Reactions of *N*-Phenyl α-Halogenophosphonamidates with Alkoxide: Migration of the Anilino Group from Phosphorus to the α Carbon Atom

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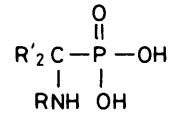
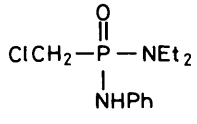
When $Me_2CClP(O)(NHPh)OMe$ is treated with 0.5M NaOMe–MeOH the anilino group migrates from phosphorus to the α carbon atom. Reaction is complete within 2 min at 60 °C and $Me_2C(NHPh)P(O)(OMe)_2$ is formed quantitatively. Similar behaviour is observed with MeCHCl-P(O)(NHPh)OMe but the reaction is *ca.* 50-times slower and in the later stages some of the resulting $MeCH(NHPh)P(O)(OMe)_2$ becomes demethylated. For the still less reactive compounds XCH_2-P(O)(NHPh)OMe (X = Cl or I) demethylation of the substrate and/or product is extensive, but with $ICH_2P(O)(NHPh)OEt$ in 0.15M NaOEt–EtOH at 60 °C the product $PhNHCH_2P(O)(OEt)_2$ can be obtained within 1 h in high yield. The relative rates of rearrangement of the various substrates are consistent with a mechanism involving a three-membered cyclic intermediate, the phosphorus analogue of an α-lactam.

Interest in the chelating ability and biological activity of α-aminophosphonic acids (**1**) and their esters has prompted the development of a wide variety of methods for their synthesis.[1] Many of these are restricted to compounds having unsubstituted amino groups (**1**; R = H)[2] although some can be used to make alkylamino derivatives (**1**; R = alkyl).[1,3] The methods available for arylamino compounds (**1**; R = aryl) are relatively few, and these are not always applicable to the simpler systems (**1**; R′ = H or alkyl).[4] In 1977 Petrov *et al.*[5] reported the transformation of the α-chlorophosphonic diamide (**2**) into the anilino compound (**3**; R = Me, Et, or Ph) (50—80%) on heating with RONa–ROH in dimethylformamide. In spite of its potential value for introducing an arylamino group onto the carbon atom adjacent to a phosphonyl centre, this type of reaction appears not to have been pursued. In particular, it has not been established whether the reaction is unique to chloromethyl compounds or can be extended to substrates having one or two alkyl groups attached to the α carbon atom. We have therefore prepared some representative 1-halogenoalkyl-*N*-phenyl-phosphonamidates and examined the possibility of transferring the anilino group from phosphorus to the adjacent carbon atom.



(**1**)



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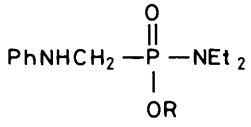
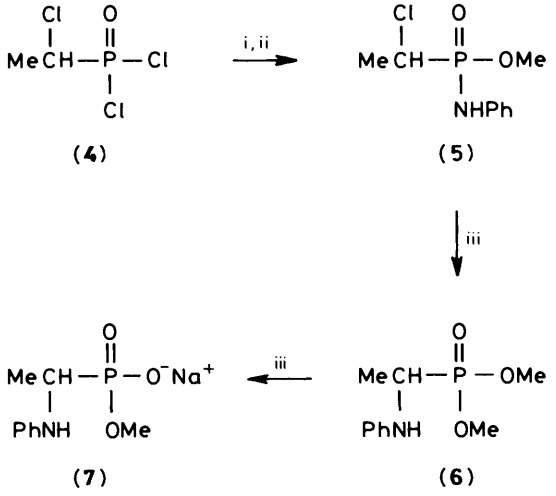


(**3**)

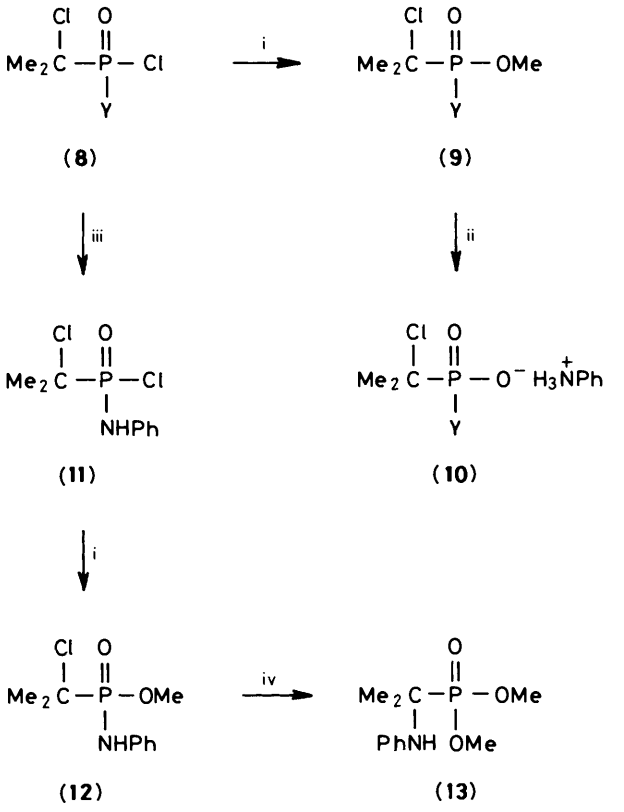
Results and Discussion

The 1-chloroethylphosphonamidate (**5**) was prepared from the corresponding phosphonic dichloride (**4**)[6] by treatment first with methanol–triethylamine (1 mol equiv.), then with aniline (Scheme 1). Although the product was crystalline, the ^1H n.m.r. spectrum showed it to be an approximately equal mixture of diastereoisomers with the signals for both the OMe (d, J_{PH} 11 Hz) and *Me*CHCl (dd, J_{PH} 17, J_{HH} 7 Hz) groups being clearly separated (Δδ 0.04 and 0.05 respectively). This material was dissolved in 0.5M NaOMe–MeOH and the progress of the reaction monitored by g.l.c. (3% OV 17 at 210 °C). The substrate (R_t 9.6 and 9.9 min for the poorly resolved diastereoisomers) was completely consumed within *ca.* 35 min at the reflux temperature, and only one g.l.c.-detectable product (R_t 8.0 min) was observed. The rearrangement product (**6**) was isolated in 71% yield (after crystallisation) and characterised. As would be expected, the diastereotopic OMe groups gave rise to separate ^1H n.m.r. signals [δ($CDCl_3$) 3.73 and 3.68; both 3 H, d, J_{PH} 11 Hz] and the most intense peak in the electron-impact mass spectrum had *m/z* 120, corresponding to the ion $[MeCHNHPh]^+$.

