J_{HCCH}$ 7.25 Hz); $^{13}C(CDCl_3)$ δ 10.31 (d, P-C-$CH_2\underline{CH_3}$, $^3J_{PCCC}$ 1.76 Hz), 16.29 (d, 2x$\underline{CH_3}CH_2O$-, $^3J_{POCC}$ 6.60 Hz), 19.92 (d, P-C-$\underline{CH_2}CH_3$, $^2J_{PCC}$ 17.04 Hz), 63.12 (d, 2x$CH_3\underline{CH_2}O$-, $^2J_{POC}$

6.54 Hz), 154.61 (d, P-C=N-OH, $^{1}J_{PC}$ 213.59 Hz); $^{31}P(CDCl_3)$ δ 11.12(s).

PREPARATION OF *O,O*-DI-n-PROPYL 1-HYDROXYIMINOPROPANE-PHOSPHONATE

O,O-Di-n-propyl 1-oxopropanephosphonate (5.10 g, 0.023 mol), was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (2.78 g, 0.040 mol) and pyridine (5.00 g, 0.063 mol), dissolved in methanol (50 cm^3), in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 20 min. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 20 cm^3) and extracted with dichloromethane (2x20 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x20 cm^3), and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O-di-n-propyl 1-hydroxyiminopropane-phosphonate* as a clear-yellow, viscous, oily residue. As much residual pyridine as possible was removed by vigourous shaking under high vacuum (0.10 mmHg), for 2 h to give the crude product (1.45 g, 27 %); (Found:

C, 47.36; H, 9.06; N, 4.69. $C_9H_{20}NO_4P$ requires: C, 45.57; H, 8.44; N, 5.91 %); $^1H(CDCl_3)$ δ 0.96 (t, 6H, 2x$CH_3CH_2CH_2O$-, $^3J_{HCCH}$ 7.31 Hz), 1.15 (t, 3H, P-C-CH_2CH_3, $^3J_{HCCH}$ 7.55 Hz), 1.73 (m, 4H, 2x$CH_3CH_2CH_2O$-), 2.54 (dq overlapping, 2H, P-C-CH_2CH_3, $^3J_{HCCH}$ 7.33 Hz), 4.05 (dt overlapping, 4H, 2x$CH_3CH_2CH_2O$-, $^3J_{HCCH}$ 7.32 Hz), 10.99 (s,br, 1H, P-C=N-OH, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 10.06 (s, 2x$CH_3CH_2CH_2O$-), 10.31 (d, P-C-CH_2CH_3, $^3J_{PCCC}$ 1.38 Hz), 20.00 (d, P-C-CH_2CH_3, $^2J_{PCC}$ 16.48 Hz), 23.87 (d, 2x$CH_3CH_2CH_2O$-, $^3J_{POCC}$ 6.60 Hz), 68.45 (d, 2x$CH_3CH_2CH_2O$-, $^2J_{POC}$ 6.60 Hz), 154.74 (d, P-C=N-OH, $^1J_{PC}$ 213.66 Hz); $^{31}P(CDCl_3)$ δ 11. 61 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-HYDROXYIMINOPROPANE-PHOSPHONATE

O,O-Di-isopropyl 1-oxopropanephosphonate (69.00 g, 0.31 mol), was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (24.32 g, 0.35 mol), and pyridine (31.64 g, 0.40 mol) dissolved in methanol (100 cm^3), in an ice-salt bath at -10 ^oC to 2 ^oC, under dry nitrogen, during a period of 1 h. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3) and extracted with

dichloromethane (2x50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O*-di-isopropyl 1-hydroxyimino-propanephosphonate[100] as a clear-yellow, viscous oily residue (73.66 g, 88 %); (Found: C, 46.03; H, 8.70; N, 5.93. Calc. for $C_9H_{20}NO_4P$: C, 45.57; H, 8.44; N, 5.91 %); $^1H(CDCl_3)$ δ 1.15 (t, 3H, P-C-$CH_2\underline{CH}_3$, $^3J_{HCCH}$ 7.00 Hz), 1.31 - 1.36 (d, 12H, 2x$(\underline{CH}_3)_2$CHO-, $^3J_{HCCH}$ 7.34 Hz), 2.51 (dq overlapping, 2H, P-C-$\underline{CH}_2CH_3$, $^3J_{HCCH}$ 7.33 Hz), 4.71-4.79 (m, 2H, 2x$(CH_3)_2\underline{CH}$O-), 11.46 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 10.37 (d, P-C-$CH_2\underline{CH}_3$, $^3J_{PCCC}$ 1.57 Hz), 19.93 (d, P-C-$\underline{CH}_2CH_3$, $^2J_{PCC}$ 16.73 Hz), 23.91 (d, 2x$(\underline{CH}_3)_2$CHO-, $^3J_{POCC}$ 4.53 Hz), 71.69 (d, 2x$(CH_3)_2\underline{CH}$O-, $^2J_{POC}$ 6.16 Hz), 155.67 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 214.35 Hz); $^{31}P(CDCl_3)$ δ 9.53 (s).

PREPARATION OF *O,O*-DI-ISOBUTYL 1-HYDROXYIMINOPROPANE-PHOSPHONATE

O,O-Di-isobutyl 1-oxopropanephosphonate (12.86 g, 0.051 mol), was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (4.17 g, 0.060 mol) and pyridine (5.54 g, 0.070 mol) dissolved in methanol (50 cm^3) in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 20 min. When the

addition had been completed, the mixture was stirred at low temperature for a further hour, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 30 cm^3) and extracted with dichloromethane (2x30 cm^3). The organic extracts were combined washed with aqueous sodium hydrogen carbonate (10 %, 2x30 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O*-di-isobutyl 1-hydroxyiminopropane-phosphonate as a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigourous shaking under high vacuum (0.10 mmHg) for 2 h to give the crude product (11.49 g, 85 %); (Found: C, 52.70; H, 9.56; N, 2.76. $C_{11}H_{24}NO_4P$ requires: C, 49.81; H, 9.06; N, 5.28 %); $^1H(CDCl_3)$ δ 0.89 (d, 12H, 2x$(CH_3)_2CHCH_2O$-, $^3J_{HCCH}$ 6.70 Hz), 1.10 (t, 3H, P-C-CH_2CH_3, $^3J_{HCCH}$ 7.63 Hz), 1.83-1.99 (m, 2H, P-C-CH_2CH_3, $^3J_{HCCH}$ 6.57 Hz), 2.39-2.56 (m, 2H, 2x$(CH_3)_2CHCH_2O$-), 3.80 (dt overlapping, 4H, 2x$(CH_3)_2CHCH_2O$-), 10.73 (s, br,1H, P-C=N-OH, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 10.25 (d, P-C-CH_2CH_3, $^3J_{PCCC}$ 1.64 Hz), 18.72 (s, 2x$(CH_3)_2CHCH_2O$-,), 20.00 (d, P-C-CH_2CH_3, $^2J_{PCC}$ 15.72 Hz), 29.19 (d, 2x$(CH_3)_2CHCH_2O$-, $^3J_{POCC}$ 5.16 Hz), 72.55 (d, 2x$(CH_3)_2CHCH_2O$-, $^2J_{POC}$ 6.67 Hz), 155.47 (d, P-C=N-OH, $^1J_{PC}$ 212.40 Hz); $^{31}P(CDCl_3)$ δ 10.67 (s).

PREPARATION OF *O,O*-DIMETHYL 1-HYDROXYIMINOBUTANEPHOSPHONATE

O,O-Dimethyl 1-oxobutanephosphonate (40.00 g, 0.22 mol), was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (16.50 g, 0.24 mol) and pyridine (20.00 g, 0.25 mol) dissolved in methanol (120 cm^3) in an ice-salt bath at -10 ^oC to 2 ^oC, under dry nitrogen, during a period of 1 h. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 60 cm^3) and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-dimethyl 1-hydroxyiminobutane-phosphonate[75] as a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigourous shaking under high vacuum (0.10 mmHg) for 2 h to give the crude product (36.50 g, 84 %); (Found: C, 36.01; H, 7.10; N, 7.07. Calc. for $C_6H_{14}NO_4P$: C, 36.92; H, 7.18; N, 7.18 %); $^1H(CDCl_3)$ δ 0.95 (t, 3H, P-C-$CH_2CH_2\underline{CH}_3$, $^3J_{HCCH}$ 7.30 Hz), 1.61 (m, 2H, P-C-$CH_2\underline{CH}_2CH_3$, $^3J_{HCCH}$ 7.50 Hz), 2.49 (m, 2H, P-C-$\underline{CH}_2CH_2CH_3$, $^3J_{HCCH}$ 7.60 Hz), 3.79 (d, 6H, 2x$\underline{CH}_3O$-, $^3J_{POCH}$ 11.10 Hz), 11.60 (s, br,

1H, P-C=N-O<u>H</u>, confirmed by absence after D_2O shake), $^{13}C(CDCl_3)$ δ 14.21 (s, P-C-$CH_2$$\underline{C}$$H_2CH_3$), 19.25 (d, P-C-$CH_2\underline{C}H_2CH_3$, $^3J_{PCCC}$ 1.19 Hz), 28.38 (d, P-C-$\underline{C}H_2CH_2CH_3$, $^2J_{PCC}$ 15.92 Hz), 53.41 (d, 2x$\underline{C}H_3O$-, $^2J_{POC}$ 6.34 Hz), 153.61 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 212.84 Hz); $^{31}P(CDCl_3)$ δ 13.92 (s).

PREPARATION OF *O,O*-DIETHYL 1-HYDROXYIMINOBUTANEPHOSPHONATE

O,O-Diethyl 1-oxobutanephosphonate (49.00 g, 0.23 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (16.13 g, 0.25 mol), and pyridine (20.50 g, 0.26 mol) dissolved in methanol (100 cm^3) in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 1 h. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3), and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-diethyl 1-hydroxyiminobutane-phosphonate[120] as a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigourous shaking under

high vacuum (0.10 mmHg) for 2 h to give the product (49.00 g, 94 %); (Found: C, 40.56; H, 8.06; N, 5.40. Calc. for $C_8H_{18}NO_4P$: C, 40.05; H, 8.28; N, 6.27 %); $^1H(CDCl_3)$ δ 0.94 (t, 3H, P-C-$CH_2CH_2\underline{CH_3}$, $^3J_{HCCH}$ 7.30 Hz), 1.33 (t, 6H, 2x$\underline{CH_3}CH_2O$-, $^3J_{HCCH}$ 7.40 Hz), 1.67 (m, 2H, P-C-$CH_2\underline{CH_2}CH_3$), 2.50 (m, 2H, P-C-$\underline{CH_2}CH_2CH_3$), 4.19 (dq overlapping, 4H, 2x$CH_3\underline{CH_2}O$-, $^3J_{HCCH}$ 7.28 Hz), 11.25 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 14.28 (s, P-C-$CH_2CH_2\underline{CH_3}$), 16.30 (d, 2x$\underline{CH_3}CH_2O$-, $^3J_{POCC}$ 6.16 Hz), 19.42 (d, P-C-$CH_2\underline{CH_2}CH_3$, $^3J_{PCCC}$ 1.57 Hz), 28.45 (d, P-C-$CH_2\underline{CH_2}CH_3$ $^2J_{PCC}$ 16.16 Hz), 63.02 (d, 2x$CH_3\underline{CH_2}O$-, $^2J_{POC}$ 5.91 Hz), 153.63 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 213.66 Hz); $^{31}P(CDCl_3)$ δ 11.12 (s).

PREPARATION OF *O,O*-DI-n-PROPYL 1-HYDROXYIMINOBUTANE-PHOSPHONATE

O,O-Di-n-propyl 1-oxobutanephosphonate (5.50 g, 0.023 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (2.78 g, 0.040 mol) and pyridine (5.00 g, 0.063 mol), dissolved in methanol (50 cm^3) in an ice-salt bath, under dry nitrogen, during a period of 1 h. When the addition was complete the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 20 cm^3) and extracted with dichloromethane (2x20 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x20 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O-di-n-propyl 1-hydroxyimino-butanephosphonate* as a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the crude product (3.50 g, 60 %); (Found: C, 45.80; H, 8.76; N, 5.63. $C_{10}H_{22}NO_4P$ requires: C, 47.81; H, 8.77; N, 5.58 %); $^1H(CDCl_3)$ δ 0.96 (t, 9H, 2x$CH_3CH_2CH_2O$- & P-C-$CH_2CH_2CH_3$, $^3J_{HCCH}$ 7.38 Hz), 1.58-1.80 (m, 6H, 2x$CH_3CH_2CH_2O$- &

P-C-$CH_2$$CH_2$$CH_3$), 2.44-2.56 (m, 2H, P-C-$CH_2$$CH_2$$CH_3$), 3.98-4.13 (m, 4H, 2x$CH_3CH_2CH_2O$-), 11.05 (s, br, 1H, P-C=N-OH, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 10.01 (s, P-C-$CH_2CH_2CH_3$), 10.04 (s, 2x$CH_3CH_2CH_2O$-), 14.30 (s, P-C-$CH_2CH_2CH_3$), 23.79 (d, 2x$CH_3CH_2CH_2O$-, $^3J_{POCC}$ 6.48 Hz), 28.47 (d, P-C-$CH_2CH_2CH_3$, $^2J_{PCC}$ 16.10 Hz), 68.27 (d, 2x$CH_3CH_2CH_2O$-, $^2J_{POC}$ 6.60 Hz), 154.31 (d, P-C=N-OH, $^1J_{PC}$ 211.90 Hz); $^{31}P(CDCl_3)$ δ 11.70 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-HYDROXYIMINOBUTANEPHOSPHONATE

O,O-Di-isopropyl 1-oxobutanephosphonate (31.01 g, 0.13 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (10.42 g, 0.15 mol) and pyridine (13.43 g, 0.17 mol), dissolved in methanol (100 cm^3), in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 30 min. When the addition had been completed the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3) and extracted with dichloromethane (2x 50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure

on a rotary evaporator to afford *0,0-di-isopropyl 1-hydroxyiminobutane-phosphonate* as a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the product (21.21 g, 82.5 %); (Found: C, 48.12; H, 9.07; N, 5.69. $C_{10}H_{22}NO_4P$ requires: C, 47.81; H, 8.77; N, 5.58 %); $^{1}H(CDCl_3)$ δ 0.95 (t, 3H, P-C-$CH_2CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.35 Hz), 1.33 (d, 12H, 2x$(\underline{CH}_3)_2$CHO-, $^{3}J_{HCCH}$ 6.86 Hz), 1.55-1.70 (m, 2H, P-C-$CH_2\underline{CH}_2CH_3$), 2.34-2.54 (m, 2H, P-C-$\underline{CH}_2CH_2CH_3$), 4.60-4.88 (m, 2H, 2x$(CH_3)_2\underline{CH}$O-), 11.05 (s, sharp, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 14.35 (s, P-C-$CH_2CH_2\underline{CH}_3$), 19.34 (s, P-C-$CH_2\underline{CH}_2CH_3$), 24.05 (d, 2x$(\underline{CH}_3)_2$CHO-, $^{3}J_{POCC}$ 3.82 Hz), 28.47 (d, P-C-$\underline{CH}_2CH_2CH_3$, $^{2}J_{PCC}$ 16.04 Hz), 71.70 (d, 2x$(CH_3)_2\underline{CH}$O- $^{2}J_{POC}$ 6.45 Hz), 154.87 (d, P-$\underline{C}$=N-OH, $^{1}J_{PC}$ 213.78 Hz); $^{31}P(CDCl_3)$ δ 9.55 (s).

PREPARATION OF *0,0*-DI-n-BUTYL 1-HYDROXYIMINOBUTANEPHOSPHONATE

0,0-Di-n-butyl 1-oxobutanephosphonate (45 g, 0.17 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (14 g, 0.20 mol) and pyridine (20 g, 0.25 mol) dissolved in methanol (100 cm^3) in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 1 h. When the addition had been completed, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day, volatile material was removed under reduced

pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 100 cm^3) and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *0,0-di-n-butyl 1-hydroxyiminobutane-phosphonate* as a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the crude product (43.50 g, 91 %); (Found: C, 49.34; H, 9.16; N, 4.86. $C_{12}H_{26}NO_4P$ requires: C, 51.61; H, 9.32; N, 5.02 %); $^1H(CDCl_3)$ δ 0.93 (2t overlapping, 9H, 2x$CH_3CH_2CH_2CH_2O$- & P-C-$CH_2CH_2CH_3$, $^3J_{HCCH}$ 7.30 Hz), 1.37-1.48 (m, 4H, 2x$CH_3CH_2CH_2CH_2O$- , $^3J_{HCCH}$ 7.49 Hz), 1.58-1.72 (m, 6H, 2x$CH_3CH_2CH_2CH_2O$ & P-C-$CH_2CH_2CH_3$), 2.43-2.52 (m, 2H, P-C-$CH_2CH_2CH_3$, $^3J_{HCCH}$ 7.00 Hz), 3.67 (m, 4H, 2x$CH_3CH_2CH_2CH_2O$-), 11.53 (s, br, 1H, P-C=N-OH, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 13.62 (s, 2x$CH_3CH_2CH_2CH_2O$-), 14.30 (s, P-C-$CH_2CH_2CH_3$), 18.81 (d, P-C-$CH_2CH_2CH_3$, $^3J_{PCCC}$ 1.76 Hz), 19.12 (s, 2x$CH_3CH_2CH_2CH_2O$-), 28.50 (d, P-C-$CH_2CH_2CH_3$, $^2J_{PCC}$ 16.10 Hz), 32.52 (d, 2x$CH_3CH_2CH_2CH_2O$, $^3J_{POCC}$ 4.97 Hz), 66.61 (d, 2x$CH_3CH_2CH_2CH_2O$-, $^2J_{POC}$ 5.91 Hz) 153.84 (d, P-C=N-OH, $^1J_{PC}$ 211.39 Hz); $^{31}P(CDCl_3)$ δ 11.12 (s).

ATTEMPTED PREPARATION OF *O,O*-DIMETHYL 1-HYDROXYIMINOCYCLOPROPYL-METHANEPHOSPHONATE

O,O-Dimethyl 1-oxocyclopropylmethanephosphonate (0.31 g, 0.058 mol), was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (4.17 g, 0.060 mol) and pyridine (4.90 g, 0.062 mol) dissolved in methanol (50 cm^3), in an ice-salt bath at -10 ^oC to 2 ^oC, under dry nitrogen, during a period of 20 min. When the addition had been completed, the mixture was stirred for a further hour at low temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 20 cm^3) and extracted with dichloromethane (3x30 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x40 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the crude product. Upon prolonged standing at room temperature the material became an off-white sticky solid (7.94 g); (Found: C, 36.92; H, 6.25; N, 5.37. $C_6H_{12}NO_4P$ requires: C, 37.31; H, 6.22; N, 7.25 %); $^1H(CDCl_3)$ δ 0.76-1.10 (m), 1.12-1.31 (m), 1.72-1.82 (m), 2.10-2.28 (m), 2.61-2.71 (m), 3.75-3.91

(dd, 2xCH_3O-), the signals were more complex than that expected on the basis of the putative structure of the target molecule indicating that the material isolated was a mixture; $^{13}C(CDCl_3)$ spectrum could not be positively interpreted confirming the observations made in the ^{1}H N.M.R. spectrum; $^{31}P(CDCl_3)$ δ -0.43, +9.36, +12.26, +22.36 (further confirmation that the material isolated was a mixture).

PREPARATION OF *O,O*-DIETHYL 1-HYDROXYIMINOCYCLOPROPYL-METHANEPHOSPHONATE

O,O-Diethyl 1-oxocyclopropylmethanephosphonate (19.37 g, 0.094 mol), was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (6.67 g, 0.096 mol) and pyridine (7.75 g, 0.098 mol) dissolved in methanol (75 cm^3), in an ice-salt bath at -10 ^{o}C to 2 ^{o}C, under dry nitrogen, during a period of 30 min. When the addition had been completed the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 30 cm^3) and extracted with dichloromethane (3x40 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x40 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the

drying agent and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O-diethyl 1-hydroxyiminocyclopropyl-methanephosphonate* as a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the product (20.80 g, 100 %); (Found: C, 43.33; H, 7.44; N, 6.58. $C_8H_{16}NO_4P$ requires: C, 43.44; H, 7.24; N, 6.34 %); $^1H(CDCl_3)$ δ 0.73-0.91 (m, 4H, C$\underline{H}_2$'s of cyclopropane ring), 1.33 (t, 6H, 2xC$\underline{H}_3$CH$_2$O-, $^3J_{HCCH}$ 7.13 Hz), 2.11-2.29 (m, 1H, C$\underline{H}$ of cyclopropane ring), 4.07-4.31 (m, 4H, 2xCH$_3$C$\underline{H}_2$O-), 11.39 (s, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 5.97 (s, C$\underline{H}_2$'s of cyclopropane ring), 8.40 (C$\underline{H}$ of cyclopropane ring, $^2J_{PCC}$ 18.43 Hz), 16.55 (d, 2xC$\underline{H}_3$CH$_2$O-, $^3J_{POCC}$ 4.66 Hz), 63.06 (d, 2xCH$_3$C$\underline{H}_2$O-, $^2J_{POC}$ 6.04 Hz), 154.12 (d, P-C$\underline{=}$N-OH, $^1J_{PC}$ 215.42 Hz); $^{31}P(CDCl_3)$ δ 9.03 (s).

PREPARATION OF *O,O*-DIMETHYL 1-HYDROXYIMINOBENZYLPHOSPHONATE

O,O-Dimethyl 1-oxobenzylphosphonate (93.47 g, 0.44 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (31.97 g, 0.46 mol) and pyridine (37.97 g, 0.46 mol), dissolved in methanol (100 cm^3), in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 1 h. When the addition had been completed the mixture was stirred for a further hour at low temperature.

The following day volatile material was removed under reduced

pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 60 cm^3) and extracted with dichloromethane (3x70 cm^3). The organic extracts were combined, washed with sodium hydrogen carbonate (10 %, 2x70 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O*-dimethyl 1-hydroxyiminobenzyl-phosphonate[79] as a deep-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h. On prolonged standing at room temperature, the product became a light brown gelatinous solid (85.7 g, 86 %); (Found: C, 47.00; H, 5.26; N, 6.03. Calc. for $C_9H_{12}NO_4P$: C, 47.16; H, 5.24; N, 6.11 %); $^1H(CDCl_3)$ δ 3.71 (d, 6H, 2x$\underline{C}H_3O$-, $^3J_{POCH}$ 11.66 Hz), 7.24-8.05 (m, 5H, $C_6\underline{H}_5$), 11.60 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 53.16 (d, 2x$\underline{C}H_3O$-, $^2J_{POC}$ 6.10 Hz), 128-130 (s, $\underline{C}_2$, $\underline{C}_3$, $\underline{C}_4$, $\underline{C}_5$ & $\underline{C}_6$ of aromatic ring), 144.91 (d, P-C-$\underline{C}_1$ of aromatic ring, $^2J_{PCC}$ 60.82 Hz), 149.91 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 220.07 Hz); $^{31}P(CDCl_3)$ δ 7.48 (s).

PREPARATION OF *O,O*-DIETHYL 1-HYDROXYIMINOBENZYLPHOSPHONATE

O,O-Diethyl 1-oxobenzylphosphonate (42.53 g, 0.18 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (12.51 g, 0.18 mol) and pyridine (14.63 g, 0.185 mol),

dissolved in methanol (100 cm^3) in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 1 h. When the addition had been completed the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3) and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-diethyl 1-hydroxyiminobenzyl-phosphonate[121] as a clear-yellow, viscous oily residue. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the product (41.23 g, 91 %); (Found: C, 51.19; H, 6.20; N, 5.37. Calc. for $C_{11}H_{16}NO_4P$: C, 51.36; H, 6.23; N, 5.45 %); $^1H(CDCl_3)$ δ 1. 26 (t, 6H, 2x$\underline{H}_3CH_2O$-, $^3J_{HCCH}$ 7.14 Hz), 4.07-4.15 (m, 4H, 2x$CH_3\underline{H}_2O$-), 7.33-7.46 (m, 3H, $\underline{H}_3$, $\underline{H}_4$, $\underline{H}_5$ of aromatic ring), 7.55-7.61 (m, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring), 11.98 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 16.13 (d, 2x$\underline{C}H_3CH_2O$-, $^3J_{POCC}$ 5.07 Hz), 63.43 (d, 2x$CH_3\underline{C}H_2O$-, $^2J_{POC}$ 5.85 Hz), 128.17 (s, $\underline{C}_3$ & $\underline{C}_4$ of aromatic ring), 128.80 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring , $^3J_{PCCC}$ 4.78 Hz), 129.88 (s, $\underline{C}_4$ of aromatic ring), 133.97 (d, $\underline{C}_1$ of aromatic ring, $^2J_{PCC}$ 20.00 Hz), 151.12 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 217.81 Hz);

$^{31}P(CDCl_3)$ δ 8.87 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-HYDROXYIMINOBENZYLPHOSPHONATE

O,O-Di-isopropyl 1-oxobenzylphosphonate (43.04 g, 0.16 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (11.47 g, 0.165 mol) and pyridine (13.45 g, 0.170 mol), dissolved in methanol (100 cm^3), in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 1 h. When the addition had been completed, the mixture was stirred for a further hour at low temperature before being left to stir overnight at room temperature.

The following day any volatile material was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3) and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O-di-isopropyl 1-hydroxyiminobenzylphosphonate* as a yellow oil. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the product (43.00 g, 95 %); (Found: C, 54.72; H, 7.13; N, 4.96. $C_{13}H_{20}NO_4P$ requires: C, 54.74; H, 7.02; N, 4.91 %); $^1H(CDCl_3)$ δ 1.25 (dd, 12H, 2x$(CH_3)_2$CHO-, $^3J_{HCCH}$ 6.15 Hz), 4.68-4.84 (m, 2H,

2x$(CH_3)_2\underline{C}H$O-), 7.28-7.41 (m, 3H $\underline{H}_3$, $\underline{H}_4$, $\underline{H}_5$ of aromatic ring), 7.60-7.73 (m, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring), 11.28 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 23.76 (dd, 2x$(\underline{C}H_3)_2$CHO-, $^3J_{POCC}$ 4.64 Hz), 72.29 (d, 2x$(CH_3)_2\underline{C}$HO-, $^2J_{POC}$ 6.43 Hz), 128.00 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 128.98 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^3J_{PCCC}$ 4.78 Hz), 129.19 (s, $\underline{C}_4$ of aromatic ring), 130.01 (d, P-C-$\underline{C}_1$ of aromatic ring, $^2J_{PCC}$ 18.30 Hz), 151.43 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 219.32 Hz); $^{31}P(CDCl_3)$ δ 7.05 (s).

PREPARATION OF *O,O*-DIETHYL 1-HYDROXYIMINO-3-METHOXYCARBONYL-PROPANEPHOSPHONATE

O,O-Diethyl 1-oxo-3-methoxycarbonylpropanephosphonate (8.00 g, 0.032 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (2.29 g, 0.033 mol) and pyridine (2.69 g, 0.034 mol), dissolved in methanol (50 cm^3) in an ice-salt bath at -10 ^oC to 2 ^oC under dry nitrogen, during a period of 20 min. When the addition was complete, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 20 cm^3) and extracted with dichloromethane (3x40 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %,

2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h. The product, *O,O-diethyl 1-hydroxyimino-3-methoxycarbonylpropanephosphonate* was afforded as a clear yellow viscous oil (6.13 g, 71.8 %); (Found: C, 40.62; H, 6.80; N, 5.20. $C_9H_{18}NO_6P$ requires: C, 40.45; H, 6.74; N, 5.24 %); $^1H(CDCl_3)$ δ 1.34 (t, 6H, 2x$\underline{CH_3}CH_2O$-, $^3J_{HCCH}$ 7.32 Hz), 2.59-2.87 (m, 4H, P-C-$\underline{CH_2}\underline{CH_2}$), 3.69 (s, 3H, $CO_2\underline{CH_3}$), 4.17 (m, 4H, 2x$CH_3\underline{CH_2}O$-), 11.61 (s, sharp, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 16.11 (d, 2x$\underline{CH_3}CH_2O$-, $^3J_{POCC}$ 6.48 Hz), 21.72 (d, P-C-$\underline{CH_2}CH_2$, $^2J_{PCC}$ 16.92 Hz), 29.64 (d, P-C-$CH_2\underline{CH_2}$, $^3J_{PCCC}$ 1.57 Hz), 51.64 (s, $CO_2\underline{CH_3}$), 63.09 (d, 2x$CH_3\underline{CH_2}O$-, $^2J_{POC}$ 6.23 Hz), 151.80 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 216.87 Hz), 172.75 (s, $\underline{CO_2}CH_3$); $^{31}P(CDCl_3)$ δ 10.06 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-HYDROXYIMINO-3-METHOXYCARBONYLPROPANEPHOSPHONATE

O,O-Di-isopropyl 1-oxo-3-methoxycarbonylpropanephosphonate (8.74 g, 0.031 mol), was slowly added dropwise to a mixture of hydroxylamine hydrochloride (2.29 g, 0.033 mol) and pyridine (2.69 g, 0.034 mol), dissolved in methanol (50 cm^3), in an ice-bath at -10 °C to 2 °C, under dry nitrogen, during a period of 20 min. When the addition

was complete, the mixture was stirred for a further hour at low temperature, before being left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 20 cm^3) and extracted with dichloromethane (3x40 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The filtrate obtained from filtration to remove the drying agent was concentrated under reduced pressure on a rotary evaporator, to afford *O,O-di-isopropyl 1-hydroxyimino-3-methoxycarbonylpropanephosphonate* as a clear yellow viscous oily residue. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the product (6.50 g, 71.08 %); (Found: C, 44.76; H, 7.46; N, 4.94. $C_{11}H_{22}NO_6P$ requires: C, 44.75; H, 7.46; N, 4.75 %); $^1H(CDCl_3)$ δ 1.33 (d, 12H, 2x$(C\underline{H}_3)_2$CHO-, $^3J_{HCCH}$ 6.71 Hz), 2.59-2.86 (m, 4H, P-C-$C\underline{H}_2C\underline{H}_2$), 3.86 (s, 3H, $CO_2C\underline{H}_3$), 4.72-4.85 (m, 2H, 2x$(CH_3)_2C\underline{H}$O-), 11.19 (s, sharp, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 21.83 (d, P-C-$\underline{C}H_2CH_2$, $^2J_{PCC}$ 16.67 Hz), 23.89 (dd, 2x$(\underline{C}H_3)_2$CHO-, $^3J_{POCC}$ 4.37 Hz), 29.78 (d, P-C-$CH_2\underline{C}H_2$, $^3J_{PCCC}$ 1.70 Hz), 51.75 (s, $CO_2\underline{C}H_3$), 72.01 (d, 2x$(CH_3)_2\underline{C}$HO-, $^2J_{POC}$ 6.04 Hz), 152.85 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 218.25 Hz), 172.97 (s, $\underline{C}O_2CH_3$); $^{31}P(CDCl_3)$ δ 8.05 (s).

PREPARATION OF *O,O*-DIMETHYL 1-HYDROXYIMINO-3-ETHOXYCARBONYL-PROPANEPHOSHONATE

O,O-Dimethyl 1-oxo-3-ethoxycarbonylpropanephosphonate (74.82 g, 0.31 mol), was slowly added dropwise, and with stirring to a mixture of hydroxylamine hydrochloride (36.98 g, 0.53 mol) and pyridine (44.23 g, 0.56 mol), dissolved in methanol (120 cm^3), in an ice-salt bath at -10 ^oC to 2 ^oC, under dry nitrogen, during a period of 1 h. When the addition was complete, the mixture was stirred for a further hour at low temperature, and then left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under vacuum on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3), and extracted with dichloromethane (5x40 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x40 cm^3), and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent and the filtrate concentrated under reduced pressure on a rotary evaporator. *O,O-Dimethyl 1-hydroxyimino-3-ethoxy-carbonylpropanephosphonate* was afforded as a clear-yellow, thick viscous oil. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10-0.20 mmHg), for 2 h to give the product (63.59 g, 80 %); (Found: C, 38.12; H, 6.26; N, 5.60. $C_8H_{16}NO_6P$ requires: C, 37.94; H, 6.32; N, 5.53 %); $^1H(CDCl_3)$ δ 1.24 (t, 3H, $CO_2CH_2\underline{CH_3}$, $^3J_{HCCH}$ 7.30 Hz), 2.64 (m, 4H, P-C-$\underline{CH_2}\underline{CH_2}$), 3.76 (d, 6H,

2x$\underline{C}H_3O$-, $^3J_{POCH}$ 10.70 Hz), 4.10 (q, 2H, $CO_2\underline{C}H_2CH_3$, $^3J_{HCCH}$ 6.70 Hz), 11.55 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 14.23 (s, $CO_2CH_2\underline{C}H_3$), 21.96 (d, P-C-$\underline{C}H_2CH_2$, $^2J_{PCC}$ 17.08 Hz), 30.06 (s, P-C-$CH_2\underline{C}H_2$), 53.60 (d, 2x$\underline{C}H_3O$-, $^2J_{POC}$ 6.10 Hz), 60.73 (s, $CO_2\underline{C}H_2CH_3$), 151.31 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 217.29 Hz), 172.52 (s, $\underline{C}O_2CH_2CH_3$); $^{31}P(CDCl_3)$ δ 10.52 (s); FAB ms (3-NOBA): m/z (%) 507 (2M+H, 1.67), 254 (M+H, 72.5), 127 (100), 109 (52.9).

PREPARATION OF *O,O*-DIETHYL 1-HYDROXYIMINO-3-ETHOXY-CARBONYLPROPANEPHOSPHONATE

O,O-Diethyl 1-oxo-3-ethoxycarbonylpropanephosphonate (19.0 g, 0.070 mol) was slowly added dropwise and with stirring, to a mixture of hydroxylamine hydrochloride (6.95 g, 0.10 mol) and pyridine (11.10 g, 0.14 mol) dissolved in methanol (100 cm^3), in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 30 min. When the addition had been completed, the mixture was stirred for a further hour at low temperature and then left to stir overnight at room temperature .

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3), and extracted with dichloromethane (3x40 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x40 cm^3) and dried over anhydrous magnesium sulphate. The

solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator. *O,O*-Diethyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate[81] was afforded as a clear-yellow thick viscous oil. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.060 mmHg) for 2 h to give the crude product (15.68 g, 78 %); (Found: C, 41.37; H, 7.04; N, 4.92. Calc. for $C_{10}H_{20}NO_6P$ C, 45.11; H, 7.52; N, 5.26 %); $^{1}H(CDCl_3)$ δ 1.16-1.46 (2xt overlapping, 9H, 2x$\underline{CH_3}CH_2O$- & $CO_2CH_2\underline{CH_3}$, $^{3}J_{HCCH}$ 7.26 Hz), 2.46-3.04 (m, 4H, P-C-$\underline{CH_2}\underline{CH_2}$), 4.00-4.40 (dq overlapping with q, 6H, 2x$CH_3\underline{CH_2}O$- & $CO_2\underline{CH_2}CH_3$, $^{3}J_{HCCH}$ 7.20 Hz), 11.60 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 14.20 (s, $CO_2CH_2\underline{CH_3}$), 16.63 (d, 2x$\underline{CH_3}CH_2O$-, $^{3}J_{POCC}$ 6.35 Hz), 22.34 (d, P-C-$\underline{CH_2}CH_2$, $^{2}J_{PCC}$ 16.98 Hz), 30.86 (d, P-C-$CH_2\underline{CH_2}$, $^{3}J_{PCCC}$ 1.45 Hz), 60.65 (s, $CO_2\underline{CH_2}CH_3$), 64.05 (d, 2x$CH_3\underline{CH_2}O$-, $^{2}J_{POC}$ 5.98 Hz), 152.35 (d, P-$\underline{C}$=N-OH, $^{1}J_{PC}$ 217.05 Hz), 172.56 (s, $\underline{CO_2}CH_2CH_3$); $^{31}P(CDCl_3)$ δ 10.27 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-HYDROXYIMINO-3-ETHOXY-CARBONYLPROPANEPHOSHONATE

O,O-Di-isopropyl 1-oxo-3-ethoxycarbonylpropanephosphonate (11.22 g, 0.038 mol) was slowly added dropwise and with stirring, to a mixture of hydroxylamine hydrochloride (2.78 g, 0.040 mol) and pyridine (3.32 g, 0.042 mol) dissolved in methanol (60 cm^3) in an ice-salt bath

at -10 to 2 °C, under dry nitrogen, during a period of 30 min. When the addition had been completed, the mixture was stirred for a further hour at low temperature and then left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 50 cm^3) and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x50 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator. *O,O-Di-isopropyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate* was afforded as a clear-yellow viscous oil. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h to give the crude product (8.04 g, 68 %); (Found: C, 47.90; H, 7.51; N, 3.33. $C_{21}H_{24}NO_6P$ requires: C, 46.60; H, 7.77; N, 4.53 %); $^1H(CDCl_3)$ δ 1.21 (t, 3H, $CO_2CH_2\underline{CH}_3$, $^3J_{HCCH}$ 7.24 Hz), 1.33-1.37 (d, 12H, $2x(\underline{CH}_3)_2CHO$-, $^3J_{HCCH}$ 7.32 Hz), 2.80 (m, 4H, P-C-$\underline{CH}_2\underline{CH}_2$), 4.16 (q, 2H, $CO_2\underline{CH}_2CH_3$, $^3J_{HCCH}$ 7.23 Hz), 4.75-4.81 (m, 2H, $2x(CH_3)_2\underline{CH}O$-), 11.53 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 14.33 (s, $CO_2CH_2\underline{CH}_3$), 22.61 (d, $2x(\underline{CH}_3)_2CHO$-, $^3J_{POCC}$ 4.46 Hz), 23.75 (d, P-C-$\underline{CH}_2CH_2$, $^2J_{PCC}$ 17.09 Hz), 30.23 (d, P-C-$CH_2\underline{CH}_2$, $^3J_{PCCC}$ 1.36 Hz), 60.78 (s, $CO_2\underline{CH}_2CH_3$), 72.39 (d, $2x(CH_3)_2\underline{CH}O$-, $^2J_{POC}$ 6.32 Hz), 152.38 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 216.79 Hz), 171.96 (s, $\underline{CO}_2CH_2CH_3$); $^{31}P(CDCl_3)$

δ 10.93 (s).

