Evaluation of Phosphinic Acid Derivatives as Reagents For Amine Protection in Peptide Synthesis[1]

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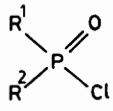
The results of a kinetic study of the acid-catalysed methanolysis of a series of N-(2-phenylethyl)phosphinamides incorporating selected substituents on phosphorus have been evaluated in order to define the optimum reagent and conditions for amine protection of α-amino acids during peptide synthesis.

The intellectual premise from which we derive our current interest in the practical exploitation of the remarkable acid lability of the phosphorus–nitrogen bond in the field of amine protection of α-amino acids during peptide synthesis has previously been established.[2] Our successful application of the diphenylphosphinoyl moiety for this purpose in the preparation of a variety of synthetically challenging peptides and peptide fragments[1–3] prompted this kinetic study of the acid-catalysed methanolysis of a series of model phosphinamides; these model compounds were derived from 2-phenylethylamine-incorporating substituents on phosphorus which were selected to define the optimum reagent for use, primarily, under the standard conditions employed in amide bond forming reactions. The objective was to prepare a range of disubstituted phosphinic chlorides (**1**) in order to investigate their potential as amine protecting groups for α-amino acids‡ during routine peptide synthesis. (In addition, the latent carboxy activating power of individual chlorides[1]—for use as mediators of acylation reactions—was also assessed and will be discussed at a later date.[4]) It was hoped that variation of the substituents R^1 and R^2 in compound (**1**) would ultimately provide a series of protecting groups with varying degrees of acid lability.



(**1**)

a; $R^1 = R^2 = PhCH_2$
b; $R^1 = R^2 = Et$
c; $R^1 = R^2 = Me$
d; $R^1 = R^2 = Bu^n$
e; $R^1 = R^2 = Ph$
f; R^1, R^2 = biphenyl-2,2′-diyl
g; $R^1 = Me, R^2 = Ph$
h; $R^1 = R^2 = Pr^i$
i; $R^1 = R^2 = Bu^i$

Choice of Phosphinic Chlorides (**1**)—Two basic chemical criteria dictated the choice of substituents in these reagents; the first was that the series should cover a reasonable range of steric effects, and the second that the groups should preferably be of low molecular weight as these would be more likely to provide water-soluble phosphinic acid derivatives that would be easily removable from the reaction mixture during aqueous work-up. Other factors considered were cost, stability of the individual chlorides, and, most importantly, ease of preparation.

Dimethyl and diethyl phosphinic chlorides were prepared by the reaction between the corresponding tetra-alkyldiphosphine disulphide and thionyl or sulphuryl chloride in dry benzene; the use of thionyl chloride was generally found to be preferable in terms of product yields and purity. Tetra-alkyldiphosphine disulphides were synthesized by the standard treatment of the appropriate alkylmagnesium halide with thiophosphoryl chloride. When the reaction of tetraethyldiphosphine disulphide with sulphuryl chloride was conducted in diethyl ether instead of benzene, diethylthiophosphinic chloride was isolated exclusively. The reaction of butylmagnesium bromide with thiophosphoryl chloride produced a mixture of products, as assessed by ^{31}P n.m.r., probably consisting of the tetrabutyldiphosphine disulphide, dibutylthiophosphinic chloride, and dibutylthiophosphinic acid. This product mixture was oxidised by 30% HNO_3 to dibutylphosphinic acid which was converted into the phosphinic chloride by reaction with thionyl chloride. The advantage of this procedure is that the phosphinic acid can be easily and rigorously purified and identified as it is a stable crystalline solid. By this method, the danger of incorporating some of the thiophosphinic acid by-product is avoided. The preparation of di-isopropylphosphinic chloride by the same procedure afforded the desired product in very low yield. Instead, this compound was synthesized more efficiently by the reaction of isopropylmagnesium chloride with phosphorus trichloride to give both dichloroisopropylphosphine [b.p. 35–40 °C (12 mmHg)] and chlorodi-isopropylphosphine [b.p. 50–55 °C (12 mmHg)] which were efficiently separated by vacuum distillation under reduced pressure. Treatment of the latter compound with oxygen gave the desired phosphinic chloride in excellent yield. Di-isobutylphosphinic acid was prepared by treating isobutylmagnesium chloride with phosphoryl chloride followed by acid hydrolysis of the resultant complex. The acid was converted into the phosphinic chloride by reaction with thionyl chloride. Dibenzylphosphinic chloride was prepared by the same method. Diphenylphosphinic chloride was readily prepared by reaction of commercially obtained dichlorophenylphosphine with aluminium trichloride followed by reaction with oxygen. 5-Chlorodibenzophosphole 5-oxide (**1f**) was

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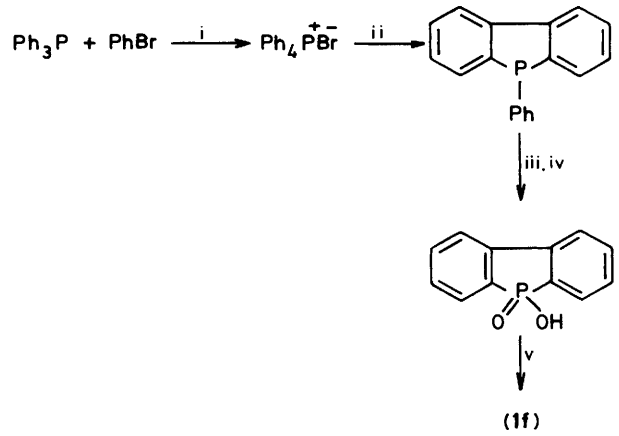
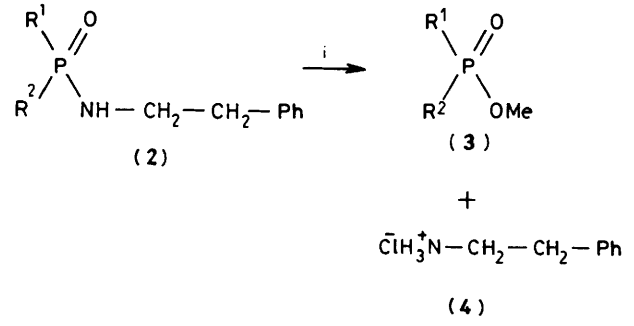
‡ With the exception of glycine, all α-amino acids are of the L-configuration and standard abbreviations are used throughout in the formulation of derivatives (IUPAC-IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, 1972, **247**, 977). In addition the following undefined abbreviations have been used: Cy, cyclohexyl; DCHA, *N,N*-dicyclohexylamine; DCM, dichloromethane; DMF, *N,N*-dimethylformamide; h.p.l.c., high pressure liquid chromatography; NMM, *N*-methylmorpholine; OBzl, benzyl ester; OPh, phenyl ester; R_t retention time; THF, tetrahydrofuran. The dibenzophospholes synthesized are all 5*H*-dibenzophospholes.



Scheme 1. Preparation of 5-chlorodibenzophosphole (**1f**). *Reagents and conditions:* i, $AlCl_3$; ii, LDEA; iii, $NH_{3(l)}$–NaH_2; iv, H_2O_2; v, $SOCl_2$



Scheme 2. Acid-catalysed methanolysis of *N*-(2-phenylethyl)-*P,P*-disubstituted phosphinamides. Derivatives (**a**—**i**) as in structure (**1**). *Reagents:* i, HCl, MeOH

synthesized by converting tetraphenylphosphonium bromide into 5-phenyldibenzophosphole using lithium diethylamide (LDEA) and this, on treatment with sodamide in liquid ammonia followed by an oxidative work-up, afforded 5-hydroxydibenzophosphole 5-oxide which was treated with thionyl chloride to provide the desired acid chloride (Scheme 1).

Preparation of N-(2-*Phenylethyl*)-P,P-*disubstituted Phosphinamides.*—One equivalent of each phosphinic chloride was allowed to react with two equivalents of 2-phenylethylamine in anhydrous dichloromethane at 0 °C. Purification of the respective *N*-(2-phenylethyl)-*P,P*-disubstituted phosphinamides was achieved by distillation under reduced pressure or by recrystallisation. The phosphinamides derived from dimethyl, diethyl, di-n-butyl and di-isobutyl phosphinic acids were very hygroscopic, low melting solids and thus were always handled in a dry box. The amides of di-isopropyl, diphenyl, and dibenzyl phosphinic acids, together with that derived from 5-hydroxydibenzophosphole 5-oxide, were, on the other hand, stable crystalline solids.

