Phospholidines incorporating an *N,N'*-dimethyl oxamide moiety: reactivity towards amines and alcohols revisited

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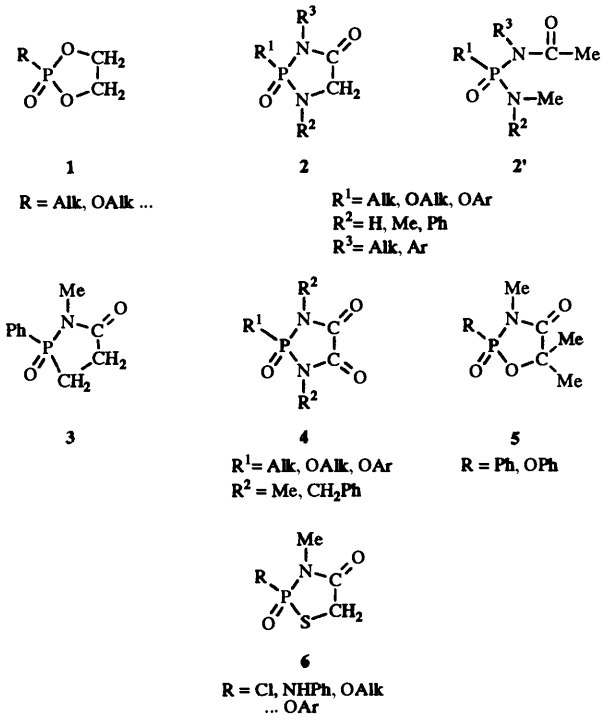
This study has established that the products of the reaction of the phenoxy derivative **4a** with *p*-anisidine are not phosphoramides **7a** and **4b**, but the salts **11a** and **12**, confirming that only ammoniolysis takes place. These results are discussed in terms of mechanism (addition–elimination with the critical deprotonation of the primary zwitterionic intermediate **A** formed) and the influence of steric hindrance. Methanolysis of the methylamino derivative **4d**, as with all phospholidines of type **4** studied so far, proceeds in two distinct stages. The monoester **8d** can be characterized, as can the analogous **8f** resulting in the opening of the amino derivative **4f**. The effect of reducing the NPN angle to *ca.* 90°, appears therefore to be of little significance for the presumed reduced rate of the first step. In the second stage of the methanolysis the regioselectivity (carbonyl *versus* phosphoryl) of attack on various monoesters **8** depends both on catalysis and substitution (R^1) of the starting phospholidines **4**. Particularly relevant is the attack on PO with a consistent reaction rate on the methylamino derivative **8d** in basic media, while the sterically equivalent methoxy derivative **8g** then undergoes attack on the carbonyl. Factors controlling the reactivity of monomethyl esters of type **8** in the second step are discussed.

In five-membered ring heterocycles which contain phosphorus (the so called phospholanes, or phospholidines when at least one nitrogen atom is located in the cyclic structure), the reactivity of the heteroatom towards nucleophiles is greatly enhanced in comparison with the acyclic analogues. This was originally observed[1] with phospholanes of type **1** to which a glycol moiety had been added (Scheme 1: heterocycles **1–6**).



Scheme 1 Five-membered cyclic phosphorus heterocycles considered, with intracyclic amide leaving group (**2–6**)

This property was utilised in the key reaction of an intramolecular peptide synthesis[2] using phospholidines **2** containing an α-aminoamide (glycinamide) moiety. As expected, alcoholysis takes place by attack on phosphorus,[3] while with the acyclic analogue **2'**, the reactivity of the phosphoryl group is so greatly diminished that attack is diverted to the carbonyl group.[4]

However, the heterocycles **2** were reluctant to undergo aminolysis,[3] precluding their facile use in peptide synthesis. This is easily explained if one considers the addition–elimination mechanism[5] which is operative with phospholanes **1** and presumably with phospholidines **2**.[3] The interpretation was substantiated by the analogous inhibition of aminolysis of the phospholidine **3** built up with a propionamide moiety[6] and was further pursued by studying the aminolysis of phospholidines **4** containing an oxamide moiety: in this case, in contrast to the situation with phospholidines **2** and **3**, the initial zwitterionic intermediate **A** can suffer pseudorotation (ψ), leading to **B** (Scheme 2). This pentacoordinated anion, **B**, which is more stable with an equatorial amino group, should give rise to the aminolysis product with retention of the cyclic structure when an exocyclic, good leaving group such as PhO– is present. We synthesised phospholidines of type **4** and found that aminolysis did indeed take place—but by attack of the carbonyl.[7]†

We were interested by the report of Modro and co-workers describing two cases of aminolysis by attack on phosphorus of the phenoxy-substituted phospholidine **4a**.[10] We had previously synthesised this compound[7] and were interested to note (*i*) the ammoniolysis we have not studied and (*ii*) the reaction with

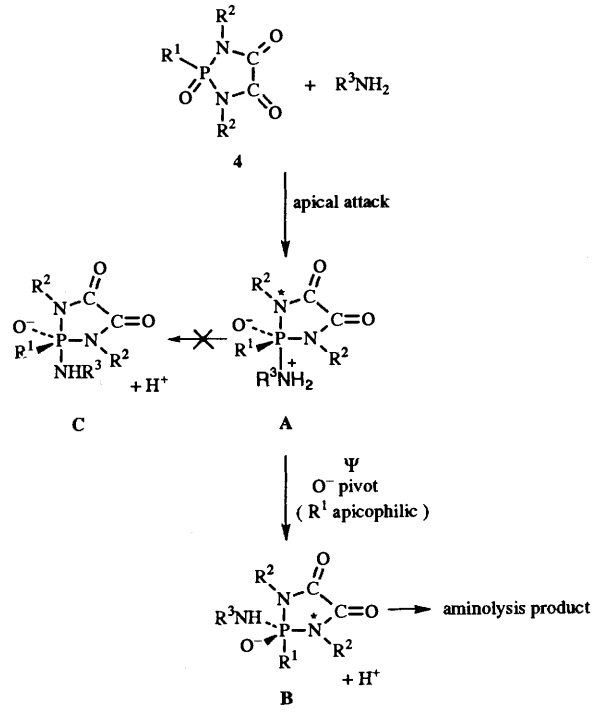
† This was interpreted by the overactivation of one carbonyl due to the presence of the second. In order to avoid this, we synthesised the phospholidine **5**, containing an α-hydroxycarboxamide moiety whose zwitterionic intermediate of type **A** can pseudorotate.[8] We found that as expected, aminolysis takes place with retention of the cyclic structure[8] (with R = OPh). The same behaviour should be observed in the aminolysis (so far not studied) of thiophospholidines **6** (R = OPh, retention; R = OAlk, opening of the heterocycle).[9] Finally, note that the observed inhibition of aminolysis by attack on phosphorus in heterocycles **2** and **3**, can be taken as evidence for the lack of equatorial attack by anionic amines which would then produce an energetically favoured pentacoordinated anion.