PREPARATION OF DI-n-BUTYL 1-HYDROXYIMINO-3-ETHOXY-CARBONYLPROPANEPHOSPHONATE

O,O-Di-n-butyl 1-oxo-3-ethoxycarbonylpropanephosphonate (7.07 g, 0.022 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (1.67 g, 0.024 mol) and pyridine (2.06 g, 0.026 mol), dissolved in methanol (50 cm^3) in an ice-salt bath at -10 ^oC to 2 ^oC, under dry nitrogen, during a period of 20 min. When the addition had been completed, the mixture was stirred for a further hour at low temperature and then left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under vacuum on a rotary evaporator. The thick viscous residue formed was treated with hydrochloric acid (10 %, 30 cm^3) and extracted with dichloromethane (3x30 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 2x20 cm^3) and dried over magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h. Crude *O,O-Di-n-butyl 1-hydroxyimino 3-ethoxycarbonylpropanephosphonate* was afforded as a clear-yellow thick viscous oil (7.40 g, 100 %); (Found: C,

55.08; H, 9.18; N, 4.59. $C_{14}H_{28}NO_6P$ requires: C, 55.40; H, 9.36; N, 4.66 %); $^1H(CDCl_3)$ δ 0.92 (t, 6H, 2x$CH_3CH_2CH_2CH_2O$-, $^3J_{HCCH}$ 7.05 Hz), 1.25 (t, 3H, $CO_2CH_2CH_3$, $^3J_{HCCH}$ 7.23 Hz), 1.42-1.86 (m, 8H, 2x$CH_3CH_2CH_2CH_2O$-), 2.45-3.00 (m, 4H, P-C-CH_2CH_2), 4.00-4.30 (m, 6H, 2x$CH_3CH_2CH_2CH_2O$- & $CO_2CH_2CH_3$), 11.70 (s, br, 1H, P-C=N-OH, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 14.46 (s, $CO_2CH_2CH_3$), 16.74 (s, 2x$CH_3CH_2CH_2CH_2O$-), 19.12 (s, 2xCH_3CH_2- CH_2CH_2O-), 24.06 (d, P-C-CH_2CH_2, $^2J_{PCC}$ 17.11 Hz), 30.09 (d, P-C-CH_2CH_2, $^3J_{PCCC}$ 1.41 Hz), 34.21 (d, 2x$CH_3CH_2CH_2CH_2O$-, $^3J_{POCC}$ 5.89 Hz), 61.92 (s, $CO_2CH_2CH_3$), 63.26 (d, 2x$CH_3CH_2CH_2CH_2O$-, $^2J_{POC}$ 6.87 Hz), 151.83 (d, P-C=N-OH, $^1J_{PC}$ 217.05 Hz), 172.03 (s, $CO_2CH_2CH_3$); $^{31}P(CDCl_3)$ δ 11.62 (s).

PREPARATION OF *O,O*-DIBENZYL 1-HYDROXYIMINO-3-ETHOXY-CARBONYLPROPANEPHOSPHONATE

Crude *O,O*-Dibenzyl 1-oxo-3-ethoxycarbonylpropanephosphonate (1.47 g, 0.012 mol) was slowly added dropwise and with stirring to a mixture of hydroxylamine hydrochloride (1.67 g, 0.024 mol) and pyridine (1.98 g, 0.025 mol) dissolved in methanol (30 cm^3), in an ice-salt bath at -10 °C to 2 °C, under dry nitrogen, during a period of 5 min. When the addition had been completed, the mixture was stirred for a further hour at low temperature and then left to stir overnight at room temperature.

The following day, as much volatile material as possible was removed under reduced pressure on a rotary evaporator. The thick viscous residue formed was extracted with hydrochloric acid (10 %, 20 cm^3) and extracted with dichloromethane (3x30 cm^3). The organic extracts were combined, washed with aqueous sodium hydrogen carbonate (10 %, 20 cm^3) and dried over anhydrous magnesium sulphate. The solution was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator. As much residual pyridine as possible was removed by vigorous shaking under high vacuum (0.10 mmHg) for 2 h. Crude *0,0-Dibenzyl 1-hydroxyimino-3-ethoxy-carbonylpropanephosphonate* was isolated as a thick, red, viscous oil. (1.3 g, 27 %); (Found: C, 58.07; H, 5.11; N, 2.98. $C_{20}H_{24}NO_6P$ requires: C, 59.26; H, 5.93; N, 3.46 %); $^1H(CDCl_3)$ δ 1.26 (t, 3H, $CO_2CH_2C\underline{H}_3$, $^3J_{HCCH}$ 7.36 Hz), 2.66-2.89 (m, 4H, P-C-$C\underline{H}_2C\underline{H}_2$), 4.06 (q, 2H, $CO_2C\underline{H}_2CH_3$, $^3J_{HCCH}$ 7.38 Hz), 5.11 (d, 4H, 2x$C_6H_5C\underline{H}_2O$-, $^3J_{POCH}$ 11.29 Hz), 7.42 (m, 10H, 2x$C_6\underline{H}_5CH_2O$-) 11.66 (s, br, 1H, P-C=N-O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 14.23 (s, $CO_2CH_2\underline{C}H_3$), 23.06 (d, P-C-$\underline{C}H_2CH_2$, $^2J_{PCC}$ 17.12 Hz), 30.08 (d, P-C-$CH_2\underline{C}H_2$, $^3J_{PCCC}$ 1.41 Hz), 62.06 (s, $CO_2\underline{C}H_2CH_3$), 65.06 (d, 2x$C_6H_5\underline{C}H_2O$-, $^2J_{POC}$ 7.16 Hz), 127.93 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 131.12 (s, $\underline{C}_4$ of aromatic ring), 135.62 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 137.09 (d, $\underline{C}_1$ of aromatic ring, $^3J_{POCC}$ 2.49 Hz), 152.79 (d, P-$\underline{C}$=N-OH, $^1J_{PC}$ 216.90 Hz), 172.66 (s, $\underline{C}O_2CH_2CH_3$); $^{31}P(CDCl_3)$ δ 14.28 (s).

4.4.7. PREPARATION OF *O,O*-DIALKYL 1-NITROALKANEPHOSPHONATES

PREPARATION OF *O,O*-DIETHYL 1-NITROETHANEPHOSPHONATE

O,O-Diethyl 1-hydroxyiminoethanephosphonate (19.5 g, 0.10 mol), dissolved in dichloromethane (250 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (17.26 g, 0.10 mol), for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x100 cm^3), water (2x100 cm^3), and brine (1x100 cm^3) before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-diethyl 1-nitroethanephosphonate[101] as a pleasant smelling, reddish-orange, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became more viscous (Crude: 8.00 g, 38 %); (Found: C, 33.95; H, 6.66; N, 6.55. Calc. for $C_6H_{14}NO_5P$: C, 34.12; H, 6.64; N, 6.64 %); $^1H(CDCl_3)$ δ 1.36 (dt overlapping, 6H, 2xCH_3CH_2O-, $^3J_{HCCH}$ 6.95 Hz), 1.75-1.84 (dd, 3H, P-$CHCH_3$, $^3J_{HCCH}$ 7.17 Hz, $^3J_{PCCH}$ 15.87 Hz), 4.21-4.30 (m, 4H, 2xCH_3CH_2O-), 5.10 (dq overlapping, P-$CHCH_3$); $^{13}C(CDCl_3)$ δ 14.44 (d, P-$CHCH_3$, $^2J_{PCC}$ 3.77 Hz), 16.33 (dd, 2xCH_3CH_2O-, $^3J_{POCC}$ 5.91 Hz), 64.30 (dd, 2xCH_3CH_2O-, $^2J_{POC}$ 7.99 Hz), 79.49 (d, P-CH, $^1J_{PC}$ 144.28 Hz); $^{31}P(CDCl_3)$ δ 11.49 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-NITROETHANEPHOSPHONATE

O,O-Di-isopropyl 1-hydroxyiminoethanephosphonate (7.89 g, 0.035 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (6.04 g, 0.035 mol), for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-di-isopropyl 1-nitroethanephosphonate[100] as a pleasant smelling, clear, yellow residue. A portion (5.08 g, 0.021 mol) of this product was distilled under high vacuum, to produce clear, free-flowing fractions of *O,O*-di-isopropyl 1-nitroethanephosphonate (Crude: 6.31 g, 75 % Distilled: 1.80 g, 35 %); b.p. 94 ^{o}C at 0.10 mmHg, (lit.[100] 81-83 ^{o}C at 0.90 mmHg); (Found: C, 40.99; H, 7.70; N, 4.99. Calc for $C_8H_{18}NO_5P$: C, 40.17; H, 7.53; N, 5.86 %); $^{1}H(CDCl_3)$ δ 1.32-1.40 (dd, 12H, 2x($C\underline{H}_3$)$_2$CHO-, $^{3}J_{HCCH}$ 6.15 Hz), 1.74-1.83 (dd, 3H, P-CHC$\underline{H}_3$, $^{3}J_{HCCH}$ 7.17 Hz), $^{3}J_{PCCH}$ 16.15 Hz), 4.72-5.04 (m, 3H, P-C$\underline{H}$ overlapping with 2x(CH_3)C$\underline{H}$O-); $^{13}C(CDCl_3)$ δ 14.46 (d, P-CH$\underline{C}H_3$, $^{2}J_{PCC}$ 3.85 Hz), 23.67 (dd, 2x($\underline{C}H_3$)$_2$CHO-, $^{3}J_{POCC}$ 5.20 Hz), 73.32 (dd, 2x(CH_3)$_2\underline{C}$HO-, $^{2}J_{POC}$ 6.93 Hz) 80.11 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 144.98 Hz); $^{31}P(CDCl_3)$ δ 11.37 (s).

PREPARATION OF *O,O*-DIMETHYL 1-NITROPROPANEPHOSPHONATE

O,O-Dimethyl 1-hydroxyiminopropanephosphonate (5.43 g, 0.030 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (6.45 g, 0.030 mol), for 1 week at room temperature. The solution was washed with: aqueous sodium hydrogen carbonate in sodium sulphate (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-dimethyl 1-nitropropanephosphonate[101] as a pleasant smelling, clear, yellow, oily residue. The product was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became an off-white gelatinous residue. No attempt was made to purify the crude nitrophosphonate further (1.95 g, 33 %); (Found: C, 32.02; H, 6.04; N, 6.17. Calc for $C_5H_{12}NO_5P$: C, 30.46; H, 6.09; N, 7.11 %); $^1H(CDCl_3)$ δ 1.06 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 7.27 Hz), 2.09-2.39 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 3.85-3.92 (dd, 6H, 2xC$\underline{H}_3$O-, $^3J_{POCH}$ 11.04 Hz), 4.92 (ddd, 1H, P-C$\underline{H}$); $^{13}C(CDCl_3)$ δ 10.99 (d, P-CHCH$_2$C$\underline{H}_3$, $^3J_{PCCC}$ 13.33 Hz), 23.05 (d, P-CHC$\underline{H}_2$CH$_3$, $^2J_{PCC}$ 2.71 Hz), 54.46 (dd, 2xC$\underline{H}_3$O-, $^2J_{POC}$ 6.70 Hz), 86.13 (d, P-C$\underline{H}$, $^1J_{PC}$ 143.84 Hz); $^{31}P(CDCl_3)$ δ 15.83 (s).

PREPARATION OF *O,O*-DIETHYL 1-NITROPROPANEPHOSPHONATE

O,O-Diethyl 1-hydroxyiminopropanephosphonate (20.9 g, 0.10 mol), dissolved in dichloromethane (250 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (17.26 g, 0.10 mol), for 1 week at room temperature. The solution was washed with: aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x100 cm^3), water (2x100 cm^3) and brine (1x100 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-diethyl 1-nitropropanephosphonate as a pleasant smelling, clear-yellow, oily residue. A portion (5.23 g, 0.023 mol) was distilled under high vacuum to produce clear, free-flowing fractions of *O,O*-diethyl 1-nitropropanephosphonate (Crude: 18.6 g, 83 % Distilled: 1.17 g, 22 %); b.p. 100-102 ^{o}C at 0.60-0.65 mmHg; (lit.[101] b.p. 130 ^{o}C at 3.0 mmHg); (Found: C, 37.51; H, 7.17; N, 5.90. Calc. for $C_7H_{16}NO_5P$: C, 37.33; H, 7.11; N, 6.22 %); $^{1}H(CDCl_3)$ δ 1.06 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{HCCH}$ 7.28 Hz), 1.34-1.41 (dt overlapping, 6H, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{HCCH}$ 7.25 Hz), 2.08-2.45 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 4.19-4.31 (m, 4H, 2xCH$_3$C$\underline{H}_2$O-), 4.84 (ddd, 1H, P-C$\underline{H}$); $^{13}C(CDCl_3)$ δ 11.08 (d, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{PCCC}$ 13.52 Hz), 16.30 (dd, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{POCC}$ 2.22 Hz), 22.99 (d, P-C$\underline{H}_2$CH$_3$, $^{2}J_{PCC}$ 2.62 Hz), 64.24 (dd, 2xCH$_3$C$\underline{H}_2$O-, $^{2}J_{POC}$ 5.86 Hz), 86.69 (d, P-C$\underline{H}$, $^{1}J_{PC}$ 142.96 Hz); $^{31}P(CDCl_3)$ δ 13.32 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-NITROPROPANEPHOSPHONATE

O,O-Di-isopropyl 1-hydroxyiminopropanephosphonate (23.70 g, 0.10 mol), dissolved in dichloromethane (250 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (17.26 g, 0.10 mol), for 1 week at room temperature. The solution was washed with: sodium hydrogen carbonate in sodium sulphite (10 %, 2x100 cm^3), water (2x100 cm^3) and brine (1x100 cm^3) before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-di-isopropyl 1-nitropropanephosphonate as a pleasant smelling, clear-yellow, oily residue. A portion of this product (3.11 g, 0.013 mol), was distilled under high vacuum to produce clear, free-flowing fractions of *O,O*-di-isopropyl 1-nitropropanephosphonate (Crude: 22.73 g, 90 % Distilled: 1.84 g, 59 %); b.p. 90-92 ^oC at 0.10 mmHg, (lit.[100] b.p. 98-101 ^oC at 1.00 mmHg) ; (Found: C, 42.63; H, 8.10; N, 5.37. Calc. for $C_9H_{20}NO_5P$: C, 42.69; H, 7.91; N, 5.53 %); $^1H(CDCl_3)$ δ 1.04 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 7.35 Hz), 1.31-1.39 (dd, 12H, 2x(C$\underline{H}_3$)$_2$CHO-, $^3J_{HCCH}$ 7.00 Hz), 2.05-2.40 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 4.71-4.87 (m, 3H, 2x(CH$_3$)$_2$C$\underline{H}$O- overlapping with P-C$\underline{H}$CH$_2$CH$_3$); $^{13}C(CDCl_3)$ δ 11.06 (d, P-CHCH$_2$C$\underline{H}_3$, $^3J_{PCCC}$ 13.46 Hz), 23.08 (d, P-CH$\underline{C}$H$_2$CH$_3$, $^2J_{PCC}$ 2.71 Hz), 23.78 (dd, 2x($\underline{C}$H$_3$)$_2$CHO-, $^3J_{POCC}$ 4.66 Hz), 73.48 (dd, 2x(CH$_3$)$_2$$\underline{C}$HO-, $^2J_{POC}$ 6.48 Hz), 87.31 (d, P-$\underline{C}$H, $^1J_{PC}$ 143.97 Hz); $^{31}P(CDCl_3)$ δ 10.55 (s).

PREPARATION OF *O,O*-DI-ISOBUTYL 1-NITROPROPANEPHOSPHONATE

O,O-Di-isobutyl 1-nitropropanephosphonate (8.17 g, 0.031 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (5.35 g, 0.031 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O-di-isobutyl 1-nitropropanephosphonate* as a pleasant smelling, clear-yellow, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the crude compound became more viscous (Crude: 8.40 g, 96 %); (Found: C, 47.28; H, 8.96; N, 4.17. $C_{11}H_{24}NO_5P$ requires: C, 46.98; H, 8.54; N, 4.98 %); $^1H(CDCl_3)$ δ 0.96 (dd, 12H, $(CH_3)_2CHCH_2O$-, $^3J_{HCCH}$ 6.62 Hz), 1.05 (t, 3H, P-$CHCH_2CH_3$, $^3J_{HCCH}$ 7.29 Hz), 1.88-2.03 (m, 2H, 2x$(CH_3)_2CHCH_2O$-), 2.04-2.42 (m, 2H, P-$CHCH_2CH_3$), 3.89-3.97 (m, 4H, 2x$(CH_3)_2CHCH_2O$-), 4.93 (ddd, 1H, P-CH); $^{13}C(CDCl_3)$ δ 11.02 (d, P-$CHCH_2CH_3$, $^3J_{PCCC}$ 13.27 Hz), 18.71 (2xs, 2x$(CH_3)_2CHCH_2O$-), 23.05 (d, P-$CHCH_2CH_3$, $^2J_{PCC}$ 2.64 Hz), 29.26 (dd, 2x$(CH_3)_2CHCH_2O$-, $^3J_{POCC}$ 5.72 Hz), 73.66 (dd, 2x$(CH_3)_2CHCH_2O$-, $^2J_{POC}$ 7.42 Hz), 86.44 (d, P-$CHCH_2CH_3$, $^1J_{PC}$ 142.59 Hz); $^{31}P(CDCl_3)$ δ 12.01 (s).

PREPARATION OF *O,O*-DIMETHYL 1-NITROBUTANEPHOSPHONATE

O,O-Dimethyl 1-hydroxyiminobutanephosphonate (6.69 g, 0.030 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (6.45 g, 0.030 mol), for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O-dimethyl 1-nitrobutanephosphonate* as a pleasant smelling, clear-yellow, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became more viscous. No attempt was made to purify the product further (4.5 g, 71 %); (Found: C, 34.03; H, 6.76; N, 6.46. $C_6H_{14}NO_5P$ requires: C, 34.12; H, 6.64; N, 6.64 %); $^1H(CDCl_3)$ δ 0.98 (t, 3H, P-CHCH$_2$CH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 7.35 Hz), 1.35-1.48 (m, 2H, P-CHCH$_2$C$\underline{H}_2$CH$_3$), 1.49-2.09 (m, 2H, P-CHC$\underline{H}_2$CH$_2$CH$_3$), 3.85-3.91 (dd, 6H, 2xC$\underline{H}_3$O-, $^3J_{POCH}$ 11.06 Hz), 5.02 (ddd, 1H, P-C$\underline{H}$); $^{13}C(CDCl_3)$ δ 13.15 (s, P-CHCH$_2$CH$_2$C$\underline{H}_3$), 19.80 (d, P-CHCH$_2$C$\underline{H}_2$CH$_3$, $^3J_{PCCC}$ 12.64 Hz), 31.11 (d, P-CHC$\underline{H}_2$CH$_2$CH$_3$, $^2J_{PCC}$ 2.83 Hz), 54.53 (dd, 2xC$\underline{H}_3$O-, $^2J_{POC}$ 6.48 Hz), 84.45 (d, P-C$\underline{H}$, $^1J_{PC}$ 143.97 Hz); $^{31}P(CDCl_3)$ δ 15.91 (s).

PREPARATION OF *O,O*-DIETHYL 1-NITROBUTANEPHOSPHONATE

O,O-Diethyl 1-hydroxyiminobutanephosphonate (6.69 g, 0.030 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (6.45 g, 0.030 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O-diethyl 1-nitrobutanephosphonate* as a pleasant smelling clear-yellow, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became more viscous. No attempt was made to purify the crude product further (Crude: 6.10 g, 85 %); (Found: C, 40.33; H, 7.48; N, 6.28. $C_8H_{18}NO_5P$ requires: C, 40.17; H, 7.53; N, 5.86 %); $^1H(CDCl_3)$ δ 0.98 (t, P-CHCH$_2$CH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 7.40 Hz), 1.32-1.40 (m, 6H, 2xC$\underline{H}_3$CH$_2$O-), 1.63-1.77 (m, 2H, P-CHCH$_2$C$\underline{H}_2$CH$_3$), 1.97-2.49 (m, P-CHC$\underline{H}_2$CH$_2$CH$_3$), 4.06-4.36 (m, 4H, 2xCH$_3$C$\underline{H}_2$O-), 4.96 (ddd, 1H, P-CH); $^{13}C(CDCl_3)$ δ 13.18 (s, P-CHCH$_2$CH$_2$C$\underline{H}_3$), 16.30 (dd, 2xC$\underline{H}_3$CH$_2$O-, $^3J_{POCC}$ 5.69 Hz), 19.83 (d, P-CHCH$_2$C$\underline{H}_2$CH$_3$, $^3J_{PCCC}$ 12.66 Hz), 31.09 (d, P-CHC$\underline{H}_2$CH$_2$CH$_3$, $^2J_{PCC}$ 2.79 Hz), 64.30 (dd, 2xCH$_3$C$\underline{H}_2$O-, $^2J_{POC}$ 6.83 Hz), 84.97 (d, P-C$\underline{H}$, $^1J_{PC}$ 142.91 Hz); $^{31}P(CDCl_3)$ δ 13.56 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-NITROBUTANEPHOSPHONATE

O,O-Di-isopropyl 1-hydroxyiminobutanephosphonate (7.53 g, 0.030 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (6.45 g, 0.030 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-di-isopropyl 1-nitrobutanephosphonate[119] as a pleasant smelling, clear-yellow, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became more viscous. No attempt was made to purify the compound further (Crude: 6.40 g, 80 %); (Found: C, 44.96; H, 8.18; N, 5.33. Calc. for $C_{10}H_{22}NO_5P$: C, 44.94; H, 8.24; N, 5.24 %); $^1H(CDCl_3)$ δ 0.97 (t, 3H, P-CHCH$_2$CH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 7.35 Hz); 1.34-1.38 (dd, 12H, 2x(C$\underline{H}_3$)$_2$CHO-, $^3J_{HCCH}$ 7.05 Hz), 1.60-1.80 (m, 2H, P-CHCH$_2$C$\underline{H}_2$CH$_3$), 1.92-2.36 (m, 2H, P-CHC$\underline{H}_2$CH$_2$CH$_3$), 4.76-4.93 (m, 3H, 2x(CH$_3$)$_2$C$\underline{H}$O- overlapping with P-C$\underline{H}$); $^{13}C(CDCl_3)$ δ 13.16 (s, P-CHCH$_2$CH$_2$C$\underline{H}_3$), 19.85 (d, P-CHCH$_2$C$\underline{H}_2$CH$_3$, $^3J_{PCCC}$ 13.27 Hz), 23.84 (dd, 2x(CH$_3$)$_2$C$\underline{H}$O-, $^3J_{POCC}$ 4.67 Hz), 31.12 (d, P-C$\underline{H}$CH$_2$CH$_2$CH$_3$, $^2J_{PCC}$ 2.79 Hz), 73.37 (d, 2x(CH$_3$)$_2$C$\underline{H}$O-, $^2J_{POC}$ 6.40 Hz), 85.63 (d, P-$\underline{C}$H, $^1J_{PC}$ 143.84 Hz); $^{31}P(CDCl_3)$ δ 11.22 (s).

PREPARATION OF *O,O*-DI-n-BUTYL 1-NITROBUTANEPHOSPHONATE

O,O-Di-n-butyl 1-hydroxyiminobutanephosphonate (8.85 g, 0.030 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (6.45 g, 0.030 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O*-di-n-butyl 1-nitrobutanephosphonate[119] as a pleasant smelling, clear-yellow, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became more viscous. No attempt was made to further purify the crude compound (Crude: 7.20 g, 81.4 %); (Found: C, 48.98; H, 8.74; N, 4.74. Calc. for $C_{12}H_{26}NO_5P$: C, 48.81; H, 8.81; N, 4.75 %); $^1H(CDCl_3)$ δ 0.95 (2xt overlapping, 9H, 2x$\underline{CH_3}CH_2CH_2CH_2O$ & P-CHCH$_2$CH$_2\underline{CH_3}$, $^3J_{HCCH}$ 7.60 Hz), 1.35-1.45 (m, 6H, 2x$CH_3\underline{CH_2}CH_2CH_2O$- & P-CHCH$_2\underline{CH_2}CH_3$), 1.60-1.80 (m, 4H, 2x$CH_3CH_2\underline{CH_2}CH_2O$-), 1.90-2.50 (m, 2H, P-CH$\underline{CH_2}$CH$_2$CH$_2$CH$_3$), 4.00-4.30 (m, 4H, 2x$CH_3CH_2CH_2\underline{CH_2}O$), 4.95 (ddd, 1H, P-$\underline{CH}$); $^{13}C(CDCl_3)$ δ 13.16 (s, P-CHCH$_2$CH$_2\underline{CH_3}$), 13.54 (s, 2x$\underline{CH_3}CH_2CH_2CH_2O$-), 18.62 (s, 2x$CH_3\underline{CH_2}CH_2CH_2O$-), 19.84 (d, P-CHCH$_2\underline{CH_2}CH_3$, $^3J_{PCCC}$ 12.83 Hz), 31.03 (d, P-CH$\underline{CH_2}$CH$_2$CH$_3$, $^2J_{PCC}$ 2.69 Hz), 32.43 (d, 2x$CH_3CH_2\underline{CH_2}CH_2O$-, $^3J_{POCC}$ 5.77 Hz), 67.95 (dd, 2x$CH_3CH_2CH_2\underline{CH_2}O$-, $^2J_{POC}$ 6.84 Hz), 84.84 (d, P-$\underline{CH}$,

$^{1}J_{PC}$ 142.64 Hz); $^{31}P(CDCl_3)$ δ 13.49 (s).

PREPARATION OF *O,O*-DIMETHYL 1-NITROBENZYLPHOSPHONATE

O,O-Dimethyl 1-hydroxyiminobenzylphosphonate (22.9 g, 0.10 mol), dissolved in dichloromethane (250 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (17.26 g, 0.10 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x100 cm^3), water (2x100 cm^3) and brine (1x100 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O-dimethyl 1-nitrobenzylphosphonate* as a pleasant smelling, clear-green, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became a gelatinous solid. No attempt was made to purify the crude product further (13.48 g, 55 %); (Crude: C, 45.64; H, 5.11; N, 5.94. $C_9H_{12}NO_5P$ requires: C, 44.08; H, 4.90; N, 5.71 %); $^{1}H(CDCl_3)$ δ 3.62-3.85 (dd, 6H, 2x$\underline{C}H_3O$-, $^{3}J_{POCH}$ 10.95 Hz), 6.14 (d, 1H, P-$\underline{C}H$, $^{2}J_{PCH}$ 16.89 Hz), 7.32-7.67 (m, 3H, $\underline{H}_3$, $\underline{H}_4$, $\underline{H}_5$ of aromatic ring), 8.00-8.04 (m, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring); $^{13}C(CDCl_3)$ δ 54.81 (dd, 2x$\underline{C}H_3O$-, $^{2}J_{POC}$ 6.67 Hz), 87.25 (d, P-$\underline{C}H$, $^{1}J_{PC}$ 150.51 Hz), 128.66 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 129.20 (s, $\underline{C}_4$ of aromatic ring), 129.48 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 132.94 (d, P-C-$\underline{C}_1$ of aromatic ring, $^{2}J_{PCC}$ 58.56 Hz); $^{31}P(CDCl_3)$ δ 12.89 (s).

PREPARATION OF *O,O*-DIETHYL 1-NITROBENZYLPHOSPHONATE

O,O-Diethyl 1-hydroxyiminobenzylphosphonate (25.70 g, 0.10 mol), dissolved in dichloromethane (250 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (17.26 g, 0.10 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x100 cm^3), water (2x100 cm^3) and brine (1x100 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O-diethyl 1-nitrobenzylphosphonate* as a pleasant smelling clear-orange, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became more viscous. No attempt was made to purify the crude product further (Crude: 25.36 g, 93 %); (Found: C, 49.64; H, 5.89; N, 4.85. $C_{11}H_{16}NO_5P$ requires: C, 48.35; H, 5.36; N, 5.13 %); $^1H(CDCl_3)$ δ 1.38 (dt overlapping, 6H, 2x$\underline{C}H_3CH_2O$-, $^3J_{HCCH}$ 7.18 Hz), 4.29 (m, 4H, 2x$CH_3\underline{C}H_2O$), 6.02 (d, 1H, P-C$\underline{H}$, $^2J_{PCH}$ 16.82 Hz), 7.35-8.30 (m, 5H, $C_6\underline{H}_5$); $^{13}C(CDCl_3)$ δ 16.30 (dd, 2x$\underline{C}H_3CH_2O$-, $^3J_{POCC}$ 4.47 Hz), 64.18 (dd, 2x$CH_3\underline{C}H_2O$-, $^2J_{POC}$ 6.92 Hz), 87.99 (d, P-$\underline{C}$H, $^1J_{PC}$ 148.88 Hz), 128.98 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 129.81 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^3J_{PCCC}$ 1.64 Hz), 134.84 (s, $\underline{C}_4$ of aromatic ring), 135.55 (d, P-C-$\underline{C}_1$, $^2J_{PCC}$ 63.78 Hz); $^{31}P(CDCl_3)$ δ 10.27 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-NITROBENZYLPHOSPHONATE

O,O-Di-isopropyl 1-hydroxyiminobenzylphosphonate (12.48 g, 0.044 mol), was dissolved in dichloromethane (250 cm^3), and stirred in the presence of *m*-chloroperbenzoic acid (7.56 g, 0.044 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x70 cm^3), water (2x70 cm^3) and brine (1x70 cm^3) before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O-di-isopropyl 1-nitrobenzylphosphonate* as a clear, orange, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg for 2 h during which time the compound became more viscous. No attempt was made to purify the crude product further (Crude: 11.22 g, 85 %); (Found: C, 52.49; H, 6.57; N, 4.14. $C_{13}H_{20}NO_5P$ requires: C, 51.83; H, 6.65; N, 4.65 %); $^1H(CDCl_3)$ δ 1.40 (dd, 12H, 2x$(C\underline{H}_3)_2$CHO-, $^3J_{HCCH}$ 6.92 Hz), 4.75 (m, 2H, 2x$(CH_3)_2C\underline{H}$O-), 6.05 (d, 1H, P-C$\underline{H}$, $^2J_{PCH}$ 16.45 Hz), 7.50-8.30 (m, 5H, $C_6\underline{H}_5$); $^{13}C(CDCl_3)$ δ 23.73 (dd, 2x$(\underline{C}H_3)_2$CHO-, $^3J_{POCC}$ 5.38 Hz), 73.76 (d, 2x$(CH_3)_2\underline{C}$HO-, $^2J_{POC}$ 6.86 Hz), 88.60 (d, P-$\underline{C}$H, $^1J_{PC}$ 149.82 Hz), 128.90 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 129.65 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^3J_{PCCC}$ 3.77 Hz), 134.57 (s, $\underline{C}_4$ of aromatic ring), 135.64 (d, P-C-$\underline{C}_1$ of aromatic ring, $^2J_{PCC}$ 63.78 Hz); $^{31}P(CDCl_3)$ δ 8.54 (s).

PREPARATION OF *O,O*-DIETHYL 1-NITRO-3-METHOXY-CARBONYLPROPANEPHOSPHONATE

O,O-Diethyl 1-hydroxyimino-3-methoxycarbonylpropanephosphonate (6.00 g, 0.023 mol) dissolved in dichloromethane (50 cm^3) was stirred in the presence of *m*-chloroperbenzoic acid (3.88 g, 0.023 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *O,O-diethyl 1-nitro-3-ethoxycarbonylpropane-phosphonate* as a plesant-smelling, clear, yellow-orange, oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became very viscous (6.50 g, 100 %); (Found: C, 38.21; H, 6.35; N, 5.03. $C_9H_{18}NO_7P$ requires: C, 38.16; H, 6.36; N, 4.95 %); $^1H(CDCl_3)$ δ 1.32-1.41 (dt overlapping, 6H, $C\underline{H}_3CH_2O$-, $^3J_{HCCH}$ 7.45 Hz), 2.40-2.88 (m, 4H, P-CHC$\underline{H}_2C\underline{H}_2$), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 4.12-4.35 (m, 4H, 2x$CH_3C\underline{H}_2O$-), 5.05-5.17 (ddd, 1H, P-C$\underline{H}$); $^{13}C(CDCl_3)$ δ 16.30 (d, 2x$\underline{C}H_3CH_2O$-, $^3J_{POCC}$ 6.29 Hz), 24.47 (d, P-CH$\underline{C}H_2CH_2$, $^2J_{PCC}$ 1.70 Hz), 29.98 (d, P-CHCH$_2\underline{C}H_2$, $^3J_{PCCC}$ 11.95 Hz), 51.99 (s, $CO_2\underline{C}H_3$), 64.55 (2x$CH_3\underline{C}H_2O$-, $^2J_{POC}$ 6.64 Hz), 83.59 (d, P-$\underline{C}$H, $^1J_{PC}$ 142.59 Hz), 172.04 (s, $\underline{C}O_2CH_3$); $^{31}P(CDCl_3)$ δ 12.22 (s).

PREPARATION OF *O,O*-DI-ISOPROPYL 1-NITRO-3-METHOXY-CARBONYLPROPANEPHOSPHONATE

O,O-Di-isopropyl 1-hydroxyimino-3-methoxycarbonylpropane-phosphonate (6.25 g, 0.021 mol), dissolved in dichloromethane (50 cm^3) was stirred in the presence of *m*-chloroperbenzoic acid (3.63 g, 0.021 mol) for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *O,O-di-isopropyl 1-nitro-3-methoxycarbonylpropanephosphonate* as a plesant-smelling, clear orange oily residue. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the compound became more viscous (6.53 g, 100 %); (Found: C, 42.31; H, 7.07; N, 4.67. $C_{11}H_{22}NO_7P$ requires: C, 42.44; H, 7.07; N, 4.50 %); $^1H(CDCl_3)$ δ 1.38 (dd, 12H, 2x$(C\underline{H}_3)_2$CHO-, $^3J_{HCCH}$ 7.06 Hz), 2.39-2.67 (m, 4H, P-CH$C\underline{H}_2C\underline{H}_2$), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 4.73-4.88 (m, 2H, 2x$(CH_3)_2C\underline{H}$O-), 4.98-5.10 (ddd, 1H, P-C$\underline{H}$); $^{13}C(CDCl_3)$ δ 23.68 (dd, 2x$(\underline{C}H_3)_2$CHO-, $^3J_{POCC}$ 6.02 Hz), 24.53 (d, P-CH$\underline{C}H_2CH_2$, $^2J_{PCC}$ 1.76 Hz), 29.99 (d, P-CHCH$_2\underline{C}H_2$, $^3J_{PCCC}$ 12.01 Hz), 73.63 (d, 2x$(CH_3)_2\underline{C}$HO-, $^2J_{POC}$ 6.92 Hz), 84.29 (d, P-$\underline{C}$H, $^1J_{PC}$ 143.28 Hz), 172.01 (s, $\underline{C}O_2CH_3$); $^{31}P(CDCl_3)$ δ 10.09 (s).