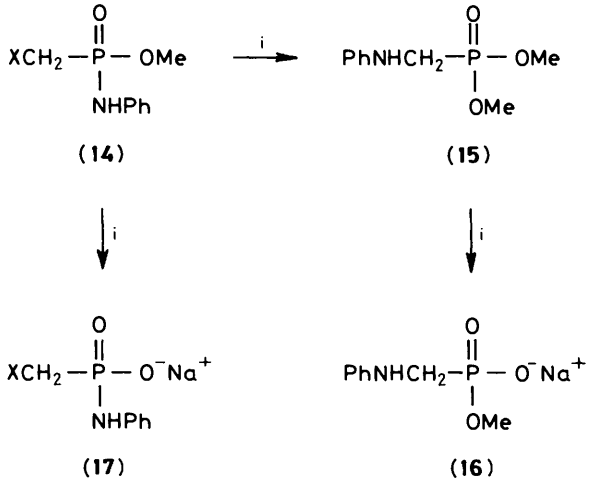


Scheme 1. *Reagents:* i, MeOH (1 mol equiv.), Et_3N; ii, $PhNH_2$, Et_3N; iii, NaOMe

In principle the diastereoisomers of phosphonamidate (**5**) may rearrange at different rates, but because of inadequate resolution the g.l.c. analysis afforded no clear evidence concerning this. On the other hand, the diastereoisomers differ significantly in their ^{31}P n.m.r. chemical shifts (δ_P 24.0 and 23.7 in 0.5M NaOMe–MeOH). The reaction of compound (**5**) was



Scheme 2. *Reagents:* i, NaOMe (1 mol equiv.); ii, $PhNH_2$; iii, LiNHPh (1 mol equiv.); iv, NaOMe



Scheme 3. *Reagent: i*, NaOMe

therefore repeated (standard conditions: 2 mol equiv. 0.50M NaOMe–MeOH at 60 °C) and its progress was monitored by ^{31}P n.m.r. spectroscopy. This showed there to be rather little difference in the reactivity of the diastereoisomers ($t_{0.5}$ 10—15 min for both),* albeit that at 85% completion the remaining substrate was almost totally devoid of the high-field diastereoisomer. It also showed that, in addition to the rearrangement product (**6**) (δ_P 29.5),† a second product (δ_P 23.3) began to be formed in the final stages of the reaction. By the time the last of the substrate had been consumed this accounted for 20% of the reaction mixture, and on continued heating it continued to be formed at the expense of the product (**6**). The ^1H n.m.r. spectrum (CD_3OD) of this compound was similar to that of compound (**6**) except that it contained only one P–OMe signal (δ 3.51, 3 H, d, J_{PH} 10 Hz), and on treatment with diazomethane (following protonation) it was converted back into (**6**). Clearly it must be the salt (**7**) formed by demethylation of the initial rearrangement product (**6**), presumably as a result of nucleophilic attack by methoxide on the carbon of a P–OMe group. From a preparative standpoint, by treatment of the rearrangement reaction mixture with diazomethane prior to work-up the isolated yield of the product (**6**) could be increased to 85% (after crystallisation).

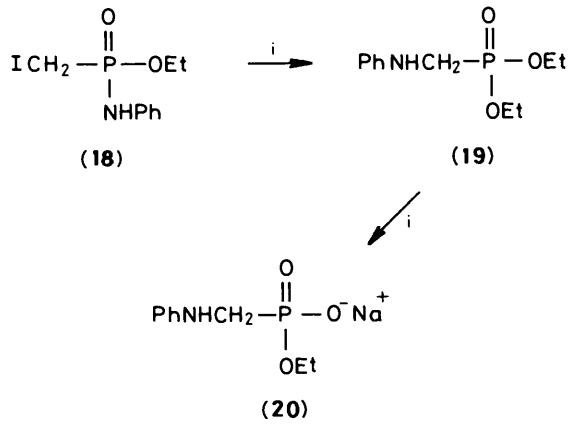
The phosphonic dichloride (**8**; Y = Cl) required for the preparation of the more highly alkylated α-chlorophosphonamidate (**12**) is not reported in the literature, but it was readily obtained in good yield from Me_2CCl_2 by a Kinnear and Perren reaction,[6] and could easily be purified by sublimation or crystallisation. It could not, however, be converted into the phosphonamidate (**12**) by first introducing the *P*-methoxy group, on account of the unexpected behaviour of the methyl phosphonochloridate (**9**; Y = Cl) (Scheme 2). This did not react with aniline under normal conditions (benzene solution, room temperature), presumably because of hindrance to nucleophilic attack at phosphorus by the bulky Me_2CCl group, and under more forcing conditions (refluxing benzene solution) the salt (**10**; Y = Cl) (85% after 3 h) was formed together with *NN*-dimethylaniline (g.l.c.). Dealkylation of a methyl phosphonate by nucleophilic attack at carbon is not in itself unusual,[7] and a control experiment showed that the dimethyl phosphonate (**9**; Y = OMe) was similarly converted into the salt (**10**; Y = OMe) with aniline in boiling benzene. However, that the P–Cl bond in (**9**; Y = Cl) should survive does seem rather remarkable. To obtain the required phosphonamidate (**12**), the phosphonic dichloride (**8**) was therefore converted first into the phosphonamidic chloride (**11**), by treatment with lithium anilide at −45 °C, and thence into the amidate (**12**) with sodium methoxide. This substrate (δ_P 25.4) showed much higher reactivity than substrate (**5**) with 0.50M NaOMe–MeOH and was cleanly converted into the rearrangement product (**13**) (δ_P 31.5) within 2 min at 60 °C ($t_{0.5}$ *ca.* 15 s). No other product was detected by g.l.c. or ^{31}P n.m.r. spectroscopy, and the phosphonate (**13**) was isolated in 95% yield.