p-anisidine leading, in less than 24 h, to a mixture of phosphoramides **7a** and **4b** (Scheme 3).

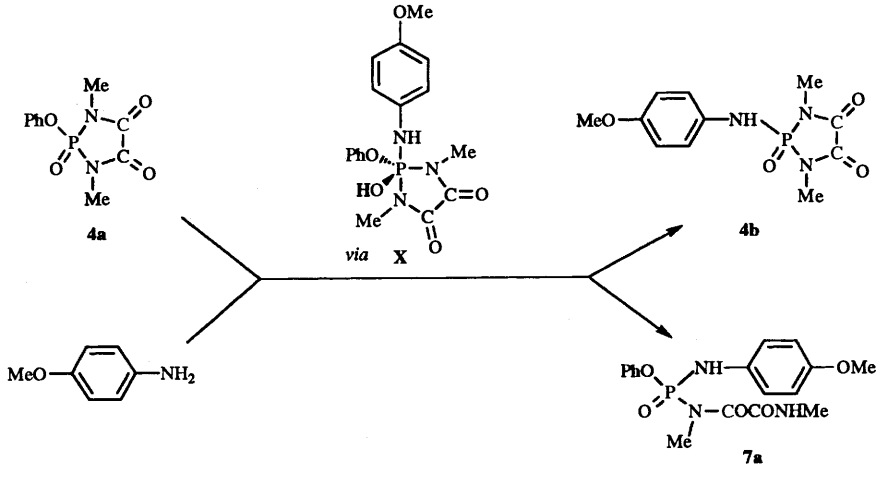
According to our interpretation, a neutral pentacoordinated intermediate **X** (corresponding to the protonated form of **C**, Scheme 2) with an apical *p*-anisidino group, and therefore an acyclic product such as **7a**, should not be so easily formed. Moreover as with the other compounds of this class,[7] this phosphoramide **7a** should cyclize almost instantaneously. Besides, we previously tried the aminolysis of the very closely related phospholidine **4c** (R^1 = PhO; R^2 = CH_2Ph) with *p*-toluidine and observed no reaction after 48 h.[7] Should such (apparently) small differences [the bulkiness of Me *versus* CH_2Ph and the p*Ka*[11] of *p*-anisidinium (5.34) *versus p*-toluidinium (5.08)] have such a spectacular effect? If this is the case, then the collapse of the pentacoordinated intermediate **X** would be a fascinating reaction with two simultaneous processes, leading to two types of bond breaking being induced by one nucleophile.

Another discrepancy appears in the methanolysis of the phospholidines **4**. The authors describing the new, symmetrical, trimethyl heterocycle **4d** with a methylamino exocyclic R^1 group (in this class we previously synthesised four unsymmetrical phospholidines and a symmetrical, tribenzyl one, whose methanolysis was not studied)[7] observe two dramatic changes compared with the four methanolyses previously described with phospholidines **4** with no amino exocyclic R^1 groups:[10] (*i*) product **8d** corresponding to the first step of methanolysis could not be detected at 60 °C (no reaction at 25 °C after 2 months) (Scheme 4) and (*ii*) the second, apparently faster, step, takes place by attack on phosphorus, despite the fact that the heteroatom is deactivated by amino substitution. Previously with non-amino exocyclic R^1 groups[7] we observed a quick first step and, *e.g.* with **8a**, a second, very slow one (it was necessary to add a base in order to accelerate the reaction), by attack on the carbonyl.

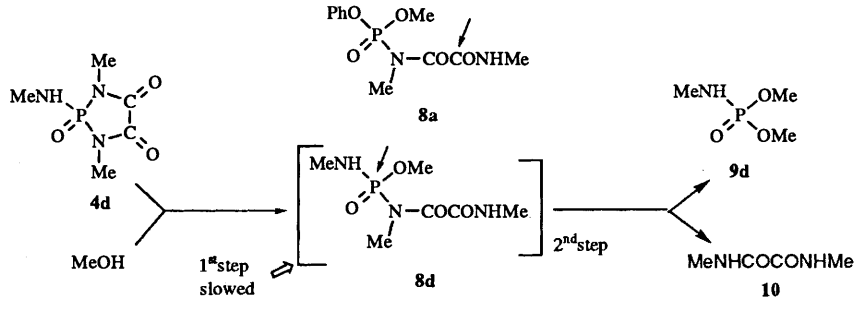
The first change (lack of accumulation of the monomethyl ester **8d**) is attributed by the authors to the reduced rate of the first step mainly as a result of an NPN angle of nearly 90°



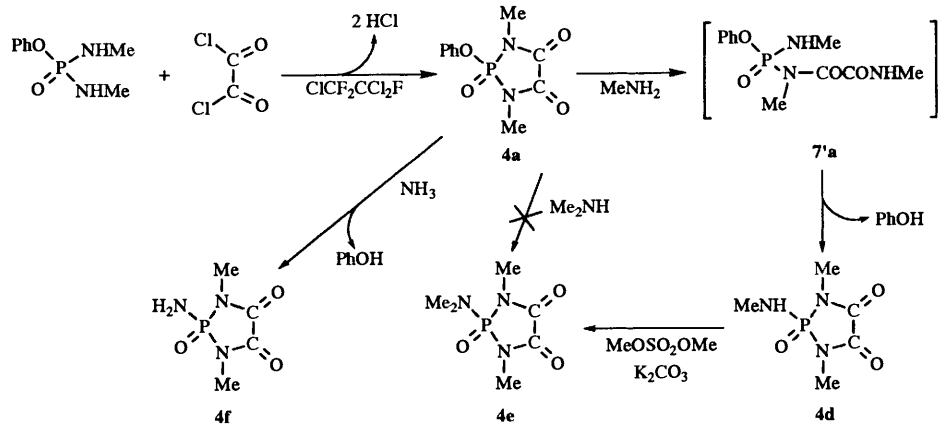
Scheme 2 Possible involvement of addition–elimination (EA) mechanism in the reaction of amines with phospholidines **4**