PREPARATION OF *O,O*-DIMETHYL 1-NITRO-3-ETHOXYCARBONYLPROPANE-PHOSPHONATE

O,O-Dimethyl 1-hydroxyimino 3-ethoxycarbonylpropanephoshonate (7.59 g, 0.030 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (6.45 g, 0.030 mol), for 1 week, at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent and concentrated under reduced pressure on a rotary evaporator. The nitrophosphonate was afforded as a pleasant-smelling, clear, orange-yellow, oily residue. This material was distilled under high vacuum to afford 3 fractions of *O,O-dimethyl 1-nitro-3-ethoxycarbonylpropanephosphonate*. N.M.R. analysis of the distillates showed that some decomposition of the product had taken place. Elemental analysis was carried out on all fractions, but the fraction distilling at 136-140 ^oC at 0.20 mmHg gave the most favourable results (Crude: 7.58 g, 99.5 %); (Found [distilled product]: C, 36.56; H, 6.12; N, 4.22. $C_8H_{16}NO_7P$ requires: C, 35.69; H, 5.95; N, 5.20 %); $^1H(CDCl_3)$ of crude material δ 1.26 (t, 3H, $CO_2CH_2\underline{C}H_3$, $^3J_{HCCH}$ 7.10 Hz), 2.38-2.80 (m, 4H, P-CH-$C\underline{H}_2C\underline{H}_2$), 3.91 (dd, 6H, 2x$C\underline{H}_3O$-, $^3J_{POCH}$ 11.18 Hz), 4.03-4.24 (q, 2H, $CO_2C\underline{H}_2CH_3$, $^3J_{HCCH}$ 7.21 Hz), 5.13-5.25 (ddd, 1H, P-$C\underline{H}CH_2CH_3$); $^{13}C(CDCl_3)$ δ 14.20 (s, $CO_2CH_2\underline{C}H_3$), 24.52 (d, P-$CH\underline{C}H_2CH_3$, $^2J_{PCC}$ 1.82 Hz),

30.20 (d, P-CHCH$_2$CH$_3$, $^3J_{PCCC}$ 11.82 Hz), 54.61 (s, $CO_2CH_2CH_3$), 61.08 (dd, 2xCH$_3$O-, $^2J_{POC}$ 7.06 Hz), 83.11 (d, P-CH, 143.91 Hz), 171.55 (s, $CO_2CH_2CH_3$); $^{31}P(CDCl_3)$ δ 15.53 (s).

PREPARATION OF *O,O*-DIETHYL 1-NITRO-3-ETHOXYCARBONYLPROPANE-PHOSPHONATE

O,O-Diethyl 1-hydroxyimino-3-ethoxycarbonylpropanephosphonate (7.86 g, 0.028 mol), dissolved in dichloromethane (90 cm^3), was stirred in the presence of *m*-chloroperbenzoic acid (4.83 g, 0.028 mol), for 1 week at room temperature. The solution was washed with aqueous sodium hydrogen carbonate in sodium sulphite (10 %, 2x50 cm^3), water (2x50 cm^3) and brine (1x50 cm^3), before being dried over anhydrous magnesium sulphate. The organic layer was filtered to remove the drying agent and concentrated under reduced pressure on a rotary evaporator. *O,O-Diethyl 1-nitro-3-ethoxycarbonylpropanephosphonate* was afforded as a pleasant smelling clear, orange-yellow, oily residue. The product was distilled under high vacuum but elemental and N.M.R. analysis, showed that the nitrophosphonate had undergone some decomposition. However good results were obtained for the crude *O,O-diethyl 1-nitro-3-ethoxycarbonyl-propanephosphonate* (Crude: 5.63 g, 63.2 %); [Found (crude): C, 41.26; H, 6.69; N, 4.10. $C_{10}H_{20}NO_7P$ requires: C, 40.54; H, 6.76; N, 4.73 %]; $^1H(CDCl_3)$ δ 1.27 (t, 3H, $CO_2CH_2CH_3$, $^3J_{HCCH}$ 7.14 Hz), 1.37 (dt overlapping, 6H, 2xCH$_3$CH$_2$O-, $^3J_{HCCH}$ 7.12 Hz), 2.36-2.69 (m, 4H,

P-CHC$\underline{H}_2$C$\underline{H}_2$), 4.10-4.32 (m, 6H, 2xCH$_3$C$\underline{H}_2$O- overlapping with CO$_2$C$\underline{H}_2$CH$_3$), 5.08-5.19 (ddd, 1H, P-C$\underline{H}$); ^{13}C(CDCl$_3$) δ 14.17 (s, CO$_2$CH$_2$C$\underline{H}_3$), 16.31 (dd, 2xC$\underline{H}_3$CH$_2$O-, $^3J_{POCC}$ 5.85 Hz), 24.53 (d, P-CHC$\underline{H}_2$CH$_3$, $^2J_{PCC}$ 1.82 Hz), 30.26 (d, P-CHCH$_2$C$\underline{H}_3$, $^3J_{PCCC}$ 12.20 Hz), 60.96 (s, CO$_2$C$\underline{H}_2$CH$_3$), 64.45 (dd, 2xCH$_3$C$\underline{H}_2$O-, $^2J_{POC}$ 6.79 Hz), 83.72 (d, P-C$\underline{H}$, $^1J_{PC}$ 142.65 Hz), 171.52 (s, C$\underline{O}_2$CH$_2$CH$_3$); ^{31}P(CDCl$_3$) δ 14.24 (s).

PREPARATION OF *O,O*-TRIMETHYLSILYL 1-NITROPROPANEPHOSPHONATE

Trimethylsilyl bromide (10.11 g, 0.066 mol), was added dropwise and with stirring to *O,O*-di-isopropyl 1-nitropropanephosphonate (5.55 g, 0.022 mol), under dry nitrogen at room temperature. After the addition had been completed, the mixture was left to stir for a further 12 h. ^{1}H N.M.R. examination at 60 MHz, showed that trimethylsilylation had taken place. The solution was concentrated under reduced pressure on a rotary evaporator and the orange oily residue afforded was distilled under high vacuum, to produce *O,O-trimethylsilyl 1-nitropropanephosphonate* as a free-flowing liquid (1.74 g, 25 %); b.p. 104-106 ^{o}C at 0.10-0.15 mmHg; (Found: C, 34.29; H, 7.79; N, 4.28. $C_9H_{24}NO_5Si_2P$ requires: C, 34.51; H, 7.67; N, 4.47 %); ^{1}H(CDCl$_3$) δ 0.29 (s, 18H, 2x(C$\underline{H}_3$)$_3$SiO-), 1.22 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 7.52 Hz), 2.30-2.62 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 4.69-4.83 (m, 1H, P-C$\underline{H}$CH$_2$CH$_3$); ^{13}C(CDCl$_3$) δ 0.61 (s, 2x(C$\underline{H}_3$)$_3$SiO-), 9.29 (d, P-CHCH$_2$C$\underline{H}_3$, $^3J_{PCCC}$ 18.11 Hz), 22.44 (s, P-CHC$\underline{H}_2$CH$_3$), 87.89 (d,

P-$\underline{C}$HCH$_2$CH$_3$, $^1J_{PC}$ 137.59 Hz); ^{31}P(CDCl$_3$) δ -26.29 (s); EI ms: m/z(%) 313 ([M]$^+$, 13.6), 298 ([M - CH$_3$]$^+$, 35.4), 267 ([M - NO$_2$]$^+$, 20.9), 225 ([M - O$_2$NCHCH$_2$CH$_3$]$^+$, 60), 167 ([M - 2x(CH$_3$)$_3$Si]$^+$, 11.79).

4.4.7.1. ATTEMPTED PREPARATION OF 1-NITROPROPANEPHOSPHONIC ACID

Trimethylsilylbromide (3.40 g, 0.023 mol) was added dropwise and with stirring to *O,O*-diethyl 1-nitropropanephosphonate (1.71 g, 0.0076 mol), under dry nitrogen at room temperature. After the addition had been completed, the mixture was left to stir for 1 h, after which a small aliquot was withdrawn and examined by ^{1}H N.M.R. at 60 MHz. The extent of *O,O*-trimethylsilylation that had taken place was observed. The mixture was stirred for a further 2 h, whereafter examination of a 2nd small aliquot by ^{1}H N.M.R., showed that the reaction was more than 90 % complete. The mixture was left for a further 12 h, and then concentrated under reduced pressure on a rotary evaporator, to afford an orange oily residue. ^{1}H N.M.R. examination of this material at 60 MHz, showed that total conversion had taken place. No attempt was made purify the *O,O*-trimethylsilyl intermediate further.

Water (50 cm^3) was added to the oily residue, and the mixture was stirred under dry nitrogen for 12 h at room temperature. The solution was concentrated by vigorous shaking under high vacuum (0.05 mmHg), for 6 h. ^{1}H N.M.R. examination at 60 MHz, of the orange

oily residue, showed that the characteristic low field multiplet of the α-proton resonating at approximately 5.50 ppm was still present. However, a large doublet resonating at high field implied that further treatment with water was necessary. The residue was re-dissolved in water, stirred under nitrogen for 12 h at room temperature, and the solution was concentrated by vigorous shaking under high vacuum, to afford an orange oily residue. High field N.M.R. examination showed that the complex multiplicity observed in the ^{1}H N.M.R. of the phosphonate precursor, and expected to be present in the corresponding nitrophosphonic acid, was not observed, indicating that the product had not been isolated. (Found: C, 45.54; H, 9.69; N, 0.76. $C_3H_8NO_5P$ requires: C, 21.30; H, 4.73; N, 8.28 %).

4.4.7.2. 2ND ATTEMPT TO PREPARE 1-NITROPROPANEPHOSPHONIC ACID

O,O-Trimethylsilyl 1-nitropropanephosphonate (1.23 g, 0.004 mol), prepared from the trimethylsilylation of *O,O*-di-isopropyl 1-nitropropanephosphonate, was dissolved in water and stirred under dry nitrogen at room temperature for 48 h. The solution was concentrated by vigorous shaking under high vacuum (0.05 mmHg) for 6 h, to afford an orange-yellow oily residue. ^{1}H N.M.R. examination at 60 MHz of this material revealed that the complex multiplicity of the α-proton resonating at approximately 5.00 ppm as in the case of the *O,O*-di-isopropyl 1-nitropropanephosphonate precursor, was not observed. This

was further confirmed by high-field N.M.R. analysis showing that the desired product had not been formed. In view of this result no other analyses were carried out on this product.

4.4.8. PREPARATION OF *O,O*-DIALKYL 1-AMINOALKANEPHOSPHONATES

CHEMICAL REDUCTION OF *O,O*-DIETHYL 1-HYDROXYIMINOPROPANE-PHOSPHONATE IN PREPARATION OF *O,O*-DIETHYL 1-AMINOPROPANE-PHOSPHONATE USING ZINC & FORMIC ACID

O,O-Diethyl 1-hydroxyiminopropanephosphonate (19.4 g, 0.09 mol) was added dropwise and with stirring to a solution of zinc (26.20 g, 0.40 g atom), in dry formic acid (100 cm^3), during a period of 30 min at 60 ^oC. The temperature was not allowed to exceed 65 ^oC. When the addition had been completed, the mixture was allowed to stir for 12 h at 60 ^oC.

The cooled solution was filtered to remove zinc formate, and the filtrate was dissolved in dichloromethane (100 cm^3). This solution was washed with aqueous sodium hydrogen carbonate (10 %, 2x100 cm^3) and dried over anhydrous sodium sulphate. After concentration under reduced pressure on a rotary evaporator, the viscous oily residue was dissolved in methanol (100 cm^3) where the solution so formed was saturated with anhydrous hydrogen chloride gas, for 3 h, at 0 ^oC. The above solution was concentrated under reduced pressure on a rotary evaporator, and the oily residue formed was dissolved in dry ether, before being saturated with dry ammonia gas, for 2 h. Ammonium chloride was removed by filtration, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford a straw-coloured viscous oily residue.

This material was distilled under high vacuum to afford *O,O*-diethyl 1-aminopropanephosphonate[122] as a colourless free-flowing liquid (Crude: 2.10 g, 12 % Distilled: 1.34 g, 7.64 %); b.p. 76 ^{o}C at 0.075 mmHg; (lit.[122] 45-47 ^{o}C at 2.6 mmHg); (Found: C, 43.15; H, 9.42; N, 6.52. Calc. for $C_7H_{18}NO_3P$: C, 43.08; H, 9.23; N, 7.18 %); $^{1}H(CDCl_3)$ δ 1.07 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{HCCH}$ 7.41 Hz), 1.34 (t, 6H, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{HCCH}$ 7.09 Hz), 1.40-1.93 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 2.82-2.92 (ddd, 1H, P-C$\underline{H}$), 4.05-4.22 (m, 4H, 2xCH$_3$C$\underline{H}_2$O-); $^{13}C(CDCl_3)$ δ 10.88 (d, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{PCCC}$ 12.47 Hz), 16.61 (d, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{POCC}$ 5.51 Hz), 24.72 (s, P-CHC$\underline{H}_2$CH$_3$), 50.38 (d, P-C$\underline{H}$, $^{1}J_{PC}$ 148.37 Hz), 61.97 (dd, 2xCH$_3$C$\underline{H}_2$O-, $^{2}J_{POC}$ 6.74 Hz); $^{31}P(CDCl_3)$ δ 28.63 (s).

CHEMICAL REDUCTION OF *O,O*-DIETHYL 1-HYDROXYIMINOBUTANE-PHOSPHONATE IN PREPARATION OF *O,O*-DIETHYL 1-AMINOBUTANE-PHOSPHONATE USING ZINC & FORMIC ACID

O,O-Diethyl 1-hydroximinobutanephosphonate (22.30 g, 0.10 mol) was added to a stirring solution of purified zinc (26.20 g, 0.40 g atom), in dry formic acid (100 cm^3), during a period of 30 min, at 60 ^{o}C. The temperature was not allowed to exceed 65 ^{o}C. When the addition had been completed, the mixture was left to stir for 12 h at 60 ^{o}C.

The cooled solution was filtered to remove zinc formate, and the filtrate was dissolved in dichloromethane (100 cm^3). This solution

was washed with aqueous sodium hydrogen carbonate (10 %, 2x100 cm^3) and dried over anhydrous sodium sulphate. After concentration under reduced pressure on a rotary evaporator, the viscous oily residue formed was dissolved in methanol (100 cm^3). This solution was saturated with anhydrous hydrogen chloride gas, for 3 h at 0 °C. The above solution was concentrated under reduced pressure on a rotary evaporator, and the oily residue formed, was dissolved in dry ether, before being saturated with dry ammonia gas, for 2 h. Ammonium chloride was removed by filtration and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford a straw-coloured viscous oily residue. This material was distilled under high vacuum to afford *O,O*-diethyl 1-aminobutanephosphonate[122] as a colourless free-flowing liquid (Crude: 7.70 g, 37 % Distilled: 4.60 g, 22 %); b.p. 86-90 °C at 0.075 mmHg); (Found: C, 45.39; H, 9.23; N, 6.55. Calc. for $C_8H_{20}NO_3P$: C, 45.93; H, 9.57; N, 6.70 %); $^1H(CDCl_3)$ δ 0.94 (t, 3H, P-CHCH$_2$CH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 6.95 Hz), 1.34 (t, 6H, 2xC$\underline{H}_3$CH$_2$O-, $^3J_{HCCH}$ 7.06 Hz), 1.40-1.92 (m, 4H, P-CHC$\underline{H}_2$C$\underline{H}_2$CH$_3$), 2.89-2.99 (ddd, 1H, P-C$\underline{H}$), 4.08-4.20 (m, 4H, 2xCH$_3$C$\underline{H}_2$O-); $^{13}C(CDCl_3)$ δ 13.84 (s, P-CHCH$_2$CH$_2$C$\underline{H}_3$), 16.63 (d, 2xC$\underline{H}_3$CH$_2$O-, $^3J_{POCC}$ 4.80 Hz), 19.37 (d, P-CHCH$_2$C$\underline{H}_2$CH$_3$, $^3J_{PCCC}$ 12.49 Hz), 33.56 (s, P-C$\underline{H}$CH$_2$CH$_2$CH$_3$), 48.53 (d, P-C$\underline{H}$, $^1J_{PC}$ 148.70 Hz), 61.99 (dd, 2xCH$_3$C$\underline{H}_2$O-, $^2J_{POC}$ 7.56 Hz); $^{31}P(CDCl_3)$ δ 28.81 (s).

CHEMICAL REDUCTION OF *O,O*-DIETHYL 1-HYDROXYIMINOETHANE-PHOSPHONATE IN PREPARATION OF *O,O*-DIETHYL 1-AMINOETHANE-PHOSPHONATE USING LITHIUM BOROHYDRIDE/TRIMETHYLSILYLCHLORIDE

Trimethylsilyl chloride (8.64 g, 0.080 mol) was added dropwise and with stirring to lithium borohydride (0.87 g, 0.040 mol) dissolved in dry THF (50 cm^3), under dry nitrogen. Upon formation of a white precipitate of lithium chloride, *O,O*-diethyl 1-hydroxyiminoethane-phosphonate (4.13 g, 0.021 mol), dissolved in dry THF (20 cm^3), was slowly added dropwise and with stirring to the mixture. A considerable amount of effervescence occurred during the addition. When the addition had been completed, the solution was left to stir at room temperature for 12 h, under dry nitrogen.

Methanol (100 cm^3) was carefully added dropwise and with stirring to the solution over a period of 30 min, amidst considerable effervescence. The solution was concentrated under reduced pressure on a rotary evaporator. The viscous oily residue formed was treated with aqueous potassium hydroxide (20 %, 40 cm^3) and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined and dried over anhydrous sodium sulphate. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford crude *O,O*-diethyl 1-aminoethane-phosphonate as a viscous yellow oil. This material was distilled under high vacuum to produce *O,O*-diethyl 1-aminoethanephosphonate[124] as a

colourless free-flowing liquid (Crude: 1.67 g, 44 % Distilled 0.90 g, 24 %); b.p. 84-85 ^{o}C at 0.20-0.30 mmHg; (Found: C, 39.50; H, 8.92; N, 7.41. Calc. for $C_6H_{16}NO_3P$: C, 39.50; H, 8.84; N, 7.74 %); $^{1}H(CDCl_3)$ δ 1.34 (dd, 3H, P-CHC$\underline{H}_3$, $^{3}J_{HCCH}$ 7.00 Hz, $^{3}J_{PCCH}$ 18.14 Hz), 1.35 (t, 6H, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{HCCH}$ 7.00 Hz), 3.10 (dq overlapping, 1H, P-C$\underline{H}$, $^{3}J_{HCCH}$ 7.25 Hz, $^{2}J_{PCH}$ 9.51 Hz), 4.15 (m, 4H, 2xCH$_3$C$\underline{H}_2$O-); $^{13}C(CDCl_3)$ δ 16.57 (d, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{POCC}$ 5.54 Hz), 16.99 (s, P-CHC$\underline{H}_3$), 44.08 (d, P-C$\underline{H}$CH$_3$, $^{1}J_{PC}$ 150.42 Hz), 62.24 (d, 2xCH$_3$C$\underline{H}_2$O-, $^{2}J_{POC}$ 7.06 Hz), $^{31}P(CDCl_3)$ δ 28.87 (s).

CHEMICAL REDUCTION OF *O,O*-DIMETHYL 1-HYDROXYIMINOPROPANE-PHOSPHONATE IN PREPARATION OF *O,O*-DIMETHYL 1-AMINOPROPANE-PHOSPHONATE USING LITHIUM BOROHYDRIDE/TRIMETHYLSILYLCHLORIDE

Trimethylsilyl chloride (17.28 g, 0.16 mol) was added dropwise and with stirring to lithium borohydride (1.74 g, 0.080 mol) dissolved in dry THF (40 cm^3), under dry nitrogen. Upon formation of a white precipitate of lithium chloride, *O,O*-dimethyl 1-hydroxyiminopropane-phosphonate (7.24 g, 0.040 mol), dissolved in dry THF (20 cm^3), was slowly added dropwise and with stirring to the mixture. A considerable amount of effervescence occurred during the addition. When the addition has been completed, the solution was left to stir for 12 h at room temperature under dry nitrogen.

Methanol (100 cm^3) was carefully added dropwise and with

stirring to the solution over a period of 30 min, amidst considerable effervescence. The solution was concentrated under reduced pressure on a rotary evaporator. The viscous oily residue that formed was treated with aqueous potassium hydroxide (20 %, 30 cm^3) and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined and dried over anhydrous sodium sulphate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure on rotary evaporator, to afford crude *O,O*-dimethyl 1-aminopropane-phosphonate as a viscous yellow oil. This material was distilled under high vacuum to produce clear, free-flowing fractions of *O,O*-dimethyl 1-aminopropanephosphonate[122] (Crude: 2.03 g, 30 % Distilled: 1.12 g, 17 %); b.p. 84 ^{o}C at 2.00 mmHg; (Found: C, 35.62; H, 8.32; N, 8.38. Calc. for $C_5H_{14}NO_3P$: C, 35.93; H, 8.38; N, 8.38 %); $^{1}H(CDCl_3)$ δ 1.07 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{HCCH}$ 7.37 Hz), 1.48-1.92 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 2.94 (ddd, 1H, P-C$\underline{H}$), 3.80 (dd, 6H, 2xC$\underline{H}_3$O-, $^{3}J_{POCH}$ 10.39 Hz); $^{13}C(CDCl_3)$ δ 10.78 (d, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{PCCC}$ 13.02 Hz), 24.69 (s, P-CH$\underline{C}$H$_2$CH$_3$), 50.00 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 149.19 Hz), 52.85 (dd, 2x$\underline{C}$H$_3$O-, $^{2}J_{POC}$ 7.68 Hz); $^{31}P(CDCl_3)$ δ 31.36 (s).

CHEMICAL REDUCTION OF *O,O*-DIETHYL 1-HYDROXYIMINOPROPANE-PHOSPHONATE IN PREPARATION OF *O,O*-DIETHYL 1-AMINOPROPANE-PHOSPHONATE USING LITHIUM BOROHYDRIDE/TRIMETHYLSILYLCHLORIDE

Trimethylsilylchloride (43.20 g, 0.40 mol) was added dropwise and with stirring to lithium borohydride (4.35 g, 0.20 mol) dissolved in dry THF (100 cm^3), under dry nitrogen. Upon formation of a white precipitate of lithium chloride, *O,O*-diethyl 1-hydroxyiminopropane-phosphonate (20.78 g, 0.099 mol) dissolved in dry THF (50 cm^3) was slowly added dropwise and with stirring to the mixture. A considerable amount of effervescence occurred during the addition, but when the addition had been completed the solution was left to stir at room temperature for 48 h under dry nitrogen.

Methanol (100 cm^3) was carefully added dropwise and with stirring to the solution over a period of 30 min, amidst considerable effervescence. The solution was concentrated under reduced pressure on a rotary evaporator. The viscous oily residue formed was treated with aqueous potassium hydroxide (20 %, 50 cm^3) and extracted with dichloromethane (3x100 cm^3). The organic extracts were combined and dried over anhydrous sodium sulphate. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford crude *O,O*-diethyl 1-aminopropane-phosphonate as a viscous yellow oil. This material was distilled under high vacuum to afford *O,O*-diethyl 1-aminopropanephosphonate[122] as a

colourless, free-flowing liquid (Crude: 13.28 g, 69 % Distilled: 5.68 g, 29 %); b.p. 95 ^{o}C at 0.10 mmHg; (Found: C, 42.98; H, 9.42; N, 7.15. Calc. for $C_7H_{18}NO_3P$: C, 43.08; H, 9.23; N, 7.18 %); $^{1}H(CDCl_3)$ δ 1.07 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{HCCH}$ 7.41 Hz), 1.34 (t, 6H, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{HCCH}$ 7.05 Hz), 1.43-1.92 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 2.83-2.93 (ddd, 1H, P-C$\underline{H}$), 4.15 (m, 4H, 2xCH$_3$C$\underline{H}_2$O-); $^{13}C(CDCl_3)$ δ 10.89 (d, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{PCCC}$ 13.13 Hz), 16.58 (d, 2xC$\underline{H}_3$CH$_2$O-, $^{3}J_{POCC}$ 5.60 Hz), 24.58 (s, P-CH$\underline{C}$H$_2$CH$_3$), 50.36 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 148.49 Hz), 62.02 (dd, 2xCH$_3\underline{C}$H$_2$O-, $^{2}J_{POC}$ 7.10 Hz); $^{31}P(CDCl_3)$ δ 29.12 (s).

CHEMICAL REDUCTION OF *O,O*-DI-ISOPROPYL 1-HYDROXYIMINOPROPANE-PHOSPHONATE IN PREPARATION OF *O,O*-DI-ISOPROPYL 1-AMINOPROPANE-PHOSPHONATE USING LITHIUM BOROHYDRIDE/TRIMETHYLSILYLCHLORIDE

Trimethylsilylchloride (43.20 g, 0.40 mol) was added dropwise and with stirring to lithium borohydride (4.35 g, 0.20 mol) dissolved in dry THF (80 cm^3), under dry nitrogen. Upon formation of a white precipitate of lithium chloride, *O,O*-di-isopropyl 1-hydroxyiminopropane-phosphonate (23.70 g, 0.10 mol) dissolved in dry THF (50 cm^3), was slowly added dropwise and with stirring to the mixture. A considerable amount of effervescence occurred during the addition. When the addition had been completed, the solution was left to stir for 48 h at room temperature under dry nitrogen.

Methanol (100 cm^3) was carefully added dropwise and with

stirring to the solution over a period of 20 min, amidst considerable effervescence. The solution was concentrated under reduced pressure on a rotary evaporator. The viscous oily residue formed was treated with aqueous potassium hydroxide (20 %, 50 cm^3) and extracted with dichloromethane (3x100 cm^3). The organic extracts were combined and dried over anhydrous sodium sulphate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford crude *O,O*-di-isopropyl 1-aminopropane-phosphonate as a viscous yellow oil. A small portion (5.00 g, 0.022 mol), of this material was distilled under high vacuum to afford *O,O-di-isopropyl 1-aminopropanephosphonate* as a colourless, free-flowing liquid (Crude: 19.42 g, 87 % Distilled: 2.34 g, 10.5 %); b.p. 86-90 ^{o}C at 0.05-0.10 mmHg (Found: C, 48.43; H, 10.00; N, 6.34. $C_9H_{22}NO_3P$ requires: C, 48.43; H, 9.87; N, 6.28 %); $^{1}H(CDCl_3)$ δ 1.07 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{HCCH}$ 7.40 Hz), 1.33 (d, 12H, 2x(C$\underline{H}_3$)$_2$CHO-, $^{3}J_{HCCH}$ 6.21 Hz), 1.37-1.96 (m, 2H, P-CHC$\underline{H}_2$), 2.78 (ddd, 1H, P-C$\underline{H}$), 4.69-4.82 (m, 2H, 2x(CH$_3$)$_2$C$\underline{H}$O-); $^{13}C(CDCl_3)$ δ 11.00 (d, P-CHCH$_2$C$\underline{H}_3$, $^{3}J_{PCCC}$ 13.09 Hz), 24.11 (d, 2x(C$\underline{H}_3$)$_2$CHO-, $^{3}J_{POCC}$ 4.32 Hz), 24.55 (s, P-CHC$\underline{H}_2$), 50.84 (d, P-C$\underline{H}$, $^{1}J_{PC}$ 148.98 Hz), 70.23 (d, 2x(CH$_3$)$_2$C$\underline{H}$O, $^{2}J_{POC}$ 7.40 Hz); $^{31}P(CDCl_3)$ δ 26.99 (s).

CHEMICAL REDUCTION OF *O,O*-DIMETHYL 1-HYDROXYIMINOBUTANE-PHOSPHONATE IN PREPARATION OF *O,O*-DIMETHYL 1-AMINOBUTANE-PHOSPHONATE USING LITHIUM BOROHYDRIDE/TRIMETHYLSILYL CHLORIDE

Trimethylsilyl chloride (8.64 g, 0.080 mol) was added dropwise and with stirring to lithium borohydride (0.87 g, 0.040 mol) dissolved in dry THF (50 cm^3), under dry nitrogen. Upon formation of a white precipitate of lithium chloride, *O,O*-dimethyl 1-hydroxyiminobutane-phosphonate (3.90 g, 0.020 mol), dissolved in dry THF (20 cm^3), was slowly added dropwise and with stirring to the mixture. A considerable amount of effervescence occurred during the addition. When the addition had been completed, the solution was left to stir for12 h at room temperature, under dry nitrogen.

Methanol (100 cm^3) was carefully added dropwise and with stirring to the solution over a period of 20 min, amidst considerable effervescence. The solution was concentrated under reduced pressure on a rotary evaporator. The viscous oily residue formed was treated with aqueous potassium hydroxide (20 %, 30 cm^3) and extracted with dichloromethane (3x50 cm^3). The organic extracts were combined and dried over anhydrous sodium sulphate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford crude *O,O*-dimethyl 1-aminobutanephosphonate as a viscous yellow oil. This material was distilled under high vacuum to afford *O,O*-dimethyl 1-aminobutanephosphonate[122] as a colourless

free-flowing liquid (Crude: 0.41 g, 11 % Distilled: 0.35 g, 10 %); b.p. 82 °C at 0.20 mmHg; (Found: C, 39.23; H, 8.46; N, 7.34. Calc. for $C_6H_{16}NO_3P$: C, 39.78; H, 8.84; N, 7.74 %); $^1H(CDCl_3)$ δ 0.95 (t, 3H, P-CHCH$_2$CH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 6.99 Hz), 1.26-1.83 (m, 4H, P-CHC$\underline{H}_2$C$\underline{H}_2$CH$_3$), 2.99 (ddd, 1H, P-C$\underline{H}$), 3.80 (dd, 6H, 2xC$\underline{H}_3$O-, $^3J_{POCH}$ 10.40 Hz); $^{13}C(CDCl_3)$ δ 13.75 (s, P-CHCH$_2$CH$_2$C$\underline{H}_3$), 19.28 (d, P-CHCH$_2$C$\underline{H}_2$CH$_3$, $^3J_{PCCC}$ 12.94 Hz), 33.38 (s, P-CHC$\underline{H}_2$CH$_2$CH$_3$), 48.18 (d, P-C$\underline{H}$, $^1J_{PC}$ 149.15 Hz), 52.96 (dd, 2xC$\underline{H}_3$O-, $^2J_{POC}$ 7.32 Hz); $^{31}P(CDCl_3)$ δ 31.61 (s).

ATTEMPT TO PREPARE *O,O*-DIETHYL 1-GUANIDINOPROPANE-PHOSPHONATE

O,O-Diethyl 1-aminopropanephosphonate (0.47 g, 0.024 mol) was added dropwise and with stirring to aminoiminomethanesulphonic acid (0.30 g, 0.024 mol), dissolved in freshly distilled methanol (10 cm^3), under dry nitrogen at room temperature, for 12 h. The solution was concentrated under reduced pressure on a rotary evaporator to afford an oily residue. This material was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the residue became extremely viscous. (5.44 g, 95 %); $^1H(CD_3OD)$ δ 0.92-1.03 (m), 1.26-1.43 (m), 1.49-1.94 (m), 4.10-4.34 (m), 5.05 (br, s); $^{13}C(CD_3OD)$ δ 13.59-14.13 (m), 16.67-16.90 (m), 19.82-20.32 (m), 47.90-49.95 (m), 63.53-65.21 (m); $^{31}P(CD_3OD)$ δ 19.96, 20.64, 22.61, 25.40, 25.89 (this spectrum confirmed that the product isolated was a mixture).

4.4.9. PREPARATION OF *N*-ALKYLIDENEBENZYLAMINES AND *N*-BENZYLIDENEBENZYLAMINES

PREPARATION OF *N*-METHYLETHYLIDENEBENZYLAMINE

Acetone (5.8 g, 0.10 mol) was added dropwise and with stirring to a solution of benzylamine (10.7 g, 0.10 mol), in ether (30 cm^3) at 0 ^oC. The solution was stirred for 1 h at room temperature in the presence of anhydrous potassium carbonate (5 g). The mixture was filtered, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford crude *N*-methylethylidenebenzylamine as a pale-yellow oily residue (14.7 g, 0.10 mol, 100 %). This material was distilled under vacuum to give pure *N*-methylethylidenebenzylamine[25] as a clear free running liquid (6.7 g, 45.6 %); b.p. 113-116 ^oC at 10-15 mmHg; (Found: C, 81.81; H, 8.69; N, 9.74. Calc. for $C_{10}H_{13}N$: C, 81.63; H, 8.84; N, 9.52 %); $^1H(CDCl_3)$ δ 1.81 (s, 3H, $C\underline{H}_3(CH_3)C=N$), 2.02 (s, 3H, $CH_3(C\underline{H}_3)C=N$), 4.38 (s, 2H, $NC\underline{H}_2$), 7.17-7.30 (m, 5H, $C_6\underline{H}_5$); $^{13}C(CDCl_3)$ δ 18.62 (s, $\underline{C}H_3(CH_3)C=N$), 29.33 (s, $CH_3(\underline{C}H_3)C=N$), 63.84 (s, $N\underline{C}H_2$), 126.62 (s, $\underline{C}_4$ of aromatic ring), 126.99 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 126.99 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 128.34 (s, $\underline{C}_1$ of aromatic ring), 167.87 (s, $CH_3(CH_3)\underline{C}=N$).

PREPARATION OF *N*-PROPYLIDENEBENZYLAMINE

Propanal (5.8 g, 0.10 mol) was added dropwise and with stirring to a solution of benzylamine (10.7 g, 0.10 mol), in ether (40 cm^3) at 0 ^oC. The solution was stirred for 1 h at room temperature, in the presence of anhydrous potassium carbonate (5 g). The mixture was filtered, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford crude *N*-propylidenebenzylamine, as a pale-yellow residue (14.7 g, 0.10 mol, 100 %). This material was distilled under vacuum to yield pure *N*-propylidenebenzylamine[25] as a clear free-running liquid (10.06 g, 68.4 %); b.p. 94-96 ^oC at 10 mmHg; (Found: C, 81.58; H, 8.92; N, 9.32. Calc. for $C_{10}H_{13}N$: C, 81.63; H, 8.84; N, 9.52 %); $^1H(CDCl_3)$ δ 1.10 (t, 3H, $CH_2\underline{C}H_3$, $^3J_{HCCH}$ 7.00 Hz), 2.25 (m, 2H, $C\underline{H}_2CH_3$), 4.50 (s, 2H, $NC\underline{H}_2$), 7.13-7.39 (m, 5H, $C_6\underline{H}_5$), 7.75 (t, 1H, $C\underline{H}CH_2$, $^3J_{HCCH}$ 7.05 Hz); $^{13}C(CDCl_3)$ δ 10.19 (s, $CH_2\underline{C}H_3$), 29.13 (s, $\underline{C}H_2CH_3$), 64.94 (s, $N\underline{C}H_2$), 126.73 (s, $\underline{C}_4$ of aromatic ring), 126.84 (s, $\underline{C}_3$ & $\underline{C}_5$, of aromatic ring), 127.81 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 129.08 (s, $\underline{C}_1$ of aromatic ring), 166.91 (s, $\underline{C}H$=N).

PREPARATION OF *N*-2-ETHYLHEXYLIDENEBENZYLAMINE

2-Ethylhexanal (12.8 g, 0.10 mol) was added dropwise and with stirring to a solution of benzylamine (10.7 g, 0.10 mol), in ether (40 cm^3), at 0 ^oC. The solution was stirred for 1 h at room temperature

in the presence of anhydrous potassium carbonate (5 g). The mixture was filtered, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford crude *N-2-ethylhexylidenebenzylamine*, as a pale-yellow oily residue (18.05 g, 83 %). This material was distilled under high vacuum to yield pure *N-2-ethylhexylidenebenzylamine* as a clear, free running liquid (15.16 g, 69.9 %); b.p. 98-102 ^{o}C at 0.15-0.20 mmHg; (Found: C, 82.80; H, 10.62; N, 6.44. $C_{15}H_{15}N$ requires: C, 82.95; H, 10.60; N, 6.45 %); ^{1}H($CDCl_3$) δ 0.88 (2xt overlapping, 6H, $CH_3(CH_2)_3CH$ & CH_2CH_3, $^{3}J_{HCCH}$ 7.43 Hz), 1.19-1.36 (m, 4H, $CH_3CH_2CH_2CH_2CH$-CH=N), 1.39-1.52 (m, 4H, $CH_3CH_2CH_2CH_2CH$-CH=N overlapping with $CHCH_2CH_3$), 2.18 (dt overlapping, 1H, $CHCH_2CH_3$, $^{3}J_{HCCH}$ 6.78 Hz), 4.51 (s, 2H, N-CH_2), 7.12-7.28 (m, 5H, C_6H_5), 7.47 (d, 1H, CH=N, $^{3}J_{HCCH}$ 6.62 Hz); ^{13}C($CDCl_3$) δ 11.69 (s, $CH_3(CH_2)_3CH$), 14.04 (s, CH_2CH_3), 22.82 (s, $CH_3CH_2CH_2CH_2$), 25.38 (s, $CH_3CH_2CH_2CH_2$), 29.43 (s, $CH_3CH_2CH_2CH_2$), 31.87 (s, $CH(CH_2CH_3)$CH=N), 46.64 (s, $CH_3(CH_2)_3CH$), 65.09 (s, NCH_2), 126.72 (s, C_4 of aromatic ring), 127.73 (s, C_3 & C_5 of aromatic ring), 128.32 (s, C_2 & C_6 of aromatic ring), 139.62 (s, C_1 of aromatic ring), 169.83 (s, CH=N).