The behaviour of the simplest phosphonamidate studied, (**14**; X = Cl) (δ_P 21.5), was very different. It reacted only slowly with 0.50M NaOMe–MeOH at 60 °C ($t_{0.5}$ *ca.* 4 h), and while ^{31}P n.m.r. spectroscopy indicated the formation of some of the rearrangement product (**15**) (δ_P 27.6) and its demethylated derivative (**16**) (δ_P 20.2) (together *ca.* 35%; $t_{0.5}$ for rearrangement *ca.* 12 h), the major product (δ_P 9.8) was neither of these. Since on protonation and treatment with diazomethane it reverted to starting material, it seems that it was simply the demethylated form (**17**; X = Cl) of the substrate (Scheme 3). This, apparently, does not rearrange.

In the hope of increasing the rate of rearrangement, and so avoiding the problem of demethylation, we turned to the iodo analogue (**14**; X = I). Diethyl iodomethylphosphonate is readily available from the Arbuzov reaction of di-iodomethane and triethyl phosphite,[8,9] and on being heated with phosphorus pentachloride (2.2 mol equiv.) at 80 °C for 3—4.5 h it formed $ICH_2P(O)Cl_2$. There was ^1H n.m.r. evidence for some halogen exchange in the product (ICH_2, δ 3.85 ⟶ $ClCH_2$, δ 4.20) but this amounted to only 5—10% so long as the period of heating was not needlessly prolonged. In any case, $ClCH_2P(O)Cl_2$ is much more volatile and could easily be removed by simple

* Only a small excess of NaOMe was employed; here and subsequently we use $t_{0.5}$ to mean the time taken for the first 50% of the substrate to be consumed.

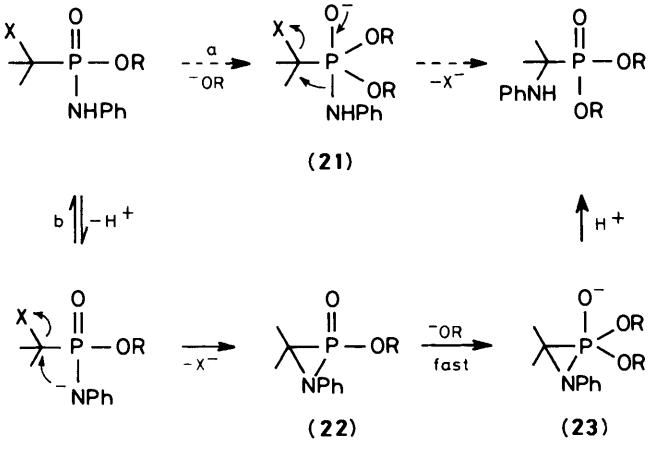
† Where no solvent is specified, ^{31}P n.m.r. chemical shifts relate to spectra recorded on reaction mixtures.



Scheme 4. *Reagent: i*, NaOEt

distillation. At room temperature the pure iodomethylphosphonic dichloride (84% yield) became highly crystalline. Sequential replacement of the chlorine atoms with methanol and aniline gave the required phosphonamidate (**14**; X = I).

The behaviour of the iodomethyl substrate (**14**; X = I) was rather disappointing. Iodide is usually *ca.* 100-times better than chloride as the leaving group in nucleophilic substitution,[10] but (**14**; X = I) rearranged only some 15-times faster than the chloro compound with 0.50M NaOMe–MeOH at 60 °C ($t_{0.5}$ 50 min). This modest increase in rate was enough largely to solve the more serious of the demethylation problems, and only 5—10% of the substrate was degraded to the unreactive salt (**17**; X = I). Demethylation of the rearrangement product (**15**) was still important, however, and even at 50% completion of reaction there was a significant amount of the salt (**16**). From such a half-complete reaction mixture the rearrangement product (**15**) (an amine) was isolated by extraction and purified by distillation (23% yield; 45% based on unrecovered starting material).

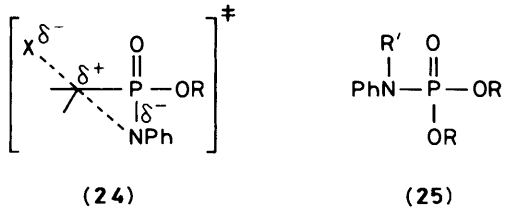


Scheme 5.

In a final attempt to overcome dealkylation the ethyl ester analogue (**18**) was prepared and examined. It rearranged rapidly with 0.50M NaOEt–EtOH at 60 °C ($t_{0.5}$ *ca.* 8 min) but even so the rearrangement product (**19**) suffered some dealkylation to salt (**20**) in the later stages of the reaction, (Scheme 4), presumably by *E*2 elimination of ethene. Reducing the concentration of NaOEt to 0.15M had only a small effect on the rate of rearrangement ($t_{0.5}$ *ca.* 11 min at 60 °C) but fortunately it reduced substantially the rate at which the product was dealkylated. Under these conditions reaction was essentially complete after 55 min, at which point dealkylation was barely perceptible. The rearrangement product (**19**) was isolated in 96% yield.