Acidolysis of N-(2-*Phenylethyl*)-P,P-*disubstituted Phosphinamides* (*Scheme 2*): *General Procedure and Results.*—It was decided to study acid-catalysed methanolysis, rather than hydrolysis, of the various phosphinamides (**2**) (Scheme 2) because several were found to be insoluble in water whilst others, for example the diethyl, di-n-propyl, and di-isobutyl, are hygroscopic and rapidly undergo hydrolysis to the respective ammonium salts. Thus, in a mechanistic study of this nature, the rigorous exclusion of moisture from the reaction medium was considered to be an expedient precaution which, together with

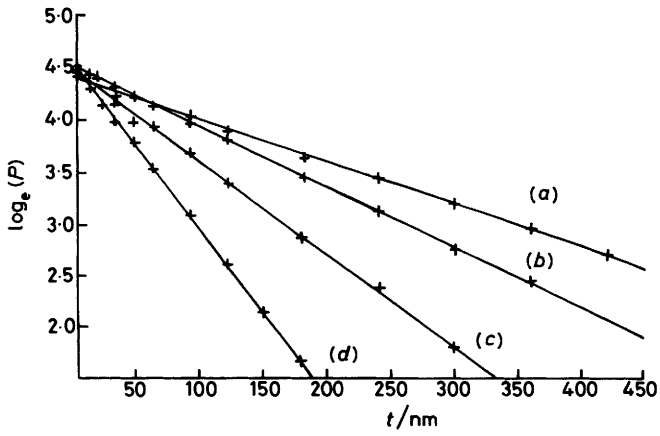


Figure 1. Acid-catalysed methanolysis of $Et_2P(O)NHCH_2CH_2Ph$ at (*a*) 25 °C; (*b*) 30 °C, (*c*) 37 °C; and (*d*) 45 °C

Table 1. Wavelength of detection λ(nm), initial concentration c_o(mmol ml^{-1}), injection volume (μl), and internal standards for the acid-catalysed methanolysis compounds (**2**)

Compound	λ	c_o	Injection volume	Internal standard
(**2a**)	254	0.0100	10	Biphenyl
(**2b**)	220	0.0090	5	Biphenyl
(**2d**)	220	0.0085	5	Toluene
(**2c**)	220	0.0081	5	Biphenyl
(**2e**)	254	0.0062	5	Anthracene
(**2f**)	254	0.0005	5	Naphthalene

the formation of methyl phosphinates as by-products, would circumvent the latter difficulty.

Initially, the disappearance of compound (**2**) upon acid cleavage was followed by thin-layer chromatography, but, although it did seem to indicate the approximate time scale of the deprotections, this method proved extremely confusing because of the interference of those spots due to the methyl phosphinates (**3**) formed as by-products of the reaction. It was found that the best method of following the deprotection reactions was to quench samples withdrawn periodically and to analyse them by h.p.l.c. techniques; this necessitated the choice of an internal standard to allow a quantitative analysis. Anthracene, biphenyl, naphthalene, and toluene all satisfied three essential prerequisites for this task, namely that they should combine adequate solubility in the solvent medium with a propitious retention time under the h.p.l.c. conditions, whilst being themselves unaffected by the experimental conditions. Calibration solutions were made up for each compound and the variation of peak height with concentration was determined. This variation was found to be linear in all cases (which covered the range of concentrations to be found in the subsequently described experiments). Peak heights, rather than areas, were considered since all the widths at half height were found to be the same for the various concentrations of each compound.

The general experimental procedure employed for each timed analysis of compounds (**2a**–**f**) was as follows. The phosphinamide (**2**) was dissolved in the appropriate volume of methanol containing a known weight of internal standard (see Table 1) and rapidly warmed, with stirring, in a thermostatted bath to the required temperature. The reaction was initiated by adding the calculated amount (3 equiv. of HCl) of a standardised methanolic solution of hydrogen chloride, pre-warmed in the bath, and timing was begun. Samples were

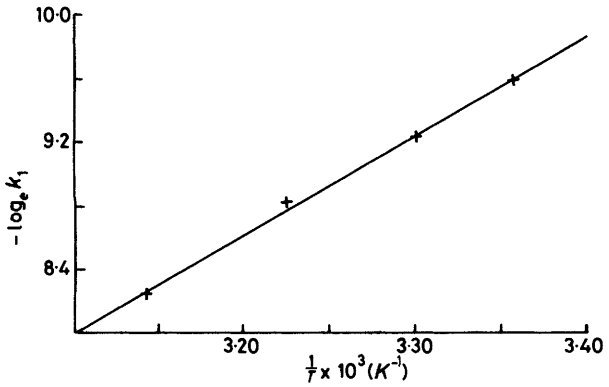


Figure 2. Arrhenius plot for the acid-catalysed methanolysis of $Et_2NHCH_2CH_2Ph$

Table 2. Rate constants ($s^{-1} \times 10^5$) and half-lives (min) for the acid-catalysed methanolysis of compounds (**2**)

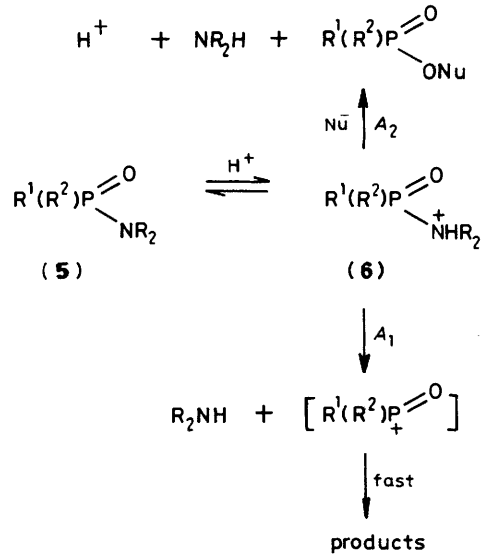
	25 °C		30 °C		37 °C		45 °C	
	k	$T_{\frac{1}{2}}$	k	$T_{\frac{1}{2}}$	k	$T_{\frac{1}{2}}$	k	$T_{\frac{1}{2}}$
(**2a**)	3.1	273	4.0	287	5.9	197	8.0	144
(**2b**)	6.8	169	9.7	118	14.8	78	26.1	44
(**2d**)	6.8	169	10.4	111	15.4	75	27.0	43
(**2c**)	145.0	8	201.0	6	326.0	4	520.0	2
(**2e**)	41.0	28	53.6	21	68.7	17	94.7	12
(**2f**)	36.0	32	52.8	22	88.0	13	153.7	8
(**2g**)	Too fast to measure by h.p.l.c.							

Table 3. Energy (kJ mol^{-1}), entropy (J mol^{-1} K^{-1}) and free energy (kJ mol^{-1}) of activation for the acid-catalysed methanolysis of compounds (**2**)

Compound	E	ΔS	ΔG
(**2a**)	37.9 ± 1.8	−204.0 ± 6.0	98.7 ± 7.7
(**2b**)	52.5 ± 1.6	−148.7 ± 5.2	96.8 ± 6.3
(**2d**)	53.2 ± 2.4	−146.2 ± 7.8	96.7 ± 9.5
(**2c**)	50.7 ± 0.9	−129.1 ± 2.8	89.2 ± 3.5
(**2e**)	32.3 ± 1.5	−201.2 ± 4.8	92.3 ± 6.4
(**2f**)	57.3 ± 0.0	−119.0 ± 0.0	93.0 ± 0.1

periodically withdrawn (*ca.* 0.5 ml), quenched with K_2CO_3 (*ca.* 10 mg), and analysed by direct injection on to the column (see Figures 1 and 2). As peak heights had been found to be directly proportional to concentrations, these values were used (after normalisation) to calculate pseudo first-order rate constants. Least mean square analysis of the plots of $\log_e$(normalised peak height) against time gave straight lines, from the slopes of which were derived the rate constants. These are collated in Table 2 and are estimated to within ±3 to ±8%. It is worth noting that the di-isobutylphosphinamide (**2i**) had undergone less than 5% conversion after 12 hours and the di-isopropylphosphinamide (**2h**) less than 10% conversion after 48 hours at 30 °C. The methylphenylphosphinamide (**2g**), on the other hand, underwent methanolysis so quickly that the reaction could not be followed by this technique. A more exhaustive examination of the potential of the latter for amine protection was not undertaken in view of the fact that it underwent acidolytic cleavage so rapidly and also because of the possible inherent problems associated with the use of such an asymmetric protecting group.

Activation parameters were obtained from Arrhenius plots



Scheme 3.

and the appropriate ancillary equations.† For the calculation of the free energy of activation (ΔG), the energy and enthalpy of activation were considered to be the same, as for reactions in solution they differ only by the term RT which at ordinary temperatures is about 2.5 kJ. The results of the calculations are shown in Table 3 and, as representative examples, the plots of $\log_e$(normalised h.p.l.c. peak height P) *versus* time over a 20 °C range in temperature (*i.e.* at 25, 30, 37, and 45 °C) for the acid-catalysed methanolysis of *N*-(2-phenylethyl)-*P*,*P*-diethylphosphinamide (**2b**) and the corresponding Arrhenius plot [$-\log_e k_1$ against $1/T \times 10^3 (K^{-1})$] are given Figures 1 and 2.