PREPARATION OF *N*-BENZYLIDENEBENZYLAMINE

Benzaldehyde (10.61 g, 0.10 mol) was added dropwise and with stirring to a solution of benzylamine (10.70 g, 0.10 mol) in ether (30 cm^3), at 0 ^{o}C. The mixture was stirred for 1 h at room temperature

in the presence of anhydrous potassium carbonate (5 g). The solution was filtered and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *N*-benzylidenebenzylamine[25] as a pale-yellow, viscous oily residue. Upon standing, the compound became a yellow crystalline solid (10.0 g, 51 %); (Found: C, 85.25; H, 7.15; N, 7.78. Calc. for $C_{14}H_{13}N$: C, 86.15; H, 6.67; N, 7.18 %); $^{1}H(CDCl_3)$ δ 4.81 (s, 2H, $NC\underline{H}_2C_6H_5$), 7.24-7.79 (m, 10H, $C_6\underline{H}_5CH{=}N$ overlapping with $NCH_2C_6\underline{H}_5$), 8.37 (s, 1H, $C\underline{H}{=}N$); $^{13}C(CDCl_3)$ δ 65.03 (s, $N\underline{C}H_2$), 126.97 (s, $\underline{C}_4$ of aromatic ring), 127.97 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 128.27 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 128.48 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 128.58 (s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring), 130.74 (s, $\underline{C}_4$ of benzylidene ring), 136.16 (s, $\underline{C}_1$ of benzylidene ring), 139.29 (s, $\underline{C}_1$ of aromatic ring), 161.96 (s, $\underline{C}H{=}N$).

PREPARATION OF *N*-2'-HYDROXYBENZYLIDENEBENZYLAMINE

Salicylaldehyde (12.2 g, 0.10 mol) was added dropwise and with stirring to a solution of benzylamine (10.7 g, 0.10 mol) in ether (50 cm^3), at 0 °C. The solution was stirred for 1 h at room temperature in the presence of anhydrous potassium carbonate (5 g). The solution was filtered and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *N-2'-hydroxybenzylidenebenzylamine* as a bright-yellow solid. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h to remove residual traces of volatile

material that may have been present (20.43 g, 97 %); (Found: C, 79.33; H, 6.25; N, 6.75. $C_{14}H_{13}NO$ requires: C, 79.62; H, 6.16; N, 6.64 %); $^1H(CDCl_3)$ δ 4.57 (s, 2H, $NC\underline{H}_2$), 6.77 (dd overlapping, 1H, $\underline{H}_5$ of benzylidene ring, $^3J_{HCCH}$ 7.41 Hz), 6.94 (d, 1H, $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.25 Hz), 7.09-7.27 (m, 7H, $\underline{H}_3$,$\underline{H}_4$ & $C_6\underline{H}_5$), 8.18 (s, 1H, $C\underline{H}$=N), 13.46 (s, br, 1H, OH, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 62.89 (s, $N\underline{C}H_2$), 116.88 (s, $\underline{C}_4$ of aromatic ring), 118.50 (s, $\underline{C}_6$ of benzylidene ring), 118.74 (s, $\underline{C}_1$ of benzylidene ring), 127.18 (s, $\underline{C}_5$ of benzylidene ring), 127.54 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 128.52 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 131.42 (s, $\underline{C}_4$ of benzylidene ring), 132.23 (s, $\underline{C}_3$ of benzylidene ring), 138.12 (s, $\underline{C}_1$ of aromatic ring), 161.06 (s, $\underline{C}$H=N), 165.59 (s, $\underline{C}_2$ of benzylidene ring).

PREPARATION OF *N*-4'-METHOXYBENZYLIDENEBENZYLAMINE

4-Methoxybenzaldehyde (13.6 g, 0.10 mol) was added dropwise and with stirring to a solution of benzylamine (10.7 g, 0.10 mol) in ether (50 cm^3) at 0 ^oC. The mixture was stirred for 1 h at room temperature in the presence of potassium carbonate (5 g). The solution was filtered, and the filtrate was concentrated under reduced pressure on a rotary evaporator, to afford *N-4'-methoxybenzylidenebenzylamine* as a bright-yellow, low-melting point solid. This material was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, to remove any residual traces of volatile material that may been present (21.53 g, 96 %); m.p.

33-35 °C; (Found: C, 79.70; H, 6.73; N, 6.15. $C_{15}H_{15}NO$ requires: C, 80.00; H, 6.67; N, 6.22 %); $^{1}H(CDCl_3)$ δ 3.67 (s, 3H, CH_3O-), 4.71 (s, 2H, NCH_2), 6.85 (d, 2H, H_2 & H_6 of benzylidene ring, $^{3}J_{HCCH}$ 8.73 Hz), 7.15 - 7.30 (m, 5H, C_6H_5), 7.68 (H_3 & H_5 of benzylidene ring, $^{3}J_{HCCH}$ 8.74 Hz), 8.21 (s, 1H, CH=N); $^{13}C(CDCl_3)$ δ 55.13 (s, CH_3O-), 64.82 (s, NCH_2), 113.90 (s, C_2 & C_6 of benzylidene ring), 126.81 (s, C_4 of aromatic ring), 127.37 (s, C_3 & C_5 of benzylidene ring), 129.04 (s, C_1 of benzylidene ring), 129.77 (s, C_2 & C_6 of aromatic ring), 139.57 (s, C_1 of aromatic ring), 161.17 (s, CH=N), 161.22 (s, C_4 of aromatic ring).

PREPARATION OF *N*-PENTAFLUOROBENZYLIDENEBENZYLAMINE

Pentafluorobenzaldehyde (5.54 g, 0.028 mol) dissolved in ether (20 cm^3) was added dropwise and with stirring to a solution of benzylamine (3.03 g, 0.028 mol) in ether (20 cm^3) at 0 °C. The solution was stirred for 1 h at room temperature in the presence of anhydrous potassium carbonate (3 g). The solution was filtered and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford *N-pentafluorobenzylidenebenzylamine* as an orange-brown, oily residue. This material was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became a sticky solid (4.50 g, 56 %); (Found: C, 59.04; H, 2.60; N, 4.94. $C_{14}F_5H_8N$ requires: C, 58.95; H, 2.81; N, 4.91 %); $^{1}H(CDCl_3)$ δ 4.86 (s, 2H, NCH_2), 7.22-7.41 (m, 5H, C_6H_5), 8.47 (s, 1H, CH=N); $^{13}C(CDCl_3)$ δ 66.48 (s, NCH_2), 110.02 (d, C_1

of fluoroaromatic ring, $^{2}J_{FCC}$ 131.45 Hz), 127.23 (s, $\underline{C}_4$ of aromatic ring), 127.78 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 128.62 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 138.49 (s, $\underline{C}_1$ of aromatic ring),

ATTEMPTED PREPARATION OF *N*-TRIFLUOROETHYLIDENE-BENZYLAMINE

Trifluoroacetaldehyde monohydrate (11.6 g, 0.10 mol), said to contain varying amounts of the ethyl hemiacetal, as specified by the manufacturers (Lancaster Synthesis), was added dropwise and with stirring to a solution of benzylamine (10.7 g, 0.10 mol) in ether (30 cm^3), at 0 ^{o}C. The mixture was stirred for 1 h at room temperature in the presence of anhydrous potassium carbonate (5 g). The solution was filtered, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford what was expected to be crude *N*-trifluoroethylidenebenzylamine. Distillation under vacuum afforded a clear free-running liquid. After standing for 1 week at room temperature, the solution turned pale-green in colour. Spectroscopic analyses showed that this observation was symptomatic of considerable decomposition. (4.5 g, 24 %); b.p. 84-88 ^{o}C at 10-15 mmHg; (Found: C, 57.68; H, 5.32; N, 8.04. $C_9F_3H_8N$ requires: C, 57.75; H, 4.28; N, 7.49 %); $^{1}H(CDCl_3)$ δ 3.85 (s, 2H, $NC\underline{H}_2$), 7.00-7.40 (m, 6H, $C_6\underline{H}_5$ overlapping with $CF_3C\underline{H}$=N); $^{13}C(CDCl_3)$ extremely complex, indicating that the expected product had not been isolated.

ATTEMPTED PREPARATION OF *N*-PENTAFLUOROPROPYLIDENE-BENZYLAMINE

Pentafluoropropanal monohydrate (3.9 g, 0.023 mol), said to contain varying amounts of the ethyl hemiacetal as specified by the manufacturers (Lancaster Synthesis), was added dropwise and with stirring to a solution of benzylamine (2.46 g, 0.023 mol) in ether (20 cm^3), at 0 ^oC. The mixture was stirred for 1 h at room temperature in the presence of anhydrous potassium carbonate (4 g). The solution was filtered, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford what was expected to be *N-pentafluoropropylidenebenzylamine* as a yellow oily residue (5.15 g). This material was distilled under vacuum to afford a clear free-running liquid. After standing for 1 week at room temperature, the solution turned pale-green in colour. Spectroscopic analyses showed that this observation was indicative of decomposition and that the expected product may not have been isolated (1.25 g, 22 %), b.p. 90-92 ^oC at 10 mmHg; (Found:C, 51.19; H, 4.72; N, 5.30. $C_{10}F_5H_8N$ requires: C, 50.63; H, 3.38; N, 5.91 %); $^1H(CDCl_3)$ δ 3.90 (s, 2H, NCH_2), 7.10-7.50 (m, 6H, C_6H_5 overlapping with CH=N); $^{13}C(CDCl_3)$ extremely complex, no positive identification of the expected product could be made.

4.4.10. PREPARATION OF *O,O*-DIALKYL 1-BENZYLAMINOALKANE- AND *O,O*-DIALKYL 1-BENZYLAMINOBENZYL- PHOSPHONATES

PREPARATION OF *O,O*-DIMETHYL 1-BENZYLAMINO-1-METHYLETHANE-PHOSPHONATE

Dimethyl phosphite (4.40 g, 0.040 mol) was added dropwise and with stirring to *N*-methylethylidenebenzylamine (5.90 g, 0.040 mol) at 0 ^{o}C. The mixture was stirred for 12 h at room temperature. The crude material was column chromatographed through silica gel, 60-200 mesh, using methanol as the eluting solvent. Fractions containing the desired phosphonate, were pooled and concentrated under reduced pressure on rotary evaporator, to afford *O,O*-dimethyl 1-benzylamino-1-methyl-ethanephosphonate[25] as a reddish-brown oily residue. This material was shaken under high vacuum (0.10 mmHg) for 2 h, during which time it became more viscous (6.50 g, 100 %); (Found: C, 55.97; H, 7.93; N, 5.61. Calc. for $C_{12}H_{20}NO_3P$: C, 56.03; H, 7.78; N, 5.45 %); ^{1}H($CDCl_3$) δ 1.36 (d, 6H, P-C($\underline{H}_3$)$_2$, $^{3}J_{PCCH}$ 15.76 Hz), 3.35 (m, 1H, P-C-C-N$\underline{H}$), 3.68 (d, 2H, NH$\underline{C}$H$_2$, $^{3}J_{NHCH}$ 1.04 Hz), 3.78 (d, 6H, 2x$\underline{C}$H$_3$O-, $^{3}J_{POCH}$ 10.20 Hz), 7.15-7.36 (m, 5H, $C_6\underline{H}_5$); ^{13}C($CDCl_3$) δ 23.19 (d, P-C($\underline{C}$H$_3$)$_2$, $^{2}J_{PCC}$ 3.15 Hz), 47.47 (d, NH$\underline{C}$H$_2$ $^{3}J_{PCNC}$ 5.35 Hz), 52.98 (d, 2x$\underline{C}$H$_3$O-, $^{2}J_{POC}$ 7.61 Hz), 53.88 (d, P-$\underline{C}$(CH$_3$)$_2$, $^{1}J_{PC}$ 145.92 Hz), 126.85 (s, $\underline{C}_4$ of aromatic ring), 128.19 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 128.31 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 140.91 (s, $\underline{C}_1$ of aromatic ring); ^{31}P($CDCl_3$)

δ 33.28 (s).

PREPARATION OF *O,O*-DIETHYL 1-BENZYLAMINO-1-METHYLETHANE-PHOSPHONATE

Diethyl phosphite (0.94 g, 0.0068 mol) was added dropwise and with stirring to *N*-methylethylidenebenzylamine (1.00 g, 0.0068 mol) at 0 ^{o}C. The mixture was stirred for 12 h at room temperature. The product was shaken under high vacuum (0.10 mmHg) for 2 h, to afford *O,O*-diethyl 1-benzylamino-1-methylethanephosphonate[25] as a reddish-brown, viscous, oily residue (1.6 g, 83 %); (Found: C, 58.76; H, 8.33; N, 4.88. Calc. for $C_{14}H_{24}NO_3P$: C, 58.95; H, 8.42; N, 4.91 %); $^{1}H(CDCl_3)$ δ 1.32 (t, 6H, 2xCH_3CH_2O-, $^{3}J_{HCCH}$ 7.07 Hz), 1.35 (d, 6H, P-C(CH_3)$_2$, $^{3}J_{PCCH}$ 15.54 Hz), 3.91 (d, 2H, NCH_2, $^{3}J_{HNCH}$ 1.10 Hz), 4.09-4.22 (dq overlapping, 4H, 2xCH_3CH_2O-, $^{3}J_{HCCH}$ 7.10 Hz), 7.19-7.36 (m, 6H, $NHCH_2$ overlapping C_6H_5); $^{13}C(CDCl_3)$ δ 16.64 (d, 2xCH_3CH_2O-, $^{3}J_{POCC}$ 5.22 Hz), 23.20 (d, P-C(CH_3)$_2$, $^{2}J_{PCC}$ 3.40 Hz), 47.54 (d, $NHCH_2$, $^{3}J_{PCNC}$ 5.16 Hz), 53.50 (d, P-$C(CH_3)_2$, $^{1}J_{PC}$ 145.92 Hz), 62.00 (d, 2xCH_3CH_2O-, $^{2}J_{POC}$ 7.61 Hz), 126.81 (s, C_4 of aromatic ring), 128.13 (s, C_3 & C_5 of aromatic ring), 128.29 (s, C_2 & C_6 of aromatic ring), 141.09 (s, C_1 of aromatic ring); $^{31}P(CDCl_3)$ δ 30.76 (s).

PREPARATION OF *O,O*-DIMETHYL 1-BENZYLAMINOPROPANEPHOSPHONATE

Dimethyl phosphite (4.40 g, 0.040 mol) was added dropwise and with stirring to a solution of *N*-propylidenebenzylamine (5.88 g, 0.040 mol), dissolved in methanol (50 cm^3), at 0 ^oC. The mixture was stirred for 12 h at room temperature. After concentration under reduced pressure on a rotary evaporator, the yellow oily residue formed, was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became more viscous. Upon standing, *O,O*-dimethyl 1-benzylaminopropanephosphonate[25] was afforded as a bright yellow, sticky, material (9.2 g, 90 %); (Found: C, 56.11; H, 7.89; N, 6.06. Calc. for $C_{12}H_{20}NO_3P$: C, 56.03; H, 7.78; N, 5.45 %); $^1H(CDCl_3)$ δ 1.01 (t, 3H, $CH_2\underline{CH}_3$, $^3J_{HCCH}$ 7.41 Hz), 1.54-1.90 (m, 2H, $\underline{CH}_2CH_3$), 2.79-2.89 (m, 1H, P-$\underline{CH}$), 3.77 (dd, 6H, 2x$\underline{CH}_3O$-, $^3J_{POCH}$ 10.37 Hz), 3.90 (d, 2H, NCH_2, $^3J_{HNCH}$ 5.84 Hz), 7.19-7.37 (m, 6H, $N\underline{H}CH_2$ overlapping $C_6\underline{H}_5$); $^{13}C(CDCl_3)$ δ 10.66 (d, $CH_2\underline{CH}_3$, $^3J_{PCCC}$ 10.31 Hz), 22.78 (d, $\underline{CH}_2CH_3$, $^2J_{PCC}$ 2.45 Hz), 52.04 (d, $NH\underline{CH}_2$, $^3J_{PCNC}$ 6.73 Hz), 52.68 (dd, 2x$\underline{CH}_3O$-, $^2J_{POC}$ 7.05 Hz), 55.10 (d, P-$\underline{CH}$, $^1J_{PC}$ 148.88 Hz), 127.08 (s, $\underline{C}_4$ of aromatic ring), 128.29 (s, $\underline{C}_2$,$\underline{C}_3$,$\underline{C}_5$,$\underline{C}_6$ of aromatic ring), 139.99 (s, $\underline{C}_1$ of aromatic ring); $^{31}P(CDCl_3)$ δ 30.67 (s).

PREPARATION OF *O,O*-DIETHYL 1-BENZYLAMINOPROPANEPHOSPHONATE

Diethyl phosphite (5.52 g, 0.040 mol) was added dropwise and with stirring to a solution of *N*-propylidenebenzylamine (5.88 g, 0.040 mol), dissolved in absolute ethanol (40 cm^3) at 0 ^oC. The mixture was stirred for 12 h at room temperature. After concentration under reduced pressure on a rotary evaporator, the pale-yellow, oily residue formed was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became more viscous. Upon standing, *O,O*-diethyl 1-benzylaminopropanephosphonate[25] was afforded as a sticky, yellow solid (11.21 g, 98 %); (Found: C, 59.36; H, 8.68; N, 4.87. Calc. for $C_{14}H_{24}NO_3P$: C, 58.95; H, 8.42; N, 4.91 %); $^1H(CDCl_3)$ δ 1.02 (t, 3H, $CH_2\underline{CH}_3$, $^3J_{HCCH}$ 7.40 Hz), 1.33 (dt overlapping, 6H, 2x$\underline{CH}_3CH_2O$, $^3J_{HCCH}$ 7.30 Hz), 1.62-1.98 (m, 2H, $\underline{CH}_2CH_3$), 2.75-2.83 (m, 1H, P-$\underline{CH}$), 3.92 (d, 2H, $NC\underline{H}_2$, $^3J_{HNCH}$ 5.65 Hz), 4.08-4.19 (m, 4H, 2x$CH_3\underline{CH}_2O$-), 7.17-7.37 (m, 6H, $N\underline{H}CH_2$ overlapping with $C_6\underline{H}_5$); $^{13}C(CDCl_3)$ δ 10.75 (d, $CH_2\underline{CH}_3$, $^3J_{PCCC}$ 10.44 Hz), 16.59 (dd, 2x$\underline{CH}_3CH_2O$-, $^3J_{POCC}$ 5.54 Hz), 22.81 (d, $\underline{CH}_2CH_3$, $^2J_{PCC}$ 2.33 Hz), 52.07 (d, $NH\underline{CH}_2$, $^3J_{PCNC}$ 6.42 Hz), 55.42 (d, P-$\underline{CH}$, $^1J_{PC}$ 148.75 Hz), 61.84 (dd, 2x$CH_3\underline{CH}_2O$-, $^2J_{POC}$ 6.79 Hz), 127.05 (s, $\underline{C}_4$ of aromatic ring), 128.25 ($\underline{C}_2$,$\underline{C}_3$,$\underline{C}_5$,$\underline{C}_6$ of aromatic ring), 140.14 (s, $\underline{C}_1$ of aromatic ring); $^{31}P(CDCl_3)$ δ 28.54 (s).

PREPARATION OF *O,O*-DIMETHYL 1-BENZYLAMINO-2'-HYDROXY-BENZYLPHOSPHONATE

Dimethyl phosphite (12.47 g, 0.113 mol) was added dropwise and with stirring to a solution of *N*-2-hydroxybenzylidenebenzylamine (23.92 g, 0.113 mol) dissolved in methanol (80 cm^3) at 0 ^oC. The mixture was stirred for 12 h at room temperature. After concentration under reduced pressure on a rotary evaporator, the pale-yellow, oily residue formed was shaken under high vacuum (0.10 mmHg) for 2 h. *O,O-dimethyl 1-benzylamino-2'-hydroxybenzylphosphonate* was afforded as a bright-yellow, sticky solid (35.50 g, 98 %); (Found: C, 59.67; H, 6.37; N, 4.42. $C_{16}H_{20}NO_4P$ requires: C, 59.81; H, 6.23; N, 4.36 %); $^1H(CDCl_3)$ δ 3.63 (dd, 6H, 2xCH_3O-, $^3J_{POCH}$ 10.45 Hz), 3.91 (d, 2H, $NHCH_2$, $^3J_{HNCH}$ 5.45 Hz), 4.23 (dd, 1H, P-CH, $^2J_{PCH}$ 19.12 Hz), 6.81-6.97 (m, 2H, H_4 & H_5 of benzylidene ring), 7.04 (d, 1H, H_6 of benzylidene ring, $^3J_{HCCH}$ 7.68 Hz), 7.18-7.37 (m, 7H, H_3 of benzylidene ring, overlapping with $NHCH_2$ & C_6H_5), 10.91 (s, br, 1H, OH, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 51.77 (d, NCH_2, $^3J_{PCNC}$ 17.08 Hz), 53.78 (dd, 2xCH_3O, $^2J_{POC}$ 7.12 Hz), 59.33 (d, P-CH, $^1J_{PC}$ 150.88 Hz), 117.22 (s, C_5 of benzylidene ring), 119.56 (s, C_4 of benzylidene ring), 127.82 (s, C_4 of aromatic ring), 128.63 (s, C_3 & C_5 of aromatic ring), 128.76 (s, C_2 & C_6 of aromatic ring), 129.70 (s, C_3 of benzylidene ring), 130.36 (d, C_6 of benzylidene ring, $^3J_{PCCC}$ 6.10 Hz), 131.90 (d, C_1 of benzylidene ring, $^2J_{PCC}$ 58.56 Hz), 137.30 (s, C_1 of aromatic ring), 157.98 (d, C_2 of

benzylidene ring, $^{3}J_{PCCC}$ 4.84 Hz); $^{31}P(CDCl_3)$ δ 25.14 (s).

PREPARATION OF *O,O*-DIMETHYL 1-BENZYLAMINO–4'-METHOXY-BENZYLPHOSPHONATE

Dimethyl phosphite (10.02 g, 0.091 mol) was added dropwise and with stirring to a solution of *N*-4'-methoxybenzylidenebenzylamine (20.49 g, 0.091 mol) dissolved in methanol (100 cm^3) at 0 ^{o}C.The mixture was stirred at room temperature for 12 h. After concentration under reduced pressure on a rotary evaporator, the bright-yellow oily residue formed was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became very viscous. Upon standing, *O,O-dimethyl 1-benzylamino-4'-methoxybenzylphosphonate*, was afforded as a bright orange-yellow, sticky solid (30.44 g, 99 %); (Found: C, 59.10; H, 6.72; N, 4.08. $C_{17}H_{22}NO_4P$ requires: C, 60.90; H, 6.57; N, 4.18 %); $^{1}H(CDCl_3)$ δ 3.39 (s, 3H, $C\underline{H}_3O$-), 3.52 (d, 2H, $NHC\underline{H}_2$, $^{3}J_{HNCH}$ 10.50 Hz), 3.74 (6H, dd overlapping, $2xC\underline{H}_3O$-, $^{3}J_{POCH}$ 10.09 Hz), 3.99 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 19.72 Hz), 6.91 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring, $^{3}J_{HCCH}$ 8.27 Hz), 7.22 (m, 8H, $\underline{H}_3$ & $\underline{H}_5$ of benzylidene ring, $N\underline{H}CH_2$, & $C_6\underline{H}_5$, overlapping); $^{13}C(CDCl_3)$ δ 50.92 (d, $NH\underline{C}H_2$, $^{3}J_{PCNC}$ 17.42 Hz), 53.51 (dd, $2x\underline{C}H_3O$-, $^{2}J_{POC}$ 7.08 Hz), 55.16 (s, -O$\underline{C}H_3$), 58.40 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 155.67 Hz), 114.05 (d, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring, $^{3}J_{PCCC}$ 1.89 Hz), 127.15 (s, $\underline{C}_4$ of aromatic ring), 128.32 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 128.38 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 129.72 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 139.21

(s, $\underline{C}_1$ of aromatic ring), 159.43 (s, $\underline{C}_4$ of benzylidene ring); $^{31}P(CDCl_3)$ δ 26.85 (s).

PREPARATION OF *O,O*-DIMETHYL 1-BENZYLAMINOBENZYLPHOSPHONATE

Dimethyl phosphite (5.55 g, 0.050 mol) was added dropwise and with stirring to a solution of *N*-benzylidenebenzylamine (9.38 g, 0.050 mol), dissolved in methanol (30 cm^3) at 0 °C. The mixture was stirred at room temperature for 12 h. After concentration under reduced pressure on a rotary evaporator, the yellow oily residue formed was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became very viscous. Upon standing *O,O*-dimethyl 1-benzylamino-benzylphosphonate[25] was afforded as a yellow, sticky solid (15.08 g, 98 %); (Found: C, 63.11; H, 6.71; N, 4.93. Calc. for $C_{16}H_{20}NO_3P$: C, 62.95; H, 6.56; N, 4.59 %); $^1H(CDCl_3)$ δ 3.51-3.74 (dd overlapping d, 8H, 2x$\underline{CH}_3O$- & NH$\underline{CH}_2$, $^3J_{POCH}$ 10.45 Hz), 4.05 (d, 1H, P-$\underline{CH}$, $^2J_{PCH}$ 20.21 Hz), 7.20-7.45 (m, 11H, P-CH$\underline{C_6H_5}$ & NH$\underline{CH_2C_6H_5}$); $^{13}C(CDCl_3)$ δ 51.16 (d, NH$\underline{CH}_2$, $^3J_{PCNC}$ 17.36 Hz), 53.56 (dd, 2x$\underline{CH}_3O$-, $^2J_{POC}$ 6.89 Hz), 59.30 (d, P-$\underline{CH}$, $^1J_{PC}$ 154.03 Hz), 127.17 (s, $\underline{C}_4$ of aromatic ring), 128.33 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 128.40 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 128.55 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 128.62 (d, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring, $^3J_{PCCC}$ 2.96 Hz), 135.51 (d, $\underline{C}_1$ of benzylidene ring, $^2J_{PCC}$ 3.84 Hz), 139.20 (s, $\underline{C}_1$ of aromatic ring); $^{31}P(CDCl_3)$ δ 25.89 (s).

PREPARATION OF *O,O*-DIMETHYL 1-BENZYLAMINO-2-ETHYL-HEXANEPHOSPHONATE

Dimethyl phosphite (6.98 g, 0.063 mol) was added dropwise and with stirring to a solution of *N*-2-ethylhexylidenebenzylamine (13.75 g, 0.063 mol) dissolved in methanol (50 cm^3) at 0 ^oC. The mixture was stirred at room temperature for 12 h. After concentration under reduced pressure on a rotary evaporator, the reddish-brown, oily residue formed, was vigourously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product, *O,O-dimethyl 1-benzylamino-2-ethylhexane-phosphonate* became more viscous (18.63 g, 90 %); (Found: C, 62.42; H, 9.36; N, 4.22. $C_{17}H_{30}NO_3P$ requires: C, 62.39; H, 9.17; N, 4.28 %); $^1H(CDCl_3)$ δ 0.74 (t, $C\underline{H}_3(CH_2)_3CH$, $^3J_{HCCH}$ 7.30 Hz), 0.88 (t, $CH(CH_2C\underline{H}_3)$, $^3J_{HCCH}$ 7.44 Hz), 1.21-1.66 (m, 8H, $CH(C\underline{H}_2CH_3)$ overlapping with $CH(C\underline{H}_2)_3CH_3$), 2.15-2.23 (m, 1H, P-CHC$\underline{H}$), 2.93-3.03 (m, 1H, P-C$\underline{H}$), 3.72-3.80 (dd overlapping d, 8H, 2x$C\underline{H}_3O$- & $NHC\underline{H}_2$, $^3J_{POCH}$ 10.35 Hz), 7.21-7.36 (m, 6H, $N\underline{H}CH_2C_6\underline{H}_5$); $^{13}C(CDCl_3)$ δ 12.00 (s, $CH(CH_2)_3\underline{C}H_3$), 14.09 (s, $CH(CH_2\underline{C}H_3)$), 22.95 (s, $CHCH_2CH_2\underline{C}H_2CH_3$), 23.00 (s, $CHCH_2\underline{C}H_2CH_2CH_3$), 23.35 (d, $CH\underline{C}H_2CH_2CH_2CH_3$, $^3J_{PCCC}$ 13.05 Hz), 29.89 (d, $CH(CH_2\underline{C}H_3)$, $^3J_{PCCC}$ 9.72 Hz), 38.39 (d, P-CH$\underline{C}$H, $^2J_{PCC}$ 3.30 Hz), 51.42 (d, $NH\underline{C}H_2$, $^3J_{PCNC}$ 7.79 Hz), 52.34 (dd, 2x$\underline{C}H_3O$-, $^2J_{POC}$ 7.01 Hz), 63.41 (d, P-$\underline{C}$H, 134.42 Hz), 127.11 (s, $\underline{C}_4$ of aromatic ring), 128.20 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 128.63 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 140.15 (s, $\underline{C}_1$ of aromatic ring); $^{31}P(CDCl_3)$ δ 31.38 (s).

PREPARATION OF *O,O*-DIETHYL 1-BENZYLAMINO-2-ETHYL-HEXANEPHOSPHONATE

Diethyl phosphite (8.60 g, 0.062 mol) was added dropwise and with stirring to a solution of *N*-2-ethylhexylidenebenzylamine (13.51 g, 0.062 mol) dissolved in absolute ethanol (50 cm^3) at 0 ^oC. The mixture was stirred at room temperature for 12 h. After concentration under reduced pressure on a rotary evaporator, the reddish-brown oily residue formed was vigourously shaken under high vacuum (0.10 mmHg) for 2 h. During this time, the product, *O,O-diethyl 1-benzylamino-2-ethylhexanephosphonate* became very viscous (20.86 g, 94 %); (Found: C, 64.28; H, 9.50; N, 4.01. $C_{19}H_{34}NO_3P$ requires: C, 64.23; H, 9.58; N, 3.94 %); $^1H(CDCl_3)$ δ 0.71-1.15 (m, 6H, terminal CH_3 overlapping with $CH(CH_2CH_3)$), 1.18-1.63 (m, 14H, $2xCH_3CH_2O$-, $CH(CH_2)_3CH_3$, $CH(CH_2CH_3)$), 2.36 (m, 1H, P-CHCH), 2.90-3.02 (m, 1H, P-CH), 4.00-4.17 (m, 6H, $2xCH_3CH_2O$- & NCH_2), 7.21-7.39 (m, 6H, $NHCH_2C_6H_5$); $^{13}C(CDCl_3)$ δ 12.16 (s, $CH(CH_2)_3CH_3$), 14.12 (s, $CH(CH_2CH_3)$), 16.52 (dd, $2xCH_3CH_2O$-, $^3J_{POCC}$ 5.66 Hz), 22.90 (s, $CHCH_2CH_2CH_2CH_3$), 23.38 (d, $CHCH_2CH_2CH_2CH_3$, $^3J_{PCCC}$ 12.83 Hz), 29.68 (d, $CH(CH_2CH_3)$, $^3J_{PCCC}$ 9.88 Hz), 41.25 (d, P-CHCH, $^2J_{PCC}$ 5.41 Hz), 53.03 (d, $NHCH_2$, $^3J_{PCNC}$ 9.18 Hz), 55.47 (d, P-CH, $^1J_{PC}$ 140.70 Hz), 61.55 (dd, $2xCH_3CH_2O$-, $^2J_{POC}$ 6.62 Hz), 127.12 (C_4 of aromatic ring), 128.24 (s, C_3 & C_5 of aromatic ring), 128.65 (s, C_2 & C_6 of aromatic ring), 140.29 (s, C_1 of aromatic ring); $^{31}P(CDCl_3)$ δ 29.69 (s).

4.4.11. PREPARATION OF *N*-BENZYLIDENEDIPHENYLMETHYLAMINES

PREPARATION OF *N*-BENZYLIDENEDIPHENYLMETHYLAMINE

Benzaldehyde (10.6 g, 0.10 mol) was added dropwise and with stirring to a solution of diphenylmethylamine (18.3 g, 0.10 mol) dissolved in ether (60 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The yellow oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became very viscous. Upon standing ***N-benzylidenediphenylmethylamine*** was afforded as a yellow solid (18.18 g, 67.08 %); (Found: C, 88.43, H, 6.30; N, 4.79. $C_{14}H_{12}N$ requires: C, 88.56; H, 6.27; N, 5.17 %); $^1H(CDCl_3)$ δ 5.54 (s, 1H, NC$\underline{H}$), 7.12-7.81 (m, 15H, $(C_6\underline{H}_5)_2$ overlapping with $C_6\underline{H}_5$), 8.33 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 78.33 (s, N$\underline{C}$H), 127.44 (s, $\underline{C}_4$'s of phenyl rings), 128.15 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.90 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 129.37 (s, $\underline{C}_4$ of benzylidene ring), 130.08 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 131.21(s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring) 144.40 (s, $\underline{C}_1$ of benzylidene ring), 161.25 (s, $\underline{C}$H=N); EI ms: m/z(%) 272 ($[M+1]^+$, 9.9), 271 ($[M]^+$, 43.9), 194 ($[M - C_6H_5]^+$, 11.7), 167 ($[M - C_6H_5CH{=}N]^+$, 100), 90 ($[M - (C_6H_5)_2CHN]^+$, 43.5).

PREPARATION OF *N*-4'-METHOXYBENZYLIDENEDIPHENYLMETHYLAMINE

4-Methoxybenzaldehyde (13.6 g, 0.10 mol) was added dropwise and with stirring to a solution of diphenylmethylamine (18.3 g, 0.10 mol) dissolved in anhydrous ether (50 cm^3), in the presence of anhydrous potassium carbonate (5 g) at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The pale-yellow oily residue formed was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became very viscous. Upon standing *N-4'-methoxybenzylidenediphenylmethylamine* was afforded as a creamy solid (26.70 g, 89 %); (Found: C, 83.74; H, 6.37; N, 4.49. $C_{21}H_{19}NO$ requires: C, 83.72; H, 6.31; N, 4.65 %); $^1H(CDCl_3)$ δ 3.79 (s, 3H, $C\underline{H}_3O$-), 5.55 (s, 1H, NC$\underline{H}$), 6.90 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of benzylidene ring, $^3J_{HCCH}$ 8.70 Hz), 7.17-7.40 (m, 10H, $(C_6\underline{H}_5)_2$), 7.76 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.73 Hz), 8.33 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 55.10 (s, $\underline{C}H_3O$), 78.20 (s, N$\underline{C}$H), 117.30 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 127.06 (s, $\underline{C}_4$'s of phenyl rings), 127.60 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 131.00 (s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring), 143.67 (s, $\underline{C}_1$'s of phenyl rings), 161.10 (s, $\underline{C}$H=N); EI ms: m/z(%) 302 ($[M+1]^+$, 57.3), 301 ($[M]^+$, 72.0), 286 ($[M - CH_3]^+$, 3.1), 224 ($[M - C_6H_5]^+$, 50.6), 167 ($[M - CH_3OC_6H_4CH{=}N]^+$, 89.8), 120 ($[M - (C_6H_5)_2CHN]^+$, 12.9).