A reasonable mechanism for the rearrangement of the α-halogenophosphonamidates could have as its first step nucleophilic attack of alkoxide at phosphorus (Scheme 5, path a). The resulting phosphorane (**21**) could then collapse directly to product, by concerted migration of the anilino group from phosphorus and displacement of the halogen from the α carbon atom. A comparable breakdown of a phosphorane has previously been postulated in the alkaline hydrolysis of some chloro- and iodo-methylphosphonium salts, although there it is a phenyl or alkyl group that migrates from phosphorus and displaces the halogen.[11] In the present case, however, the relative reactivities of the different 1-chloroalkylphosphonamidates seem incompatible with such a mechanism. Nucleophilic attack at a phosphoryl centre is known to be strongly retarded by bulky ligands,[12] but the rate of the phosphonamidate rearrangement increases by a factor of ~3 000 as the *P*-alkyl group changes $ClCH_2 \rightarrow MeCHCl \rightarrow Me_2CCl$. Also, the fact that rearrangement is faster with NaOEt–EtOH than with NaOMe–MeOH suggests that the alkoxide acts initially as a base rather than a nucleophile. We therefore prefer the alternative mechanism (path b) shown in Scheme 5. This is essentially the same as that proposed by Petrov *et al.*[5] for the α-chlorophosphonic diamide (**2**), and has as its most notable feature the cyclic intermediate (**22**). Three-membered rings containing a P=O group have attracted considerable attention in recent years,[13] both as short-lived reaction intermediates[14] and, in special cases, as stable, isolable products.[15] However, the particular system of concern here, the phosphorus analogue of an α-lactam,[16] has been largely ignored. The P=O group in a three-membered ring is expected to be highly reactive towards a nucleophile such as methoxide, especially if a pentaco-ordinate intermediate [*e.g.* (**23**)] is formed,[17] so it is not surprising that we were unable to detect the cyclic species (**22**) by ^{31}P n.m.r. spectroscopy. As regards the relative reactivities of the chloroalkylphosphonamidates, it has long been recognised that cyclisation reactions generally benefit from the presence of alkyl groups, especially *gem*-dimethyl substituents, in the developing ring.[18,19] A pertinent example is provided by the base-induced conversion of chlorohydrins into epoxides;[20] the relative reactivities of $ClCH_2CH_2OH$, $MeCHClCH_2OH$, and Me_2CClCH_2OH are 1.0, 5.5, and 248. In the present case the 50—60-fold increase in the rate of rearrangement (ring closure) as each hydrogen on the α carbon atom is replaced by a methyl group may be just another manifestation of the general phenomenon. On the other hand, it could be that the ring closure has some S_N1 character, in which case methyl groups would help to stabilise the partial positive charge on the α carbon atom in the cyclisation transition state (**24**).*

Nucleophilic attack on the cyclic intermediate (**22**) can, in



* The rather small increase in the rate of rearrangement on going from the chloromethyl substrate (**14**; X = Cl) to its iodomethyl analogue (**14**; X = I) can be understood in terms of path b in Scheme 5: the beneficial effect of iodine on the second step (I better leaving group than Cl) will be partially cancelled out by its adverse effect on the first step [I less electronegative than Cl; (**14**; X = I) less acidic than (**14**; X = Cl)].

principle, bring about ring opening in two ways. The isolated rearrangement products are all the result of P–N bond cleavage, and given the anionic character of the leaving group, and the presence of the phenyl substituent on nitrogen, it is not surprising that this should be preferred. If instead the P–C bond had broken, the products would have been the phosphoramidates (**25**; R′ = Me, Et, or Pr^{i}). Even small amounts of these products would constitute important evidence for the cyclic intermediate (**22**). Authentic samples were therefore prepared by conventional methods, and the rearrangements were then re-examined. Even with the aid of the authentic samples [δ_P(MeOH) 8.3—8.5] no trace of the phosphoramidates (**25**) could be detected by ^{31}P n.m.r. spectroscopy.

In conclusion, while we have no direct evidence for a three-membered cyclic intermediate in the rearrangements of the 1-halogenoalkyl-*N*-phenylphosphonamidates, the indirect evidence is strongly in favour of the mechanism shown in Scheme 5, path b. And whatever the mechanism, the rearrangement can provide an efficient and probably quite general way of introducing an anilino group onto the carbon atom adjacent to a phosphonyl centre.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 298 instrument, and ^{1}H n.m.r. spectra with a Varian EM390 spectrometer. ^{31}P N.m.r. spectra (^{1}H-decoupled) were recorded at 24.3 MHz with a JEOL JNM-FX60 spectrometer; positive chemical shifts are downfield from external 85% H_3PO_4. Routine mass spectra were obtained with a V.G. Micromass 16B instrument; high-resolution spectra were recorded by PCMU Harwell. Methanol and ethanol were purified by distillation from their magnesium salts. 2,2-Dichloropropane was prepared from acetone and phosphorus pentachloride, with phosphoryl trichloride as a suspension medium.[21]

Phosphonic Dichlorides.—The following were prepared by the method of Kinnear and Perren,[6] except that conc. hydrochloric acid was used in place of water in the work-up: chloromethylphosphonic dichloride, b.p. 78—80 °C at 5 mmHg (lit.,[6] 50 °C at 0.5 mmHg); $\delta_H(CDCl_3)$ 4.20 (d, J_{PH} 6 Hz); 1-chloroethylphosphonic dichloride (**4**), b.p. 67—69 °C at 5.5 mmHg (lit.,[6] 57 °C at 3 mmHg); $\delta_H(CDCl_3)$ 4.41 (1 H, dq, J_{PH} 2, J_{HH} 7 Hz) and 1.89 (3 H, dd, J_{PH} 24, J_{HH} 7 Hz).

1-*Chloro*-1-*methylethylphosphonic dichloride* (**8**; Y = Cl). 2,2-Dichloropropane (10.0 g, 0.089 mol), phosphorus trichloride (24.4 g, 0.178 mol), and aluminium chloride (23.7 g, 0.178 mol) were mixed in order and stirred for 3 h. The mixture was diluted with dichloromethane (160 ml) and cooled to −20 °C. Conc. hydrochloric acid (40 ml) was added in portions with thorough mixing. After 0.25 h the coagulated salts were removed by filtration. The filtrate was evaporated to dryness and the product was extracted from the residue with hot light petroleum (b.p. 40—60 °C)–dichloromethane (6:1), to give the *phosphonic dichloride* (**8**; Y = Cl) (14.0 g, 81%), m.p. ~80 °C; sublimes at 70 °C/1.5 mmHg; *m/z* 200, 198, 196, 194 (M^+, 10%), and 79, and 77 (Me_2CCl^+, 100); $\nu_{max.}$(Nujol) 1 280 cm^{-1}; $\delta_H(CDCl_3)$ 1.94 (d, J_{PH} 22 Hz) (Found: C, 18.5; H, 3.1; Cl, *ca.* 53.3. $C_3H_6Cl_3OP$ requires C, 18.4; H, 3.1; Cl, 54.4%).