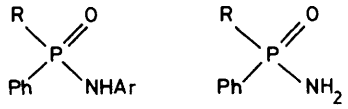
Discussion

The remarkably facile cleavage of the phosphorus–nitrogen bond under acidic conditions has received much attention in recent years in terms of mechanistic and stereochemical studies as well as synthetic application. For the phosphoryl and phosphinoyl derivatives $R^1(R^2)P(O)NR_2$ (**5**), the principal mechanistic problems involve the structure of the substrate conjugate acid (*i.e. N- versus O*-protonation) and the nature of the rate determining step; *i.e.* a bimolecular displacement (an associative A_2 mechanism) *versus* a unimolecular collapse of the protonated substrate (a dissociative A_1 mechanism) (Scheme 3). It was the realisation that an A_2 mechanism (if this were found to be the operating mechanism) for phosphinamide cleavage would be more advantageous than the alternative A_1 mechanism that led to the search for an alternative mode of amine protection.

The well-established t-butyloxycarbonyl (Boc) group suffers from undesired side-reactions occasioned by the reaction of t-butyl carbocations, produced during Boc deprotection, with reactive side chain functionalities of Met, Trp, and Tyr. In the same way, the alternative A_1 mechanism for phosphorus cleavage would involve a highly reactive, charged phosphorus species which would be very undesirable.

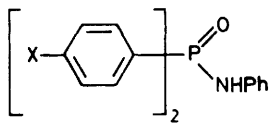
Although conclusive evidence for *N*-protonation has yet to be presented, the species (**6**) is currently considered to be the most probable reactive form of the substrate in solvolysis

† (1) $k_1 = Ae^{-E/RT}$; (2) $A = \frac{kT}{h} e^{S/R}$ (at standard temperature 298 °K); (3) $\Delta G = \Delta H - T\Delta S$; (4) $t_{\frac{1}{2}} = \log_e 2/k_1$.



(7) (8)

(8a) R = Pr^i, Bu^t, 1-methylcyclopropyl
(8b) R = Et, cyclopropyl



(9)

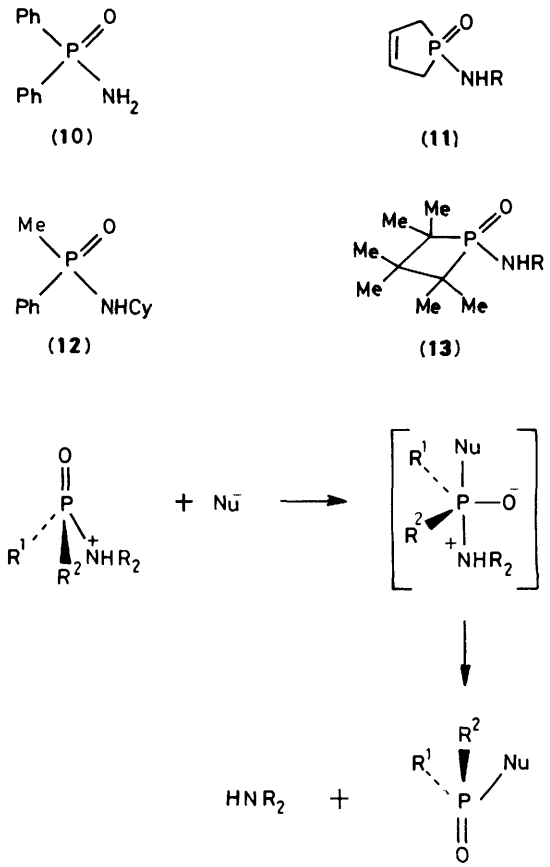
X = H, Me, OMe, NMe_2, Cl, NO_2

reactions. Indirect evidence for *N*-protonation has been provided by Haake and Koizumi[5] which is supported by the limited *X*-ray data available on phosphinamides.[2,6]

Our observations that the rates of scission of the phosphorus—nitrogen bond in di-isobutyl (**2i**) and di-isopropyl (**2h**) substituted phosphinamides were so much slower than those for the analogous diethyl (**2b**) and di-n-butyl (**2c**) compounds strongly suggests that steric factors influence the reaction, with bulky groups on phosphorus drastically retarding the cleavage. Furthermore, a change from dimethyl (**2d**) to diethyl substituents causes a 21-fold decrease in the rate of reaction, whilst the substitution of benzyl for ethyl causes a further 2-fold decrease in rate. Interestingly, the diethyl and di-n-butyl phosphinamide reactions have almost the same rate constants which seems to imply that beyond two carbons in a straight alkyl chain, steric hindrance becomes less important. The effect of bulky groups on phosphorus on the rate of reaction was stressed by Harger in his studies of the acid-catalysed methanolysis of compound (**7**)[7] and the acid-catalysed hydrolysis of (**8**).[8] He reported that the phosphinamides (**8a**) formed stable hydrochlorides in dilute hydrochloric acid at room temperature, whilst the amides (**8b**), where there is less steric interference, hydrolysed to ammonium chloride. The effect of steric crowding at phosphorus in retarding the acidolysis reaction has also been emphasised by other workers.[9]

The difference in rates of cleavage for the compounds with dimethyl and diphenyl substituents may be explained by electronic and inductive effects. The phenyl group may be considered as a net electron withdrawing group and is thus expected to have a retarding effect on the rate of protonation compared with the methyl group which is electron donating. Electronic and inductive effects on the rate of the acid-catalysed hydrolysis of a series of *p*-aryl substituted phosphinamides (**9**) were investigated by Tomaschewski and Kühn[10] who found that the first-order rate constants decreased in the order H > Me > OMe > NMe_2 > Cl > NO_2, where these groups are represented by the *p*-substituent 'X' in structure (**9**). A similar observation has been reported by Haake *et al.*[11] In addition, a comparison of the rate constants for the methanolysis of the phosphinamide derived from 5-hydroxybenzophosphole 5-oxide (**2f**) and that of the diphenylphosphinamide (**2e**) suggests that the orientation of the phenyl rings has very little effect on the rate of reaction. However, the activation entropy for compound (**2f**) is much lower in absolute value than that of (**2e**) which could possibly be due to the planarity of the dibenzophosphole system.

If the activation energies are, in general, rather low, more important are the highly negative activation entropies which

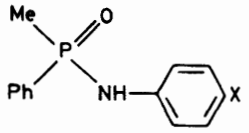


Scheme 4.

usually signify highly ordered transition states. Such unusual values have also been reported for the acid-catalysed hydrolysis of *P,P*-diphenylphosphinamide (**10**) where the following activation parameters were reported:[12] ΔH +39.0 kJ mol^{-1} ΔS −146.5 kJ mol^{-1} K^{-1}, and ΔG +82.8 kJ mol^{-1}. It has been argued[11] that an even higher negative value for ΔS would be expected as the leaving group, H_2N–R, becomes more nucleophilic. This prediction agrees with our value for the phosphinamide (**2e**) where one hydrogen on the nitrogen of compound (**10**) is replaced by an alkyl group; caution should be exercised in such comparisons, however, as the reaction in our case involves methanolysis.

In a more recent publication, similarly unusual values of activation parameters were reported[13] for the acid-catalysed hydrolysis of compounds (**11**) where it was observed that in those phosphinamides with R = H, Ar, or Bu^t there is an increase in the activation energy whereas there is a diminution with aliphatic substituents, including the benzyl group.

A great deal of work has been carried out to establish the actual nature of the rate-determining step. The evidence in support of either an associative or a dissociative mechanism depends largely upon the class of compound being studied. Generally, with compounds where the two substituents on phosphorus are the same, an associative mechanism *via* a pentaco-ordinate transition state is favoured (Scheme 4). In our present studies, the large, negative values of the activation entropies support this associative mechanism as that being operative. These large values are probably due in part to the entropy change on generation of the protonated substrate because of the strong solvation requirements of the H_2N^+–R group and in part to the bimolecular reaction of the protonated substrate with methanol. Some workers[11] have suggested that