PREPARATION OF *N*-2'-HYDROXYBENZYLIDENEDIPHENYLMETHYLAMINE

Salicylaldehyde (2.27 g, 0.019 mol), was added dropwise and with stirring to a solution of diphenylmethylamine (3.41 g, 0.019 mol), dissolved in anhydrous ether (20 cm^3) in the presence of anhydrous potassium carbonate (2 g), at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The yellow oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became very viscous. Upon standing *N-2'-hydroxybenzylidenediphenylmethylamine* was afforded as a bright-yellow solid (5.34 g, 100 %); (Found: C, 83.98; H, 5.93; N, 4.51. $C_{20}H_{17}NO$ requires: C, 83.62; H, 5.92; N, 4.88 %); $^1H(CDCl_3)$ δ 5.56 (s, 1H, NC<u>H</u>), 6.79-7.77 (m, 14H, $(C_6\underline{H}_5)_2$ & $C_6\underline{H}_4$), 8.39 (s, 1H, C<u>H</u>=N), 13.54 (s, br, 1H, O<u>H</u>, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 76.72 (s, N<u>C</u>H), 116.95 (s, <u>C</u>$_5$ of benzylidene ring), 118.73 (s, <u>C</u>$_6$ of benzylidene ring), 127.35 (s, <u>C</u>$_4$'s of phenyl rings), 127.40 (s, <u>C</u>$_3$'s & <u>C</u>$_5$'s of phenyl rings), 128.64 (s, <u>C</u>$_2$'s & <u>C</u>$_6$'s of phenyl rings), 131.66 (s, <u>C</u>$_4$ of benzylidene ring), 132.56 (s, <u>C</u>$_3$ of benzylidene ring), 142.49 (<u>C</u>$_1$'s of phenyl rings), 161.01 (s, <u>C</u>H=N), 164.98 (s, <u>C</u>$_2$-OH of benzylidene ring); EI ms: m/z(%) 288 ($[M+1]^+$, 31.7), 287 ($[M]^+$, 74.7), 210 ($[M - C_6H_5]^+$, 4.8), 167 ($[M - 2(OH)C_6H_4CH=N]^+$, 100), 106 ($[M - (C_6H_5)_2CHN]^+$, 53.4).

PREPARATION OF *N*-4'-ISOPROPYLBENZYLIDENEDIPHENYLMETHYLAMINE

4-Isopropylbenzaldehyde (cuminicaldehyde, 14.82 g, 0.10 mol) was added dropwise and with stirring to a solution of diphenylmethylamine (18.30 g, 0.10 mol) dissolved in anhydrous ether (70 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 ^oC The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The orange oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became very viscous. Upon standing *N-4'-isopropylbenzylidenediphenylmethylamine* was afforded as an orange solid (26.77 g, 86 %); (Found: C, 87.96; H, 7.40; N, 4.49. $C_{23}H_{23}N$ requires: C, 88.18; H, 7.35; N, 4.47 %); $^1H(CDCl_3)$ δ 1.21 (d, 6H, $CH(C\underline{H}_3)_2$, $^3J_{HCCH}$ 6.91 Hz), 2.88 (dq overlapping, 1H, $C\underline{H}(CH_3)_2$, $^3J_{HCCH}$ 6.90 Hz), 5.55 (s, 1H, NC$\underline{H}$), 7.16-7.40 (m, 12H, $(C_6\underline{H}_5)_2$ overlapping $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring), 7.74 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of benzylidene ring, $^3J_{HCCH}$ 8.16 Hz), 8.35 (s, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 23.79 (s, $(\underline{C}H_3)_2CH$), 34.08 (s, $(CH_3)_2\underline{C}H$), 77.80 (s, N$\underline{C}$H), 126.58 (s, $\underline{C}_4$'s of phenyl rings), 126.86 (s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring), 127.67 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.35 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 128.52 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 134.14 (s, $\underline{C}_4$ of benzylidene ring), 144.00 (s, $\underline{C}_1$'s of phenyl rings), 151.66 (s, $\underline{C}_1$ of benzylidene ring), 160.59 (s, $\underline{C}$H=N); EI ms: m/z(%) 314 ($[M+1]^+$, 35.9), 313 ($[M]^+$, 72.2), 270 ($[M - (CH_3)_2CH]^+$, 15.5), 236 ($[M - C_6H_5]^+$, 13.1), 167 ([M -

$(CH_3)_2CHC_6H_4CH=N]^+$, 100), 132 ([M - $(C_6H_5)_2CHN]^+$, 5.8).

PREPARATION OF *N*-4'-METHYLBENZYLIDENEDIPHENYLMETHYLAMINE

4-Methylbenzaldehyde (9.69 g, 0.081 mol) was added dropwise and with stirring to a solution of diphenylmethylamine (14.69 g, 0.081 mol) dissolved in anhydrous ether (60 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The yellow oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. Upon standing *N-4'-methylbenzylidenediphenylmethylamine* was afforded as a bright yellow solid (20.89 g, 91 %); (Found: C, 88.28; H, 6.72; N, 4.85. $C_{21}H_{19}N$ requires: C, 88.42; H, 6.67; N, 4.91 %); $^1H(CDCl_3)$ δ 2.34 (s, 3H, C_4-$\underline{C}H_3$), 5.57 (s, 1H, NCH), 7.14-7.41 (m, 12H, $(C_6\underline{H}_5)_2$ overlapping $\underline{H}_3$ & $\underline{H}_5$ of benzylidene ring), 7.71 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.10 Hz), 8.35 (s, 1H, $C\underline{H}$=N); $^{13}C(CDCl_3)$ δ 21.48 (s, C_4-$\underline{C}H_3$), 77.82 (s, N$\underline{C}$H), 126.88 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 127.67 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.41 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 129.20 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 133.72 (s, $\underline{C}_4$ of benzylidene ring), 140.97 (s, $\underline{C}_1$ of benzylidene ring), 143.99 (s, $\underline{C}_1$'s of phenyl rings), 160.68 (s, $\underline{C}$H=N); EI ms: m/z(%) 286 ($[M+1]^+$, 46.7), 285 ($[M]^+$, 61.1), 270 ([M - $CH_3]^+$, 7.0), 208 ([M - $C_6H_5]^+$, 41.2), 194 ([M - $C_7H_7]^+$, 12.5), 167 ([M - $CH_3C_6H_4CH=N]^+$, 93.8), 104 ([M - $(C_6H_5)_2CHN]^+$, 48.4).

PREPARATION OF *N*-3'-METHOXY-4'-HYDROXYBENZYLIDENEDIPHENYL-METHYLAMINE

3-Methoxy-4-hydroxybenzaldehyde (vanillin, 15.2 g, 0.10 mol) dissolved in anhydrous ether (100 cm^3) was added dropwise and with stirring to a solution of diphenylmethylamine (18.33 g, 0.10 mol) dissolved in anhydrous ether (60 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 °C. The solution was stirred at room temperature for 1 h, before being filtered and concentrated under reduced pressure on a rotary evaporator. The extremely viscous, yellow-green residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. Upon standing *N-3'-methoxy-4'-hydroxybenzylidene-diphenylmethylamine* was afforded as a lime green solid (28.08 g, 89 %); (Found: C, 83.67; H, 6.37; N, 4.57. $C_{21}H_{19}NO_2$ requires: C, 83.72; H, 6.31; N, 4.65 %); $^1H(CDCl_3)$ δ 3.68 (s, 3H, $C\underline{H}_3O$-), 5.56 (s, 1H, NC$\underline{H}$), 6.79 (d, 1H, $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.05 Hz); 7.04-7.38 (m, 11H, $(C_6\underline{H}_5)_2$ overlapping H_5 of benzylidene ring); 7.50 (s, 1H, $\underline{H}_2$ of benzylidene ring), 8.23 (s, 1H, C$\underline{H}$=N), 13.20 (s, br, 1H, O$\underline{H}$, confirmed by absence after D_2O shake); $^{13}C(CDCl_3)$ δ 55.63 (s, $\underline{C}H_3O$-), 77.61 (s, N$\underline{C}$H), 108.82 (s, $\underline{C}_6$ of benzylidene ring), 114.25 (s, $\underline{C}_5$ of benzylidene ring), 124.17 (s, $\underline{C}_2$ of benzylidene ring), 126.91 ($\underline{C}_4$'s of phenyl rings), 127.77 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.34 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 143.66 (s, $\underline{C}_1$'s of phenyl rings), 147.13 (s, $\underline{C}_1$ of benzylidene ring), 148.64 (s, $\underline{C}_3$ of benzylidene ring), 160.95 (s, $\underline{C}$H=N),

180.50 (s, $\underline{C}_4$ of benzylidene ring); EI ms: m/z(%) 318 ($[M+1]^+$, 64.3), 317 ($[M]^+$, 61.5), 316 ($[M - H]^+$, 76.5), 301 ($[M - CH_4]^+$, 19.6), 286 ($[M - CH_3O]^+$, 4.3), 240 ($[M - C_6H_5]^+$, 50.3), 194 ($[M - C_7H_7O_2]^+$, 13.8), 167 ($[M - C_8H_8NO_2]^+$, 69.8), 151 ($[M - (C_6H_5)_2C]^+$, 57.4), 150 ($[M - (C_6H_5)_2CH]^+$, 59.4), 136 ($[M - (C_6H_5)_2CHN]^+$, 21.0).

PREPARATION OF *N*-2'-NITROBENZYLIDENEDIPHENYLMETHYLAMINE

2-Nitrobenzaldehyde (3.09 g, 0.021 mol) dissolved in dichloromethane (20 cm^3) was added dropwise and with stirring to a solution of diphenylmethylamine (3.75 g, 0.021 mol) dissolved in dichloromethane (20 cm^3), in the presence of anhydrous potassium carbonate (3 g) at 0 ^oC. The solution was stirred for 1.5 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The yellow oily residue was vigorously shaken under high vacuum (0.10 mmHg) for 1.5 h. The product, *N-2'-nitrobenzylidenediphenylmethylamine* was afforded as a yellow solid (6.57 g, 100 %); (Found: C, 76.03; H, 5.00; N, 8.84. $C_{20}H_{16}N_2O_2$ requires: C, 75.95; H, 5.06; N, 8.86 %); $^1H(CDCl_3)$ δ 5.71 (s, 1H, NC$\underline{H}$); 7.21-7.42 (m, 10H, 2x$C_6\underline{H}_5$), 7.46-7.67 (m, 2H, $\underline{H}_4$ & $\underline{H}_5$ of benzylidene ring), 7.98 (d, 1H, $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.12 Hz), 8.20 (d, 1H, $\underline{H}_3$ of benzylidene ring, $^3J_{HCCH}$ 7.75 Hz), 8.87 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 77.80 (s, N$\underline{C}$H), 126.69 (s, $\underline{C}_4$'s of phenyl rings), 127.43 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.32 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl

rings), 129.86 ($\underline{C}_4$ of benzylidene ring), 130.58 ($\underline{C}_5$ of benzylidene ring), 130.88 (s, $\underline{C}_6$ of benzylidene ring), 133.20 ($\underline{C}_1$'s of phenyl rings), 142.76 (s, $\underline{C}_3$ of benzylidene ring), 148.67 (s, $\underline{C}_1$ of benzylidene ring), 156.63 (s, $\underline{C}$H=N), 178.34 (s, $\underline{C}_2$-NO_2); EI ms: m/z(%) 317 ($[M+1]^+$, 1.1), 316 ($[M]^+$, 5.0), 286 ($[M - NO]^+$, 1.2), 239 ($[M - C_6H_5]^+$, 5.3), 168 ($[M - NO_2C_6H_4C{=}N]^+$, 80.3), 167 ($[M - NO_2C_6H_4CH{=}N]^+$, 100), 135 ($[M - (C_6H_5)_2CHN]^+$, 9.3).

PREPARATION OF *N*-4'-NITROBENZYLIDENEDIPHENYLMETHYLAMINE

4-Nitrobenzaldehyde (7.56 g, 0.050 mol) dissolved in dichloromethane (50 cm^3) was added dropwise and with stirring to a solution of diphenylmethylamine (9.16 g, 0.050 mol) dissolved in dichloromethane (50 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The orange oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product, *N-4'-nitrobenzylidenediphenylmethylamine* was afforded as an orange solid (16.00 g, 100 %); (Found: C, 76.02; H, 4.97; N, 8.96. $C_{20}H_{16}N_2O_2$ requires: C, 75.95; H, 5.06; N, 8.86 %); $^1H(CDCl_3)$ δ 5.64 (s, 1H, NC$\underline{H}$), 7.19-7.42 (m, 10H, $(C_6\underline{H}_5)_2$), 7.93 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.88 Hz), 8.20 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of benzylidene ring, $^3J_{HCCH}$ 8.84 Hz), 8.45 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 78.08 (s, N$\underline{C}$H),

123.78 (s, $\underline{C}_4$'s of phenyl rings), 127.31 (s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring), 127.58 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.61 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 129.11 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 141.64 (s, $\underline{C}_1$ of benzylidene ring), 143.23 (s, $\underline{C}_1$ of phenyl rings), 149.05 (s, $\underline{C}_4$ of benzylidene ring), 158.61 (s, CH=N); EI ms: m/z(%) 317 ($[M+1]^+$, 22.8), 316 ($[M]^+$, 59.3), 270 ($[M - NO_2]^+$, 6.9), 239 ($[M - C_6H_5]^+$, 37.8), 167 ($[M - O_2NC_6H_4CH=N]^+$, 76.7), 150 ($[M - (C_6H_5)_2C]^+$, 18.1), 149 ($[M - (C_6H_5)_2CH]^+$, 7.6), 135 ($[M - (C_6H_5)_2CHN]^+$, 5.2).

PREPARATION OF *N*-4'-DIMETHYLAMINOBENZYLIDENEDIPHENYLMETHYLAMINE

4-Dimethylaminobenzaldehyde (14.92 g, 0.10 mol) dissolved in dichloromethane (30 cm^3) was added dropwise and with stirring to a solution of diphenylmethylamine (18.33 g, 0.10 mol), dissolved in dichloromethane (30 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered, and then concentrated under reduced pressure on a rotary evaporator. The orange-brown oily residue formed was vigorously shaken under high vacuum (0.10 mmHg), for 2 h. Upon standing, *N-4'-dimethylaminobenzylidenediphenylmethylamine*, was afforded as a hard orange-brown solid (32.0 g, 100 %); (Found: C, 83.97; H, 14.00; N, 8.95. $C_{22}H_{22}N_2$ requires: C, 84.08; H, 7.01; N, 8.92 %); $^1H(CDCl_3)$ δ 2.93 (s, 6H, $(\underline{CH}_3)_2N$), 5.52 (s, 1H, $NC\underline{H}$), 6.65 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.91 Hz), 7.15-7.40 (m, 10H, $(C_6\underline{H}_5)_2$),

7.70 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of benzylidene ring, $^3J_{HCCH}$ 8.91 Hz), 8.26 (s, C$\underline{H}$=N); ^{13}C($CDCl_3$) δ 40.13 (s, $(\underline{C}H_3)_2N$), 77.66 (s, N$\underline{C}$H), 111.48 (s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring), 126.69 (s, $\underline{C}_4$'s of phenyl rings), 127.73 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.80 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 144.43 (s, $\underline{C}_1$'s of phenyl rings), 152.06 (s, $\underline{C}_4$ of benzylidene ring), 160.60 (s, $\underline{C}$H=N); EI ms: m/z(%) 315 ($[M+1]^+$, 24.3), 314 ($[M]^+$, 57.2), 237 ($[M - C_6H_5]^+$, 23.0), 167 ($[M - (CH_3)_2NC_6H_4CH{=}N]^+$, 91.3), 148 ($[M - (C_6H_5)_2C]^+$, 100), 147 ($[M - (C_6H_5)_2CH]^+$, 41.5), 133 ($[M - (C_6H_5)_2CHN]^+$, 22.5).

PREPARATION OF *N*-3'-,4'-,5'-TRIMETHOXYBENZYLIDENEDIPHENYL-METHYLAMINE

3,4,5-Trimethoxybenzaldehyde (9.80 g, 0.05 mol) dissolved in dichloromethane (100 cm^3), was added dropwise and with stirring to a solution of diphenylmethylamine (9.16 g, 0.05 mol) dissolved in dichloromethane (50 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 °C. The solution was stirred for 1.5 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The yellow oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. Upon standing *N-3'-,4'-,5'-trimethoxybenzylidenediphenylmethylamine* was afforded as a hard yellow-orange solid (18.21 g, 100 %); (Found: C, 76.54; H, 6.41; N, 3.73. $C_{23}H_{23}NO_3$ requires: C, 76.45; H, 6.37; N, 3.88 %); ^{1}H($CDCl_3$) δ

3.87 (s, 9H, ($C\underline{H}_3O$-)$_3$), 5.60 (s, 1H, NC$\underline{H}$), 7.08 (s, 2H, $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring), 7.18-7.40 (m, 10H, ($C_6\underline{H}_5$)$_2$), 8.30 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 56.29 (s, C_3-$\underline{C}H_3O$, C_5-$\underline{C}H_3O$ of benzylidene ring), 61.00 (s, C_4-$\underline{C}H_3O$ of benzylidene ring), 77.75 (s, N$\underline{C}$H), 105.54 (s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring), 127.13 (s, $\underline{C}_4$'s of phenyl rings), 127.88 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.55 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings) 131.95 (s, $\underline{C}_1$ of benzylidene ring), 140.50 (s, $\underline{C}_4$ of benzylidene ring), 143.80 (s, $\underline{C}_1$'s of phenyl rings), 153.48 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 160.60 (s, $\underline{C}$H=N); EI ms: m/z(%) 362 ([M+1]$^+$, 10.9), 361 ([M]$^+$, 43.4), 284 ([M - C_6H_5]$^+$, 1.8), 195 ([M - $(C_6H_5)_2C$]$^+$, 5.1), 180 ([M - $(C_6H_5)_2CHN$]$^+$, 3.9), 167 ([M - $(CH_3O)_3C_6H_2CH$=N]$^+$, 100).

PREPARATION OF *N*-4'-ETHYLBENZYLIDENEDIPHENYLMETHYLAMINE

4-Ethylbenzaldehyde (6.71 g, 0.050 mol) was added dropwise and with stirring to solution of diphenylmethylamine (9.16 g, 0.050 mol) dissolved in dichloromethane (50 cm^3), in the presence of anhydrous potassium carbonate (5 g) at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered, and concentrated under reduced pressure on a rotary evaporator. The deep-yellow oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. Upon standing, *N-4'-ethylbenzylidenediphenylmethylamine*, was afforded as a hard orange solid (15.88 g, 100 %); (Found: C, 86.12; H, 7.12; N, 4.55. $C_{22}H_{21}N$ requires: C, 88.29; H, 7.02; N, 4.68 %); $^1H(CDCl_3)$ δ 1.19 (t,

3H, $C\underline{H}_3CH_2$, $^3J_{HCCH}$ 7.61 Hz), 2.61 (q, 2H, $CH_3C\underline{H}_2$, $^3J_{HCCH}$ 7.55 Hz), 5.55 (s, 1H, NC$\underline{H}$), 7.14-7.40 (m, 12H, $(C_6\underline{H}_5)_2$ overlapping with $\underline{H}_3$ & $\underline{H}_5$ of benzylidene ring), 7.73 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.15 Hz), 8.34 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 15.42 (s, $\underline{C}H_3CH_2$), 28.81 (s, $CH_3\underline{C}H_2$), 77.79 (s, N$\underline{C}$H), 126.87 (s, $\underline{C}_4$'s of phenyl rings), 127.52 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.01 (s, $\underline{C}_3$ & $\underline{C}_5$ of benzylidene ring), 128.34 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 128.49 (s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring), 133.92 (s, $\underline{C}_4$ of benzylidene ring), 147.28 (s, $\underline{C}_1$ of benzylidene ring), 160.67 (s, $\underline{C}$H=N); EI ms: m/z(%) 300 ($[M+1]^+$, 9.7), 299 ($[M]^+$, 41.8), 270 ($[M - CH_3CH_2]^+$, 3.4), 222 ($[M - C_6H_5]^+$, 13.4), 167 ($[M - CH_3CH_2C_6H_4CH{=}N]^+$, 100), 133 ($[M - (C_6H_5)_2C]^+$, 11.5), 118 ($[M - (C_6H_5)_2CHN]^+$, 2.5).

PREPARATION OF *N*-2'-ETHOXYBENZYLIDENEDIPHENYLMETHYLAMINE

2-Ethoxybenzaldehyde (7.51 g, 0.05 mol), was added dropwise and with stirring to a solution of diphenylmethylamine (9.16 g, 0.05 mol), dissolved in dichloromethane (50 cm^3), in the presence of potassium carbonate (10 g) at 0 ^oC. The solution was stirred at room temperature for 1 h, before being filtered, and concentrated under reduced pressure on a rotary evaporator. The deep-yellow oily residue formed was vigorously shaken under high vacuum (0.10 mmHg), for 2 h. Upon standing, *N-2'-ethoxybenzylidenediphenylmethylamine*, was afforded as an orange-yellow solid (16.0 g, 100 %); (Found: C, 83.77; H, 6.63; N, 4.40.

$C_{22}H_{21}NO$ requires: C, 83.81; H, 6.67; N, 4.44 %); $^{1}H(CDCl_3)$ δ 1.37 (t, 3H, $OCH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 6.97 Hz), 3.98 (q, 2H, $OCH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 6.96 Hz), 5.59 (s, 1H, N$\underline{CH}$), 6.81 (d, 1H, $\underline{H}_6$ of benzylidene ring, $^{3}J_{HCCH}$ 8.34 Hz), 6.94 (dd overlapping, 1H, $\underline{H}_5$ of benzylidene ring, $^{3}J_{HCCH}$ 7.50 Hz), 7.12-7.42 (m, 11H, 2x$C_6\underline{H}_5$ overlapping $\underline{H}_4$ of benzylidene ring), 8.18 (d, 1H, $\underline{H}_3$ of benzylidene ring, $^{3}J_{HCCH}$ 7.70 Hz), 8.90 (s, 1H, $\underline{CH}$=N); $^{13}C(CDCl_3)$ δ 49.05 (s, $OCH_2\underline{CH}_3$), 63.60 (s, $O\underline{CH}_2CH_3$), 97.13 (s, N$\underline{CH}$), 105.77 (s, $\underline{C}_6$ of benzylidene ring), 109.97 (s, $\underline{C}_1$ of benzylidene ring), 112.04 (s, $\underline{C}_4$'s of phenyl rings), 112.88 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 112.94 (s, $\underline{C}_5$ of benzylidene ring), 113.57 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 117.13 (s, $\underline{C}_4$ of benzylidene ring), 129.51 (s, $\underline{C}_1$'s of phenyl rings), 142.01 (s, $\underline{C}_3$ of benzylidene ring), 143.51 (s, $\underline{C}_2$ of benzylidene ring), 160.50 (s, $\underline{C}$H=N); EI ms: m/z(%) 316 ($[M+1]^+$, 14.9), 315 ($[M]^+$, 46.1), 300 ($[M - CH_3]^+$, 45.9), 286 ($[M - CH_3CH_2]^+$, 19.1), 270 ($[M - CH_3CH_2O]^+$, 7.4), 238 ($[M - C_6H_5]^+$, 10), 167 ($[M - CH_3CH_2OC_6H_4CH{=}N]^+$, 100), 134 ($[M - (C_6H_5)_2CHN]^+$, 9.5).

PREPARATION OF *N*-2'-FLUOROBENZYLIDENEDIPHENYLMETHYLAMINE

2-Fluorobenzaldehyde (2.37 g, 0.019 mol), was added dropwise and with stirring to a solution of diphenylmethylamine (3.50 g, 0.019 mol), dissolved in dry ether (60 cm^3) in the presence of anhydrous potassium carbonate (5 g) at 0 °C. The solution was stirred at room temperature for 1 h, before being filtered and concentrated under

reduced pressure on a rotary evaporator. The viscous yellow residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. *N-2'-fluorobenzylidenediphenylmethylamine* was afforded as a sticky, orange-yellow solid (5.50 g, 99 %); (Found: C, 83.01; H, 5.53; N, 4.86. $C_{20}FH_{15}N$ requires: C, 83.05; H, 5.54; N, 4.84. $^{1}H(CDCl_3)$ δ 5.60 (s, 1H, NC$\underline{H}$), 7.02 (dd overlapping, 1H, $\underline{H}_3$ of aromatic ring, $^{3}J_{HCCH}$ 8.45 Hz), 7.11-7.41 (m, 12H, 2x$C_6\underline{H}_5$, $\underline{H}_4$ & $\underline{H}_5$ of aromatic ring overlapping), 8.18 (ddd overlapping, 1H, $\underline{H}_6$ of aromatic ring, $^{3}J_{HCCH}$ 7.51 Hz, $^{4}J_{FH}$ 1.73 Hz), 8.74 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 78.38 (s, N$\underline{C}$H), 115.63 (d, $\underline{C}_3$ of aromatic ring, $^{2}J_{FCC}$ 21.13 Hz), 123.86 (d, $\underline{C}_1$ of aromatic ring, $^{2}J_{FCC}$ 9.37 Hz), 124.24 (d, $\underline{C}_4$ of aromatic ring, $^{3}J_{FCCC}$ 3.59 Hz), 127.03 (s, $\underline{C}_4$'s of phenyl rings), 127.59 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.07 (d, $\underline{C}_5$ of aromatic ring, $^{4}J_{FC}$ 2.83 Hz), 128.45 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 132.31 (d, $\underline{C}_6$ of aromatic ring, $^{3}J_{FCCC}$ 8.55 Hz), 154.02 (d, $\underline{C}$H=N, $^{3}J_{FCCC}$ 4.78 Hz), 162.33 (d, $\underline{C}_2$ of aromatic ring, $^{1}J_{FC}$ 252.47 Hz); $^{19}F(CDCl_3)$ δ - 124.57 (d); EI ms: m/z(%) 290 ($[M+1]^+$, 20.6), 289 ($[M]^+$, 49.8), 270 ($[M - F]^+$, 6.3), 212 ($[M - C_6H_5]^+$, 25.9), 182 ($[M - FC_6H_4C]^+$, 23.2), 181 ($[M - FC_6H_4CH]^+$, 18.6), 167 ($[M - FC_6H_4CH{=}N]^+$, 100), 108 ($[M - (C_6H_2)_2CHN]^+$, 35.1).

PREPARATION OF *N*-4'-TRIFLUOROMETHYLBENZYLIDENEDIPHENYL-METHYLAMINE

4-Trifluoromethylbenzaldehyde (8.0 g, 0.046 mol), dissolved in dichloromethane (20 cm^3) was added dropwise and with stirring to a solution of diphenylmethylamine (8.42 g, 0.046 mol) dissolved in dichloromethane (40 cm^3) in the presence of anhydrous potassium carbonate (10 g) at 0 ^oC. The solution was stirred at room temperature for 1.5 h, before being filtered and concentrated under reduced pressure on a rotary evaporator. The oily, orange residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. *N-4'-trifluoromethylbenzylidenediphenylmethylamine* was afforded as an orange solid (15.36 g, 99 %); (Found: C, 74.30; H, 4.82; N, 4.07. $C_{21}F_3H_{16}N$ requires: C, 74.34; H, 4.72; N, 4.13 %); $^1H(CDCl_3)$ δ 5.61 (s, 1H, NC$\underline{H}$), 7.19-7.41 (m, 10H, 2x$C_6\underline{H}_5$), 7.62 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of benzylidene ring, $^3J_{HCCH}$ 8.16 Hz), 7.90 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of benzylidene ring, $^3J_{HCCH}$ 8.01 Hz), 8.41 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 77.98 (s, N$\underline{C}$H), 125.49 (q, $\underline{C}_4$ of benzylidene ring, $^2J_{FCC}$ 3.77 Hz), 127.19 (s, $\underline{C}_4$'s of phenyl rings), 127.61 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.55 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 128.65 (s, $\underline{C}_2$ & $\underline{C}_6$ of benzylidene ring), 132.29 (q, $\underline{C}F_3$, $^1J_{FC}$ 259.34 Hz), 139.35 (s, $\underline{C}_1$ of benzylidene ring), 143.49 (s, $\underline{C}_1$'s of phenyl rings), 159.37 (s, $\underline{C}$H=N); EI ms: m/z(%) 340 ($[M+1]^+$, 16.5), 339 ($[M]^+$, 54.8), 320 ($[M - F]^+$, 25.2), 262 ($[M - C_6H_5]^+$, 29.4), 194 ($[M - CF_3C_6H_4]^+$, 4.7), 182 ($[M - CF_3C_6H_4C]^+$, 5.9), 181 ([M -

$CF_3C_6H_4CH]^+$, 4.0), 167 ([M - $CF_3C_6H_4CH{=}N]^+$, 100), 158 ([M - $(C_6H_5)_2CHN]^+$, 22.0).

PREPARATION OF *N*-3'-TRIFLUOROMETHOXYBENZYLIDENEDIPHENYL-METHYLAMINE

3-Trifluoromethoxybenzaldehyde (5.13 g, 0.027 mol), dissolved in dichloromethane (20 cm^3) was added dropwise and with stirring to a solution of diphenylmethylamine (4.95 g, 0.027 mol), dissolved in dichloromethane (50 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 °C. The solution was stirred at room temperature for 1.5 h, before being filtered and concentrated under reduced pressure on a rotary evaporator. The light brown, oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. *N-3'-Trifluoromethoxybenzylidenediphenylmethylamine* was afforded as a light brown viscous oil (8.41 g, 88 %); (Found: C, 70.89; H, 4.54; N, 3.84. $C_{21}F_3H_{16}NO$ requires: C, 70.99; H, 4.51; N, 3.94 %); $^1H(CDCl_3)$ δ 5.60 (s, 1H, NC<u>H</u>), 7.18-7.42 (m, 12H, 2x$C_6\underline{H}_5$ overlapping with $\underline{H}_5$ & $\underline{H}_6$ of benzylidene ring), 7.70 (m, 2H, $\underline{H}_2$ & $\underline{H}_4$ of benzylidene ring), 8.37 (s, 1H, C<u>H</u>=N); $^{13}C(CDCl_3)$ δ 77.86 (s, N<u>C</u>H), 120.43 (s, $\underline{C}_6$ of benzylidene ring), 120.49 (q, $\underline{C}F_3O$, $^1J_{FC}$ 257.50 Hz), 123.02 (s, $\underline{C}_5$ of benzylidene ring), 126.94 (s, $\underline{C}_4$ of benzylidene ring), 127.14 (s, $\underline{C}_4$'s of phenyl rings), 127.61 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.52 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 129.93 (s, $\underline{C}_2$ of benzylidene ring), 138.37 (s, $\underline{C}_1$ of

benzylidene ring), 143.54 (s, $\underline{C}_1$'s of phenyl rings), 149.58 (q, $\underline{C}_3$ of benzylidene ring, $^3J_{FCOC}$ 1.89 Hz), 159.18 (s, $\underline{C}$H=N); EI ms: m/z(%) 356 ($[M+1]^+$, 39.2), 355 ($[M]^+$, 57.8), 278 ($[M - C_6H_5]^+$, 41.5), 270 ($[M - CF_3O]^+$, 23.2), 194 ($[M - CF_3OC_6H_4]^+$, 7.7), 174 ($[M - (C_6H_2)_2CHN]^+$, 3.2), 167 ($[M - CF_3OC_6H_4CH{=}N]^+$, 94.6).

PREPARATION OF *N*-[3'(3''-TRIFLUOROMETHYL)PHENOXYBENZYLIDENE]-DIPHENYLMETHYLAMINE

3-[3-(Trifluoromethyl)phenoxy]benzaldehyde (2.90 g, 0.011 mol) was added dropwise and with stirring to a solution of diphenylmethylamine (2.00 g, 0.011 mol) dissolved in anhydrous ether (20 cm^3) in the presence of anhydrous potassium carbonate (2 g) at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The orange, oily residue formed, was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time *N-[3-(3-trifluoromethyl)-phenoxybenzylidene]diphenylmethylamine*, was afforded as a very viscous, oily orange residue (4.66 g, 98 %); (Found: C, 78.02; H, 4.80; N, 3.37. $C_{27}F_3H_{20}NO$ requires: C, 78.07; H, 4.82; N, 3.37 %); $^1H(CDCl_3)$ δ 5.58 (s, NC$\underline{H}$), 7.02-7.40 (m, 18H, $(C_6\underline{H}_5)_2$ overlapping with $C_6\underline{H}_4$ of ring B & $\underline{H}_5$, $\underline{H}_6$ of ring A), 7.58 (m, 2H, $\underline{H}_2$ & $\underline{H}_4$ of ring A); 8.37 (s, 1H, C$\underline{H}$=N); $^{13}C(CDCl_3)$ δ 77.86 (s, N$\underline{C}$H), 115.26 (q, $\underline{C}_4$ of ring A, $^3J_{FCCC}$ 3.77 Hz), 118.85 (s, $\underline{C}_6$ of ring B), 119.79 (q, $\underline{C}_2$ of ring A, $^3J_{FCCC}$ 3.82 Hz),

121.54 (s, $\underline{C}_2$ of ring B), 121.74 (s, $\underline{C}_5$ of ring B), 124.58 (s, $\underline{C}_4$ of ring B), 127.09 (s, $\underline{C}_4$'s of phenyl rings), 127.62 (s, $\underline{C}_3$'s & $\underline{C}_5$'s of phenyl rings), 128.45 (s, $\underline{C}_2$'s & $\underline{C}_6$'s of phenyl rings), 130.17 (s, $\underline{C}_5$ of ring A), 130.39 (s, $\underline{C}_6$ of ring A), 132.25 (q, $\underline{C}_3$ of ring A, $^2J_{FCC}$ 32.69 Hz), 132.89 (q, $\underline{C}F_3$ $^1J_{FC}$ 261.43 Hz), 138.54 (s, $\underline{C}_1$ of ring B), 143.67 (s, $\underline{C}_1$'s of phenyl rings), 156.41 (s, $\underline{C}_3$ of ring B), 157.41 (s, $\underline{C}_3$ of ring B), 157.64 (s, $\underline{C}_1$ of ring A), 159.79 (s, $\underline{C}$H=N); $^{19}F(CDCl_3)$ δ - 65.12 (s); EI ms: m/z(%) 432 ($[M+1]^+$, 16.1), 431 ($[M]^+$, 58.6), 412 ($[M - F]^+$, 3.5), 354 ($[M - C_6H_5]^+$, 3.8), 265 ($[M - (C_6H_5)_2C]^+$, 17.1), 167 ($[M - CF_3C_6H_4OC_6H_4CH=N]^+$, 100).

PREPARATION OF *N*-PENTAFLUOROBENZYLIDENEDIPHENYLMETHYLAMINE

Pentafluorobenzaldehyde (23.11 g, 0.12 mol), dissolved in dichloromethane (20 cm^3), was added dropwise and with stirring to a solution of diphenylmethylamine (21.60 g, 0.12 mol), dissolved in dichloromethane (70 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 ^oC. The solution was stirred at room temperature for 1.5 h, before being filtered and concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. *N-Pentafluorobenzylidenediphenylmethylamine* was afforded as a bright yellow solid (42.28 g, 99 %); (Found: C, 66.67; H, 3.39; N, 3.91. $C_{20}F_5H_{12}N$ requires: C, 66.48; H, 3.32; N, 3.38 %); $^1H(CDCl_3)$ δ 5.72 (s,

1H, NC<u>H</u>), 7.18-7.41 (m, 10H, 2x$C_6\underline{H}_5$), 8.52 (s, 1H, C<u>H</u>=N); $^{13}C(CDCl_3)$ δ 79.78 (s, NC<u>H</u>), 111.34 (dd overlapping, <u>C</u>$_1$ of aromatic ring, $^2J_{FCC}$ 11.56 Hz), 127.37 (s, <u>C</u>$_4$'s of phenyl rings), 127.46 (s, <u>C</u>$_3$'s & <u>C</u>$_5$'s of phenyl rings), 128.63 (s, <u>C</u>$_2$'s & <u>C</u>$_6$'s of phenyl rings), 137.77 (dm, <u>C</u>$_3$ & <u>C</u>$_5$ of aromatic ring, $^1J_{FC}$ 249.82 Hz), 141.89 (dm, <u>C</u>$_4$ of aromatic ring, $^1J_{FC}$ 268.13 Hz), 143.02 (s, <u>C</u>$_1$'s of phenyl rings), 146.05 (dm, <u>C</u>$_2$ & <u>C</u>$_6$ of aromatic ring, $^1J_{FC}$ 255.36 Hz), 149.10 (d, <u>C</u>H=N, $^3J_{FCCC}$ 2.52 Hz); EI ms: m/z(%) 362 ($[M+1]^+$, 8.5), 361 ($[M]^+$, 34.2), 342 ($[M - F]^+$, 7.6), 284 ($[M - C_6H_5]^+$, 31.7), 180 ($[M - (C_6H_5)_2CHN]^+$, 73.8), 167 ($[M - C_6F_5CH=N]^+$, 100).