Iodomethylphosphonic dichloride. Based on literature procedures,[8,9] triethyl phosphite (0.070 mol, 11.6 g) was added to di-iodomethane (0.11 mol, 29.5 g) at 180 °C and the mixture was heated for a further 0.5 h. Distillation gave diethyl iodomethylphosphonate (9.7 g, 50%), b.p. 110—113 °C at 2.5 mmHg (lit.,[9] 96—99 °C at 0.5 mmHg); $\delta_P(CDCl_3)$ 20.4; $\delta_H(CDCl_3)$ 4.16 (4 H, dq, J_{PH} 7, J_{HH} 7 Hz), 3.01 (2 H, d, J_{PH} 11 Hz), and 1.33 (6 H, t, J_{HH} 7 Hz).

The phosphonate (2.78 g, 10.0 mmol) was stirred at room temperature and phosphorus pentachloride (4.6 g, 22 mmol) was added in portions during 15 min. The mixture was then heated at 80 °C for 3—4.5 h. [The progress of the reaction was monitored by ^{1}H n.m.r. spectroscopy (ICH_2 signals) so that the period of heating, and hence the risk of halogen exchange ($ICH_2 \longrightarrow ClCH_2$), could be kept to a minimum.] Volatile material was removed at 80 °C/15 mmHg and the residue was distilled (Kugelrohr) to give iodomethylphosphonic dichloride (2.17 g, 84%), b.p. 105 °C (oven temp.) at 2 mmHg, which solidified at room temperature (m.p. *ca.* 40 °C); *m/z* 262, 260, 258 (M^+, 100) 141 (ICH_2^+, 50), 135, 133, and 131 (M^+ − I, 95); $\nu_{max.}$(melt) 1 270 cm^{-1}; $\delta_P(CDCl_3)$ 33.9; $\delta_H(CDCl_3)$ 3.85 (d, J_{PH} 8 Hz). This compound hydrolyses very rapidly on exposure to air and elemental analysis was not attempted.

Methyl P-(*Chloromethyl*)-N-*phenylphosphonamidate* (**14**; X = Cl).—A mixture of methanol (0.32 g, 10.0 mmol) and triethylamine (1.01 g, 10.0 mmol) in ether (20 ml) was added dropwise to a stirred solution of chloromethylphosphonic dichloride (1.68 g, 10.0 mmol) in ether (25 ml) at 0 °C, and the mixture was kept at room temperature for 1 h. A mixture of aniline (1.02 g, 11.0 mmol) and triethylamine (1.01 g, 10.0 mmol) in ether (10 ml) was then added. After a further 2 h at room temperature the mixture was filtered. The filtrate was washed successively with water (containing sufficient HCl to react with any remaining $PhNH_2$), aqueous potassium carbonate, and water, and was dried (Na_2SO_4). Evaporation of the solvent gave an oil which was crystallised from ether–light petroleum (b.p. 60—80 °C) to give *methyl* P-(*chloromethyl*)-N-*phenylphosphonamidate* (**14**; X = Cl) (1.38 g, 63%), m.p. 73—75 °C; δ_P(ether) 19.6; *m/z* 221, 219 (M^+, 100%), and 170 (M^+ − $ClCH_2$, 80); $\nu_{max.}$(Nujol) 3 160 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.35—6.85 (5 H, m), 6.57 (1 H, br, NH), 3.80 (3 H, d, J_{PH} 12 Hz), and 3.63 (2 H, d, J_{PH} 10 Hz) (Found: C, 43.7; H, 5.05; N, 6.45. $C_8H_{11}ClNO_2P$ requires C, 43.75; H, 5.05; N, 6.4%).

Methyl P-(*Iodomethyl*)-N-*phenylphosphonamidate* (**14**; X = I).—This was prepared from iodomethylphosphonic dichloride as above except that the final mixture was heated under reflux for 1 h prior to filtration. Crystallisation from ether–light petroleum (b.p. 60—80 °C) afforded *methyl* P-(*iodomethyl*)-N-*phenylphosphonamidate* (**14**; X = I) (64%), m.p. 89—90 °C (after recrystallisation from ether containing a little dichloromethane); δ_P(ether) 20.8; *m/z* 311 (M^+, 75%) and 106 (100); $\nu_{max.}$(Nujol) 3 150 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.3—6.85 (5 H, m), 6.73 (1 H, br, NH), 3.77 (3 H, d, J_{PH} 11 Hz), and 3.17 (2 H, d, J_{PH} 9 Hz) (Found: C, 31.0; H, 3.55; N, 4.5. $C_8H_{11}INO_2P$ requires C, 30.9; H, 3.6; N, 4.5%).

Ethyl P-(*Iodomethyl*)-N-*phenylphosphonamidate* (**18**).—This was similarly prepared from iodomethylphosphonic dichloride by treatment with ethanol–triethylamine (2 h at room temperature) and then aniline–triethylamine (overnight at room temperature). The initial oil was stirred vigorously with light petroleum (b.p. 60—80 °C) to give the crude solid product (60%). This was purified by dissolution in ether and filtration to remove an insoluble impurity [$\delta_P(CH_2Cl_2)$ 18.1]. Crystallisation from aqueous ethanol gave *ethyl* P-(*iodomethyl*)-N-*phenylphosphonamidate* (**18**) (35%), $\delta_P(CH_2Cl_2)$ 20.2; m.p. 106—106.5 °C; *m/z* 325 (M^+, 80%) and 106 (100); $\nu_{max.}$(Nujol) 3 180 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.3—6.85 (5 H, m), 6.78 (1 H, d, J_{PH} 6 Hz, NH), 4.20 (2 H, dq, J_{PH} 12, J_{HH} 6 Hz), 3.20 (2 H, d, J_{PH} 9 Hz), and 1.34 (3 H, t, J_{HH} 6 Hz) (Found: C, 33.2; H, 4.0; N, 4.3. $C_9H_{13}INO_2P$ requires C, 33.25; H, 4.0; N, 4.3%).