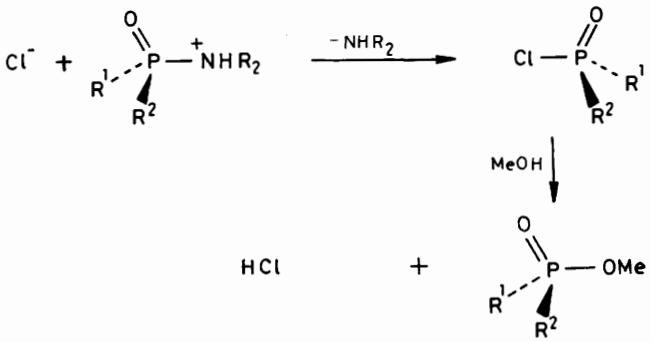


(14)

a; X = H
b; X = NO_2
c; X = OMe

as the leaving group in the protonated substrate becomes more nucleophilic, the associative A_2 mechanism becomes more dominant. This is because full participation of the attacking species is required to reach an A_2-like transition state, whereas when the leaving group has low nucleophilicity it departs so readily that little or no assistance is required to reach an A_1-like transition state. Stereochemical evidence for an associative A_2 mechanism is provided by the report[14] that the acid-catalysed methanolysis of *N*-cyclohexyl-*P*-methyl-*P*-phenylphosphinamide (**12**) proceeded with virtually complete stereochemical inversion of configuration irrespective of the acidity of the medium. Even the phosphetane amides (**13**), which are normally resistant to hydrochloric, sulphuric, and trifluoroacetic acids, were found to undergo methanolysis in the presence of BF_3 with considerable inversion of configuration at phosphorus.[15] Similarly, Harger[16] has shown that *N*-*p*-nitrophenyl-*P*-methyl-*P*-phenylphosphinamide rapidly undergoes solvolysis in methanol containing 0.15M-hydrochloric acid, also with complete inversion of configuration. Indeed, Harger has further substantiated the stereospecific course of acid-catalysed, nucleophilic attack upon phosphinamides.[16,17] Using hydrogen chloride as the catalyst in the methanolysis of a series of phosphinamides (**14**), he found that the *p*-nitroanilide (**14b**) undergoes methanolysis with less deviation from complete inversion of configuration than does compound (**14a**), although (**14b**) is more favourably disposed to react by a dissociative A_1 mechanism. Also, with sufficiently high concentrations of hydrogen chloride, both compounds (**14a**) and (**14b**) give predominantly phosphinate with retention of configuration. With trifluoromethanesulphonic acid as the catalyst, complete inversion of the configuration was observed at low and high acid concentrations. However, introducing lithium chloride into the trifluoromethanesulphonic acid catalysed reaction medium caused the formation of some phosphinate with retention of configuration. This finding was interpreted by Harger as suggesting an associative mechanism involving the participation of chloride ion as the nucleophile. The extent to which the reaction proceeds with retention of configuration depends upon the nucleophilicity of the leaving group in the amide, which decreases in the order (**14c**) > (**14a**) > (**14b**). The mechanism whereby nucleophilic participation of chloride ion resulting in retention of configuration can occur is depicted in Scheme 5.

In our work, the acid-catalysed methanolysis of *N*-(2-phenylethyl)-*P*-methyl-*P*-phenylphosphinamide was not studied in detail because, even at 25 °C, it appeared to be complete within eight minutes of the reaction starting. However, h.p.l.c. traces of reaction samples withdrawn during the first few minutes indicated that in addition to the peak due to the phosphinamide, another broad peak of longer retention time was seen to be formed but this soon disappeared along with the phosphinamide peak. Tentatively, this broad peak could be due to an intermediate phosphinic chloride. If so, the participation of chloride ion is implicated. Interestingly, this phenomenon was not observed with any of the other compounds studied.



Scheme 5.

Application of the Dimethylphosphinoyl Group for α-Amino Protection.—As can be seen from the rate constants (Table 2) for the acid-catalysed methanolysis of the phosphinamides (**2a—f**), with the exception of compound (**2f**), the dimethylphosphinoyl group is the most acid labile of the series, being about 3.5 times more labile than the diphenylphosphinoyl group. Thus it was decided to investigate its suitability for α-amino protection in peptide synthesis, particularly as there are several recent reports of the successful application of the analogous dimethylthiophosphinoyl (Mpt) group as a general acid-labile protecting group for α-amino acids in the solid phase synthesis of Leu[5]-enkephalin (H.Tyr-Gly-Gly-Phe-LeuOH) and its (D)Ala[2] analogue,[18a] as well as for the protection of the side chains of tyrosine[18b] and cysteine.[18c]

As in the preparation of MptGly·DCHA, which defied efficient preparation and recrystallisation,[18a] repeated attempts to bring about the reaction of glycine benzyl ester tosylate ($TosO^-H_2{}^+GlyOBzl$) and dimethylphosphinic chloride in the presence of two equivalents of *N*-methylmorpholine at 0 °C led to the formation of dimethylphosphinoylglycine benzyl ester in very low yield as an intractable oil which could not be fully characterised. Catalytic hydrogenolysis followed by the addition of one equivalent of dicyclohexylamine produced no identifiable salt. Presumably either the fully protected benzyl ester was very unstable and sensitive to moisture or the partially deprotected material is unstable and an autocatalytic* hydrolysis reaction can take place as the benzyl ester is cleaved, yielding fully deprotected material. In a similar way, dimethylphosphinoyl-leucine benzyl ester (DmpLeuOBzl) was isolated as a yellow oil (characterised only by ^1H n.m.r. spectroscopy) in low yield by reaction between leucine benzyl ester hydrochloride and dimethylphosphinic chloride in the presence of two equivalents of *N*-methylmorpholine. Hydrogenolysis followed by the addition of one equivalent of dicyclohexylamine resulted in a thick oil which upon trituration with anhydrous diethyl ether formed a white solid. This was isolated and shown by elemental analysis to be totally devoid of phosphorus and thus was not further examined. However, evaporation of the ethereal solution, under reduced pressure, provided the desired DCHA salt in low yield. Again, it appears that catalytic hydrogenolysis in ethanol affords the free acid which in turn allows an autocatalytic deprotection to occur. At this stage, the dimethylphosphinoyl group was considered to be too labile to be of use in peptide synthesis and we turned our attention to the assessment of the efficacy of the homologous diethylphosphinoyl group.

* See earlier section on the acidolysis of *N*-(2-phenylethyl)-*P*,*P*-disubstituted phosphinamides.

Applicability of the Diethylphosphinoyl Group for α-Amino Protection.—As the values of the rate constants show, the diethylphosphinoyl (Dep) group is removed relatively slowly by acid-catalysed methanolysis; it is cleaved some 21 times more slowly than the dimethylphosphinoyl group and about five times more slowly than the diphenylphosphinoyl group.

In contrast to the difficulties encountered in the attempted synthesis of Dmp amino acids, both DepIleOH and DepValOH were prepared in excellent yields and isolated as stable crystalline solids. The protected dipeptides DepIle-AlaOPh and DepVal-GlyOBzl were prepared, *via* the mixed anhydride derived from diphenylphosphinic chloride,[19] in yields of 51 and 62% respectively. DepIleOH was also successfully employed in the synthesis of DepIle-Asp(OBu^t)-PheNH$_2$.

Conclusion

The underlying conclusion to be drawn from the evidence presented is that the optimum choice for α-amino protection is the diphenylphosphinoyl group.[2] It is easily introduced using readily available starting materials, it provides indefinitely stable, crystalline α-amino acid derivatives which can be activated with little risk of racemisation (an important constraint in the choice of a protecting group), and it provides peptides of similar crystallinity and stability from which it can be readily removed under mild acid conditions.

Experiments within this work were repeated to determine the dependence of the rate of reaction on the acid concentration by both doubling and halving it—in which case the rate constants were measured to be either double or half the corresponding values; from this it is deduced that the rate is first order in both [acid] and [phosphinamide]. As a direct consequence of this observation, routine cleavage of the diphenylphosphinoyl group is now carried out in the presence of six equivalents of methanolic HCl.[2] The by-products of deprotection obtained under these conditions have the advantage of not being available for recapture by reactive α-amino acid side chains and furthermore it is possible to routinely optimise reaction parameters with the aid of ^{31}P n.m.r. spectroscopy.

Whilst it would appear that the *P*-methyl-*P*-phenylphosphinoyl group exhibits the optimum combination of steric and electronic effects for facile methanolysis, it has the disadvantages of its rapid cleavage and potential chiral-induction problems. The dimethylphosphinoyl group is too hygroscopic to be of use in peptide synthesis, but the diethyl, di-n-butyl, and dibenzyl groups do show potential for side chain protection where relatively greater acid stability is required.

In this latter respect, the results of our efforts to apply the findings of this work to the development of a range of acid-labile phosphorus-based protecting groups for use in conjunction with routine diphenylphosphinoyl protection will be reported in due course.

Experimental

The general experimental methods, abbreviations and solvent systems for thin-layer chromatography employed in this work are those previously reported[2,19] into which should be incorporated the following: high pressure liquid chromatography (h.p.l.c.) analysis of all samples was carried out by isocratic elution with 80% h.p.l.c. grade methanol: 20% doubly distilled water (efficiently degassed prior to use) at a flow rate of 2.5 ml min^{-1} generated by an ACS reciprocating pump model 750/03. The volume injected onto the analytical reverse phase column (10 cm) packed with Partisil ODS2 was kept constant for each system both during calibration and kinetic investigations and the resulting eluant was monitored for u.v. absorbance at a preselected wavelength (see Table 1) by means of a Cecil UV detector model CE212 within the absorbance range 0—0.2. Thionyl chloride was distilled from linseed oil before use. Toluene was dried over sodium wire. Nitrogen was dried and purified by passage through Fieser's solution,[20] lead acetate solution, concentrated sulphuric acid, and finally through potassium hydroxide pellets.