4.4.11.1. PREPARATION OF *N*-[3-PYRIDYLMETHYLIDENE]DIPHENYL-METHYLAMINE

Pyridine-3-carboxaldehyde (5.36 g, 0.05 mol) was added dropwise and with stirring to a solution of diphenylmethylamine (9.15 g, 0.05 mol), dissolved in anhydrous ether (50 cm^3), in the presence of anhydrous potassium carbonate (5 g) at 0 °C. The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The yellow oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product became very viscous. Upon standing, ***N-[3-pyridylmethylidene]diphenylmethylamine*** was afforded as an orange-yellow solid (11.68 g, 86 %); (Found: C, 83.74; H, 5.66; N,

10.31. $C_{19}H_{16}N_2$ requires: C, 83.82; H, 5.88; N, 10.29 %); $^1H(CDCl_3)$ δ 5.60 (s, 1H, NC<u>H</u>), 7.18-7.41 (m, 11H, <u>H</u>$_4$ of pyridine ring overlapping with $(C_6\underline{H}_5)_2$), 8.17 (d, 1H, <u>H</u>$_5$ of pyridine ring, $^3J_{HCCH}$ 7.49 Hz), 8.40 (s, 1H, C<u>H</u>=N), 8.60 (d, 1H, <u>H</u>$_6$ of pyridine ring, $^3J_{HCCH}$ 6.49 Hz), 8.90 (s, <u>H</u>$_2$ of pyridine ring); $^{13}C(CDCl_3)$ δ 78.05 (s, NC<u>H</u>), 123.58 (s, <u>C</u>$_4$'s of phenyl rings), 127.14 (s, <u>C</u>$_3$'s & <u>C</u>$_5$'s of phenyl rings), 127.53 (s, <u>C</u>$_2$'s & <u>C</u>$_6$'s of phenyl rings), 128.49 (s, <u>C</u>$_1$'s of phenyl rings), 134.78 (s, <u>C</u>$_4$ & <u>C</u>$_5$ of pyridine ring), 150.37 (s, <u>C</u>$_2$ & <u>C</u>$_6$ of pyridine ring), 151.52 (s, <u>C</u>$_3$ of pyridine ring), 157.94 (s, <u>C</u>H=N); EI ms: m/z(%) 273 ($[M+1]^+$, 13.8), 272 ($[M]^+$, 54.1), 195 ($[M - C_6H_5]^+$, 9.4), 167 ($[M - C_5H_4NCH{=}N]^+$, 100), 91 ($[M - (C_6H_5)_2CHN]^+$, 20.6).

4.4.11.2. PREPARATION OF *N*-2-ETHYLHEXYLIDENEDIPHENYLMETHYLAMINE

2-Ethylhexanal (12.82 g, 0.10 mol) was added dropwise and with stirring to a solution of diphenylmethylamine (18.30 g, 0.10 mol) dissolved in anhydrous ether (70 cm^3), in the presence of anhydrous potassium carbonate (10 g) at 0 ^oC. The solution was stirred for 1 h at room temperature, before being filtered and concentrated under reduced pressure on a rotary evaporator. The reddish-brown oily residue formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h. During this time the product, *N-2-ethylhexylidenediphenylmethylamine* became very viscous (21.83 g, 75 %); (Found: C, 86.16; H, 9.37; N, 4.83. $C_{21}H_{27}N$ requires: C, 86.01; H, 9.22; N, 4.78 %; $^1H(CDCl_3)$ δ 0.86 (2xt

overlapping, 6H, $CH_3(CH_2)_3CH$ & $CH(CH_2CH_3)$, $^3J_{HCCH}$ 7.27 Hz), 1.23-1.36 (m, 4H, $CH_3CH_2CH_2CH_2CH$), 1.40-1.53 (m, 4H, $CH_3CH_2CH_2CH_2CH$ overlapping with $CH(CH_2CH_3)$), 2.27 (m, 1H, $CH(CH_2CH_3)$, $^3J_{HCCH}$ 6.85 Hz), 5.35 (s, NCH), 7.14-7.46 (m, 10H, $NCH(C_6H_5)_2$), 7.58 (d, CH=N, 1H, $^3J_{HCCH}$ 6.67 Hz); $^{13}C(CDCl_3)$ δ 11.68 (s, $CH_3(CH_2)_3CH$), 13.96 (s, $CH(CH_2CH_3)$), 22.70 (s, $CH_3CH_2CH_2CH_2CH$), 25.43 (s, $CH_3CH_2CH_2CH_2CH$), 29.43 (s, $CH_3CH_2CH_2CH_2CH$), 31.64 (s, $CH(CH_2CH_3)$), 46.60 (s, $CH_3(CH_2)_3CH$), 78.17 (s, NCH), 126.79 (s, C_4's of phenyl rings), 127.64 (s, C_3's & C_5's of phenyl rings), 128.31 (s, C_2's & C_6's of phenyl rings), 143.94 (C_1's of phenyl rings), 169.29 (s, CH=N); EI ms: m/z(%) 294 ($[M+1]^+$, 2.9), 293 ($[M]^+$, 11.0), 264 ($[M - CH_2CH_3]^+$, 3.8), 237 ($[M - C_4H_8]^+$, 79.7), 167 ($[M - CH_3(CH_2)_3CH(CH_2CH_3)CH=N]^+$, 100), 112 ($[M - (C_6H_5)_2CHN]^+$, 2.8).

4.4.12. PREPARATION OF 1-AMINOBENZYLPHOSPHONIC ACIDS USING *N*-BENZYLIDENEDIPHENYLMETHYLAMINES

PREPARATION OF 1-AMINOBENZYLPHOSPHONIC ACID

N-Benzylidenediphenylmethylamine (14.68 g, 0.054 mol), and diethyl phosphite (7.48 g, 0.054 mol), were heated at 120-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl 1-diphenylmethylaminobenzylphosphonate intermediate. Concentrated hydrochloric acid (80 cm^3) was added, and the resultant deep red solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x50 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue that formed was dissolved in methanol and treated with propylene oxide at 40 - 50 ^{o}C, to afford a white crystalline solid. The product 1-aminobenzylphosphonic acid, was filtered off, washed with acetone and dry ether, before being dried in a vacuum oven for 2 h at 70 ^{o}C (4.22 g, 41.6 %); m.p. 286-289 ^{o}C (lit.[34] 280-282 ^{o}C); (Found: C, 45.10; H, 5.29; N, 7.25. Calc. for $C_7H_{10}NO_3P$: C, 44.92; H, 5.35; N, 7.49 %); ^{1}H(NaOD) δ 4.24 (d, 1H, P-C$\underline{H}$C$_6$H$_5$, $^{2}J_{PCH}$ 14.84 Hz), 7.42-7.47 (m, 5H, C$_6\underline{H}_5$); ^{13}C($CDCl_3$) δ 57.85 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 127.30 Hz), 130.56 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 4.40 Hz), 130.88 (s, $\underline{C}_4$ of aromatic ring), 131.56 (d, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring, $^{4}J_{PC}$ 1.57 Hz), 138.03 (d, $\underline{C}_1$ of aromatic ring, $^{2}J_{PCC}$ 4.65 Hz); ^{31}P(NaOD) δ 9.94 (s).

PREPARATION OF 1-AMINO-4'-METHOXYBENZYLPHOSPHONIC ACID

N-4'-Methoxybenzylidenediphenylmethylamine (25.45 g,0.085 mol), and diethyl phosphite (11.74 g, 0.085 mol), were heated at 120-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl-1-diphenylmethylamino-4'-methoxybenzylphosphonateintermediate. Concentrated hydrochloric acid (100 cm^3), was added, and the resultant deep purple solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x30 cm^3), and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue that formed was dissolved in methanol, and treated with propylene oxide at 40-50 ^{o}C, to afford a white crystalline solid. The product 1-amino-4'-methoxybenzylphosphonic acid[116] was filtered off, washed with acetone and dry ether and dried in a vacuum oven for 2 h at 70 ^{o}C (6.32 g, 35 %); m.p. 285-288 ^{o}C; (Found: C, 44.18; H, 5.52; N, 6.00. Calc. for $C_8H_{12}NO_4P$: C, 44.24; H, 5.53; N, 6.45 %); ^{1}H(NaOD) δ 3.79 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 18.52 Hz), 3.83 (s, 3H, OC$\underline{H}_3$), 6.98 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic ring, $^{3}J_{HCCH}$ 8.54 Hz), 7.37 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring, $^{3}J_{HCCH}$ 7.21 Hz); ^{13}C(NaOD) δ 57.55 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 132.65 Hz), 58.19 (s, O$\underline{C}H_3$), 116.24 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 131.55 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 5.22 Hz), 137.61 (s, $\underline{C}_4$-OCH_3 of aromatic ring), 159.92 (d, P-C-$\underline{C}_1$ of aromatic ring, $^{2}J_{PCC}$ 2.01 Hz); ^{31}P(NaOD) δ 18.66 (s).

PREPARATION OF 1-AMINO-2'-HYDROXYBENZYLPHOSPHONIC ACID

N-2'-Hydroxybenzylidenediphenylmethylamine (4.11 g, 0.0143 mol), and diethyl phosphite (2.00 g, 0.0143 mol) were heated at 120-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl 1-diphenylmethylamino-2'-hydroxybenzylphosphonate intermediate. Concentrated hydrochloric acid (40 cm^3) was added, and the resultant reddish-purple solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x20 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue was dissolved in methanol, and treated with propylene oxide at 40-50 ^{o}C, to afford a white crystalline solid. The product, *1-amino-2'-hydroxybenzylphosphonic acid* was filtered off, washed with acetone and dry ether, and dried in a vacuum oven for 2 h at 70 ^{o}C. (0.50 g, 17 %); m.p. 310-313 ^{o}C; (Found: C, 41.21; H, 4.92; N, 6.37. $C_7H_{10}NO_4P$ requires: C, 41.38; H, 4.93; N, 6.90 %); ^{1}H(NaOD) δ 4.32 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 14.35 Hz), 6.60 (dd overlapping, 2H, $\underline{H}_4$ & $\underline{H}_5$, $^{3}J_{HCCH}$ 7.44 Hz), 7.05 (dd overlapping, 1H, $\underline{H}_6$ of aromatic ring, $^{3}J_{HCCH}$ 7.36 Hz), 7.44 (d, $\underline{H}_3$ of aromatic ring, $^{3}J_{HCCH}$ 7.42 Hz); ^{13}C($CDCl_3$) δ 49.57 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 137.55 Hz), 116.76 (s, $\underline{C}_5$ of aromatic ring), 121.58 (s, $\underline{C}_4$ of aromatic ring), 131.34 (d, $\underline{C}_6$ of aromatic ring), 166.73 (d, $\underline{C}_2$-OH of aromatic ring, $^{3}J_{PCCC}$ 7.49 Hz); ^{31}P(NaOD) δ 20.82 (s).

PREPARATION OF 1-AMINO-4'-ISOPROPYLBENZYLPHOSPHONIC ACID

N-4-Isopropylbenzylidenediphenylmethylamine (24.57 g, 0.079 mol), and diethyl phosphite (10.83 g, 0.079 mol) were heated at 120-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl 1-diphenylmethylamino-4'-isopropylbenzylphosphonate intermediate. Concentrated hydrochloric acid (80 cm^3) was added and the resultant purple solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x40 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue that had formed was dissolved in methanol and treated with propylene oxide at 40-50 ^{o}C, to afford a white crystalline solid. The product 1-amino-4'-isopropylbenzylphosphonic acid, was filtered off, washed with acetone and dry ether and later dried in a vacuum oven for 2 h at 70 ^{o}C (4.87 g, 27 %); m.p. 286-288 ^{o}C; (Found: C, 52.46; H, 6.98; N, 5.75. Calc. for $C_{10}H_{16}NO_3P$: C, 52.46; H, 6.98; N, 5.75 %); ^{1}H(NaOD) δ 1.23 (d, 6H, $CH(C\underline{H}_3)_2$, $^{3}J_{HCCH}$ 6.94 Hz), 2.93 (m, 1H, $C\underline{H}(CH_3)_2$, $^{3}J_{HCCH}$ 6.93 Hz), 3.79 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 15.30 Hz), 7.28 - 7.41 (m, 4H, $C_6\underline{H}_4$); ^{13}C(NaOD) δ 26.18 (s, $CH(\underline{C}H_3)_2$), 35.98 (s, $\underline{C}H(CH_3)_2$), 58.07 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 130.95 Hz), 128.79 (d, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring, $^{4}J_{PC}$ 1.26 Hz), 130.64 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 4.91 Hz), 150.28 (d, $\underline{C}_1$ of aromatic ring, $^{2}J_{PCC}$ 2.45 Hz); ^{31}P(NaOD) δ 9.94 (s).

PREPARATION OF 1-AMINO-4'-METHYLBENZYLPHOSPHONIC ACID

N-4'-Methylbenzylidenediphenylmethylamine (9.60 g, 0.034 mol), and dimethyl phosphite (5.50 g, 0.050 mol) were heated at 140 °C for 30 min. No attempt was made to isolate the *O,O*-dimethyl 1-diphenylmethylamino-4'-methylbenzylphosphonate intermediate. Concentrated hydrochloric acid (60 cm^3) was added, and the resultant deep purple solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x30 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue that had formed, was treated with propylene oxide at 40-50 °C, to afford a white crystalline solid. The product 1-amino-4'-methylbenzylphosphonic acid, was filtered off, washed with acetone and dry ether and dried in a vacuum oven for 2 h at 70 °C (0.24 g, 4 %); m.p. 275-278 °C; (lit.[34] 276 °C); (Found: C, 45.32; H, 5.91; N, 6.01. Calc. for $C_8H_{12}NO_3P$: C, 47.76; H, 5.96; N, 6.97 %); ^{1}H(NaOD) δ 2.33 (s, 3H, C_4-C$\underline{H}_3$), 3.77 (d, 1H, P-C$\underline{H}$, $^2J_{PCH}$ 15.28 Hz), 7.21 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic ring, $^3J_{HCCH}$ 8.17 Hz), 7.30 (dd, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring, $^3J_{HCCH}$ 8.12 Hz, $^4J_{PH}$ 1.76 Hz); ^{13}C(NaOD) δ 22.94 (s, $\underline{C}H_3$), 58.04 (d, P-$\underline{C}$H, $^1J_{PC}$ 131.52 Hz), 130.48 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^3J_{PCCC}$ 4.91 Hz), 131.37 (d, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring, $^4J_{PC}$ 1.57 Hz), 138.97 (s, $\underline{C}_4$ of aromatic ring), 141.72 (d, $\underline{C}_1$ of aromatic ring, $^2J_{PCC}$ 2.64 Hz); ^{31}P(NaOD) δ 18.42 (s).

PREPARATION OF 1-AMINO 3'-METHOXY-4'-HYDROXYBENZYLPHOSPHONIC ACID

N-3'-Methoxy-4'-hydroxybenzylidenediphenylamine (5 g, 0.016 mol), and dimethyl phosphite (4 g, 0.036 mol) were heated at 140 ^{o}C for 30 min. No attempt was maded to isolate the *O,O*-dimethyl 1-diphenylmethylamino-3'-methoxy-4'-hydroxybenzylphosphonate intermediate. Concentrated hydrochloric acid (60 cm^3) was added and the resultant orange solution was heated under reflux for 4 h. Upon cooling, the reaction mixture was extracted with toluene (3x40 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous deep yellow residue that had formed was dissolved in methanol, and treated with propylene oxide at 40-50 ^{o}C, to afford a yellow paste-like material. This material was dissolved in water and upon dropwise addition of ethanol at 0 ^{o}C, produced a white crystalline solid. The product expected to be 1-amino-3'-methoxy-4'-hydroxybenzylphosphonic acid was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 70 ^{o}C (0.042 g, 1 %); m.p. 290-294 ^{o}C; (Found [crude]: C, 37.88; H, 6.18; N, 3.76. $C_8H_{12}NO_5P$ requires: C, 41.20; H, 5.15; N, 6.01 %); ^{1}H(NaOD) δ 3.64 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 14.36 Hz), 3.79 (s, 3H, OC$\underline{H}_3$), 6.58 (d, 1H, $\underline{H}_6$ of aromatic ring, $^{3}J_{HCCH}$ 7.97 Hz), 6.78 (s, $\underline{H}_5$ of aromatic ring), 6.95 (s, $\underline{H}_2$ of aromatic ring); ^{13}C($CDCl_3$) δ 57.96 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 136.86 Hz), 115.77 (d, $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 4.91 Hz), 120.53 (s, $\underline{C}_5$ of aromatic ring), 152.97 (s, $\underline{C}_3$ of aromatic ring), 152.97 (s, $\underline{C}_4$ of aromatic ring); ^{31}P(NaOD) δ 19.33 (s).

PREPARATION OF 1-AMINO-4'-ETHYLBENZYLPHOSPHONIC ACID

N-4'-Ethylbenzylidenediphenylmethylamine (5 g, 0.017 mol) and diethyl phosphite (2.35 g, 0.017 mol) were heated at 140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl 1-diphenylmethyl-amino-4'-ethylbenzylphosphonate intermediate. Concentrated hydrochloric acid (60 cm^3) was added and the resultant red solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x50 cm^3), and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue that formed was dissolved in methanol, and treated with propylene oxide at 40-50 ^{o}C to afford a white crystalline solid. The product 1-amino-4'-ethylbenzylphosphonic acid, was filtered off, washed with acetone and dry ether, and dried in a vacuum oven for 2 h at 70 ^{o}C (1.52 g, 42 %); m.p. 284-286 ^{o}C; (Found: C, 50.15; H, 6.48; N, 6.50. Calc. for $C_9H_{14}NO_3P$: C, 50.23; H, 6.51; N, 6.51 %); ^{1}H(NaOD) δ 1.20 (t, 3H, $CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.61 Hz), 2.64 (q, 2H, $\underline{CH}_2CH_3$, $^{3}J_{HCCH}$ 7.57 Hz), 3.78 (d, 1H, P-$\underline{CH}$, $^{2}J_{PCH}$ 15.31 Hz), 7.25 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic ring, $^{3}J_{HCCH}$ 8.13 Hz), 7.34 (dd, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring, $^{3}J_{HCCH}$ 8.06 Hz), $^{4}J_{PH}$ 1.48 Hz); ^{13}C(NaOD) δ 18.12 (s, $\underline{C}H_3CH_2$), 30.69 (s, $CH_3\underline{C}H_2$), 58.02 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 131.83 Hz), 130.23 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 130.59 (d, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 4.78 Hz), 142.05 (s, $\underline{C}_4$ of aromatic ring), 145.61 (s, $\underline{C}_1$ of aromatic ring); ^{31}P(NaOD) δ 18.42 (s)

PREPARATION OF 1-AMINO-2'-FLUOROBENZYLPHOSPHONIC ACID

N-2'-Fluorobenzylidenediphenylmethylamine (4.07 g, 0.14 mol), and dimethyl phosphite (2.00 g, 0.014 mol), were heated at 120-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-dimethyl-1-diphenylmethylamino-2'-fluorobenzylphosphonate intermediate. Concentrated hydrochloric acid (80 cm^3) was added and the resultant red solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x30 cm^3), and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous reddish-orange residue that had formed was dissolved in methanol and treated with propylene oxide at 40-50 ^{o}C, to afford a white powdery, crystalline material. The product, *1-amino-2'-fluorobenzylphosphonic acid*, was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 80 ^{o}C (0.80 g, 28 %); m.p. 270-273 ^{o}C; (Found: C, 41.05; H, 4.41; N, 6.61. $C_7FH_9NO_3P$ requires: C, 40.98; H, 4.39; N, 6.38 %); ^{1}H(NaOD) δ 4.41 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 16.10 Hz), 7.07-7.34 (m, 3H, $\underline{H}_4$, $\underline{H}_5$, $\underline{H}_6$ of aromatic ring), 7.46 (m, 1H, $\underline{H}_3$ of aromatic ring); ^{13}C(NaOD) δ 50.96 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 132.14 Hz, $^{3}J_{FCCC}$ 1.18 Hz), 117.74 (d, $\underline{C}_3$ of aromatic ring, $^{2}J_{FCC}$ 22.77 Hz), 126.69 (s, $\underline{C}_5$ of aromatic ring), 130.53 (dd, $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 2.39 Hz, $^{3}J_{FCCC}$ 8.30 Hz), 131.55 (dd overlapping, $\underline{C}_4$ of aromatic ring, $^{3}J_{FCCC}$ 8.05 Hz), 131.82 (dd overlapping, $\underline{C}_1$ of aromatic ring, $^{2}J_{PCC}$ 1.89 Hz), 162.69 (dd, $\underline{C}_2$ of aromatic ring, $^{1}J_{FC}$ 242.62 Hz); ^{31}P(NaOD) δ 17.59 (d, $^{4}J_{FP}$ 3.94 Hz); ^{19}F(NaOD) δ - 117.97 (s).

PREPARATION OF 1-AMINO-4'-TRIFLUOROMETHYLBENZYLPHOSPHONIC ACID

N-4'-Trifluoromethylbenzylidenediphenylmethylamine (5 g, 0.015 mol), and dimethyl phosphite (4.00 g, 0.036 mol), were heated at 120-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-dimethyl 1-diphenylmethylamino-4'-trifluoromethylbenzylphosphonate intermediate. Concentrated hydrochloric acid (80 cm^3) was added and the resultant reddish-orange solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x50 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous light-green residue that had formed was dissolved in methanol and treated with propylene oxide at 40-50 ^{o}C, to afford a white crystalline solid. The product, *1-amino-4'-trifluoromethylbenzylphosphonic acid*, was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 80 ^{o}C (1.71 g, 46 %); m.p. 287-289 ^{o}C; (Found: C, 37.50; H, 3.55; N, 5.40. $C_8F_3H_9NO_3P$ requires: C, 37.65; H, 3.53; N, 5.49 %); ^{1}H(NaOD) δ 3.95 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 16.41 Hz), 7.57 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring, $^{3}J_{HCCH}$ 7.96 Hz), 7.67 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic ring, $^{3}J_{HCCH}$ 8.13 Hz); ^{13}C(NaOD) δ 58.27 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 128.06 Hz), 127.34 (q, $\underline{C}F_3$, $^{1}J_{FC}$ 271.17 Hz), 127.54 (s, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring), 130.05 (q, $\underline{C}_4$ of aromatic ring, $^{2}J_{FCC}$ 63.84 Hz), 130.62 (d, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring, $^{3}J_{FCCC}$ 4.65 Hz), 149.09 (s, $\underline{C}_1$ of aromatic ring); ^{31}P(NaOD) δ 16.96 (s); ^{19}F(NaOD) δ - 61.94 (s); FAB ms (thioglycerol): m/z(%) 511 (2M+H, 20.6), 256 (M+H, 52.5), 186 (14.6), 176 (M+H - HPO_3, 12.1), 174 (M+H - H_3PO_3,

100), 155 (M+H - F, 29.2), 130 (72.7).

PREPARATION OF 1-AMINO-4'-FLUOROBENZYLPHOSPHONIC ACID

N-4'-Fluorobenzylidenediphenylmethylamine (5 g, 0.0173 mol) and diethyl phosphite (2.76 g, 0.020 mol) were heated at 120-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl 1-diphenylmethylamino-4'-fluorobenzylphosphonate intermediate. Concentrated hydrochloric acid (80 cm^3) was added and the resultant orange solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x60 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue that had formed, was dissolved in methanol and treated with propylene oxide at 40-50 ^{o}C, to afford a white crystalline solid. The product, *1-amino-4'-fluorobenzylphosphonic acid* was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 80 ^{o}C (1.95 g, 55 %); m.p. 278-282 ^{o}C; (Found: C, 40.98; H, 4.93; N, 6.80. $C_7FH_9NO_3P$ requires: C, 40.98; H, 4.39; N, 6.83 %); ^{1}H(NaOD) δ 3.86 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 15.36 Hz), 7.11 (dd overlapping, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic ring, $^{3}J_{HCCH}$ 8.91 Hz), 7.40 (dd overlapping, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring, $^{3}J_{HCCH}$ 6.28 Hz); ^{13}C(NaOD) δ 57.52 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 131.08 Hz), 117.41 (d, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring, $^{2}J_{FCC}$ 21.64 Hz), 131.90 (dd, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 5.06 Hz, $^{3}J_{FCCC}$ 7.83 Hz), 139.82 (s, $\underline{C}_1$ of aromatic ring), 164.12 (d, $\underline{C}_4$ of aromatic ring, $^{1}J_{FC}$ 243.53 Hz); ^{31}P(NaOD) δ 17.03 (d, $^{6}J_{PF}$ 2.95 Hz).

PREPARATION OF 1-AMINO-3'-TRIFLUOROMETHOXYBENZYLPHOSPHONIC ACID

N-3'-Trifluoromethoxybenzylidenediphenylmethylamine (5 g, 0.014 mol), and diethyl phosphite (2.21 g, 0.016 mol), were heated at 120-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl 1-diphenylmethylamino-3'-trifluoromethoxybenzylphosphonate intermediate. Concentrated hydrochloric acid (80 cm^3) was added and the resultant reddish-orange solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x60 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous light-green residue that had formed was dissolved in methanol and treated with propylene oxide at 40-50 ^{o}C, to afford a white crystalline solid. The product, *1-amino-3'-trifluoromethoxybenzylphosphonic acid* was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 80 ^{o}C(1.63 g, 43 %); m.p. 277-280 ^{o}C; (Found: C, 36.62; H, 3.54; N, 5.40. $C_8F_3H_9NO_3P$ requires: C, 36.65; H, 3.35; N, 5.49 %); ^{1}H(NaOD) δ 3.87 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 16.24 Hz), 7.21 (s, 1H, $\underline{H}_2$ of aromatic ring), 7.33-7.47 (m, 3H, $\underline{H}_4$, $\underline{H}_5$, $\underline{H}_6$ of aromatic ring); ^{13}C(NaOD) δ 57.93 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 129.75 Hz), 121.13 (s, $\underline{C}_5$ of aromatic ring), 122.69 (d, $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 4.53 Hz), 123.03 (q, O$\underline{C}F_3$, $^{1}J_{FC}$ 255.80 Hz), 128.90 (d, $\underline{C}_2$ of aromatic ring, $^{3}J_{PCCC}$ 4.72 Hz), 132.00 (s, $\underline{C}_4$ of aromatic ring), 147.46 (s, $\underline{C}_1$ of aromatic ring), 151.24 (s, $\underline{C}_3$ of aromatic ring); ^{31}P(NaOD) δ 17.29 (s); ^{19}F(NaOD) δ - 57.62 (d); FAB ms (3-NOBA): m/z(%) 308 (100), 290 (70.8), 272 (M+H, 24.6), 254 (M+H - H_2O, 28.5), 189

(15.8), 166 (51.7).

PREPARATION OF 1-AMINOPENTAFLUOROBENZYLPHOSPHONIC ACID

N-Pentafluorobenzylidenediphenylmethylamine (5 g, 0.014 mol), and diethyl phosphite (2.07 g, 0.015 mol), were heated at 135 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl 1-diphenylmethylaminopentafluorobenzylphosphonate intermediate. Concentrated hydrochloric acid (80 cm^3) was added and the resultant deep-purple solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x50 cm^3), and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous yellow residue that formed was dissolved in methanol and treated with propylene oxide at 40-50 ^{o}C, to afford a grey paste-like residue. This material was dissolved in water, heated in the presence of decolourising charcoal, filtered, cooled, and precipitated by the addition of ethanol to the filtrate, generating a white crystalline solid. The product, *1-pentafluorobenzylphosphonic acid*, was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 80 ^{o}C (0.67 g, 18 %); m.p. 268-270 ^{o}C; (Found: C, 31.04; H, 2.15; N, 5.38. $C_7F_5H_5NO_3P$ requires: C, 31.15; H, 2.03; N, 5.69 %); ^{1}H(NaOD) δ 4.20 (d, 1H, P-C<u>H</u>, $^{2}J_{PCH}$ 17.53 Hz); ^{13}C(NaOD) δ 50.23 (d, P-<u>C</u>H, $^{1}J_{PC}$ 130.89 Hz), 118.45 (dd overlapping, <u>C</u>$_1$ of aromatic ring, $^{2}J_{FCC}$ 16.23 Hz), 140.14 (ddd overlapping overlapping, <u>C</u>$_3$ & <u>C</u>$_5$ of aromatic ring, $^{1}J_{FC}$ 246.30 Hz), 142.09 (dm, <u>C</u>$_4$ of aromatic ring, $^{1}J_{FC}$ 249.38 Hz), 147.58 (d, <u>C</u>$_2$ & <u>C</u>$_6$ of

aromatic ring, $^{1}J_{FC}$ 243.03 Hz); ^{31}P(NaOD) δ 15.32 (d); ^{19}F(NaOD) δ - 9.47 (m), - 25.96 (m), - 31.22 (m); FAB ms (thioglycerol): m/z(%) 555 (2M+H, 40.2), 386 (M+H+T, 2.7), 278 (M+H, 74.6), 196 (M+H - H_3PO_3, 100), 178 (67.9).

PREPARATION OF 1-AMINO-4'-NITROBENZYLPHOSPHONIC ACID

N-4'-Nitrobenzylidenediphenylmethylamine (5 g, 0.016 mol) and diethyl phosphite (2.35 g, 0.017 mol) were mixed and heated at 130-140 ^{o}C for 30 min. No attempt was made to isolate the *O,O*-diethyl 1-diphenylmethylamino-4'-nitrobenzylphosphonate intermediate. Concentrated hydrochloric acid (60 cm^3) was added and the resultant orange solution was heated under reflux for 3 h. Upon cooling, the reaction mixture was extracted with toluene (3x50 cm^3) and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The viscous deep yellow residue formed was dissolved in methanol and treated with propene oxide (40-50 ^{o}C) to afford a deep yellow powdery solid. The product, 1-amino-4'-nitrobenzylphosphonic acid was filtered off, washed with acetone and dry ether, before being dried in a vacuum oven for 2 h at 70 ^{o}C. (1.79 g, 48 %); m.p. 230-234 ^{o}C; (lit.[27] 234-238 ^{o}C); (Found: C, 36.25; H, 3.82; N, 11.94. Calc for $C_7H_9N_2O_5P$: C, 36.21; H, 3.79; N, 12.07 %); ^{1}H(NaOD) δ 4.01 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 17.29 Hz), 7.59 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic ring, $^{3}J_{HCCH}$ 7.73 Hz), 8.20 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring, $^{3}J_{HCCH}$ 8.40 Hz); ^{13}C(NaOD) δ 58.60 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 126.36 Hz), 126.01 (s, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring), 130.95 (d, $\underline{C}_2$ & $\underline{C}_6$ of

aromatic ring, $^{3}J_{PCCC}$ 4.28 Hz), 148.61 (s, $\underline{C}_4$ of aromatic ring), 153.70 (d, $\underline{C}_1$ of aromatic ring, $^{2}J_{PCC}$ 2.45 Hz); ^{31}P(NaOD) δ 16.64 (s); FAB ms (3-NOBA): m/z(%) 539 (M+H+2N, 5.8), 465 (2M+H, 24), 386 (M+H+N, 15.8), 233 (M+H, 47.5), 153 (M+H - HPO_3, 27.1), 151 (M+H - H_3PO_3, 100.0)

4.4.13. THE PREPARATION OF 1-AMINOPHOSPHONOUS ACIDS

PREPARATION OF 1-AMINOETHANEPHOSPHONOUS ACID

Acetaldehyde (8.81 g, 0.20 mol) dissolved in water (50 cm^3), was added dropwise to a refluxing mixture of diphenylmethylamine hydrochloride (43.94 g, 0.20 mol), and aqueous hypophosphorous acid (50 %, 26.4 g, 0.20 mol), in water (50 cm^3). When 2/3 of the aldehyde solution had been added, precipitation of the phosphonous acid intermediate had begun to occur. When the addition had been completed, the solution was heated under reflux for 2 h. After cooling, the 1-diphenylmethylaminoethanephosphonous acid intermediate was filtered off, washed with acetone and dried in a vacuum oven for 2 h at 60 ^{o}C.

1-Diphenylmethylaminoethanephosphonous acid (22 g, 0.08 mol), was heated under reflux in the presence of concentrated hydrochloric acid (18 %, 200 cm^3), for 4 h. The 2-phase solution which formed on cooling, was concentrated under reduced pressure on a rotary evaporator, to afford a creamy gelatinous residue. After dissolving in the minimum of water, this solution was exhaustively extracted with ether, and then concentrated under reduced pressure on a rotary evaporator, to produce a clear-yellow viscous oily residue. This material was dissolved in methanol (50 cm^3) and treated with propylene oxide (40-50 ^{o}C), to afford a white crystalline solid. The product, 1-aminoethanephosphonous acid, was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 60 ^{o}C (8.12 g, 90 %); m.p. 223-226 ^{o}C (lit.[4]

m.p. 223-224 ^{o}C); (Found: C, 22.41; H, 7.27; N, 12.64. Calc. for $C_2H_8NO_2P$: C, 22.02; H, 7.34; N, 12.84 %); ^{1}H(NaOD) δ 1.33 (dd, 3H, P-CHC$\underline{H}_3$, $^{3}J_{HCCH}$ 7.14 Hz, $^{3}J_{PCCH}$ 16.28 Hz), 3.08 (dq overlapping, 1H, P-C$\underline{H}$CH$_3$, $^{3}J_{HCCH}$ 7.74 Hz), 5.84 & 7.92 (d, 1H, $\underline{H}$-P, $^{1}J_{PH}$ 520.91 Hz); ^{13}C(NaOD) δ 14.89 (s, P-CH$\underline{C}$H$_3$), 48.57 (d, P-$\underline{C}$HCH$_3$, $^{1}J_{PC}$ 92.22 Hz); ^{31}P(NaOD) δ 24.65 (s).

PREPARATION OF 1-AMINOPROPANEPHOSPHONOUS ACID

Propanal (11.6 g, 0.20 mol) dissolved in water (50 cm^3), was added dropwise to a refluxing mixture of diphenylmethylamine hydrochloride (43.94 g, 0.20 mol), and aqueous hypophosphorous acid (50 %, 26.4 g, 0.20 mol), in water (50 cm^3). When 2/3 of the aldehyde solution had been added, precipitation of the phosphonous acid intermediate had begun to occur. When the addition had been completed the solution was heated under reflux for 2 h. After cooling, the 1-diphenylmethylaminopropanephosphonous acid intermediate was filtered off, washed with acetone and dried in a vacuum oven for 2 h at 60 ^{o}C.

1-Diphenylmethylaminopropanephosphonous acid (23.07 g, 0.08 mol), was heated under reflux in the presence of concentrated hydrochloric acid (18 %, 200 cm^3), for 4 h. The 2 phase solution which had formed on cooling, was concentrated under reduced pressure on a rotary evaporator, to afford an off-white gelatinous residue, which was then dissolved in a small quantity of water. This solution was exhaustively extracted with ether, before being concentrated under

reduced pressure on a rotary evaporator, to produce a clear-yellow viscous oily residue. This material was dissolved in ethanol (100 cm^3), and treated with propylene oxide at 40-50 ^oC, to afford a white crystalline solid. The product, 1-aminopropanephosphonous acid, was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 60 ^oC (9.22 g, 38 %); m.p. 225-227 ^oC (lit.[115] 226-227 ^oC); (Found: C, 30.21; H, 8.41; N, 11.40. Calc. for $C_3H_{10}NO_2P$: C, 29.27; H, 8.13; N, 11.38 %); ^1H(NaOD) δ 1.05 (t, 3H, P-CHCH$_2$C$\underline{H}_3$, $^3J_{HCCH}$ 7.49 Hz), 1.47-1.90 (m, 2H, P-CHC$\underline{H}_2$CH$_3$), 2.70-2.80 (m, 1H, P-C$\underline{H}$CH$_2$CH$_3$), 5.82 & 7.87 (dd, 1H, $\underline{H}$-P, $^1J_{HP}$ 513.32 Hz, $^3J_{HPCH}$ 1.42 Hz); ^{13}C(NaOD) δ 12.86 (d, P-CHCH$_2$C$\underline{H}_3$, $^3J_{PCCC}$ 10.69 Hz), 24.13 (s, P-$\underline{C}$HCH$_2$), 54.69 (d, P-$\underline{C}$H, $^1J_{PC}$ 97.09 Hz); ^{31}P(NaOD) δ 28.02 (s).

PREPARATION OF 1-AMINO-4-METHYLBUTANEPHOSPHONOUS ACID

Isovaleraldehyde (4-methylbutanal, 9.92 g, 0.12 mol), dissolved in water (50 cm^3), was added dropwise to a refluxing mixture of diphenylmethylmethylamine hydrochloride (25.30 g, 0.12 mol), and aqueous hypophosphorous acid (50 %, 15.20 g, 0.12 mol), in water (50 cm^3). When 2/3 of the aldehyde solution had been added, precipitation of the phosphonous acid intermediate had begun to occur. When the addition was complete, the solution was heated under reflux for 2 h. After cooling, the 1-diphenylmethylamino-4-methylbutanephosphonous acid intermediate was filtered off, washed with acetone and dried in a vacuum oven for 2 h at 60 ^oC.