Methyl P-(1-*Chloroethyl*)-N-*phenylphosphonamidate* (**5**).—This was prepared from 1-chloroethylphosphonic dichloride (**4**)

by the method described for amidate (**14**; X = Cl). The initial oil was chromatographed on alumina. Elution with ether containing 3% methanol gave a crystalline mixture (*ca.* 1:1) of the diastereoisomers of *methyl* P-(1-*chloroethyl*)-N-*phenylphosphonamidate* (**5**) (47%), $\delta_P(CH_2Cl_2)$ 23.8 and 22.9; m.p. 66—67 °C [from light petroleum (b.p. 60—80 °C) containing a little ether]; *m/z* 235 and 233 (M^+, 100%), 198 (M^+ − Cl, 20), and 170 (M^+ − MeCHCl, 65); $\nu_{max.}$(Nujol) 3 140 and 3 080 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.35—6.85 (5 H, m), 6.1 (1 H, br, NH), 4.08 (1 H, dq, J_{PH} 7, J_{HH} 7 Hz), 3.83 and 3.79 (total 3 H; both d, J_{PH} 11 Hz), and 1.69 and 1.64 (total 3 H; both dd, J_{PH} 16, J_{HH} 7 Hz) (Found: C, 46.0; H, 5.6; N, 5.9. $C_9H_{13}ClNO_2P$ requires C, 46.3; H, 5.6; N, 6.0%).

P-(1-*Chloro*-1-*methylethyl*)-N-*phenylphosphonamidic Chloride* (**11**).—A solution of lithium anilide (10.5 mmol) (prepared from aniline and n-butyl-lithium) in tetrahydrofuran (THF)–hexane (9 ml) was added during 5 min to a stirred solution of 1-chloro-1-methylethylphosphonic dichloride (**8**; Y = Cl) (1.00 g, 5.12 mmol) in THF (6 ml) at −45 °C. The mixture was allowed to warm to room temperature and a solution of trifluoroacetic acid (1.45 g, 12.8 mmol) in THF (8 ml) was added. Most of the solvent was evaporated off and the residue, dissolved in dichloromethane (30 ml), was washed with water (10 ml). Crystallisation from ether–light petroleum (b.p. 60—80 °C) gave the *phosphonamidic chloride* (**11**) (0.95 g, 74%), m.p. 107—108 °C; *m/z* 255, 253, 251 (M^+, 100%), 218, 216 (M^+ − Cl, 20), and 177 and 175 (M^+ − C_3H_5Cl, 70); $\nu_{max.}$(Nujol) 3 140 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.3—6.95 (5 H, m), 5.80 (1 H, br d, J_{PH} 10 Hz, NH), and 1.88 (6 H, d, J_{PH} 18 Hz) (Found: C, 42.8; H, 4.7; N, 5.5. $C_9H_{12}Cl_2NOP$ requires C, 42.9; H, 4.8; N, 5.6%).

Methyl P-(1-*Chloro*-1-*methylethyl*)-N-*phenylphosphonamidate* (**12**).—A solution of the phosphonamidic chloride (**11**) (0.67 g, 2.7 mmol) in methanol (5 ml) was cooled in ice while sodium methoxide (2.8 mmol; 1M solution) was added dropwise. After 15 min at room temperature the excess of methoxide was neutralised (NH_4Cl) and the solvent was evaporated off. The residue, dissolved in dichloromethane (15 ml), was washed with water (7 ml). Crystallisation from ether–dichloromethane afforded *methyl* P-(1-*chloro*-1-*methylethyl*)-N-*phenylphosphonamidate* (**12**) (0.58 g, 87%); $\delta_P(CDCl_3)$ 25.3; m.p. 164—165 °C; *m/z* 249, 247 (M^+, 100%), 212 (M^+ − Cl, 40), and 170 (M^+ − Me_2CCl, 90); $\nu_{max.}$(Nujol) 3 160 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.25—6.8 (5 H, m), 5.25 (1 H, br d, J_{PH} 6 Hz), 3.81 (3 H, d, J_{PH} 11 Hz), 1.72 (3 H, d, J_{PH} 15 Hz), and 1.69 (3 H, d, J_{PH} 15 Hz) (Found: C, 48.3; H, 5.9; N, 5.8. $C_{10}H_{15}ClNO_2P$ requires C, 48.5; H, 6.1; N, 5.7%).

Anilinium 1-*Chloro*-1-*methylethylphosphonochloridate* (**10**; Y = Cl).—Sodium methoxide (3.85 mmol; 1M solution) was added to a solution of 1-chloro-1-methylethylphosphonic dichloride (**8**; Y = Cl) (0.75 g, 3.85 mmol) in ether. After 0.5 h the solvent was evaporated off and the residue was extracted with dichloromethane. The extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave methyl 1-chloro-1-methylethylphosphonochloridate (**9**; Y = Cl) as an oil that was not purified; *m/z* 157, 155 (M^+ − Cl, 40%), 79 and 77 (Me_2CCl^+, 100); $\delta_H(CDCl_3)$ 3.95 (3 H, d, J_{PH} 12 Hz) and 1.86 (6 H, d, J_{PH} 18 Hz).

The chloridate (0.50 g, 2.6 mmol) was dissolved in benzene, and aniline (0.49 g, 5.2 mmol) was added. No reaction was apparent at room temperature but on heating a solid began to precipitate. After the mixture had been boiled for 3 h, *anilinium* 1-*chloro*-1-*methylethylphosphonochloridate* (**10**; Y = Cl) (0.60 g, 85%) was collected by filtration, m.p. 186 °C (decomp.); $\nu_{max.}$(Nujol) 3 100—2 000 cm^{-1} (NH); $\delta_H(CD_3OD)$ 7.6—7.3 (5 H, m) and 1.74 (6 H, d, J_{PH} 16 Hz) (Found: C, 40.0; H, 5.2; N, 5.3; Cl, *ca.* 26.9. $C_9H_{14}Cl_2NO_2P$ requires C, 40.0; H, 5.2; N, 5.2; Cl, 26.25%).

Anilinium Methyl 1-*Chloro*-1-*methylethylphosphonate* (**10**; Y = OMe).—1-Chloro-1-methylethylphosphonic dichloride (**8**; Y = Cl) was treated with sodium methoxide (2 equiv.; as above) to give *dimethyl* 1-*chloro*-1-*methylethylphosphonate* (**9**; Y = OMe), b.p. 80 °C (oven temp.) at 0.2 mmHg; *m/z* 151 (M^+ − Cl, 30%) and 110 (M^+ − C_3H_5Cl, 100); $\delta_H(CDCl_3)$ 3.88 (6 H, d, J_{PH} 10 Hz) and 1.75 (6 H, d, J_{PH} 15 Hz) (Found: C, 32.1; H, 6.6; P, 16.5. $C_5H_{12}ClO_3P$ requires C, 32.2; H, 6.5; P, 16.6%).