Dibenzylphosphinic Chloride (**1a**).—Dibenzylphosphinic acid[21] (7.0 g, 28.4 × 10^{-3} mol) in dry toluene (20 ml) was cooled to 0 °C under nitrogen and thionyl chloride (3.69 g, 31.2 × 10^{-3} mol) was added. The reaction, which began immediately, was terminated by refluxing for 30 min. Evaporation to dryness afforded crude dibenzylphosphinic chloride which was purified by distillation under reduced pressure to give pure compound (**1a**) as a white crystalline powder (7.2 g, 96%), m.p. (sealed tube) 173—175 °C (Found: C, 63.4; H, 5.2; Cl, 13.0; P, 11.7. Calc. for $C_{14}H_{14}ClOP$: C, 63.5; H, 5.3; Cl, 13.4; P, 11.7%); $\nu_{max.}$(Nujol) 3 080—3 025 (arom. C-H), 1 450 (Bzl-P), and 1 230 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.3 (10 H, s, aromatic), 3.4 (4 H, d, $^2J_{P-H}$ 15 Hz, -CH_2); $\delta_P(CDCl_3)$ + 51.

Diethylphosphinic Chloride (**1b**).—By following the standard literature procedure,[22—24] pure diethylphosphinic chloride was isolated as a clear, colourless liquid (88%), b.p. 60—62 °C (0.4 mmHg) [lit.,[22] 62.5—64.5 °C (0.7 mmHg)]; $\delta_P(CDCl_3)$ + 74.

Di-n-butylphosphinic Chloride (**1c**).—The reaction of di-n-butylphosphinic acid[24] (17.8 g, 0.1 mol) with thionyl chloride (13 g, 0.11 mol) as described for (**1a**) afforded pure di-n-butylphosphinic chloride (**1c**) as a pale yellow liquid (18.1 g, 92%), b.p. 103—105 °C (0.5 mmHg) [lit.,[24] 56—57 °C (0.11 mmHg)] (Found: C, 48.7; H, 9.3; Cl, 18.4; P, 15.5. Calc. for $C_8H_{18}ClOP$: C, 48.8; H, 9.2; Cl, 18.0; P, 15.7%); $\delta_P(CDCl_3)$ + 69 (lit.,[25] + 71).

Dimethylphosphinic Chloride (**1d**).—Pure dimethylphosphinic chloride was isolated as white, acicular crystals from the reaction of thionyl chloride (11.9 g, 0.1 mol) with tetramethyldiphosphine disulphide[26,27] (9.3 g, 0.05 mol)[22] (10.5 g, 93%), m.p. (sealed tube) 69 °C (lit.,[22] 66.5—68.4 °C); $\delta_H[(CD_3)_2SO]$ 1.5 (6 H, d, $^2J_{P-H}$ 14.6 Hz, CH_3); $\delta_P(CDCl_3)$ +59 (lit.,[28] + 63).

Diphenylphosphinic Chloride (**1e**).—Dry oxygen was bubbled through a stirred solution of dichlorophenylphosphine (55.1 g, 0.25 mol) in dry toluene (200 ml) for 4 h. Initially, the solution became hot, but slowly cooled to ambient temperature. Distillation of the crude residue remaining upon evaporation of the reaction solvent gave pure diphenylphosphinic chloride as a clear, colourless liquid (56.1 g, 95%), b.p. 148—150 °C (0.4 mmHg) [lit.,[9] 199—201 °C (8.0 mmHg)] (Found: C, 60.9; H, 4.2; Cl, 15.0; P, 13.1. Calc. for $C_{12}H_{10}ClOP$: C, 60.7; H, 4.4; Cl, 15.3; P, 12.8%); $\nu_{max.}$ 3 060 (aromatic C–H), 1 440 (Ph–P), and 1 180 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.1—7.3 (10 H, m, aromatic); $\delta_C(CDCl_3)$ 136.5—127.3 (m, aromatic); $\delta_P(CDCl_3)$ + 43 (lit.,[28] + 43).

5-Hydroxydibenzophosphole 5-Oxide.—A mixture of powdered, freshly sublimed aluminium chloride (50 g, 0.37 mol), triphenylphosphine (50 g, 0.19 mol) and bromobenzene (60 g, 0.38 mol) was heated under dry nitrogen at 230 °C for 2 h. During this time a gentle reflux was observed. The mixture was heated for 1 h at 250 °C, then cooled to 120 °C and poured into distilled water (500 ml). Decolourising charcoal (2 g) was added and the solution heated for 20 min, filtered and left to cool overnight. The brown crystals which formed were filtered off, washed with anhydrous diethyl ether (2 × 100 ml), and subsequently dissolved in DCM (250 ml). Following extraction of the aqueous mother-liquor with DCM (2 × 100 ml), the combined organic phases were washed with distilled water (2 ×

100 ml) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a brown solid which was filtered and washed with THF (200 ml). Recrystallisation from water afforded pure tetraphenylphosphonium bromide which was dried in a vacuum oven at 110 °C for 10 h (45.2 g, 57%), m.p. 295—296 °C (lit.,[29] 298—300 °C); $\delta_P[(CD_3)_2SO$–$CDCl_3]$ + 21. To stirred anhydrous diethyl ether (75 ml) containing lithium (3.9 g, 0.56 mol) under dry nitrogen was added distilled bromobenzene (45.8 g, 0.29 mol) in anhydrous diethyl ether (150 ml) during 50 min whilst the reaction mixture was kept gently at reflux. After a further 90 min at reflux this was cooled in ice and treated with distilled diethylamine (20.3 g, 0.29 mol). After 15 min, dry, powdered tetraphenylphosphonium bromide (35 g, 83.5 × 10^{-3} mol) was added. The mixture was stirred at room temperature for 20 h before being again cooled in ice; 4M-aqueous hydrochloric acid (150 ml) was added during 50 min, the reactants were filtered, and the two layers separated. The aqueous layer was washed with diethyl ether (2 × 100 ml) and the combined ethereal solutions were washed with brine, saturated $NaHCO_3$, and water before being dried ($MgSO_4$). Evaporation of the solvent afforded 5-phenyldibenzophosphole as a red solid which was purified by recrystallisation from ethanol (13.5 g, 62.2%), m.p. 91—92 °C (lit.,[29] 95—97 °C) (Found: C, 83.0; H, 5.1; P, 11.9. Calc. for $C_{18}H_{13}P$: C, 83.1; H, 5.0; P, 11.9%); $\nu_{max.}$ 3 050 (aromatic C–H), 1 440 (Ph–P), 760 (*o*-disubstituted benzene), 740 and 700 cm^{-1} (monosubstituted benzene); $\delta_H(CDCl_3)$ 8.0—7.1 (13 H, m, aromatic); $\delta_P(CDCl_3)$ −13 (lit.,[30] − 10). Powdered 5-phenyldibenzophosphole (10 g, 38.4 × 10^{-3} mol) was added to vigorously stirred liquid ammonia (200 ml) at −50 °C under nitrogen immediately followed by sodium (2 g, 86.9 × 10^{-3} mol) which was added during 2 h. After a further 1 h ammonium chloride (2.3 g, 42.9 × 10^{-3} mol) was added, the cooling bath removed and the solution stirred rapidly to evaporate the ammonia. Towards the end, diethyl ether saturated with water (50 ml) was added and finally the mixture was placed in a warm water-bath. Distilled water (75 ml) and THF (50 ml) were then added and the solution stirred at 45 °C whilst hydrogen peroxide (10 ml; 30%) was added during 1 h, the temperature being kept below 53 °C. The mixture was then left to stir at room temperature for 16 h, sodium hydroxide (6 g, 0.15 mol) was added and the solution stirred and heated at 100 °C until most of the ammonia had been lost (60 min). After being cooled in ice, the sodium salt was collected, washed with saturated brine (2 × 30 ml), and dissolved in water (500 ml). The solution was stirred and heated at 60 °C whilst 5M-hydrochloric acid (40 ml) was added. After a further 15 min at 60 °C, the mixture was cooled in ice and concentrated hydrochloric acid (50 ml) added. The product, 5-hydroxydibenzophosphole 5-oxide, was collected by filtration, washed with water (2 × 100 ml) and dried in a vacuum oven at 100 °C (5.3 g, 66.3%), m.p. 238—240 °C (lit.,[29] 242—244 °C); $\delta_P[(CD_3)_2SO$–$CDCl_3]$ + 32.