Scheme 3 One case of aminolysis of the phenoxy derivative **4a** as described by Modro and co-workers[10]



Scheme 4 Methanolysis of the methylamino derivative **4b** as described by Modro and co-workers[10]



Scheme 5 Syntheses of phospholidines **4**

(observed in the RX structure of the methylamino-substituted phospholidine, **4d**). Unfortunately, the RX structure of the phenoxy derivative **4a**, which should show an 'NPN angle significantly larger' than in **4d** and the observation of the same reduction in rate with other phospholidines **4** with an exocyclic amino R group were not given; both of which would corroborate the hypothesis. Moreover, as far as the second change (regioselectivity of attack on the phosphoryl or carbonyl groups) is concerned, no explanation was given and remains a question to be answered.

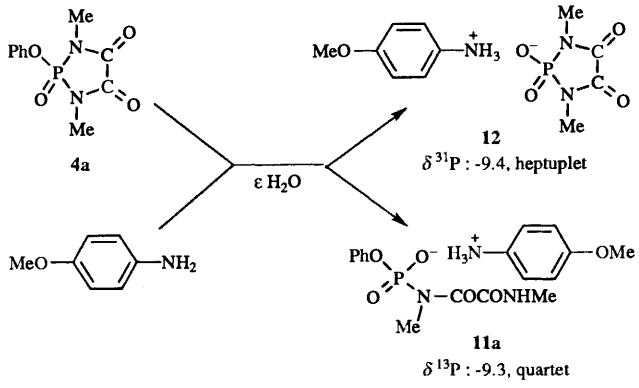
Results

In this study we utilized not only the phospholidines **4a** and **4d**, but also, the amino derivative **4f** and the novel heterocycle **4e** (Scheme 5). The preparation of the first compound **4a** was improved (90% yield) compared with our initial report,[7] by using genetron 113 (1,1,2-trichloro-1,2,2-trifluoroethane), a solvent in which, owing to the near insolubility of both hydrogen chloride and phosphorus compounds, acidolysis of P–N bonds is prevented. Compound **4d** was synthesised by reaction of **4a** with methylamine. In this case, unless using C-deuteriated methylamine, it is not possible to determine the site of the primary attack (the carbonyl or phosphoryl group), which leads in each case to the same product, **7'a**. However, similar reactions are proven to proceed by primary attack on the carbonyl.[7] Accordingly, **4e** could not be synthesised with dimethylamine (where no cyclization is possible after the attack on carbonyl), so it was necessary to use **4d** and *N*-alkylate it. In order to synthesise **4f**, attack on the carbonyl must be excluded as it would yield, after cyclization (*cf.* **7'a**→**4d**), MeNH as the exocyclic group.

Aminolysis

Under rigorous exclusion of moisture, no reaction at all takes place between the phenoxy derivative **4a** and *p*-anisidine as indicated in Scheme 3. After a week, because hydrolysis products could catalyse the reaction, we deliberately opened the reaction vessel for contact with the atmosphere. Under these conditions, the reaction was quick and complete and we obtained a mixture of the two salts **11a** and **12** (Scheme 6) easily identified even in the undecoupled ^{31}P NMR spectra (phosphorus coupled with one or two methyl groups: quartet or heptet).

The ratio **11a**/**12** is dependent on the rate of introduction of water: it increases with stirring, more acid being formed by hydrolysis of **4a** (with less free *p*-anisidine remaining). In a control experiment we hydrolysed **4a**, in a few minutes, and obtained only the phosphorus acid which was remarkably



Scheme 6 Hydrolysis of the phenoxy derivative **4a** in the presence of *p*-anisidine

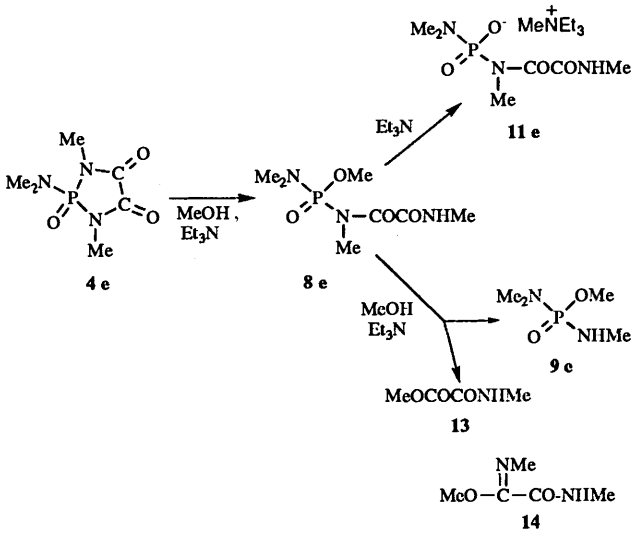
stable. After addition of *p*-anisidine we isolated the corresponding salt **11a** in 67% yield with melting point 128–132 °C, [139–142 °C after recrystallization in DMF (*N*,*N*-dimethylformamide)] and ^1H NMR spectrum both identical to that described by Modro and co-workers for the phosphoramide **7a**[10] (except, in the NMR spectrum, for the NH_3^+ protons δ 9.67 was previously not given). The pure salt **11a** is remarkably reluctant to cyclize. In the presence of greater amounts of *p*-anisidine, **12** is obtained increasingly easily (94% isolated yield after 3 days at 70 °C) and, with sodium hydroxide, the base catalysed cyclization is over in less than 3 min. The ^1H NMR spectrum of **12** is identical to that given for the phosphoramide **4b**,[10] (except for the NH_3^+ protons δ 6.61 previously not mentioned). By recrystallization from DMF the purest form melts at 215–217 °C (compared with 183–185 °C from acetone).[10] Note that Modro's products **7a** and **4b** (Scheme 3) were proven to be hydrated by elemental analysis (but water was not indicated in the ^1H NMR spectrum), which is unusual for phosphoramides.[10] Moreover no IR or mass spectra data were given and it appears that owing to their precipitation in the reaction mixture, they were more polar than anticipated for phosphoramides.