The phosphonous acid intermediate was heated under reflux in the presence of concentrated hydrochloric acid (18 %, 200 cm^3), for 4 h. The 2-phase solution which formed on cooling, was concentrated under reduced pressure on a rotary evaporator, to afford an off-white oily residue. After dissolving in the minimum of water, this solution was exhaustively extracted with ether, and concentrated under reduced pressure on a rotary evaporator, to produce a clear-yellow viscous oily residue. This material was dissolved in ethanol (100 cm^3), and treated with propylene oxide at 40-50 ^oC, to afford a white crystalline solid. The product, 1-amino-4-methylbutanephosphonous acid, was filtered off washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 60 ^oC (3.77 g, 21 %); m.p. 203-206 ^oC; (lit.[4] 201-202 ^oC); (Found: C, 39.81; H, 9.06; N, 9.31. Calc. for $C_5H_{14}NO_2P$: C, 39.74; H, 9.27; N, 9.27 %); ^1H(NaOD) δ 1.37 (m, 2H, $C\underline{H}_2CH(CH_3)CH_3$), 1.80 (m, 1H, $CH_2C\underline{H}(CH_3)CH_3$), 2.70 (ddd, 1H, P-C$\underline{H}$), 4.84 & 7.70 (dd, 1H, $\underline{H}$-P, $^1J_{PH}$ 501.47 Hz, $^3J_{HPCH}$ 1.30 Hz); ^{13}C(NaOD) δ 23.51 (s, $CH(CH_3)\underline{C}H_3$), 25.88 (s, $CH(\underline{C}H_3)CH_3$), 26.65 (d, P-$CHCH_2\underline{C}H$, $^3J_{PCCC}$ 12.05 Hz), 41.01 (s, P-$CH\underline{C}H_2CH$), 51.55 (d, P-$\underline{C}H$, $^1J_{PC}$ 99.43 Hz); ^{31}P(NaOD) δ 25.44 (s).

PREPARATION OF 1-AMINO-2'-HYDROXYBENZYLPHOSPHONOUS ACID

Salicylaldehyde (20.39 g, 0.17 mol), was added dropwise to a refluxing mixture of diphenylmethylamine hydrochloride (36.64 g, 0.17 mol), and aqueous hypophosphorous acid (50 %, 11.02 g, 0.17 mol), in water (50 cm^3). When the addition had been completed, the solution

was heated under reflux for 5 h. After cooling, the 1-diphenylmethylamino-2'-hydroxybenzylphosphonous acid intermediate was filtered off, washed with acetone and dried in a vacuum oven for 2 h at 60 ^{o}C.

Without weighing the amount of 1-diphenylmethylamino-2'-hydroxybenzylphosphonous acid that been isolated, this intermediate was heated under reflux in the presence of concentrated hydrochloric acid (18 %, 200 cm^3), for 4 h. The solution, on cooling, was concentrated under reduced pressure on a rotary evaporator, to afford a thick viscous yellow residue. After dissolving in the minimum of water, this solution was exhaustively extracted with ether, and then concentrated under reduced pressure on a rotary evaporator, to produce a viscous yellow residue. This material was dissolved in ethanol (100 cm^3) and treated with propylene oxide at 40-50 ^{o}C, to afford a white crystalline solid. The product *1-amino-2'-hydroxybenzylphosphonous acid*, was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 60 ^{o}C. (4.26 g, 13 %); m.p. 217-220 ^{o}C; (Found: C, 43.69; H, 5.03; N, 6.84. $C_7H_{10}NO_3P$ requires: C, 44.92; H, 5.35; N, 7.49 %); ^{1}H(NaOD) δ 4.34 (d, 1H, P-C$\underline{H}$, $^{2}J_{PCH}$ 12.46 Hz), 6.64 (dd overlapping, 2H, $\underline{H}_3$ & $\underline{H}_4$ of aromatic ring, $^{3}J_{HCCH}$ 7.32 Hz), 7.12 (dd overlapping, 2H, $\underline{H}_5$ & H_6 of aromatic ring, $^{3}J_{HCCH}$ 7.31 Hz), 5.79 & 7.84 (d, 1H, $\underline{H}$-P, $^{1}J_{PH}$ 512.96 Hz); ^{13}C(NaOD) δ 51.92 (d, P-$\underline{C}$H, $^{1}J_{PC}$ 92.29 Hz), 116.63 (d, $\underline{C}_5$ of aromatic ring, $^{4}J_{PC}$ 2.33 Hz), 121.56 (s, $\underline{C}_4$ of aromatic ring), 129.74 (s, $\underline{C}_1$ of aromatic ring), 130.24 (d, $\underline{C}_6$ of aromatic ring, $^{3}J_{PCCC}$ 5.66 Hz), 131.14 (d, $\underline{C}_3$ of aromatic ring, $^{4}J_{PC}$ 2.20 Hz), 167.10 (d, $\underline{C}_2$

of aromatic ring, $^{3}J_{PCCC}$ 5.47 Hz); ^{31}P(NaOD) δ 30.33 (s).

PREPARATION OF 1-AMINO-4'-ETHYLBENZYLPHOSPHONOUS ACID

4-Ethylbenzaldehyde (6.71 g, 0.050 mol), was added dropwise to a refluxing mixture of diphenylmethylamine hydrochloride (11 g, 0.05 mol), and aqueous hypophosphorous acid (50 %, 6.6 g, 0.05 mol), in water (40 cm^3). When the addition had been completed the solution was heated under reflux for 5 h. After cooling, the 1-diphenylmethylamino-4'-ethylbenzylphosphonous acid intermediate was filtered off, washed with acetone and dried in a vacuum oven for 2 h at 60 ^{o}C.

Without weighing the amount of 1-diphenylmethylamino-4'-ethylbenzylphosphonous acid that had been isolated, the intermediate was heated under reflux in the presence of concentrated hydrochloric acid (18 %, 100 cm^3) for 4 h. The solution, on cooling, was concentrated under reduced pressure on a rotary evaporator, to afford a thick viscous gelatinous residue. After dissolving in the minimum of water, this solution was exhaustively extracted with ether, and then concentrated under reduced pressure on a rotary evaporator, to produce a viscous clear-yellow residue. This material was dissolved in ethanol (50 cm^3), and treated with propylene oxide at 40-50 ^{o}C, to afford a white crystalline solid. The product, *1-amino-4'-ethylbenzylphosphonous acid*, was filtered off, washed with acetone and dry ether, before being dried in a vacuum oven for 2 h at 60 ^{o}C (3.23 g, 32 %); m.p. 245-247 ^{o}C; (Found: C, 54.66; H, 7.07; N, 6.52. $C_9H_{14}NO_2P$ requires: C, 54.27; H,

7.04; N, 7.04 %); ^{1}H(NaOD) δ 1.18 (t, 3H, $\underline{CH_3}CH_2$, $^{3}J_{HCCH}$ 7.61 Hz), 2.60 (q, 2H, $CH_3\underline{CH_2}$, $^{3}J_{HCCH}$ 7.58 Hz), 3.86 (dd, 1H, P-$\underline{CH}$, $^{2}J_{PCH}$ 13.44 Hz, $^{3}J_{HPCH}$ 1.03 Hz), 7.27 (m, 4H, $\underline{H_2}$, $\underline{H_3}$, $\underline{H_5}$, $\underline{H_6}$ of aromatic ring), 5.76 & 7.82 (dd, $\underline{H}$-P, $^{1}J_{HP}$ 514.32 Hz, $^{3}J_{HPCH}$ 1.17 Hz); ^{13}C(NaOD) δ 17.96 (s, $CH_2\underline{CH_3}$), 30.71 (s, $\underline{CH_2}CH_3$), 58.93 (d, P-$\underline{CH}$, $^{1}J_{PC}$ 94.22 Hz), 130.25 (d, $\underline{C_2}$ & $\underline{C_6}$ of aromatic ring, $^{3}J_{PCCC}$ 5.28 Hz), 130.81 (s, $\underline{C_3}$ & $\underline{C_5}$ of aromatic ring), 138.02 (s, $\underline{C_4}$ of aromatic ring), 146.56 (s, $\underline{C_1}$ of aromatic ring); ^{31}P(NaOD) δ 29.97 (s).

PREPARATION OF 1-AMINO-4'-FLUOROBENZYLPHOSPHONOUS ACID

4-Fluorobenzaldehyde (6.21 g, 0.050 mol) was added dropwise to a refluxing mixture of diphenylmethylamine hydrochloride (11 g, 0.050 mol), and aqueous hypophosphorus acid (50 %, 6.6 g, 0.050 mol), in water (40 cm^3). When the addition had been completed, the solution was heated under reflux for 5 h. After cooling, the 1-diphenylmethylamino-4'-fluorobenzylphosphonous acid intermediate was filtered off, washed with acetone, and dried in a vacuum oven for 2 h at 60 ^{o}C.

No attempt was made to isolate and characterise the 1-diphenylmethylamino-4'-fluorobenzylphosphonous acid, which was heated under reflux in the presence of concentrated hydrochloric acid (18 %, 100 cm^3), for 4 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator, to afford a viscous creamy residue. After dissolving in the minimum amount of water, this solution was exhaustively extracted with ether, and then concentrated under reduced

pressure on a rotary evaporator, to produce a clear-yellow residue. This material was dissolved in ethanol (50 cm^3), and treated with propylene oxide at 40 - 50 ^oC, to afford a white crystalline product. The product, *1-amino-4'-fluorobenzylphosphonous acid* was filtered off, washed with acetone and dry ether, and later dried in a vacuum oven for 2 h at 60 ^oC. (1.15 g, 12 %); m.p. 242-244 ^oC; (Found: C, 45.22; H, 5.10; N, 6.32. $C_7FH_9NO_2$ requires: C, 44.44; H, 4.76; N, 7.41 %); ^1H(NaOD) δ 3.90 (d, 1H, P-C$\underline{H}$, $^2J_{PCH}$ 13.16 Hz), 7.17 (dd overlapping, 2H, $\underline{H}_3$ & $\underline{H}_5$ of aromatic ring, $^3J_{HCCH}$ 8.91 Hz), 7.32-7.38 (m, 2H, $\underline{H}_2$ & $\underline{H}_6$ of aromatic ring), 5.78-7.83 (dd, 1H, $\underline{H}$-P, $^1J_{PH}$ 514.98 Hz, $^3J_{HCPH}$ 1.09 Hz); ^{13}C(NaOD) δ 58.42 (d, P-$\underline{C}$H, $^1J_{PC}$ 93.97 Hz), 118.05 (dd, $\underline{C}_3$ & $\underline{C}_5$ of aromatic ring, $^2J_{FCC}$ 21.51 Hz, $^4J_{PC}$ 2.01 Hz), 131.76 (dd, $\underline{C}_2$ & $\underline{C}_6$ of aromatic ring, $^3J_{PCCC}$ 5.22 Hz, $^3J_{FCCC}$ 8.18 Hz), 136.51 (s, $\underline{C}_1$ of aromatic ring), 164.60 (d, $\underline{C}_4$ of aromatic ring, $^1J_{FC}$ 245.29 Hz); ^{31}P(NaOD) δ 29.51 (d, $^6J_{PF}$ 3.94 Hz); ^{19}F(NaOD) δ - 116.23 (s).

4.4.13.1.

ATTEMPT TO PREPARE 1-GUANIDINOPROPANEPHOSPHONOUS ACID USING AMINOIMINOMETHANESULPHONIC ACID IN THE PRESENCE OF SODIUM HYDROXIDE

A mixture of 1-aminopropanephosphonous acid (0.62 g, 0.005 mol) and sodium hydroxide (0.20 g, 0.005 mol) dissolved in water (10 cm^3), was added dropwise to a stirring suspension of aminoiminomethanesulphonic acid (0.62 g, 0.005 mol), under dry nitrogen.

The solution was left to stir at room temperature for 48 h. The solution was concentrated under reduced pressure on a rotary evaporator, to afford a creamy residue. This material was dissolved in the minimum of cold water and treated with ethanol at 0 ^{o}C, to produce a turbid solution. After leaving to stand at 4 ^{o}C for 12 h, a white crystalline precipitate had formed. This material was filtered off, washed with acetone and dried in a vacuum oven for 2 h at 60 ^{o}C. Elemental analysis showed that guanidation had not taken place. (0.21 g); (Found: C, 2.75; H, 0.79; N, 2.27. $C_4H_{12}N_3O_2P$ requires: C, 29.09; H, 7.27; N, 25.46 %).

4.4.13.2.

ATTEMPT TO PREPARE 1-GUANIDINOPROPANEPHOSPHONOUS ACID USING AMINOIMINOMETHANESULPHONIC ACID IN THE PRESENCE OF EXCESS SODIUM HYDROXIDE

A mixture of 1-aminopropanephosphonous acid (0.62 g, 0.005 mol) and sodium hydroxide (0.40 g, 0.010 mol) dissolved in water (10 cm^3) was added dropwise to a stirring suspension of aminoiminomethanesulphonic acid (0.62 g, 0.005 mol), under dry nitrogen. The solution was left to stir at room temperature for 48 h. The solution was concentrated under reduced pressure on a rotary evaporator, to afford a creamy residue. This creamy material was dissolved in the minimum of cold water and treated with ethanol at 0 ^{o}C, producing a turbid solution. After leaving this solution to stand at 4 ^{o}C for 12 h, a white crystalline solid had precipitated. The material was filtered off, washed with

acetone and dried in a vacuum oven for 2 h at 60 ^{o}C. Elemental analysis showed that guanidation had not taken place. (0.51 g of material recovered); (Found: C, 1.69; H, 0.42; N, 1.24. $C_4H_{12}N_3O_2P$ requires: C, 29.09; H, 7.27; N, 25.46 %).

4.4.14. THE PREPARATION OF PYRIDINE PHOSPHONIC ACIDS AND THEIR DERIVATIVES

PREPARATION OF 2-[2'-(DIETHOXYPHOSPHINYL)ETHYL]PYRIDINE

A solution of sodium ethoxide in ethanol (0.7 g of sodium in 20 cm^3 of ethanol) was added dropwise and with stirring to a mixture of 2-vinyl pyridine (21 g, 0.20 mol) and diethyl phosphite (27.6 g, 0.20 mol). After the addition was completed the mixture was stirred at room temperature for a further 12 h. The dark brown reaction mixture was dissolved in dichloromethane (200 cm^3), washed with water (2x20 cm^3) and dried over anhydrous magnesium sulphate. The solution was concentrated under reduced pressure on a rotary evaporator, and the brown oily residue was distilled under high vacuum in the presence of a few milligrams of hydroquinone, to afford 2-[2'-(diethoxyphosphinyl)-ethyl]pyridine as a colourless, free-flowing liquid (36.50 g, 75 %); b.p. 124-126 ^oC at 0.050-0.075 mmHg (lit.[109] 101 ^oC at 0.050 mmHg and 112-113 ^oC at 0.20 mmHg); (Found: C, 53.66; H, 7.74; N, 5.86. Calc. for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76 %); $^1H(CDCl_3)$ δ 1.30 (t, 6H, 2x$\underline{H}_3CH_2O$-, $^3J_{HCCH}$ 7.06 Hz), 2.19-2.32 (m, 2H, $CH_2\underline{H}_2P$), 3.03-3.14 (m, 2H, $\underline{H}_2CH_2P$), 4.11 (dq overlapping, 4H, 2x$CH_3\underline{H}_2O$), 7.10-7.21 (m, 2H, $\underline{H}_3$ & $\underline{H}_4$ of pyridine ring), 7.61 (dd overlapping, 1H, $\underline{H}_5$ of pyridine ring, $^3J_{HCCH}$ 7.67 Hz), 8.53 (m, 1H, $\underline{H}_6$ of pyridine ring); $^{13}C(CDCl_3)$ δ 16.64 (d, 2x$\underline{C}H_3CH_2O$-P, $^3J_{POCC}$ 5.79 Hz), 24.90 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 141.26 Hz),

30.71 (d, $\underline{C}H_2CH_2P$, $^2J_{PCC}$ 4.21 Hz), 61.22 (d, $2xCH_3\underline{C}H_2O$, $^2J_{POC}$ 6.48 Hz), 121.25 (s, $\underline{C}_3$ of pyridine ring), 122.54 (s, $\underline{C}_4$ of pyridine ring), 136.20 (s, $\underline{C}_5$ of pyridine ring), 159.91 (d, $\underline{C}_2$ of pyridine ring, $^3J_{PCCC}$ 16.29 Hz); $^{31}P(CDCl_3)$ δ 30.76 (s).

PREPARATION OF 4-[2'-(DIETHOXYPHOSPHINYL)ETHYL]PYRIDINE

A solution of sodium ethoxide in ethanol (0.7 g of sodium in 20 cm^3 of ethanol) was added dropwise and with stirring to a mixture of 4-vinyl pyridine (21 g, 0.20 mol) and diethyl phosphite (27.6 g, 0.20 mol). When 2/3 of sodium ethoxide had been added the reaction mixture had begun to effervesce considerably. By the time the addition had been completed the solution the effervescence had subsided considerably and the solution was left to stir at room temperature for 12 h. The dark brown solution that had formed, was dissolved in dichloromethane (200 cm^3), washed with water (2x20 cm^3) and dried over magnesium sulphate. The solution was concentrated under reduced pressure on a rotary evaporator, and the brown oily residue was distilled under high vacuum, in the presence of a few milligrams of hydroquinone, to afford 4-[2'-(diethoxyphosphinyl)ethyl]pyridine as a colourless, free-flowing liquid. Upon standing for a prolonged period at room temperature, the compound turned deep red in colour, however this was not symptomatic of extensive decomposition as evidenced by the results of the structural characterisation carried out on the product

(19.80 g, 41 %); b.p. 136-140 °C at 0.05 mmHg (lit.[109] 117 °C at 0.20 mmHg); (Found: C, 54.21; H, 8.09; N, 6.18. Calc. for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76 %); $^1H(CDCl_3)$ δ 1.30 (t, 6H, 2x$\underline{C}H_3CH_2O$, $^3J_{HCCH}$ 7.04 Hz), 2.02 - 2.16 (m, 2H, $CH_2\underline{C}H_2P$), 2.86-2.97 (m, 2H, $\underline{C}H_2CH_2P$), 4.09 (dq overlapping, 4H, 2x$CH_3\underline{C}H_2O$, $^3J_{HCCH}$ 7.33 Hz), 7.18 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of pyridine ring, $^3J_{HCCH}$ 5.81 Hz), 8.50 (dd, 2H, $\underline{H}_2$ & $\underline{H}_6$ of pyridine ring, $^3J_{HCCH}$ 4.41 Hz); $^{13}C(CDCl_3)$ δ 16.47 (d, 2x$\underline{C}H_3CH_2O$, $^3J_{POCC}$ 5.66 Hz), 26.19 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 141.32 Hz), 28.05 (d, $\underline{C}H_2CH_2P$, $^2J_{PCC}$ 4.40 Hz), 61.54 (d, 2x$CH_3\underline{C}H_2O$, $^2J_{POC}$ 6.42 Hz), 123.55(s, $\underline{C}_3$ & $\underline{C}_5$ of pyridine ring), 149.76 (d, $\underline{C}_4$ of pyridine ring, $^3J_{PCCC}$ 16.98 Hz), 149.93 (s, $\underline{C}_2$ & $\underline{C}_6$ of pyridine ring); $^{31}P(CDCl_3)$ δ 29.04 (s).

THE PREPARATION OF *N*-METHYL-2-[2'-(DIETHOXYPHOSPHINYL)ETHYL]-PYRIDINIUM IODIDE

Methyl iodide (7.1 g, 0.050 mol) was added dropwise and with stirring to 2-[2'-(diethoxyphosphinyl)ethyl]pyridine (12.15 g, 0.050 mol), at room temperature. After 2 h, the mixture had become very viscous, and after 12 h the material had become a thick reddish-brown residue. The product was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, to afford *N*-methyl-2-[2'-(diethoxyphosphinyl)-ethyl]pyridinium iodide[113] as a sticky brownish-orange solid (19 g, 99 %); (Found: C, 38.24; H, 5.96; N, 4.19. Calc. for $C_{12}H_{21}INO_3P$: C, 37.40; H, 5.46; N, 3.64 %); $^1H(CDCl_3)$ δ 1.28-1.35 (dt, 6H, 2x$\underline{C}H_3CH_2O$-,

$^{3}J_{HCCH}$ 7.44 Hz), 2.31-2.46 (m, 2H, $CH_2\underline{CH}_2P$), 3.45-3.56 (m, 2H, $\underline{CH}_2CH_2P$), 4.00-4.20 (m, 4H, $2xCH_3\underline{CH}_2O$-), 4.56 (s, 3H, N-$\underline{CH}_3$), 8.04 (dd overlapping, 1H, $\underline{H}_4$ of aromatic ring, $^{3}J_{HCCH}$ 7.61 Hz), 8.16 (d, 1H, $\underline{H}_3$ of pyridine ring, $^{3}J_{HCCH}$ 7.62 Hz), 8.56 (dd overlapping, 1H, $\underline{H}_5$ of pyridine ring, $^{3}J_{HCCH}$ 7.74 Hz), 9.34 (d, 1H, $\underline{H}_6$ of pyridine ring, $^{3}J_{HCCH}$ 6.14 Hz); $^{13}C(CDCl_3)$ δ 16.57 (d, $2x\underline{C}H_3CH_2O$-, $^{3}J_{POCC}$ 6.23 Hz), 23.74 (d, $CH_2\underline{C}H_2P$, $^{1}J_{PC}$ 142.59 Hz), 26.99 (d, $\underline{C}H_2CH_2P$, $^{2}J_{PCC}$ 3.84 Hz), 47.21 (s, N-$\underline{C}H_3$), 62.49 (d, $2xCH_3\underline{C}H_2O$-, $^{2}J_{POC}$ 6.48 Hz), 126.48 (s, $\underline{C}_3$ of pyridine ring), 129.01 (s, $\underline{C}_4$ of pyridine ring), 145.73 (s, $\underline{C}_5$ of pyridine ring), 147.09 (s, $\underline{C}_6$ of pyridine ring), 157.06 (d, $\underline{C}_2$ of pyridine ring, $^{3}J_{PCCC}$ 14.34 Hz); $^{31}P(CDCl_3)$ δ 27.35 (s).

THE PREPARATION OF *N*-METHYL-4-[2'-(DIETHOXYPHOSPHINYL)ETHYL]-PYRIDINIUM IODIDE

Methyl iodide (3.55 g, 0.025 mol) was added dropwise and with stirring to 4-[2'-(diethoxyphosphinyl)ethyl]pyridine (6.08 g, 0.025 mol), at room temperature. After 1 h, the mixture had become very viscous and after being left to stir at room temperature for 12 h, the material had become a very thick dark-brown residue. The product was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, to afford *N*-methyl-4-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide[113] as a sticky dark-brown residue (9.12 g, 95 %); (Found: C, 36.57; H, 5.58; N, 3.63. Calc. for $C_{12}H_{21}INO_3P$: C, 37.40; H, 5.46; N, 3.64 %); $^{1}H(CDCl_3)$ δ

1.34 (t, 6H, 2x$\underline{CH_3}CH_2O$-, $^3J_{HCCH}$ 7.07 Hz), 2.15-2.29 (m, 2H, $CH_2\underline{CH_2}P$), 3.19- 3.30 (m, 2H, $\underline{CH_2}CH_2P$), 4.05-4.19 (m, 4H, 2x$CH_3\underline{CH_2}O$-), 4.66 (s, 3H, N-$\underline{CH_3}$), 8.05 (d, 2H, $\underline{H_3}$ & $\underline{H_5}$ of pyridine ring, $^3J_{HCCH}$ 6.64 Hz), 9.27 (d, 2H, $\underline{H_2}$ & $\underline{H_6}$ of pyridine ring, $^3J_{HCCH}$ 6.67 Hz); $^{13}(CDCl_3)$ δ 16.55 (d, 2x$\underline{CH_3}CH_2O$-, $^3J_{POCC}$ 6.29 Hz), 25.10 (d, $CH_2\underline{CH_2}P$, $^1J_{PC}$ 142.71 Hz), 28.92 (d, $\underline{CH_2}CH_2P$, $^2J_{PCC}$ 4.21 Hz), 48.89 (s, N-$\underline{CH_3}$), 62.23 (d, 2x$CH_3\underline{CH_2}O$-, $^2J_{POC}$ 6.60 Hz), 128.06 (s, $\underline{C_3}$ & $\underline{C_5}$ of pyridine ring), 145.21 (s, $\underline{C_2}$ & $\underline{C_6}$ of aromatic ring), 160.83 (d, $\underline{C_4}$ of pyridine ring, $^3J_{PCCC}$ 15.22 Hz); $^{31}P(CDCl_3)$ δ 28.55 (s).

THE PREPARATION OF *N*-ETHYL-2-[2'-(DIETHOXYPHOSPHINYL)ETHYL]-PYRIDINIUM IODIDE

Ethyl iodide (1.56 g, 0.010 mol) was added dropwise and with stirring to 2-[2'-(diethoxyphosphinyl)ethyl]pyridine (2.43 g, 0.010 mol), at room temperature. When the addition had been completed, the mixture was left to stir at room temperature for 12 h. The very thick dark-brown residue that formed, was vigorously shaken under high vacuum (0.10 mmHg), for 2 h, to afford *N*-ethyl-2-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide[113] as a sticky, dark-brown solid (3.58 g, 90 %), (Found: C, 39.20; H, 6.24; N, 3.91. Calc. for $C_{13}H_{23}INO_3P$: C, 39.10; H, 5.76; N, 3.51 %); $^1H(CDCl_3)$ δ 1.31 (t, 6H, 2x$\underline{CH_3}CH_2O$-, $^3J_{HCCH}$ 7.10 Hz), 1.70 (t, 3H, N-$CH_2\underline{CH_3}$, $^3J_{HCCH}$ 7.47 Hz), 2.35-2.49 (m, 2H, $CH_2\underline{CH_2}P$), 3.37-3.66 (m, 2H, $\underline{CH_2}CH_2P$), 4.00-4.19 (dq

overlapping, 4H, 2x$CH_3\underline{C}H_2O$-, $^3J_{HCCH}$ 7.06 Hz), 4.90 (q, 2H, N-$\underline{C}H_2CH_3$, $^3J_{HCCH}$ 7.79 Hz), 8.19 (dd overlapping, 1H, $\underline{H}_4$ of pyridine ring, $^3J_{HCCH}$ 8.47 Hz), 8.49-8.62 (m, 2H, $\underline{H}_3$ & $\underline{H}_5$ of pyridine ring, $^3J_{HCCH}$ 7.79 Hz), 9.45 (d, $\underline{H}_6$ of pyridine ring, $^3J_{HCCH}$ 7.36 Hz); $^{13}C(CDCl_3)$ δ 16.55 (d, 2x$\underline{C}H_3CH_2O$-, $^3J_{POCC}$ 6.23 Hz), 16.71 (s, N-$CH_2\underline{C}H_3$), 25.42 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 142.40 Hz), 26.20 (d, $\underline{C}H_2CH_2P$, $^2J_{PCC}$ 3.71 Hz), 53.97 (s, N-$\underline{C}H_2CH_3$), 62.52 (d, 2x$CH_3\underline{C}H_2O$-, $^2J_{POC}$ 6.60 Hz), 127.13 (s, $\underline{C}_3$ of pyridine ring), 129.58 (s, $\underline{C}_4$ of pyridine ring), 145.47 (s, $\underline{C}_5$ of pyridine ring), 146.08 (s, $\underline{C}_6$ of pyridine ring), 156.11 (d, $\underline{C}_2$ of pyridine ring, $^3J_{PCCC}$ 14.22 Hz); $^{31}P(CDCl_3)$ δ 27.56 (s).

THE PREPARATION OF *N*-ETHYL-4-[2'-(DIETHOXYPHOSPHINYL)ETHYL]-PYRIDINIUM IODIDE

Ethyl iodide (1.56 g, 0.010 mol) was added dropwise and with stirring to 4-[2'-(diethoxyphosphinyl)ethyl]pyridine (2.43 g, 0.010 mol), at room temperature. When the addition had been completed, the mixture was left to stir for a further 12 h. The dark brown residue that formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, after which *N*-ethyl-4-[2'-diethoxyphosphinyl)ethyl]pyridinium iodide[113] was afforded as a sticky, dark-brown solid (3.68 g, 92 %); (Found: C, 39.54; H, 5.90; N, 3.42. Calc. for $C_{13}H_{23}INO_3P$: C, 39.10; H, 5.76; N, 3.51 %); $^1H(CDCl_3)$ δ 1.33 (t, 6H, 2x$\underline{C}H_3CH_2O$, $^3J_{HCCH}$ 7.03 Hz), 1.75 (t, N-$CH_2\underline{C}H_3$, $^3J_{HCCH}$ 7.23 Hz), 2.21-2.34 (m, 2H, $CH_2\underline{C}H_2P$), 3.22-3.34 (m, 2H,

$C\underline{H}_2CH_2P$), 4.08-4.20 (m, 4H, $2xCH_3C\underline{H}_2O$), 5.01 (q, 2H, $N\text{-}C\underline{H}_2CH_3$, $^3J_{HCCH}$ 7.12 Hz), 8.14 (d, 1H, $\underline{H}_3$ & $\underline{H}_5$ of pyridine ring, $^3J_{HCCH}$ 6.40 Hz), 9.45 (d, 1H, $\underline{H}_2$ & $\underline{H}_6$ of pyridine ring, $^3J_{HCCH}$ 6.51 Hz); $^{13}C(CDCl_3)$ δ 16.50 (d, $2xC\underline{H}_3CH_2O$-, $^3J_{POCC}$ 5.85 Hz), 17.27 (s, $N\text{-}CH_2\underline{C}H_3$), 25.03 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 142.33 Hz), 28.86 (d, $\underline{C}H_2CH_2P$, $^2J_{PCC}$ 4.15 Hz), 56.60 (s, $N\text{-}\underline{C}H_2CH_3$), 62.11 (d, $2xCH_3\underline{C}H_2O$-, $^2J_{POC}$ 6.54 Hz), 128.34 (s, $\underline{C}_3$ & $\underline{C}_5$ of pyridine ring), 144.20 (s, $\underline{C}_2$ & $\underline{C}_6$ of pyridine ring), 160.85 (d, $\underline{C}_4$ of pyridine ring, $^3J_{PCCC}$ 15.10 Hz); $^{31}P(CDCl_3)$ δ 28.44 (s).

PREPARATION OF 2-(2'-PHOSPHONOETHYL)PYRIDINE

2-[2'-(Diethoxyphosphinyl)ethyl]pyridine (10 g, 0.041 mol) was heated under reflux in the presence of concentrated hydrochloric acid (100 cm^3) for 5 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator to afford a clear-yellow viscous oily residue. This material was dissolved in methanol, and treated with propene oxide (40-50 °C) to afford a white crystalline solid. The product, 2-(2'-phosphonoethyl)pyridine was recrystallised from ethanol and water, filtered off, washed with acetone and dry ether, and dried in a vacuum oven for 2 h at 60 °C (5.55 g, 72 %); (Found: C, 45.02; H, 5.41; N, 7.32. Calc. for $C_7H_{10}NO_3P$: C, 44.92; H, 5.35; N, 7.49 %); m.p. 153-155 °C (lit.[109] 149-150 °C); $^1H(D_2O)$ δ 2.12 (m, 2H, $CH_2C\underline{H}_2P$), 3.31 (m, 2H, $C\underline{H}_2CH_2P$), 7.86 (dd, overlapping, 1H, $\underline{H}_4$ of pyridine ring, $^3J_{HCCH}$ 6.66 Hz), 7.95 (d, 1H, $\underline{H}_3$ of pyridine ring, $^3J_{HCCH}$ 8.14 Hz), 8.46 (dd

overlapping, 1H, $\underline{H}_5$ of pyridine ring, $^3J_{HCCH}$ 7.88 Hz), 8.64 (d, 1H, $\underline{H}_6$ of pyridine ring, $^3J_{HCCH}$ 5.69 Hz); $^{13}C(D_2O)$ δ 29.72 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 133.72 Hz), 30.82 (d, $\underline{C}H_2CH_2P$, $^2J_{PCC}$ 5.47 Hz), 127.35 (s, $\underline{C}_4$ of pyridine ring), 129.57 (s, $\underline{C}_3$ of pyridine ring), 144.04 (s, $\underline{C}_6$ of pyridine ring), 148.77 (s, $\underline{C}_5$ of pyridine ring), 159.76 (d, $\underline{C}_2$ of pyridine ring, $^3J_{PCCC}$ 15.10 Hz); $^{31}P(D_2O)$ δ 21.52 (s); FAB ms (3-NOBA): m/z(%) 375 (2M+H, 19.4), 188 (M+H, 100.0), 170 (M+H - H_2O, 13.8), 106 (M+H - H_3PO_3, 15.0).

PREPARATION OF 4-(2'-PHOSPHONOETHYL)PYRIDINE

4-[2'-(Diethoxyphosphinyl)ethyl]pyridine (10 g, 0.041 mol) was heated under reflux in the presence of concentrated hydrochloric acid (100 cm^3) for 5 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator to afford a clear yellow viscous residue. This material was dissolved in methanol, and treated with propene oxide (40-50 ^oC) to afford a white crystalline solid. The product 4-(2'-phosphonoethyl)pyridine was recrystallised from ethanol and water, filtered off, washed with acetone and ether, and dried in a vacuum oven for 2 h at 60 ^oC (7.35 g, 95 %); (Found: C, 45.47; H, 5.47; N, 7.39. Calc. for $C_7H_{10}NO_3P$: C, 44.92; H, 5.35; N, 7.49 %); m.p. 244-246 ^oC (lit.[109] 225-227 ^oC); $^1H(D_2O)$ δ 2.04 (m, 2H, $CH_2\underline{C}H_2P$), 3.14 (m, 2H, $\underline{C}H_2CH_2P$), 7.85 (d, 2H, $\underline{H}_3$ & $\underline{H}_4$ of pyridine ring, $^3J_{HCCH}$ 6.37 Hz), 8.61 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of pyridine ring, $^3J_{HCCH}$ 6.33 Hz); $^{13}C(D_2O)$ δ 30.69 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 133.21 Hz), 32.65 (d, $\underline{C}H_2CH_2P$, $^2J_{PCC}$

3.02 Hz), 129.03 (s, $\underline{C}_3$ & $\underline{C}_5$ of pyridine ring), 145.24 (s, $\underline{C}_2$ & $\underline{C}_6$ of pyridine ring), 164.38 (d, $\underline{C}_4$ of pyridine ring, $^3J_{PCCC}$ 16.54 Hz); $^{31}P(D_2O)$ δ 22.38 (s); FAB ms (3-NOBA): m/z(%) 308 (100.0), 290 (66.0), 188 (M+H, 39.8), 166 (43.1), 136 (94), 127 (27.1), 106 (M+H - H_3PO_3, 86.3).

PREPARATION OF *N*-METHYL-2-(2'-PHOSPHONOETHYL)PYRIDINE

N-Methyl-2-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide (15 g, 0.040 mol) was heated under reflux in the presence of concentrated hydrochloric acid for 12 h. After cooling, the dark-brown solution was exhaustively extracted with toluene, and the aqueous solution was concentrated under reduced pressure on a rotary evaporator, to afford a viscous, greyish-blue residue. This material was dissolved in methanol, and treated with propylene oxide (40-50 ^oC), to produce a dark-grey crystalline solid. This material was decolourised with charcoal, and recrystallised from acetone/water, to afford the light-grey crystalline product, *N*-methyl-2-(2'-phosphonoethyl)pyridine monohydrate,[113] which was filtered off, washed with acetone and ether and then dried in a vacuum oven for 2 h at 60 ^oC (7.26 g, 90 %); (Found: C, 43.22; H, 6.45; N, 6.22. Calc. for $C_8H_{12}NO_3P.H_2O$: C, 43.84; H, 6.39; N, 6.39 %); $^1H(D_2O)$ δ 2.10 (m, 2H, $CH_2\underline{CH}_2P$), 3.34 (m, 2H, $\underline{CH}_2CH_2P$), 4.34 (s, 3H, N-$\underline{CH}_3$), 7.86 (dd overlapping, 1H, $\underline{H}_4$ of pyridine ring, $^3J_{HCCH}$ 6.83 Hz), 8.01 (d, 1H, $\underline{H}_3$ of pyridine ring, $^3J_{HCCH}$ 7.88 Hz), 8.45 (dd

overlapping, 1H, $\underline{H}_5$ of pyridine ring, $^3J_{HCCH}$ 7.73 Hz), 8.72 (d, 1H, $\underline{H}_6$ of pyridine ring, $^3J_{HCCH}$ 6.06 Hz); $^{13}C(CDCl_3)$ δ 28.28 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 133.28 Hz), 30.20 (s, $\underline{C}H_2CH_2P$), 48.24 (s, N-$\underline{C}H_3$), 128.39 (s, $\underline{C}_4$ of pyridine ring), 131.04 (s, $\underline{C}_3$ of pyridine ring), 148.98 (s, $\underline{C}_6$ of pyridine ring), 161.21 (d, $\underline{C}_2$ of pyridine ring, $^3J_{PCCC}$ 17.61 Hz); $^{31}P(D_2O)$ δ 21.96 (s); FAB ms (glycerol): m/z(%) 403 (2M+H, 4.6), 294 (M+H+G, 19.6), 202 (M+H, 100), 186 (9.4), 122(M+H - HPO_3, 5.0) 120 (M+H - H_3PO_3, 12.7).