5-Chlorodibenzophosphole 5-Oxide (**1f**).—5-Hydroxydibenzophosphole 5-oxide (2.4 g, 11.1 × 10^{-3} mol) was heated with an excess of thionyl chloride and the residue distilled under reduced pressure (0.2 mmHg) to give *5-chlorodibenzophosphole 5-oxide* as a white powder (2.45 g, 93.7%), m.p. (sealed tube) 136—137 °C (Found: C, 61.5; H, 3.6; Cl, 15.1; P, 13.3. $C_{12}H_8ClOP$ requires C, 61.4; H, 3.4; Cl, 15.1; P, 13.2%); $\delta_P(CDCl_3)$ + 43.

Di-isopropylphosphinic Chloride (**1h**).—A solution of chloro-di-isopropylphosphine[31] (22.8 g, 0.15 mol) in dry benzene (100 ml) was heated with a stream of dry oxygen during 2 h. The solution became hot, boiled gently under reflux, and cooled to ambient temperature as the reaction subsided. Evaporation of solvent gave crude di-isopropylphosphinic chloride which was distilled under reduced pressure to afford pure compound (**1h**) as a clear, colourless liquid (22.1 g, 88%), b.p. 110—112 °C (15 mmHg) [lit.,[32] 109—110.5 °C (12 mmHg)]; $\nu_{max.}$ 2 975, 2 945, 2 880 (alkyl C–H), 1 470 (C–P), 1 220 cm^{-1} (P=O); $\delta_P(CDCl_3)$ + 83.

Di-isobutylphosphinic Chloride (**1i**).—Di-isobutylphosphinic acid[33] (17.8 g, 0.1 mol) was treated with an excess of thionyl chloride by the method described for compound (**1a**). The resulting crude di-isobutylphosphinic chloride was distilled under reduced pressure to afford pure compound (**1i**) as a clear, colourless oil (18.5 g, 94.4%), b.p. 60—63 °C (0.1 mmHg) [lit.,[24] 61 °C (0.15 mmHg)] (Found: C, 48.7; H, 9.4; Cl, 18.5; P, 15.4. Calc. for C_8H_8ClOP: C, 48.8; H, 9.2; Cl, 18.0; P, 15.7%); $\delta_P(CDCl_3)$ + 66.

N-(2-*Phenylethyl*)-P,P-*dibenzylphosphinamide* (**2a**).—This compound was prepared from compound (**1a**) (1 g, 3.78 × 10^{-3} mol) and 2-phenylethylamine (0.92 g, 7.56 × 10^{-3} mol) by following the general procedure described in the text. The product, N-(2-*phenylethyl*)-P,P-*dibenzylphosphinamide*, was purified by recrystallisation from anhydrous diethyl ether–light petroleum (60—80 °C) (1.16 g, 88%), m.p. 103—104 °C (Found: C, 75.8; H, 6.6; N, 4.0; P, 8.8. $C_{22}H_{24}NOP$ requires C, 75.6; H, 6.8; N, 4.0; P, 8.8%); $\nu_{max.}$ 3 220, 3 100—3 025 (N–H), 1 460 ($PhCH_2$–P), and 1 175 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.1 (15 H, s, aromatic), and 3.2—2.2 [9 H, m, $NH(CH_2)_2$]; $\delta_P(CDCl_3)$ + 33.

N-(2-*Phenylethyl*)-P,P-*diethylphosphinamide* (**2b**).—Diethylphosphinic chloride (**1b**) (2 g, 14.2 × 10^{-3} mol) and 2-phenylethylamine (3.44 g, 28.4 × 10^{-3} mol) were treated together as described in the general procedure (above). Evaporation of the reaction solvent gave a green oil which was rapidly eluted down a short column of dry basic alumina (pH 9) using dry DCM. Removal of the solvent under reduced pressure and distillation of the residue [b.p. 158—160 °C (0.2 mmHg)] gave pure N-(2-*phenylethyl*)-P,P-*diethylphosphinamide* as a pale yellow oil. On standing at room temperature for several days the oil solidified giving a very hygroscopic white powder (2.3 g, 72%), m.p. (sealed tube) 28—29 °C (Found: C, 63.9; H, 9.2; N, 6.2; P, 13.4. $C_{12}H_{20}NOP$ requires C, 64.0; H, 9.0; N, 6.2; P, 13.7%); $\delta_H(CDCl_3)$ 7.3 (5 H, s, aromatic), 3.4—2.7 [5 H, m, $NH(CH_2)_2$], 1.9—0.9 [10 H, m, $(CH_3CH_2)_2PO$]; $\delta_P(CDCl_3)$ +44; *m/z* 225.1275 (M^+, 84.2%), 196.0883 [M^+ −29, 22.8, $CH_3CH_2P^+$ (=O)$NH(CH_2)_2Ph$], 134.0742 [M^+ −91, 100.0, $(CH_3CH_2)_2P(=O)N^+(H)=CH_2$], 120.0814 ($M^+$ −105, 3.1%, $H_2N^+=CH{\cdot}CH_2Ph$), 105.0422 (M^+ −120, 28.2%, $(CH_3CH_2)_2P^+=O$].

N-(2-*Phenylethyl*)-P,P-*di-n-butylphosphinamide* (**2c**).—A solution of compound (**1c**) (3 g, 15.2 × 10^{-3} mol) in anhydrous DCM (20 ml) was slowly added to a stirred solution of 2-phenylethylamine (3.7 g, 30.4 × 10^{-3} mol) in anhydrous DCM (30 ml) at 0 °C under dry nitrogen. Work-up gave a yellow oil which was passed through a short column (10 cm) of basic alumina (pH 9) eluting with anhydrous DCM. Evaporation of the solvent under reduced pressure gave a pale yellow oil which was distilled under reduced pressure [b.p. 180 °C (0.05 mmHg)] to give pure N-(2-*phenylethyl*)-P,P-*di-n-butylphosphinamide* as a very hygroscopic white, crystalline solid (4.1 g, 96%), m.p. (sealed tube) 32—33 °C (Found: C, 68.5; H, 10.1; N, 4.8; P, 10.8. $C_{16}H_{28}NOP$ requires C, 68.3; H, 10.0; N, 5.0; P, 11.0%); $\nu_{max.}$(HCB mull) 3 180, 3 090—3 025 (N–H), 1 460 (CH_2–P), and 1 160 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.2 (5 H, s, aromatic), 3.4—2.7 [5 H, m, $NH(CH_2)_2$], 1.9—1.1 [12 H, m, $(CH_2)_3P(=O)$], and 1.1—0.8 (6 H, m, CH_3); $\delta_P(CDCl_3)$ +41.

N-(2-*Phenylethyl*)-P,P-*dimethylphosphinamide* (**2d**).—The reaction of compound (**1d**) (2 g, 17.7 × 10^{-3} mol) with 2-

Table 4. Methyl *P,P*-disubstituted phosphinates

	M.p. (°C)/B.p. (°C, mmHg)	Literature m.p. (°C)/B.p. (°C, mmHg)	Yield (%)	δ_P[a]
(3a)	76	75[33]	88	28
(3b)	82—83 (12)	86 (12)[34]	87	59
(3d)	85—86 (1)	95 (3)[35]	85	56
(3c)	68—70 (12)	78.5—79.5 (14)[36]	85	55
(3e)	55		92	33
(3h)	100—103 (12)	89.5—90.5 (12)[37]	82	61
(3i)	75 (0.8)		83	54

[a] Measured in $CDCl_3$.

phenylethylamine (4.2 g, 35.4 × 10^{-3} mol) as described for compound (**2b**) led to the isolation of crude N-(2-*phenylethyl*)-P,P-*dimethylphosphinamide* as a pale green oil which was distilled under reduced pressure to give the pure product as a very hygroscopic white powder (2.4 g, 69%), m.p. (sealed tube) 49—50 °C (Found: C, 60.9; H, 8.1; N, 6.9; P, 15.3. $C_{10}H_{16}NOP$ requires C, 60.9; H, 8.2; N, 7.1; P, 15.7%); $\delta_H(CDCl_3)$ 7.3 (5 H, s, aromatic), 3.3—2.7 [5 H, m, $NH(CH_2)_2$], 1.4 [6 H, d $^3J_{P-H}$ 14 Hz, $(CH_3)_2P(O)$]; $\delta_P(CDCl_3)$ +36; *m/z* 197.0964 (M^+, 20.5%), 182.0728 [M^+ −15, 1.4% $CH_3P^+(=O)NH(CH_2)_2Ph$], 120.0813 (M^+ −77, 4.3%, $H_2N^+=CHCH_2Ph$), 106.0426 [M^+ −91, 100.0%, $(CH_3)_2P(=O)N^+(H)=CH_2$], 104.0628 [M^+ −93, 4.7%, $(H_2C=CH\cdot Ph)^+$], and 91.0551 (M^+ −106, 22.9%, $C_7H_7^+$).