With ammonia, even at low temperatures (−50 °C), we observed by ^{31}P NMR, in a few minutes, only one signal δ = 8.79 (no other signal *e.g.* δ *ca.* 10 for an opened form of type **7** or δ *ca.* −50 for a pentacoordinate species). The isolated product is identical (melting point; ^1H NMR spectrum, with the NH_2 group unsplit by phosphorus) to **4f**.[10] The IR spectrum shows no NH_4^+ absorption and the identity is confirmed by synthesis of the monomethyl ester of type **8**.

Alcoholysis

Neutral conditions. The stable derivative **8f** with the exocyclic NH_2 group is isolated (60% yield). The $t_{\frac{1}{2}}$ of the reaction in excess CD_3SOCD_3–MeOH is *ca.* 15 min. Under the same conditions, the derivatives of the phospholidine **4a** are formed in a few minutes for the methyl ester **8a**, already synthesised,[7] and for the benzyl ester **8'a**, a possible source by debenzylation[12] and addition of *p*-anisidine, of the salt **11a**. The $t_{\frac{1}{2}}$ for monomethanolysis of the methylamino-substituted phospholidine **4d** (see Scheme 4) is *ca.* 6 days under these conditions. It was not possible to achieve the reaction without formation of **9d**, the product of bismethanolysis, which suddenly appeared after *ca.* 80% completion of the first reaction: therefore we stopped it at *ca.* 70% by evaporation of the methanol and easily characterized the monoester **8d** by comparison with the analogous **8f**. Without cosolvent, in methanol alone, in which **4d** is slightly soluble, the complete double methanolysis leading to **9d** and **10** is performed in less than 1 h (previously no reaction was observed).[10] With the two amino compounds **8d** and **8f** we observed that the second attack is still on phosphoryl at a significant rate although lower than in the first step. In contrast **8a**, having no amino exocyclic substituent, reacts very slowly. At elevated temperatures (60 °C), a complex reaction takes place and it is clear that neither phenol (cyclization) nor amide **13** (CO attack) moieties are released and the dimethyloxamide **10** is isolated instead, indicating that attack on PO is probably complicated by auto-alkylation (*cf.* further **8e**→**11e**). The *exo*-*N*,*N*-dimethyl phospholidine **4e** proved to be inert even after three days at 60 °C.

Basic conditions. In the presence of triethylamine, however, the dimethylamino derivative **4e** is methanolysed (Scheme 7).

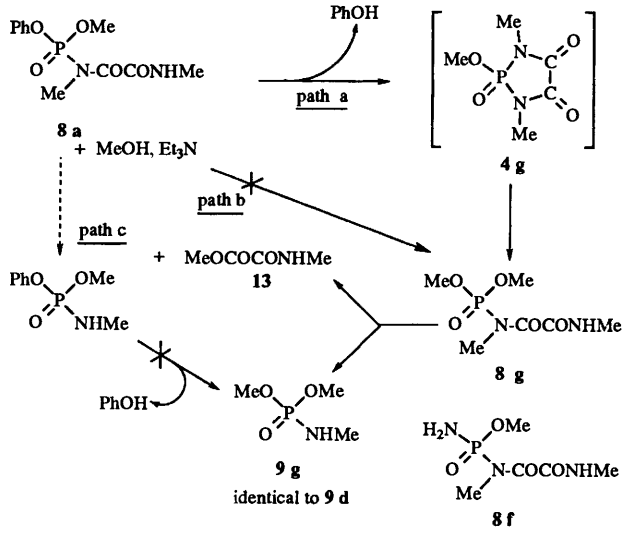


Guide to compounds: **a** to **f** families

4: Heterocycles
7: Non-cyclized phosphordiamides
8: Product of monomethanolysis
9: Phosphorus compound, product of the second methanolysis step
11: Salt corresponding to **8**

Scheme 7 Methanolysis of the dimethylamino derivative **4e**

The ^{31}P NMR spectra show at completion of the reaction (7 days) formation of two signals δ +21.8 (40%) and +2.8 (60%). Separation and ^1H NMR analysis of the reaction mixture established that the former is from **9e** and the latter, from the corresponding salt, **11e**, resulting from the alkylation of triethylamine (as previously observed with **8c**)[7] by **8e**, δ +11, transiently detected.



Scheme 8 Methanolysis of the phenoxymethoxy diester **8a** in basic medium

So, the second step proceeds here by attack on the carbonyl as observed previously with the phenoxy derivative **8a**.[7] For the latter the ^{31}P NMR spectra showed that the second methanolysis takes place on the dimethyl ester **8g** formed by transesterification and release of phenol (Scheme 8, path a). Path b is excluded as direct displacement of phenol is not observed under these conditions with analogues of **8a**.[13] In contrast, the amino derivative **8f** is methanolysed by attack (*ca.* 95%) on phosphoryl. Of course, the regioselectivity of the second alcoholysis can be ascertained as well by analysis of the oxalyl derivatives **10** or **13** and in a control experiment we verified that **10** is not converted to **13** under basic conditions. It is worth mentioning that no imino ether **14**, indicating the involvement of an N→O phosphoryl migration as observed with some *N*-benzoyl phosphoramides,[14–16] could be detected.