The dimethyl phosphonate (0.30 g, 1.55 mmol) and aniline (0.29 g, 3.1 mmol) were dissolved in benzene. The solution was heated under reflux overnight to give a precipitate of *anilinium methyl* 1-*chloro*-1-*methylethylphosphonate* (**10**; Y = OMe) (0.31 g, 82%), m.p. 152—154 °C; $\nu_{max.}$(Nujol) 3 100—1 900 cm^{-1} (NH); $\delta_H(CD_3OD)$ 7.4—7.2 (5 H, m), 3.66 (3 H, d, J_{PH} 10 Hz), and 1.67 (6 H, d, J_{PH} 13 Hz) (Found: C, 45.1; H, 6.3; N, 5.4. $C_{10}H_{17}ClNO_3P$ requires C, 45.2; H, 6.45; N, 5.3%). This compound was also obtained when the chloride (**10**; Y = Cl) was heated in methanol.

Reactions of Alkyl P-(1-*Halogenoalkyl*)-N-*phenylphosphonamidates.*—(a) *Methyl* P-(1-*chloroethyl*)-N-*phenylphosphonamidate* (**5**). The substrate (**5**) (187 mg, 0.80 mmol) was heated at 60 °C with 0.50M methanolic sodium methoxide (3.2 ml, 1.60 mmol) and the progress of the reaction was monitored by ^{31}P n.m.r. spectroscopy. During 100 min the substrate peaks (δ_P 24.0 and 23.7; diastereoisomers) were completely replaced by signals at δ_P 29.5 (80%) and 23.3 (20%). The mixture was acidified (methanolic HCl), concentrated, treated with diazomethane (δ_P 23.3 converted into δ_P 29.5), and evaporated to dryness. Extraction with dichloromethane and crystallisation from light petroleum (b.p. 60—80 °C)–dichloromethane gave *dimethyl* 1-*anilinoethylphosphonate* (**6**) (156 mg, 85%), m.p. 98—100 °C; $\delta_P(CDCl_3)$ 29.5; *m/z* 229 (M^+, 8%) and 120 ($PhNHCHMe^+$, 100); $\nu_{max.}$(Nujol) 3 310 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.25—7.05 (2 H, m), 6.75—6.55 (3 H, m), ~3.8 (1 H, m), 3.73 (3 H, d, J_{PH} 11 Hz), 3.68 (3 H, d, J_{PH} 11 Hz), 3.3 (1 H, br, NH), and 1.42 (3 H, dd, J_{PH} 17, J_{HH} 7 Hz); $\delta_H(C_6D_6)$ includes 3.69 (1 H, dq, J_{PH} 16, J_{HH} 7 Hz), 3.38 (3 H, d, J_{PH} 11 Hz), 3.33 (3 H, d, J_{PH} 11 Hz), and 1.30 (3 H, dd, J_{PH} 17, J_{HH} 7 Hz) (Found: C, 52.45; H, 7.0; N, 6.1. $C_{10}H_{16}NO_3P$ requires C, 52.4; H, 7.0; N, 6.1%). The same product (**6**) was isolated in reduced yield (71%) from a similar reaction [refluxing methanolic NaOMe (3 mol equiv.); *ca.* 35 min] when the diazomethane treatment was omitted. When the period of heating was increased to 8 h (at 60 °C) the product consisted entirely of the compound with δ_P 23.3. This had a ^1H n.m.r. spectrum showing $\delta_H(CD_3OD)$ 7.15—6.9 (2 H, m), 6.7—6.4 (3 H, m), *ca.* 3.6 (1 H, m), 3.51 (3 H, d, J_{PH} 10 Hz), and 1.31 (3 H, dd, J_{PH} 15, J_{HH} 7 Hz), consistent with it being the salt (**7**). On protonation and treatment with diazomethane it was converted into the product (**6**).

(b) *Methyl* P-(1-*chloro*-1-*methylethyl*)-N-*phenylphosphonamidate* (**12**). When the substrate (**12**) (124 mg, 0.50 mmol) was heated with 0.50M methanolic sodium methoxide (2.0 ml, 1.0 mmol) at 60 °C the peak δ_P 25.4 was replaced quantitatively by one at δ_P 31.5 during *ca.* 2 min. The excess of methoxide was neutralised (NH_4Cl), the methanol was evaporated off, and the residue was partitioned between chloroform and water. Evaporation of the chloroform portion afforded pure *dimethyl* 1-*anilino*-1-*methylethylphosphonate* (**13**) (115 mg, 95%), crystallised from light petroleum (b.p. 60—80 °C), m.p. 92—93 °C; $\delta_P(CDCl_3)$ 31.5; *m/z* 243 (M^+, 2%), 134 ($PhNHCMe_2^+$, 30), 133 (45), and 118 (100); $\nu_{max.}$(Nujol) 3 325 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.25—6.75 (5 H, m), 3.68 (6 H, d, J_{PH} 10 Hz), 3.4 (1 H, br, NH), and 1.45 (6 H, d, J_{PH} 15 Hz)

(Found: C, 54.3; H, 7.4; N, 5.7. $C_{11}H_{18}NO_3P$ requires C, 54.3; H, 7.5; N, 5.8%).

(c) *Methyl* P-(*chloromethyl*)-N-*phenylphosphonamidate* (**14**; X = Cl). The reaction of substrate (**14**; X = Cl) with 0.50M methanolic sodium methoxide (2 mol equiv.) at 60 °C was examined by ^{31}P n.m.r. spectroscopy [see Results and Discussion section; an unidentified minor product, with δ_P 14.3 (unaffected by CH_2N_2), was also observed] but was not pursued.