N-(2-*Phenylethyl*)-P,P-*diphenylphosphinamide* (**2e**).—Diphenylphosphinic chloride (**1e**) (5 g, 21.1 × 10^{-3} mol,) was allowed to react with 2-phenylethylamine (5.1 g, 42.1 × 10^{-3} mol) in the usual way to give crude N-(2-*phenylethyl*)-P,P-*diphenylphosphinamide* as a white powder which was purified by recrystallisation from ethyl acetate with light petroleum (60—80 °C) (6.2 g, 92%), m.p. 140—141 °C (Found: C, 74.6; H, 6.1; N, 4.1; P, 9.5. $C_{20}H_{20}NOP$ requires C, 74.8; H, 6.3; N, 4.3; P, 9.6%); $\nu_{max.}$ 3 100, 3 050 (N–H), 1 440 (Ph–P), and 1 190 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.0—7.1 (15 H, m, aromatic) and 3.4—2.6 [5 H, m, $NH(CH_2)_2$]; $\delta_P(CDCl_3)$ +21.

5-[N-(2-*Phenylethyl*)*amino*]*dibenzophosphole* 5-*Oxide* (**2f**).—Powdered compound (**1f**) (1 g, 4.26 × 10^{-3} mol) was slowly added in small portions to a stirred solution of 2-phenylethylamine (1.03 g, 8.52 × 10^{-3} mol) in dry DCM (60 ml) at 0 °C under dry nitrogen. Stirring was continued at this temperature for 1 h and for 2 h more at room temperature. The solvent was evaporated and the resultant residual white solid residue was stirred with water (100 ml) for 30 min. Filtration gave 5-[N-(2-*phenylethyl*)*amino*]*dibenzophosphole* 5-*oxide* as a fine white powder which was recrystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) (1.1 g, 81%), m.p. 152 °C (Found: C, 75.1; H, 5.7; N, 4.3; P, 9.7. $C_{20}H_{18}NOP$ requires C, 75.2; H, 5.7; N, 4.4; P, 9.7%); $\nu_{max.}$(HCB mull) 3 220 (N–H), 1 420 (Ph–P), and 1 180 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.9—6.9 (13 H, aromatic), 3.2—2.5 [5 H, m, $NH(CH_2)_2$]; δ_P +37.

N-(2-*Phenylethyl*)-P,P-*di-isopropylphosphinamide* (**2h**).—The reaction of compound (**1h**) (3 g, 17.8 × 10^{-3} mol) with 2-phenylethylamine (4.3 g, 35.6 × 10^{-3} mol) under the usual conditions led to the isolation of N-(2-*phenylethyl*)-P,P-*di-isopropylphosphinamide* as a white powder which was recrystallised from anhydrous diethyl ether–light petroleum (b.p. 60—80 °C) (3.7 g, 82%), m.p. 82—83 °C (Found: C, 66.4; H, 9.6; N, 5.8; P, 11.9. $C_{14}H_{24}NOP$ requires C, 66.4; H, 9.5; N, 5.5; P, 12.2%); $\nu_{max.}$(HCB mull) 3 200 (N–H), 1 460 (Pr^i–P), and 1 180 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.2 (5 H, s, aromatic), 3.5—3.1 (3 H, m, $NHCH_2CH_2$), 2.8 (2 H, t, $NHCH_2$), 2.2—1.7 [2 H, m, $CH(CH_3)_2$], 1.2 (6 H, dd $^3J_{P-H}$ 17 Hz, $^3J_{H-H}$ 6.5 Hz) and 1.1 [6 H, dd, $^3J_{P-H}$ 17 Hz, $^3J_{H-H}$ 6.5 Hz, $CH(CH_3)_2$]; $\delta_P(CDCl_3)$ +49.

N-(2-*Phenylethyl*)-P,P-*di-isobutylphosphinamide* (**2i**).—By following the procedure given for compound (**2c**), the desired product, N-(2-*phenylethyl*)-P,P-*di-isobutylphosphinamide* was isolated from the reaction of (**1i**) (3 g, 15.2 × 10^{-3} mol) with 2-phenylethylamine (3.7 g, 30.4 × 10^{-3} mol) as very hygroscopic white crystals (3.8 g, 90%), m.p. (sealed tube) 30 °C [b.p. 175 °C (0.5 mmHg)] (Found: C, 68.1; H, 10.3; N, 5.0; P, 10.7. $C_{16}H_{28}NOP$ requires C, 68.3; H, 10.0; N, 5.0; P, 11.0%); $\nu_{max.}$(neat) 3 200 (N–H), 1 460 (Bu^i–P), and 1 160 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.2 (5 H, s, aromatic), 3.4—2.5 (5 H, m, $NHCH_2CH_2$), 1.7—1.2 [6 H, m, $P(O)CH_2CH$], and 1.1—0.9 [12 H, d, $CH(CH_3)_2$]; $\delta_P(CDCl_3)$ +41.

General Procedure for The Preparation Of Methyl P,P-*Disubstituted Phosphinates*.—The appropriate *P,P*-disubstituted phosphinic chloride was slowly added to a vigorously stirred solution of triethylamine (1 equiv.) in an excess of dry methanol. After 3 h, the reaction solvent was removed under reduced pressure and water (20 ml) was added to the residue. The aqueous solution was extracted twice with DCM and the organic phases combined and dried ($MgSO_4$). The residue obtained upon evaporation of the solvent under reduced pressure was distilled or recrystallised as summarised in Table 4.

Nα-*Dimethylphosphinoyl-leucine Dicyclohexylammonium Salt* DmpLeuOH·DCHA.—Leucine benzyl ester hydrochloride[38] (1.72 g, 6.7 × 10^{-3} mol) was stirred with NMM (1.35 g, 13.4 × 10^{-3} mol) in dry ethyl acetate (50 ml) at 0 °C for 20 min under dry nitrogen. Dimethylphosphinic chloride (**1d**) (0.75 g, 6.7 × 10^{-3} mol) in ethyl acetate (10 ml) was slowly added in such a way that the temperature of the reaction mixture remained at 0 °C. After 30 min at low temperature the solvent was evaporated under reduced pressure and anhydrous diethyl ether (100 ml) was added to the residual oil. The precipitated amine hydrochloride was filtered off and the ether removed to yield an oily solid (1.9 g, 95%) which was shown by 220 MHz ^1H n.m.r. spectroscopy to be N$_\alpha$-*dimethylphosphinoyl-leucine benzyl ester*, DmpLeuOBzl. This was taken up in dry ethanol (70 ml) and hydrogenolysed at room temperature and pressure over 5% palladium on charcoal (0.1 g) catalyst; the uptake of hydrogen ceased after 30 min. Filtration of the catalyst and evaporation of the ethanol afforded an oily residue (1.2 g), to which was added DCHA (1.3 g, 7.2 × 10^{-3} mol) in anhydrous diethyl ether (50 ml) and the resulting mixture stirred for a further 20 min at room temperature. The precipitate thus formed was filtered off but, although found by microanalysis and n.m.r. to be free of phosphorus, was not fully characterised. Evaporation of the ethereal filtrate gave Nα-*dimethylphosphinoyl-leucine, dicyclohexylammonium salt* as a white powder which was filtered off

and dried (0.75 g, 53.5%), m.p. 140—141 °C (Found: C, 61.5; H, 10.8; N, 6.9; P, 8.4. $C_{20}H_{41}N_2O_3P$ requires C, 61.8; H, 10.6; N, 7.2; P, 8.0%); $\nu_{max.}$(HCB mull) 3 280, 3 100—2 100 ($^+NR_4$), 1 450 (CH_3–P), and 1 180 cm^{-1} (P=O); $\delta_H(D_2O)$ 3.2 (1 H, m, Leu α–CH), 2.2—0.8 [37 H, m, Leu β–CH_2, γ–CH and δ–CH_3, $(CH_3)_2$P(=O), $(C_6H_{11})_2$N]; $\delta_P[(CD_3)_2SO]$ +40.

Nα-*Diethylphosphinoylisoleucine*, DepIleOH.—To a stirred solution of isoleucine benzyl ester toluene-*p*-sulphonate[39] (3.93 g, 10 × 10^{-3} mol) in DCM (25 ml) at 0 °C were added NMM (2.0 ml, 20 × 10^{-3} mol) and a solution of compound (**1b**) (1.4 g, 10 × 10^{-3} mol) after which the reaction mixture was stirred at low temperature for 1 h and worked up as described for DmpLeuOBzl to give Nα-*diethylphosphinoylisoleucine benzyl ester*, DepIleOBzl, as a pale yellow oil (2.9 g, 90%); $\delta_P(CDCl_3)$ + 44. This oil (2.9 g, 9.0 × 10^{-3} mol) was hydrogenolysed in ethanol (100 ml) at room temperature and pressure over 5% palladium on charcoal catalyst (0.3 g) for 1 h. Removal of the catalyst and evaporation of the solvent afforded Nα-*diethylphosphinoylisoleucine*, as a white solid which was recrystallised from methanol–anhydrous diethyl ether (1.75 g, 92%), m.p. 158 °C (Found: C, 51.0; H, 9.7; N, 5.8. $C_{10}H_{22}NO_3P$ requires C, 51.0; H, 9.4; N, 5.9%); $\nu_{max.}$(HCB mull) 3 450—2 850 (acid OH), 3 200 (N–H), 1 710 (ester C=O), 1 460 (Et–P), and 1 190 cm^{-1} (P=O); δ_H [$(CD_3)_2SO$] 5.5—3.4 (5 H, m) and 2.0—0.5 (17 H, m); $\delta_P[(CD_3)_2SO]$ +49.