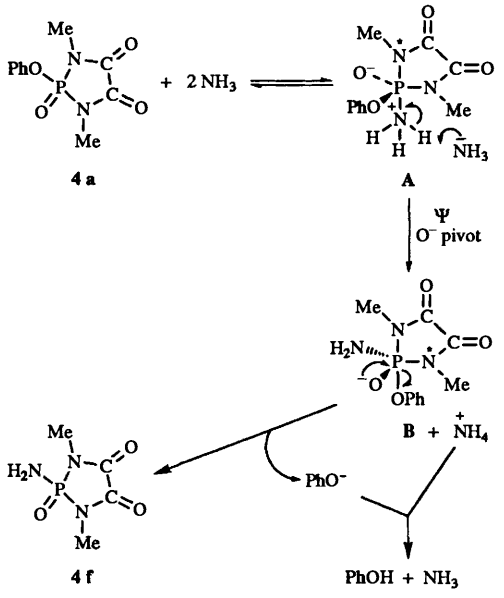
Discussion

Having completed this study we think that the major contradictions between the two preceding reports[7,10] may be resolved with respect to both aminolysis and alcoholysis.

Aminolysis

Concerning the two cases of aminolysis described by Modro and co-workers, the first (ammoniolysis of **4a**) is correct.[10] However, it is clear that the second (Scheme 3) is not. Salts (Scheme 6) are formed rather than phosphoramides. This behaviour (favoured hydrolysis) was also established with the heterocycles **2** and **3**,[3,9] and recently Modro himself recognized that the closed phospholidines **6** are also very sensitive to hydrolysis.[17] As noted in our original paper[7] and proved by elemental analysis, the phenoxy-substituted phospholidine **4a** as the ethoxy is, as later recognized, 'highly hygroscopic'[10] and 'doivent être utilisés juste après leur synthèse.'[7] One can speculate that the **4a** used by Modro and co-workers had decomposed [an indication being the rather low yield (30%) of the benzylaminolysis product of **4a** compared with 91% as originally described].[10] The apparently different rates of formation of **12** (not **4b**) in the reaction mixture (rapid: 'almost immediately') and after isolation (slower: 'reflux at least 0.5 h') is well explained as suggested by a referee[10] and proved in this study by base catalysis of cyclization with *p*-anisidine present in larger (at the beginning) or lesser (at the end) amounts, and not as believed by two different pathways: pseudorotation (rapid) and cyclization (slow).

All amines so far studied either react with phospholidines **4** on one of the two carbonyls or do not react at all. The only proven exception is the ammoniolysis of **4a**, *i.e.* the smallest amine nucleophile with the smallest *O*-aryl phospholidine **4** electrophile (built up with the smallest *N,N*-dialkyl oxamide). This aminolysis is of course easily explained as previously anticipated (Scheme 2).[7] Phospholidines **4** are very sensitive to steric hindrance[7] and one has to examine in this respect the deprotonation–pseudorotation step of the primary zwitterionic intermediate **A**, leading to **B** (Scheme 9).



Scheme 9 Postulated mechanism of ammoniolysis of the phenoxy derivative **4a**, with base catalysis of the deprotonation–pseudorotation step

This could be in a type of amplification of steric hindrance, as deduced in the kinetic study of aminolysis of *p*-nitrobis(chloromethyl)phosphinate,[18] base-catalysed by a second molecule of ammonia; with other amines such catalysis would be ineffective as amplified crowding in the immediate vicinity of phosphorus would be too high and therefore attack should be diverted to one of the two carbonyls.

Taking into account the ammoniolysis of **4a** and the aminolysis[8] of the phenoxyphospholidine **5** it appears that as initially postulated[3,6] the reluctance to aminolysis of phospholidines **2** and **3** results not merely from the absence of interaction of amines with phosphorus, but from the inhibition of deprotonation of the primary zwitterionic intermediate formed, as in these latter cases no pseudorotation is possible. Direct proof of this would be given by the observation of signals at δ *ca.* −50 ppm in the ^{31}P NMR spectra at low temperature having added amines.

This could be due to the fact that the usual carboxamide group associated with compounds **2–6** (Scheme 1) (for oxamides the pK_a can be estimated to be *ca.* 13, by comparison with literature values[19,20] of thioanalogues) is not a good leaving group (pK_a *ca.* 14)[21] preventing direct collapse of the initial zwitterion. This is precisely what is observed[3] with the phospholidine **2** with the much better leaving group *p*-nitroanilide in R[3]. Another effect of a better leaving group [the mechanism in this instance coming closer to giving the SN_2P transition state, than the addition–elimination (AE) intermediate] should be enhanced stabilization of the zwitterion: it is a well known fact that pentacoordinated compounds are energetically more stable when substituted with more electron-withdrawing species.

For the same reason, if one examines the competition between aminolysis and alcoholysis, hydroxy-phosphorane intermediates with a nitrogen substituent should be energetically disfavoured compared with those with an oxygen (more electronegative). In fact, they have been observed only with the more stabilized P–F compounds.[22] Therefore, (not taking into account catalysis), alcoholysis should intrinsically be easier than aminolysis, especially, as described here, with poor leaving groups. With very good ones, aminolysis can become selective[23] as the character of bond formation with a nucleophile in a transition state becomes then relatively more important than bond breaking from the leaving group. This situation is then closer to that encountered with carbonyl derivatives,[24] where aminolysis is generally selective.

Alcoholysis

Reconsidering (as described in the introduction) the first change observed by Modro and co-workers (Scheme 4),[10] it appears that it is elusive: monoester **8d** is indeed detected and characterized. As it is very sensitive, one can speculate that the phospholidine, **4d** used, synthesised in a manner such that HCl was evolved, could contain some acidic impurities that catalyse the second step [as indicated by the poor percentage of nitrogen found (22% instead of the theoretical 20.9%) in the elemental analysis and the complete solubility in methanol and $CDCl_3$]. Another explanation could be a possible precipitation of **8d** with **10** which therefore would not appear in the NMR samples.

Moreover the analogous monoester **8f** is formed without any diester **9f**. This is inconsistent with the advanced effect of the NPN angle of *ca.* 90° observed in the RX structure of **4d**,[10] as this must be observed also with **4f**. Recently, sophisticated studies have appeared concerning the reactivity of phospholanes **1**,[25,26] indicating that strain is not a major factor for the enhancement of the reactivity of **1**.[26,27] In a sense our results can be considered as an indirect, experimental, proof of that. Moreover one should note that lack of accumulation of monoesters **8d** or **8f** may result in the enhancement of the rate of the second step as well.