PREPARATION OF *N*-METHYL-4-(2'-(PHOSPHONOETHYL)PYRIDINE

N-Methyl-4-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide (9.12 g, 0.024 mol) was heated under reflux in the presence of concentrated hydrochloric acid for 5 h. After cooling, the dark-brown reaction was exhaustively extracted with ether and toluene, and the aqueous solution was concentrated under reduced pressure on a rotary evaporator, to produce a dark brown viscous residue. This material was dissolved in methanol and treated with propylene oxide at 40-50 °C. No precipitation occurred, even after leaving the solution to stand in a fridge for 12 h. The volatile components were removed from the solution under reduced pressure on a rotary evaporator to produce a viscous residue. This material was dissolved in the minimum of water, extracted with toluene, and concentrated under reduced pressure on a rotary evaporator. The viscous residue that formed, was shaken under high

vacuum (0.10 mmHg) for 2 h. The product, *N*-methyl-4-(2'-phosphonoethyl)pyridine[113] was afforded as a very viscous residue. Microanalysis showed that the product contained a large proportion of water (5.8 g, product+H_2O); (Found: C, 34.93; H, 6.21; N, 3.38. Calc. for C $H_{12}NO_3P$ + 4.4 H_2O : C, 34.26; H, 7.42; N, 5.00 %); $^1H(D_2O)$ δ 2.05-2.18 (m, 2H, $CH_2\underline{CH}_2P$), 3.20-3.30 (m, 2H, $\underline{CH}_2CH_2P$), 4.46 (s, 3H, N-$C\underline{H}_3$), 8.06 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of pyridine ring, $^3J_{HCCH}$ 6.64 Hz), 8.79 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of pyridine ring, $^3J_{HCCH}$ 6.62 Hz); $^{13}C(D_2O)$ δ 30.47 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 133.15 Hz), 32.35 (d, $\underline{C}H_2CH_2P$, $^2J_{PCC}$ 2.83 Hz), 50.14 (s, N-$\underline{C}H_3$), 130.18 (s, $\underline{C}_3$ & $\underline{C}_5$ of pyridine ring), 147.04 (s, $\underline{C}_2$ & $\underline{C}_6$ of pyridine ring), 165.13 (d, $\underline{C}_4$ of pyridine ring, $^3J_{PCCC}$ 16.16 Hz); $^{31}P(D_2O)$ δ 22.25 (s); FAB ms (thioglycerol): m/z(%) 260 (18.5), 246 (18.5), 202 (M+H, 82.9), 184 (16.7), 122 (M+H - HPO_3, 8.8) 120 (M+H - H_3PO_3, 100), 91 (47.3).

PREPARATION OF *N*-ETHYL-2-(2'-PHOSPHONOETHYL)PYRIDINE

N-Ethyl-2-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide (3 g, 0.0075 mol) was heated under reflux in the presence of concentrated hydrochloric acid for 12 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator. The dark brown oily residue that formed, was dissolved in water and extracted exhaustively with toluene. The aqueous solution was concentrated under reduced pressure on a rotary evaporator to afford a dark-brown viscous

residue. This material was shaken high vacuum (0.10 mmHg) for 2 h, during which time the product, *N*-ethyl-2-(2'-phosphonoethyl)pyridine[113] became very viscous. Microanalysis showed that the product possessed a high proportion of water (2.06 g, product+H_2O); (Found: C, 36.91; H, 7.65; N, 4.55. Calc. for $C_9H_{14}NO_3P$ + 3.8 H_2O : C, 38.10; H, 7.62; N, 4.94 %); $^1H(D_2O)$ δ 1.68 (t, 3H, N-$CH_2\underline{CH_3}$, $^3J_{HCCH}$ 7.29 Hz), 2.09-2.22 (m, 2H, $CH_2\underline{CH_2}P$), 3.38-3.48 (m, 2H, $\underline{CH_2}CH_2P$), 4.73 (q, 2H, N-$\underline{CH_2}CH_3$, $^3J_{HCCH}$ 7.28 Hz), 7.95 (dd overlapping, 1H, $\underline{H_4}$ of pyridine ring, $^3J_{HCCH}$ 6.84 Hz), 8.07 (d, 1H, $\underline{H_3}$ of pyridine ring, $^3J_{HCCH}$ 8.08 Hz), 8.48 (dd overlapping, 1H, $\underline{H_5}$ of pyridine ring, $^3J_{HCCH}$ 7.86 Hz), 8.83 (d, 1H, $\underline{H_6}$ of pyridine ring, $^3J_{HCCH}$ 6.12 Hz); $^{13}C(D_2O)$ δ 21.51 (s, N-$CH_2\underline{CH_3}$), 32.76 (d, $CH_2\underline{CH_2}P$, $^1J_{PC}$ 133.47 Hz), 33.07 (d, $\underline{CH_2}CH_2P$, $^2J_{PCC}$ 2.58 Hz), 59.54 (s, N-$\underline{CH_2}CH_3$), 132.25 (s, $\underline{C_3}$ of aromatic ring), 135.09 (s, $\underline{C_4}$ of pyridine ring), 150.92 (s, $\underline{C_6}$ of aromatic ring), 151.52 (s, $\underline{C_5}$ of aromatic ring), 163.98 (d, $\underline{C_2}$ of aromatic ring, $^3J_{PCCC}$ 17.67 Hz); $^{31}P(D_2O)$ δ 21.58 (s); FAB ms (glycerol): m/z(%) 431 (2M+H, 16.5), 274 (23.8), 216 (M+H, 100), 136 (M+H - HPO_3, 7.9) 134 (M+H - H_3PO_3, 27.5).

PREPARATION OF *N*-ETHYL-4-(2'-PHOSPHONOETHYL)PYRIDINE

N-Ethyl-4-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide (3.50 g, 0.090 mol) was heated under reflux in the presence of concentrated hydrochloric acid for 12 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator. The

dark-brown oily residue that formed was dissolved in water and extracted exhaustively with toluene. The aqueous solution was concentrated under reduced pressure on a rotary evaporator, to afford a very sticky, dark-brown viscous residue. This material was vigorously shaken under high vacuum (0.10 mmHg), for 2 h, during which time the product, *N*-ethyl-4-(2'-phosphonoethyl)pyridine[113] became very thick. No attempt was made to microanalyse the product, which due to its appearance, and in the light of earlier results of similar compounds, was presumed to possess a significant amount of water $^{1}H(D_2O)$ δ 1.75 (t, 3H, N-$CH_2\underline{C}H_3$, $^{3}J_{HCCH}$ 7.30 Hz), 2.10-2.23 (m, 2H, $CH_2\underline{C}H_2P$), 3.24-3.35 (m, 2H, $\underline{C}H_2CH_2P$), 4.75 (q, 2H, N-$\underline{C}H_2CH_3$, $^{3}J_{HCCH}$ 6.05 Hz), 8.12 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of pyridine ring, $^{3}J_{HCCH}$ 6.05 Hz), 8.90 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of pyridine ring, $^{3}J_{HCCH}$ 6.18 Hz); $^{13}C(D_2O)$ δ 18.45 (s, N-$CH_2\underline{C}H_3$), 30.40 (d, $CH_2\underline{C}H_2P$, $^{1}J_{PC}$ 133.53 Hz), 32.26 (s, $\underline{C}H_2CH_2P$), 59.05 (s, N-$\underline{C}H_2CH_3$), 130.41 (s, $\underline{C}_3$ & $\underline{C}_5$ of pyridine ring), 145.86 (s, $\underline{C}_2$ & $\underline{C}_6$ of pyridine ring), 165.21 (d, $\underline{C}_4$ of pyridine ring, $^{3}J_{PCCC}$ 15.85 Hz); $^{31}P(D_2O)$ δ 21.66 (s).

PREPARATION OF *N*-ISOPROPYL-2-(2'-PHOSPHONOETHYL)PYRIDINE

2-[2'-(Diethoxyphosphinyl)ethyl]pyridine (2.43 g, 0.010 mol) was heated under reflux with isopropyl iodide (1.70 g, 0.010 mol), for 12 h. No attempt was made to characterise *N*-isopropyl-2-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide which had formed as a very hard intractable residue. The intermediate was heated

under reflux in the presence of concentrated hydrochloric acid for 12 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator, to produce a dark-brown oily residue. This material was dissolved in water and exhaustively extracted with toluene, and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The dark-brown oil that had formed, was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product, *N-isopropyl-2-(2'-phosphonoethyl)pyridine* was afforded as a sticky brown solid (3.5 g, product+water); ^{1}H(NaOD) δ 1.65 (dd overlapping, 6H, N-CH($\underline{CH}_3$)$_2$, $^{3}J_{HCCH}$ 7.34 Hz), 2.17-2.31 (m, 2H, $CH_2\underline{CH}_2P$), 3.37-3.48 (m, 2H, $\underline{CH}_2CH_2P$), 4.70 (q, 1H, N-$\underline{CH}$(CH_3)$_2$, $^{3}J_{HCCH}$ 7.34 Hz), 7.97 (dd overlapping, 1H, $\underline{H}_4$ of pyridine ring, $^{3}J_{HCCH}$ 7.36 Hz), 8.05 (d, 1H, $\underline{H}_3$ of pyridine ring, $^{3}J_{HCCH}$ 7.57 Hz), 8.48 (dd overlapping, 1H, $\underline{H}_5$ of pyridine ring, $^{3}J_{HCCH}$ 7.90 Hz), 8.84 (d, 1H, $\underline{H}_6$ of pyridine ring, $^{3}J_{HCCH}$ 6.27 Hz); ^{13}C(NaOD) δ 18.06 (s, N-CH($\underline{CH}_3$)$_2$), 28.57 (d, $CH_2\underline{CH}_2P$, $^{1}J_{PC}$ 134.72 Hz), 29.03 (d, $\underline{CH}_2CH_2P$, $^{2}J_{PCC}$ 2.58 Hz), 56.03 (s, N-$\underline{CH}$(CH_3)$_2$), 128.88 (s, $\underline{C}_3$ of pyridine ring), 131.52 (s, $\underline{C}_4$ of aromatic ring), 147.49 (s, $\underline{C}_6$ of pyridine ring), 159.74 (d, $\underline{C}_2$ of pyridine ring, $^{3}J_{PCCC}$ 17.61 Hz); ^{31}P(D_2O) δ 23.22 (s); FAB ms (3-NOBA): m/z(%) 459 (2M+H, 2.9), 230 (M+H, 50.0), 212 (M+H - H_2O, 1.7), 150 (M+H - HPO_3, 3.8), 148 (M+H - H_3PO_3, 7.5).

PREPARATION OF *N*-ISOPROPYL-4-(2'-PHOSPHONOETHYL)PYRIDINE

4-[2'-(Diethoxyphosphinyl)ethyl]pyridine (2.43 g, 0.01 mol) was heated under reflux with isopropyl iodide (1.70 g, 0.01 mol), for 12 h. No attempt was made to characterise *N*-isopropyl-4-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide which had formed as a very hard intractable residue. The intermediate was heated under reflux in the presence of concentrated hydrochloric acid for 12 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator, to produce a dark-brown oily residue. This material was dissolved in water, extracted with toluene and the aqueous solution was concentrated under reduced pressure on a rotary evaporator. The dark-brown oil that formed was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product, *N-isopropyl-2-(4'-phosphonoethyl)-pyridine* was afforded as a dark-brown sticky, viscous solid. The product was not microanalysed, as by its appearance, and in the light of earlier results for similar compounds, it was presumed that it contained a significant proportion of water (3.2 g, product+H_2O); $^{1}H(D_2O)$ δ 1.71 (d, 6H, N-CH($\underline{CH_3}$)$_2$, $^{3}J_{HCCH}$ 6.05 Hz), 2.32 (m, 2H, $CH_2\underline{CH_2}P$), 3.26 (m, 2H, $\underline{CH_2}CH_2P$), 4.66 (m, 1H, NC$\underline{H}$(CH$_3$)$_2$), 8.03 (d, 2H, $\underline{H_5}$ & $\underline{H_6}$ of pyridine ring, $^{3}J_{HCCH}$ 7.46 Hz), 8.84 (d, 2H, $\underline{H_2}$ & $\underline{H_6}$ of pyridine ring, $^{3}J_{HCCH}$ 7.57 Hz); $^{13}C(D_2O)$ δ 24.59 (s, NCH($\underline{C}H_3$)$_2$), 28.43 (d, $CH_2\underline{C}H_2P$, $^{1}J_{PC}$ 136.67 Hz), 30.69 (s, $\underline{C}H_2CH_2P$), 66.63 (s, N$\underline{C}$H(CH$_3$)$_2$), 130.26 (s, $\underline{C_3}$ & $\underline{C_5}$ of pyridine ring), 144.14 (s, $\underline{C_2}$ & $\underline{C_6}$ of pyridine ring), 163.62 (d, C_4

of pyridine ring, $^{3}J_{PCCC}$ 15.22 Hz); $^{31}P(D_2O)$ δ 31.27 (s); FAB ms (thioglycerol): m/z(%) 230 (M+H, 74.6), 216 (24.0), 150 (M+H - HPO_3, 16.3) 148 (M+H - H_3PO_3, 47.3), 134 (41.7), 106 (100).

PREPARATION OF *N*-PROPYL-2-(2'-(PHOSPHONOETHYL)PYRIDINE

2-[2'-(Diethoxyphosphinyl)ethyl]pyridine (2.43 g, 0.01 mol) was heated under reflux with propyl iodide (1.70 g, 0.01 mol), for 12 h. No attempt was made to characterise *N*-propyl-2-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide which formed as a very hard intractable residue. The intermediate was heated under reflux in the presence of concentrated hydrochloric acid for 12 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator, to afford a dark brown oily residue. This material was dissolved in water, extracted exhaustively with toluene and the aqueous solution was concentrated under reduced pressure on a rotary evaporator. The dark-brown oil that formed was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product, *N*-propyl-2-(2'-phosphonoethyl)pyridine[113] was afforded as a brown sticky solid. (3.6 g, product+H_2O); $^{1}H(NaOD)$ δ 1.07 (t, 3H, N-$CH_2CH_2CH_3$, $^{3}J_{HCCH}$ 7.37 Hz), 1.95-2.14 (m, 4H, CH_2CH_2P overlapping with N-$CH_2CH_2CH_3$), 3.33-3.43 (m, 2H, CH_2CH_2P), 4.63 (t, 2H, N-$CH_2CH_2CH_3$, $^{3}J_{HCCH}$ 7.64 Hz), 7.97 (dd overlapping, 1H, H_4 of pyridine ring, $^{3}J_{HCCH}$ 6.93 Hz), 8.07 (d, 1H, H_3 of pyridine ring, $^{3}J_{HCCH}$ 7.79 Hz), 8.48 (dd overlapping, 1H, H_5

of pyridine ring, $^{3}J_{HCCH}$ 7.87 Hz), 8.81 (d, 1H, H_6 of pyridine ring, $^{3}J_{HCCH}$ 7.65 Hz); ^{13}C(NaOD) δ 12.94 (s, N-$CH_2CH_2CH_3$), 30.29 (d, CH_2CH_2P, $^{1}J_{PC}$ 129.69 Hz), 30.40 (s, CH_2CH_2P), 61.82 (s, $NCH_2CH_2CH_3$), 128.40 (s, C_3 of pyridine ring), 131.64 (s, C_4 of pyridine ring), 147.78 (s, C_6 of pyridine ring), 148.06 (s, C_5 of pyridine ring), 161.39 (d, C_2 of pyridine ring, $^{3}J_{PCCC}$ 18.18 Hz); ^{31}P(NaOD) δ 19.30 (s); FAB ms (3-NOBA): m/z(%) 459 (2M+H, 26.7), 230 (M+H, 100), 212 (M+H - H_2O, 11.7), 150 (M+H - HPO_3, 6.5), 148 (M+H - H_3PO_3, 45.0).

PREPARATION OF *N*-PROPYL-4-(2'-PHOSPHONOETHYL)PYRIDINE

4-[2'-(Diethoxyphosphinyl)ethyl]pyridine (2.43 g, 0.01 mol) was heated under reflux with propyl iodide (1.70 g, 0.01 mol), for 12 h. No attempt was made to characterise *N*-propyl-2-[4'-(diethoxyphosphinyl)ethyl]pyridinium iodide which had formed as a very hard intractable residue. The intermediate was heated under reflux in the presence of concentrated hydrochloric acid for 12 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator, to produce a dark-brown oily residue. This material was dissolved in water, extracted exhaustively with toluene and the aqueous layer was concentrated under reduced pressure on a rotary evaporator. The dark-brown oil that formed, was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product, *N*-propyl-4-(2'-phosphonoethyl)pyridine[113] was afforded as a dark-brown viscous

liquid. No attempt was made to microanalyse the product which by its appearance, and in the light of earlier results for similar compounds, was presumed to possess a significant amount of water (3.66 g, product+H_2O); $^{1}H(D_2O)$ δ 1.01 (t, 3H, N-$CH_2CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.36 Hz), 2.10 (m, 2H, N-$CH_2\underline{CH}_2CH_3$, $^{3}J_{HCCH}$ 7.30 Hz), 2.30-2.44 (m, 2H, $CH_2\underline{CH}_2P$), 3.25-3.37 (m, 2H, $\underline{CH}_2CH_2P$), 4.63 (t, 2H, N-$\underline{CH}_2CH_2CH_3$, $^{3}J_{HCCH}$ 7.22 Hz), 8.08 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of pyridine ring, $^{3}J_{HCCH}$ 6.38 Hz), 8.85 (d, 2H, $\underline{H}_2$ & $\underline{H}_6$ of pyridine ring, $^{3}J_{HCCH}$ 6.46 Hz); $^{13}C(D_2O)$ δ 12.45 (s, N-$CH_2CH_2\underline{CH}_3$), 26.43 (s, N-$CH_2\underline{CH}_2CH_3$), 28.24 (d, $CH_2\underline{CH}_2P$, $^{1}J_{PC}$ 136.23 Hz), 30.69 (d, $\underline{CH}_2CH_2P$, $^{2}J_{PCC}$ 3.52 Hz), 64.88 (s, N-$\underline{CH}_2CH_2CH_3$), 130.18 (s, $\underline{C}_3$ & $\underline{C}_5$ of pyridine ring), 145.93 (s, $\underline{C}_2$ & $\underline{C}_6$ of pyridine ring), 163.43 (d, $\underline{C}_4$ of pyridine ring, $^{3}J_{PCCC}$ 15.91 Hz); $^{31}P(D_2O)$ δ 28.08 (s); FAB ms (thioglycerol): m/z(%) 230 (M+H, 100), 212 (M+H - H_2O, 24.0), 150 (M+H - HPO_3, 16.3), 148 (M+H - H_3PO_3, 92.7), 106 (72.9).

PREPARATION OF *N*-BUTYL-2-(2'-PHOSPHONOETHYL)PYRIDINE

2-[2'-(diethoxyphosphinyl)ethyl]pyridine (4.86 g, 0.02 mol) was heated under reflux with butyl iodide (3.68 g, 0.02 mol), for 12 h. No attempt was made to characterise *N*-butyl-2-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide which formed as a very hard intractable residue. The intermediate was heated under reflux in the presence of concentrated hydrochloric acid for 12 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator,

to produce a dark-brown oily residue. This material was dissolved in water, extracted exhaustively with toluene, and the aqueous solution was concentrated under reduced pressure on a rotary evaporator. The dark-brown oil that formed was shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product, *N-butyl-2-(2'-phosphonoethyl)-pyridine* was afforded as a brown viscous residue. No attempt was made to microanalyse the product which by its appearance, and in the light of earlier results for similar compounds, was presumed to possess a significant amount of water (4.8 g, product+water); $^{1}H(D_2O)$ δ 0.99 (t, 3H, N-$CH_2CH_2CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.34 Hz), 1.48 (m, 2H, N-$CH_2CH_2\underline{CH}_2CH_3$, $^{3}J_{HCCH}$ 7.42 Hz), 1.92-2.18 (m, 4H, N-$CH_2\underline{CH}_2CH_2CH_3$ overlapping with $CH_2\underline{CH}_2P$), 3.34-3.44 (m, 2H, $\underline{CH}_2CH_2P$), 4.65 (m, 2H, N-$\underline{CH}_2CH_2CH_2CH_3$), 7.91 (dd overlapping, 1H, $\underline{H}_4$ of aromatic ring, $^{3}J_{HCCH}$ 6.76 Hz), 8.04 (d, 1H, $\underline{H}_3$ of pyridine ring, $^{3}J_{HCCH}$ 8.13 Hz), 8.46 (dd overlapping, 1H, $\underline{H}_5$ of pyridine ring, $^{3}J_{HCCH}$ 7.91 Hz), 8.79 (d, 1H, $\underline{H}_6$ of pyridine ring, $^{3}J_{HCCH}$ 6.47 Hz); $^{13}C(D_2O)$ δ 15.69 (s, N-$CH_2CH_2CH_2\underline{CH}_3$), 21.92 (s, N-$CH_2CH_2\underline{CH}_2CH_3$), 29.35 (d, $CH_2\underline{CH}_2P$, $^{1}J_{PC}$ 133.40 Hz), 29.67 (s, $\underline{CH}_2CH_2P$), 30.06 (s, N-$CH_2\underline{CH}_2CH_2CH_3$), 60.56 (s, N-$\underline{CH}_2CH_2CH_2CH_3$), 128.84 (s, $\underline{C}_3$ of pyridine ring), 131.68 (s, $\underline{C}_4$ of pyridine ring), 147.50 (s, $\underline{C}_5$ of pyridine ring), 148.11 (s, $\underline{C}_5$ of pyridine ring), 160.57 (d, $\underline{C}_2$ of pyridine ring, $^{3}J_{PCCC}$ 17.80 Hz); $^{31}P(D_2O)$ δ 21.54 (s); FAB ms (thioglycerol): m/z(%) 302 (10.4), 244 (M+H, 100), 226 (M+H - H_2O, 12.9), 216 (51.9), 188 (15.4), 164 (M+H - HPO_3, 19.6), 162 (M+H - H_3PO_3, 36.9), 134 (60.8), 106 (76.9).

PREPARATION OF *N*-BUTYL-4-(2'-PHOSPHONOETHYL)PYRIDINE

4-[2'-(diethoxyphosphinyl)ethyl]pyridine (4.86 g, 0.02 mol) was heated under reflux with butyl iodide (3.68 g, 0.02 mol) for 12 h. No attempt was made to characterise *N*-butyl-4-[2'-(diethoxyphosphinyl)ethyl]pyridinium iodide which formed as a very hard intractable residue. The intermediate was heated under reflux in the presence of concentrated hydrochloric acid for 12 h. The cooled solution was concentrated under reduced pressure on a rotary evaporator, to produce a dark-brown oily residue. This material was dissolved in water, extracted exhaustively with toluene, and the aqueous solution was concentrated under reduced pressure on a rotary evaporator. The dark-brown oil that had formed was vigorously shaken under high vacuum (0.10 mmHg) for 2 h, during which time the product, *N-butyl-4-(2'-phosphonoethyl)pyridine* was afforded as a brown, extremely viscous residue. No attempt was made to microanalyse the product which by its appearance, and in the light of earlier results for similar compounds, was presumed to possess a significant amount of water (5.6 g, product+H_2O); $^{1}H(D_2O)$ δ 0.95 (t, 3H, N-$CH_2CH_2CH_2\underline{CH}_3$, $^{3}J_{HCCH}$ 7.34 Hz), 1.36 (m, 2H, N-$CH_2CH_2\underline{CH}_2CH_3$, $^{3}J_{HCCH}$ 7.50 Hz), 1.93-2.12 (m, 4H, N-$CH_2\underline{CH}_2CH_2CH_3$ overlapping $CH_2\underline{CH}_2P$), 3.13-3.24 (m, 2H, $\underline{CH}_2CH_2P$), 4.57 (t, 2H, $N\underline{CH}_2CH_2CH_2CH_3$, $^{3}J_{HCCH}$ 7.22 Hz), 7.98 (d, 2H, $\underline{H}_3$ & $\underline{H}_5$ of pyridine ring, $^{3}J_{HCCH}$ 6.58 Hz), 8.72 (d, $\underline{H}_2$ & $\underline{H}_6$ of pyridine ring, $^{3}J_{HCCH}$ 6.67 Hz); $^{13}C(D_2O)$ δ 15.53 (s, N-$CH_2CH_2CH_2\underline{CH}_3$), 21.53 (s,

N-$CH_2CH_2\underline{C}H_2CH_3$), 30.39 (d, $CH_2\underline{C}H_2P$, $^1J_{PC}$ 133.97 Hz), 32.40 (d, $\underline{C}H_2CH_2P$, $^2J_{PCC}$ 3.08 Hz), 35.30 (s, N-$CH_2\underline{C}H_2CH_2CH_3$), 63.72 (s, N-$\underline{C}H_2CH_2CH_2CH_3$), 130.58 (s, $\underline{C}_3$ & $\underline{C}_5$ of pyridine ring), 146.31 (s, $\underline{C}_2$ & $\underline{C}_6$ of pyridine ring), 165.54 (d, $\underline{C}_4$ of pyridine ring, $^3J_{PCCC}$ 16.23 Hz); $^{31}P(D_2O)$ δ 23.22 (s); FAB ms (glycerol): m/z(%) 487 (2M+H, 18.1), 302 (16.7), 272 (42.7), 244 (M+H, 100), 226 (M+H - H_2O, 22.3), 164 (M+H - HPO_3, 2.9), 162 (M+H - H_3PO_3, 78.5), 106 (44.2).

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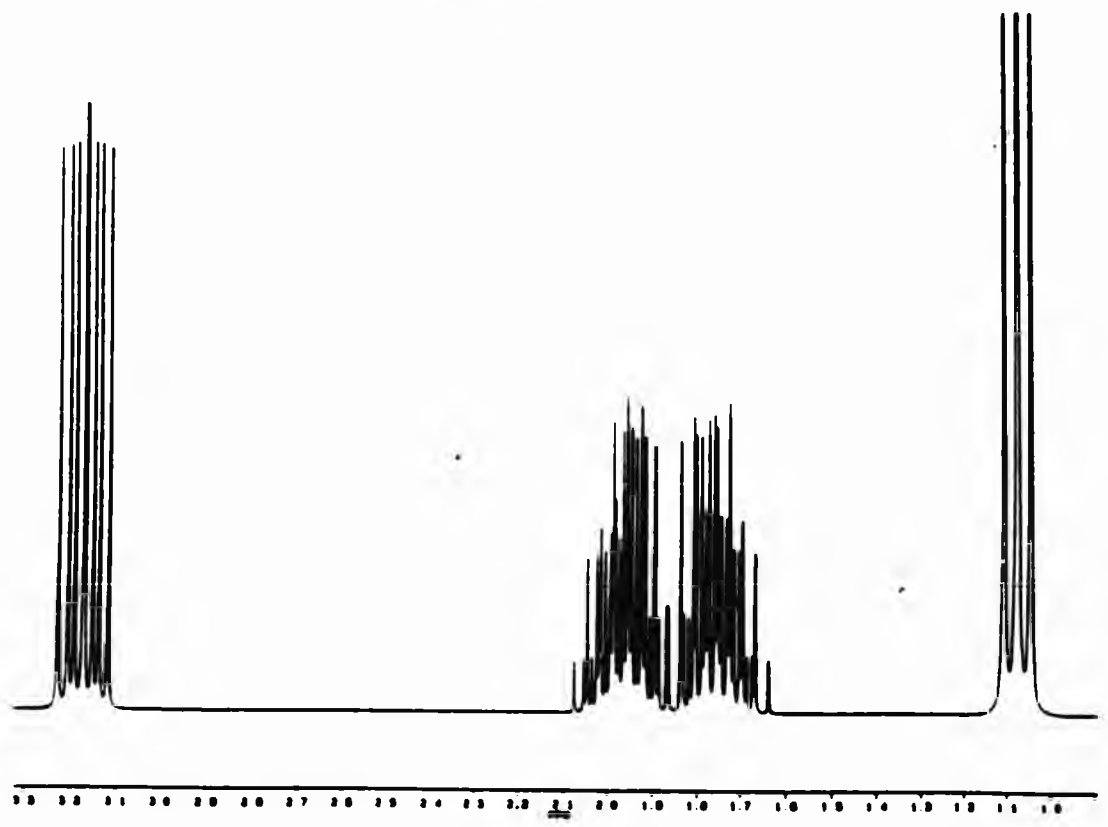
APPENDIX

Simulated and experimental ^{1}H N.M.R. spectra (in D_2O at 250 MHz)



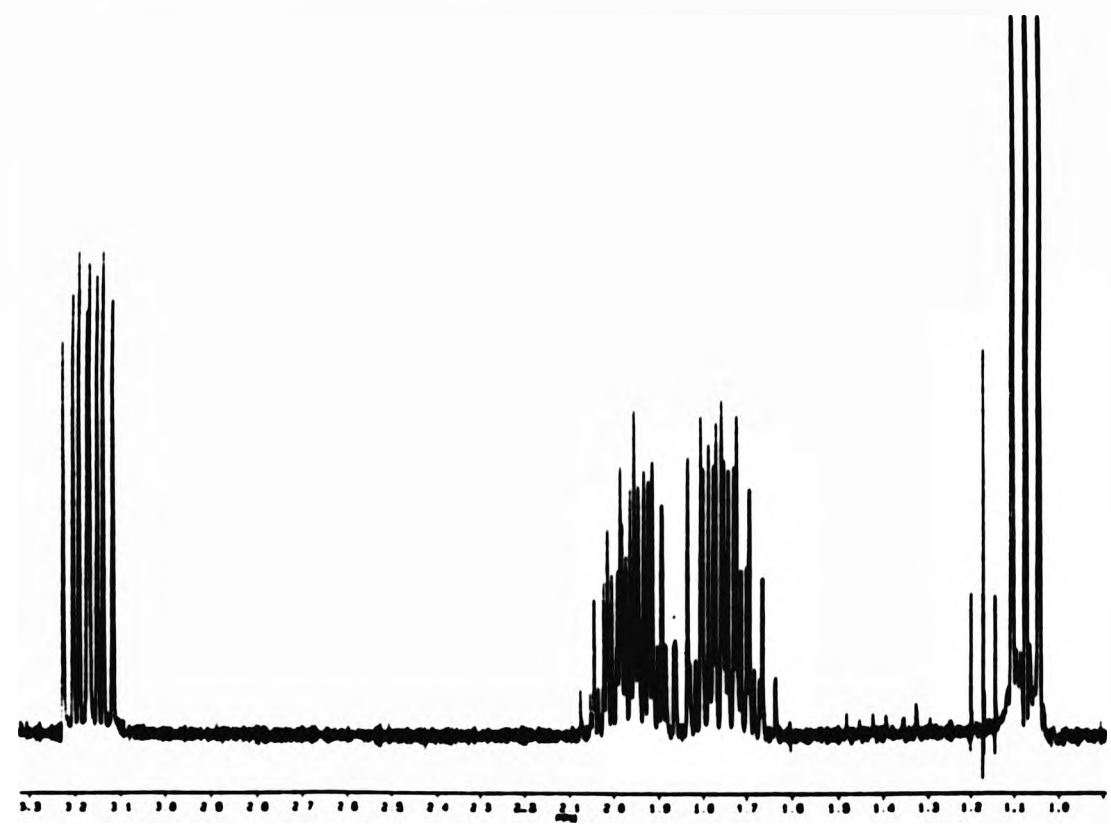


Fig 1

Expansion of the methylene proton multiplets

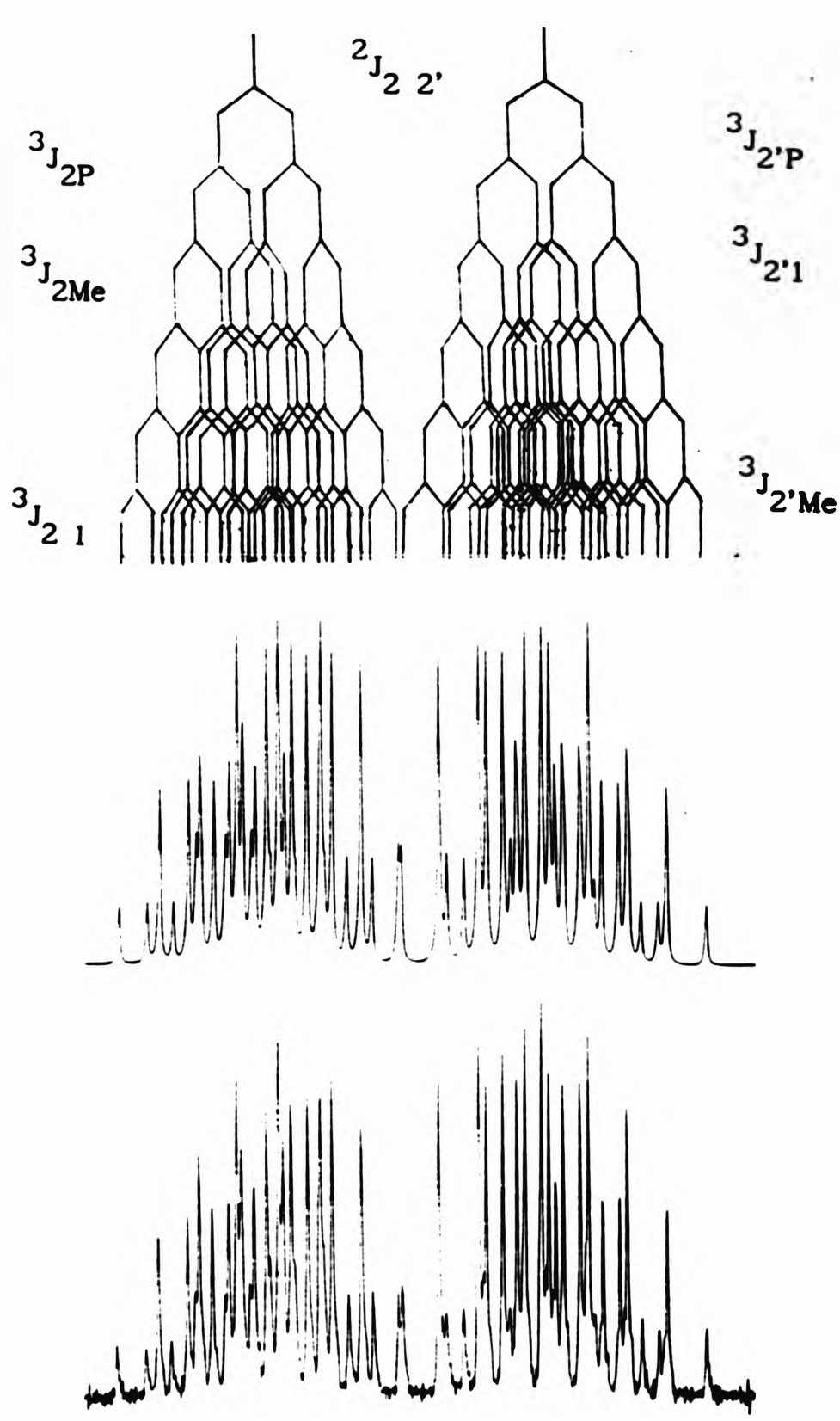


Fig 1 (a)

^{1}H nmr RESULTS

δ/ppm	multiplicity	assignment
1.08	dd	CH_3-2
1.76	m	H-2
1.96	m	H-2'
3.17	ddd	H-1

Couplings/Hz			
$^{3}J_{2Me}$	7.4	$^{3}J_{2'Me}$	7.6
$^{2}J_{22'}$	-14.4	$^{3}J_{12}$	8.9
$^{3}J_{2P}$	12.0	$^{3}J_{12'}$	5.3
$^{3}J_{2'P}$	10.1	$^{2}J_{1P}$	13.2

DX

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