Nα-*Diethylphosphinoylvaline*, DepValOH.—Valine benzyl ester toluene-*p*-sulphonate[39] (5.4 g, 14.2 × 10^{-3} mol) in DCM (80 ml) was allowed to react with compound (**1b**) (2 g, 14.2 × 10^{-3} mol) in the presence of NMM (3.1 ml, 28.4 × 10^{-3} mol) as described for DepIleOBzl. The resulting Nα-*diethylphosphinoylvaline benzyl ester*, DepValOBzl [(3.8 g, 86%, 12.2 mmol); $\delta_P(CDCl_3)$ +44] was hydrogenolysed in ethanol (100 ml) at room temperature and pressure over 5% palladium on charcoal catalyst (0.3 g). After removal of the catalyst by filtration through Celite, the solution was evaporated to yield a white powder which was recrystallised from the ethanol with anhydrous diethyl ether to give pure Nα-*diethylphosphinoylvaline* (2.3 g, 85%), m.p. 144—145 °C (Found: C, 48.7; H, 9.3; N, 6.1. $C_9H_{20}NO_3P$ requires C, 48.8; H, 9.1; N, 6.3%); $\nu_{max.}$ 3 200 (N–H), 3 250—2 750 (acid OH), 1 710 (C=O), 1 460 (Et–P) and 1 200 cm^{-1} (P=O); $\delta_P(D_2O)$ + 59.

Nα-*Diethylphosphinoylisoleucylalanine Phenyl Ester*, DepIle-Ala OPh.—A suspension of Nα-diethylphosphinoylisoleucine (0.61 g, 2.6 × 10^{-3} mol) and NMM (0.28 ml, 2.6 × 10^{-3} mol) in dry ethyl acetate (50 ml) was vigorously stirred at −20 °C for 10 min. Diphenylphosphinic chloride (**1e**) (0.61 g, 2.6 × 10^{-3} mol) in dry ethyl acetate (20 ml) was slowly added[19] and stirring was continued for a further 20 min when a solution of alanine phenyl ester hydrobromide[40] {m.p. 117—118 °C (Found: C, 43.8; H, 5.1; N, 5.9; Br, 32.1. Calc. for $C_9H_{12}BrNO_2$: C, 43.9; H, 4.9; Br, 32.5; N, 5.7%); t.l.c.-H[19] R_F 0.75 (N, I);[2] $[\alpha]_D^{23}$ +6.8° (*c* 1 in MeOH); $\nu_{max.}$ 3 300—2 400 ($^+NH_3$), 1 760 (ester C=O), and 1 190 cm^{-1} (COPh); $\delta_H(D_2O)$ 7.4—6.7 (5 H, m, aromatic), 4.4 (1 H, q, $^3J_{\alpha\text{-CH}-\beta\text{-CH}_3}$ 7.2 Hz, Ala α-CH), 1.9 (3 H, d $^3J_{\alpha\text{-CH}-\beta\text{-CH}_3}$ Ala β–CH_3); $\delta_C(D_2O)$ 169.1 (Ala CO), 151.0 (ester C-1), 132.8 (ester C-3 and C-5), 129.6 (ester C-4), 123.7 (ester C-2 and C-6), 49.8 (Ala α-C), 22.7 (Ala β-C)} (0.53 g, 2.2 × 10^{-3} mol) and NMM (0.24 ml, 2.2 × 10^{-3} mol) in chloroform (40 ml) was added during 15 min. After a further hour at low temperature the reaction solvents were evaporated and the residue partitioned between ethyl acetate and water. The organic phase was isolated and washed with saturated $NaHCO_3$ (×3) and water (×3) before being dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a white powder which was recrystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) to give pure Nα-*diethylphosphinoylisoleucylalanine phenyl ester* (0.42 g, 51%), m.p. 146 °C (Found: C, 59.4; H, 8.5; N, 7.4. $C_{19}H_{31}N_2O_4P$ requires C, 59.6; H, 8.2; N, 7.3%); amino acid analysis Ala_1 1.00, Ile_1 0.98; $\nu_{max.}$ 3 260 (N–H), 1 760 (ester C=O), 1 660 (amide C=O), 1 570 (CONH), 1 460 (Et–P), and 1 170 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 8.0 (1 H, d, Ala NH), 7.4—7.0 (5 H, m, aromatic), 4.7 (1 H, t, Ile NH), 3.6 (1 H, m, Ala α-CH), 3.0 (1 H, t, Ile α-CH), 2.0—0.8 [22 H, m, Ile β-CH, γ-CH_2, γ-CH_3, and δ-CH_3, Ala β-CH_3, $(CH_3CH_2)_2$P(O)]; $\delta_P(CDCl_3)$ +45.

Nα-*Diethylphosphinoylisoleucyl*(β-*t-butyl*)*aspartylphenylalanine amide*, DepIle-Asp(OBu^t)-PheNH_2.—A solution of diphenylphosphinic chloride (**1e**) (2.0 g, 0.85 × 10^{-3} mol) in dry ethyl acetate (10 ml) was slowly added[19] to a stirred mixture of DepIleOH (0.2 g, 0.85 × 10^{-3} mol) and NMM (0.09 ml, 0.85 × 10^{-3} mol) in dry ethyl acetate (15 ml) at 0 °C. Stirring was continued for 30 min when a solution of (β-t-butyl)aspartylphenylalanine amide[41] (0.24 g, 0.72 × 10^{-3} mol) in dry ethyl acetate (20 ml) was added. After a further 20 min the reaction was worked up as described for DepIle-AlaOPh to give Nα-*diethylphosphinoylisoleucyl*(β-*t-butyl*)*aspartylphenylalanine amide* as a white powder which was purified by recrystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) (0.31 g, 78%), m.p. 226—227 °C (Found: C, 58.7; H, 8.1; N, 9.8. $C_{27}H_{45}N_4O_6P$ requires C, 58.6; H, 8.2; N, 10.1%); amino acid analysis Asp_1 0.97, Ile_1 1.01; $\nu_{max.}$ (HCB mull) 3 500, 3 400, 3 375 (N–H), 1 730 (ester C=O), 1 690, 1 640 (amide C=O), 1 580 (CONH), 1 450 (Et–P), and 1 170 cm^{-1} (P=O); $\delta_P[(CD_3)_2SO]$ +47.

Nα-*Diethylphosphinoylvalylglycine Benzyl Ester*, DepVal-GlyOBzl.—To a stirred solution of DepValOH (0.6 g, 2.7 × 10^{-3} mol) in dry DCM (20 ml) cooled to 0 °C were added NMM (0.30 ml, 2.7 × 10^{-3} mol) and a solution of compound (**1e**) (0.64 g, 2.7 × 10^{-3} mol) in dry DCM (10 ml). Following an activation period of 15 min a pre-cooled solution of glycine benzyl ester toluene-*p*-sulphonate[39] (0.76 g, 2.2 × 10^{-3} mol) and NMM (0.24 ml, 2.2 × 10^{-3} mol) in DCM (10 ml) was added during 15 min. After the resulting mixture had been stirred for a further 1 h the reaction was worked up as described for DepIle-AlaOPh to give Nα-*diethylphosphinoylvalylglycine benzyl ester* as a white powder which was purified by recrystallisation from ethyl acetate with light petroleum (b.p. 60—80 °C) (0.5 g, 60%), m.p. 157 °C (Found: C, 58.9; H, 7.9; N, 7.5. $C_{18}H_{29}N_2O_5P$ requires C, 58.7; H, 7.9; N, 7.6%) amino acid analysis Gly_1 1.00, Val_1 1.00; $\nu_{max.}$ 3 280 (N–H), 1 725 (ester C=O), 1 660 (amide C=O), 1 430 (Et–P), and 1 165 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 7.4 (5 H, s, aromatic), 5.2 (2 H, s, CH_2Ph), 4.1—4.0 (2 H, d, Gly CH_2), 3.7—3.5 (2 H, m, Val α–CH and Val NH), 1.9—1.5 [4 H, m, $(CH_3CH_2)_2$], and 1.4—0.8 [13 H, m, Val β-CH and γ-CH_3, $(CH_3CH_2)_2$]; $\delta_P(CDCl_3)$ +50.

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