To some extent this appears to be the case. Particularly striking in this respect is the comparison of the second step of neutral methanolysis of amino derivatives **8d** or **8f** and the diester **8a**: with **8d** and **8f** the reaction is much more rapid than with the latter. This is the opposite to what would be predicted if one considers only the polarity of phosphorus (corresponding to bond formation with the nucleophile). Therefore in a search for an explanation for this paradox one needs merely look at the bond breaking process of the leaving group and so examine also the second divergence (in regioselectivity of methanolysis) noted in the introduction. In fact the contradiction between the methanolysis of **8d** and, as described before,[7] of **8a**, is only apparent as the CO attack was, in the latter case, observed only in basic conditions:[7] in neutral conditions (this study), as for **8d**, PO attack takes place.

However in basic conditions PO attack is still observed with amino compounds **8d** and **8f**, while CO attack occurs with the dimethyl ester **8g** or the *exo-N*-dimethylamide **8e**. Diversion of the attack of methanol onto the carbonyl imide of **8g** is easily explained as considered above, by the relative greater sensitivity to the bond formation process and dependence of the nucleophilicity in carbonyl compounds than in phosphoryl ones. However the observed paradox of both relative rate enhancement and regioselectivity of attack on phosphoryl still in basic conditions observed with **8d** and **8f** bearing an exocyclic amino R group can be *a priori* the result of at least four different factors involving this R group: (*i*) steric hindrance, (*ii*) stereoelectronic effect;[28] (*iii*) change in mechanism, to elimination–addition (EA)[29] and (*iv*) hydrogen bonding. Point (*i*) can

be discarded as **8g**, which is practically as crowded as **8d** (*O*Me instead of *NH*Me), suffers CO attack. A stereoelectronic effect (*ii*) would mean that the nitrogen in R of **8d**, **8f**, would be sp^2 hydridized to have its lone pair *trans* (antiperiplanar) to the P–NCO apical bond of pentacoordinated intermediate (not a transition state, however more likely). This is inconsistent with the fact that a similar effect must also be involved with the *N*-dimethylamino derivative **8e** in which CO attack is then observed. An EA mechanism[29] (*iii*) can of course be involved only with **8d** and **8f** bearing an ionizable NH group (not with **8e** or **8g**) and in basic media. The results in neutral media cannot be explained. As regards point (*iv*) the KBr IR spectrum of the phenoxy derivative **8a** shows, as expected, two distinct prominent carbonyl bands at 1715 cm^{-1} and 1665 cm^{-1} due to the imide (PONMe*CO*) and amide (*CO*NHMe), respectively, and in striking contrast, only one broad band at 1670 cm^{-1} is observed with the amino derivative **8f**. It is tempting to attribute this to a shift of the imide band onto the amide one, as a result of hydrogen bonding between NH_2 and the imide carbonyl, with the improvement of the leaving group ability of the oxamide, in a sort of an intramolecular acid catalysis. Both the observed decrease in rate by addition to MeOH of the cosolvent CD_3SOCD_3, and the very different NMR spectra of the amino derivative **8f** in CD_3SOCD_3 and $CDCl_3$ fit well with this hypothesis. However, while the analogous compound[4] $PhCH_2NHP(O)(OPh)N(Bzl)COMe$ shows the carbonyl band still as low as 1660 cm^{-1}, methanolysis takes place by attack on CO. This could mean that crowding around phosphorus, in this latter case, should divert the attack on carbonyl even when the leaving group is made better by hydrogen bonding. Detailed studies would be necessary in order to clarify the respective importance of the different factors involved. At the present stage, a change in mechanism (EA) and hydrogen bond formation, in basic and neutral media, respectively, appear to us the most likely.

Experimental

Melting points were determined with capillaries (Dr Tottoli's apparatus) and are uncorrected. ^1H, ^{13}C (*J* modulated) and ^{31}P NMR spectra were recorded on a Bruker AC 80 spectrometer (respectively, 80.13, 20.15 and 32.44 MHz) with lock-on internal or external deuteriated solvents. *J* and δ values are given respectively in Hz and in ppm relative to tetramethylsilane. All reactions were monitored using ^{31}P NMR. IR spectra (KBr pellets or Nujol mulls for solids, films for liquids) were recorded on a Fourier transform Perkin-Elmer 1600 apparatus. Solvents were dried by repeated static exposure to actived molecular sieves (5 h, 350 °C, 0.5 mm) except for tetrahydrofuran (THF) which was distilled just before use from naphthalene–sodium. Commercial (Aldrich) *p*-anisidine was purified in the presence of 5% activated carbon in methanol and was recrystallized from CCl_4. All operations were performed with the usual protection against atmospheric moisture (*e.g.* dry argon was used, solutions were transferred through septa using syringes with needles and the use of $CaCl_2$ guards), unless stated otherwise.

Synthesis of the starting 1,3,2-diaza-λ⁵-phospholidine-2,4,5-triones

2-Phenoxy derivative, 4a. A mixture of $PhO–PO(NHMe)_2$ (5.54 g, 27.7 mmol), $ClCF_2CCl_2F$ (*ca.* 45 g) and oxalyl chloride (2.62 cm^3, 30 mmol) was heated under reflux with magnetic stirring; the HCl evolved was detected visually at the beginning and with wet hydrion paper at the end. After 3 h the suspension was centrifuged (10 min, 5000 rpm) and the solvent decanted. The pellet was dried (P_4O_{10}) leaving the product as a white solid (6.43 g, 91%), mp 115–117 °C (lit.,[7] 117–118 °C); $\delta_P(CD_3SOCD_3)$ −0.06; $\delta_C(CD_3SOCD_3)$ 24.96 ($2CH_3$), 120.59 (d, ^3J 4.2, C *ortho*), 126.5 (C *para*), 130.36 (2 C *meta*), 149.17 (d, ^2J 9.5, C *ipso*) and 156.77 (d, *J* 13.3, 2 CO).