(d) *Methyl* P-(*iodomethyl*)-N-*phenylphosphonamidate* (**14**; X = I). The substrate (**14**; X = I) (405 mg, 1.30 mmol) was heated with 0.50M methanolic sodium methoxide (5.2 ml, 2.60 mmol) at 60 °C for 50 min. Examination by ^{31}P n.m.r. spectroscopy indicated unchanged substrate (δ_P 22.6) (*ca.* 50%), one substantial product (δ_P 27.4) (*ca.* 30%), and three minor products (δ_P 20.0, 14.7, and 9.3). The excess of methoxide was neutralised (methanolic HCl), volatile material was evaporated off, and the residue was partitioned between 2M aqueous HCl (1 ml) and dichloromethane (0.5 ml). The aqueous portion was washed with ether and then basified (NaOH); extraction with ether and distillation of the resulting oil gave *dimethyl anilinomethylphosphonate* (**15**) (65 mg, 23%), b.p. 130 °C (oven temp.) at 0.25 mmHg; $\delta_P(CDCl_3)$ 27.3; *m/z* 215 (M^+, 17%) and 106 ($PhNHCH_2^+$, 100); $\nu_{max.}$(film) 3 320 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.3—7.05 (2 H, m), 6.8—6.6 (3 H, m), 3.73 (6 H, d, J_{PH} 11 Hz), 3.48 (2 H, d, J_{PH} 12 Hz), and 3.42 (1 H, s, NH) (Found: M^+, 215.0728. $C_9H_{14}NO_3P$ requires *M*, 215.0711). Evaporation of the combined dichloromethane portion and ether washings gave unchanged substrate (**14**; X = I) (215 mg, 53%) of *ca.* 95% purity. The crude product from a similar experiment was acidified and treated with diazomethane. The minor components, with δ_P 20.0 and 9.3, were transformed into the product (**15**) (δ_P 27.4) and the substrate (**14**; X = I) (δ_P 22.6) respectively.

(e) *Ethyl* P-(*iodomethyl*)-N-*phenylphosphonamidate* (**18**). The substrate (**18**) (163 mg, 0.50 mmol) (δ_P 19.6) was heated with 0.15M ethanolic sodium ethoxide (6.7 ml, 1.0 mmol) at 60 °C until ^{31}P n.m.r. spectroscopy showed the reaction to be >95% complete (55 min). There was then one dominant product (δ_P 24.7) (*ca.* 95%) and one trace product (δ_P 18.2) (1—2%). The excess of ethoxide was neutralised (AcOH), volatile material was evaporated off, and the residue was partitioned between chloroform and water. Distillation of the chloroform portion gave *diethyl anilinomethylphosphonate* (**19**) (117 mg, 96%), b.p. 135 °C (oven temp.) at 0.1 mmHg; $\delta_P(CDCl_3)$ 24.1; *m/z* 243 (M^+, 35%) and 106 ($PhNHCH_2^+$, 100); $\nu_{max.}$(film) 3 320 cm^{-1} (NH); $\delta_H(CDCl_3)$ 7.25—7.05 (2 H, m), 6.8—6.6 (3 H, m), 4.10 (4 H, dq, J_{PH} 7, J_{HH} 7 Hz), 3.95 (1 H, br, NH), 3.47 (2 H, d, J_{PH} 12 Hz), and 1.27 (6 H, t, J_{HH} 7 Hz) (Found: C, 53.0; H, 7.5; N, 5.6. $C_{11}H_{18}NO_3P{\cdot}0.4H_2O$ requires C, 53.0; H, 7.6; N, 5.6%. Found: M^+, 243.1024. $C_{11}H_{18}NO_3P$ requires *M*, 243.1024).

Dimethyl N-*Alkyl*-N-*phenylphosphoramidates*.—These compounds were examined as possible products of the rearrangement reactions. Authentic samples were prepared and characterised as indicated below. Using these samples it was possible to establish by ^{31}P n.m.r. spectroscopy that they were not formed in the reactions of the phosphonamidates (**5**), (**12**), and (**14**; X = I) with NaOMe–MeOH (1% would have been detected).

(a) Treatment of dimethyl phosphorochloridate with *N*-methylaniline or *N*-ethylaniline (2 mol equiv.) in ether at room temperature for 24 h gave dimethyl *N*-methyl-*N*-phenylphosphoramidate (**25**; R = R′ = Me), b.p. 100 °C (oven temp.) at 0.5 mmHg (lit.,[22] 92 °C at 0.5 mmHg); δ_P(MeOH) 8.5; or *dimethyl* N-*ethyl*-N-*phenylphosphoramidate* (**25**; R = Me, R′ = Et), b.p. 110 °C (oven temp.) at 0.4 mmHg; δ_P(MeOH) 8.3; $\delta_H(CDCl_3)$ 7.3—7.1 (5 H, m), 3.65 (6 H, d, J_{PH} 11 Hz), 3.56 (2 H, dq, J_{PH} 10, J_{HH} 7 Hz), and 1.12 (3 H, t, J_{HH} 7 Hz) (Found: M^+, 229.0865. $C_{10}H_{16}NO_3P$ requires *M*, 229.0868).

(b) Phosphoryl trichloride was treated with an equimolar mixture of *N*-isopropylaniline[23] and pyridine (1 mol equiv.) in benzene to give N-*isopropyl*-N-*phenylphosphoramidic dichloride*, b.p. 125 °C (oven temp.) at 0.4 mmHg; m.p. 44—45 °C; *m/z* 255, 253, and 251 (M^+, 17%) (Found: C, 43.3; H, 4.9; N, 5.5. $C_9H_{12}Cl_2NOP$ requires C, 42.9; H, 4.8; N, 5.6%). This was converted by sodium methoxide in methanol into *dimethyl* N-*isopropyl*-N-*phenylphosphoramidate* (**25**; R = Me, R′ = Pr^i), a hygroscopic solid; m.p. *ca.* 40 °C; δ_P(MeOH) 8.3; *m/z* 243 (M^+, 15%); $\delta_H(CDCl_3)$ 7.4—7.1 (5 H, m), 4.12 (1 H, d × septet, J_{PH} 9, J_{HH} 7 Hz), 3.65 (6 H, d, J_{PH} 11 Hz), and 1.10 (6 H, d, J_{HH} 7 Hz) (Found: C, 54.3; H, 7.4; N, 5.7. $C_{11}H_{18}NO_3P$ requires C, 54.3; H, 7.5; N, 5.8%).

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