NMR data for the starting diamide (not available in ref. 7): $\delta_P(CD_3SOCD_3)$ +15.8; $\delta_C(CD_3SOCD_3)$ 26.41 (d, ^2J 2.2, 2 CH_3), 120.4 (d, ^3J 4.2, C *ortho*), 123.9 (C *para*), 129.3 (2 C, *meta*) and 151.1 (d, ^2J 6.9, C *ipso*).

2-Methylamino derivative, 4d. Methylamine, dried through two columns of KOH (pellets), was bubbled into a solution of the phenoxy derivative **4a** (4.15 g, 16.33 mmol) in CH_2Cl_2 (50 g) for *ca.* 5 min. An increase in weight of 0.7 g (*ca.* 22.5 mmol) was achieved. Crystallization began after 20 min. After 20 h at 4 °C, the solid was rapidly filtered, rinsed twice (CH_2Cl_2) and dried leaving the product **4d** (0.94 g) as needles, mp 204–206 °C (lit.,[10] 205–207 °C). The filtrate was concentrated (strong smell of phenol), suspended in Et_2O and filtered to give the product as a white solid (1.38 g after drying, total yield, 74%); ν_{max}(Nujol)/cm^{-1} 3233 (NH), 1738–1754 (CO); $\delta_H(CD_3SOCD_3)$ 2.45 (3 H, dd, $^3J_{NHCH_3}$ 3.3, $^3J_{PNCH_3}$ 14.15, d, *J* 14.3, with irr. δ 5.6, NH*Me*), 2.88 (6 H, d, ^3J 8.49, 2 CONMe) and 5.6 (1 H, br s, NH); $\delta_P(CD_3SOCD_3)$ +9.6; $\delta_C(CD_3SOCD_3)$ 23.82 (d, ^2J 3.63, 2 *endo* CH_3), 26.19 (*exo* CH_3) and 157.6 (d, *J* 12.69, 2 CO).

2-Dimethylamino derivative, 4e. A suspension of anhydrous K_2CO_3 (1.08 g, 7.8 mmol, 5 equiv.) in a solution of **4d** (0.3 g, 1.57 mmol) and dimethyl sulfate (0.4 g, 3.17 mmol, 4 equiv.) in MeCN (8 g) was stirred until complete disappearance (1 week) of **4d** [formation of **4e** (95%) and of a product (5%), δ 5.7]. After filtration and concentration to dryness, the residue was treated with 10 g of hot AcOEt. The product **4e** was allowed to crystallize for 1 day at room temperature. The crystals were collected and dried (0.15 g, 47%), mp 173–174 °C (Found: C, 34.5; H, 5.8; N, 20.2. $C_6H_{12}NO_3P$ requires C, 35.1; H, 5.9; N, 20.5%); ν_{max}(Nujol)/cm^{-1} no NH band left, 1752–1754 (CO), 1263 (as intense as CO, PO); $\delta_H(CDCl_3)$ four equal signals; most probable assignment 2.62 (6 H, d, ^3J 10.9, NMe_2) and 2.8 (6 H, d, ^3J 8.74, 2 *endo* Me); $\delta_P(CDCl_3)$ +10.4; $\delta_C(CDCl_3)$ 24.4 (d, ^2J 2.82, $N(CH_3)_2$ 35.9 (d, ^2J 5.24, 2 *endo* CH_3) and 157.73 (d, *J* 12.49, 2 CO).

2-Amino derivative, 4f. The same procedure as for **4d** was used with $CHCl_3$ as a solvent.[10] Steady bubbling with ammonia led to 2 equiv. after *ca.* 5 min. The product **4f** (87%) crystallized over 5 days and was recrystallized in DMF–MeCN, mp 228–230 °C, turning slightly brown at *ca.* 200 °C (lit.,[10] 223–227 °C); ν_{max}(Nujol)/cm^{-1} 3327, 3376 (NH_2), no NH_4^+ bands observed (at 2500–2700), 1735–1755 (CO); $\delta_H(CD_3SOCD_3)$, 2.87 (6 H, d, ^3J 8.51, 2 Me) and 5.46 (2 H, s, NH_2); $\delta_P(CD_3SOCD_3)$ +8.8 (undecoupled: heptet ^3J 8.5); $\delta_C(CD_3SOCD_3)$ 23.85 (d, ^2J 3.4, CH_3) and 157.62 (d, *J* 13, CO).

^{31}P NMR spectra from −50 °C to +32 °C of a precooled (−50 °C) $CDCl_3$ solution of *ca.* 30 equiv. of ammonia and 1 equiv. of **4a** showed the single heptet of **4f**.

Reaction of 4a in the presence of *p*-anisidine

A clear yellow solution of **4a** (0.5 g, 1.97 mmol) and of *p*-anisidine (0.24 g, 1 equiv.) in THF (4 cm^3) was kept under argon in a septum capped 10 mm NMR tube. Practically no change in either the ^{31}P NMR spectra or the solution (slight turbidity) was observed after 2 days and no change after a further 6 days. The solution was then transferred to an open flask, diluted with THF and left stirring. The mixture turned brown and a white precipitate was formed in a few minutes. After 24 h, using ^{31}P NMR, no **4a** was detectable in the supernatant and the insoluble material dissolved in DMF was shown to be a mixture of two products δ_P −4.93 (heptet, ^3J 7.5, 22%) and −9.3 (quartet, ^3J 6.5, 78%). After 3 days at 70 °C in MeCN containing 6 equiv. of *p*-anisidine only the heptet was detected.

After cooling the solid formed was proven to be identical in all respects (^{31}P, ^{1}H, ^{13}C NMR spectra and IR) to **12**.

When the initial solution was left in contact with air without stirring the reaction was complete in 3 days and 51% and 49%, respectively, of the heptet and quartet were detected.

Acid hydrolysis of 4a; isolation of 11a ‡

With rapid stirring, **4a** (3.56 g, 14 mmol) was added to 20 g water (pH *ca.* 3 by addition of a few mg of citric acid). After 2 min a slightly turbid solution pH *ca.* 1 was obtained. ^{31}P NMR showed only one signal, δ −8.04 (q, ^{3}J 7) and ^{1}H NMR (+D_2O) signals δ 2.59 (3 H, s, CONH*Me*), 2.85 (3 H, d, ^{3}J 7, PONMe) and 7.05 (5 H, mf, OPh) with no release of phenol (coinjection) or dimethyl oxamide **10** (as indicated in ref. 10, p. 22). One equivalent of *p*-anisidine was then added with dioxan (25 g) to ensure complete solubilization. After evaporation of the solvent, crystallization from MeCN afforded the white product **11a** (3.64 g, 66%), mp 128–132 °C (139–142 °C after recrystallization in THF); ν_{max}(Nujol)/cm^{-1} 3282 (NH), 2647 (NH_3^+), 1676 (CO imide), 1643 (CO amide) and 1236 (PO); δ_H(CD_3SOCD_3) 2.59 (3 H, d, ^{3}J 4.3, NH*Me*), 2.83 (3 H, d, ^{3}J 6.6, PONMe), 3.74 (3 H, s, OMe), 7.09 (4 H, q, J_{AB} 8.7, C_6H_4), 7.2 (5 H, s, OPh), 7.97 (1 H, q, ^{3}J 4.3, N*H*Me) and 9.67 (3 H, s, NH_3); δ_P(CD_3SOCD_3) −10.15 (q, ^{3}J 6.7); δ_C(CD_3SOCD_3) 25.05 ($NHCH_3$), 30.96 ($PONCH_3$), 55.30 (OCH_3) for COPh: 120.1 (d, ^{3}J 4.9, 2 C *ortho*), 122.74 (C *para*), 129.01 (2 C, *meta*) and 152.6 (d, ^{2}J 7.3 C *ipso*), for the aromatic C of *p*-anisidine: 114.54 and 126.06 (2 C, *ortho* and/or *meta*), 127.17 (CNH_3), 157.4 (C–OMe), all signals arising from the *p*-anisidinium cation are more intense than those of the anion; 164.44 (d, ^{2}J 8, CO imide) and 165.46 (CO amide).

Cyclization of 11a; isolation of 12 §

A DMF (15 g) solution of **11a** (2.24 g, 5.87 mmol) and of *p*-anisidine (2.62 g, 21.27 mmol, 3.6 equiv.) was heated at 70 °C until complete conversion (3 days) of the initial quartet to the final heptet. The solvent was evaporated and the product was crystallized from AcOEt as a white powder (1.6 g, 90%), mp 170–180 °C dec. This could be recrystallized satisfactorily from DMF (mp 215–217 °C) instead of acetone[10] (mp 183–185 °C) (Found: C, 43.6; H, 5.4; N, 13.9. $C_{11}H_{16}N_3O_5P$ requires C, 43.9; H, 5.4; N, 13.9%); ν_{max}(Nujol)/cm^{-1} 2610s (NH_3^+), 1736s (CO) and 1702w; δ_H(CD_3SOCD_3) 2.73 (6 H, d, ^{3}J 7.5, 2 NMe), 3.71 (3 H, s, OMe), 7.05 (4 H, q, $^{3}J_{AB}$ 9, C_6H_4) and 6.61 (s, NH_3); δ_P(DMF) −4.9 (heptet, ^{3}J 7.46); δ_C(CD_3SOCD_3) 23.82 (d, ^{2}J 3.5, $2NCH_3$), 55.28 (OCH_3), 114.73 (2 C *ortho*), 122.95 (2 C, *meta*), 126.42 (CNH_3), 157.57 (C–OMe) and 157.98 (d, *J* 12, 2 CO).

The ratio (*b*) of cyclization in DMF at 70 °C for 24 h depends on the amount (*a*) of *p*-anisidine introduced: $a = 0$; $b = 0$; $a = 1$; $b = 20\%$; $a = 4$; $b = 50\%$. Cyclization of the sodium salt in the presence of 1 equiv. of NaOH is over in less than 4 min.

First step of neutral alcoholysis of phospholidines 4: isolation of monoesters 8 ¶

Phenoxy derivative, 8a: methanolysis. See ref. 7 for mp, ^{1}H NMR and IR spectra. In CH_2Cl_2–MeOH (excess) the reaction was over in less than 20 min; δ_P($CDCl_3$) −2.6; δ_C($CDCl_3$) 25.96 ($NHCH_3$), 33.29 (d, ^{2}J 1, $PONCH_3$), 55.23 (d, ^{2}J 5.8, OCH_3), 120.05 (d, ^{3}J 4.8, 2 C *ortho*), 125.54 (C *para*), 129.95 (2 C, *meta*), 150.04 (d, ^{2}J 4.8, C *ipso*), 162.53 (CO amide) and 167.55 (d, ^{2}J 8.5, CO imide).

Phenoxy derivative 8'a: treatment with benzyl alcohol. The reaction was over after 4 days in the presence of 1 equiv. of benzyl alcohol in CH_2Cl_2, leaving the product as an oil in quantitative yield; R_F = 0.1 on Merck Kieselgel 60 F_{254} with cyclohexane–Et_2O (1 : 1); ν_{max}(film)/cm^{-1} 3298 (NH), 1690 (CO imide) and 1670 (CO amide); δ_H($CDCl_3$) 2.78 (3 H, d, ^{3}J 5, NH*Me*), 3 (3 H, d, ^{3}J 8, PONMe), 5.24 (2 H, d, ^{3}J 8.8, CH_2), 7.2 and 7.3 (10 H, 2 s, OPh and/or CH_2*Ph*); δ_P($CDCl_3$) −4.58; δ_C($CDCl_3$) 26.14 ($NHCH_3$), 32.64 (d, ^{2}J 6.1, $PNCH_3$), 70.7 (d, ^{2}J 5.5, CH_2), 120.3 (d, ^{3}J 5, 2 C *ortho* OPh), 125.66 (C *para* OPh), 128.32 and 128.67 (2 s, 2 C *ortho* and/or *meta* Bzl), 128.83 (s, C *para* Bzl), 129.91 (2 C, *meta* OPh), 135.19 (d, ^{3}J 6.9, C *ipso* Bzl), 150.05 (d, ^{2}J 7, C *ipso* OPh), 162.27 (CO amide) and 167.5 (d, ^{2}J 8.7, CO imide).

Methylamino derivative 8d. A CD_3SOCD_3 solution of **4d** (0.06 g, 0.3 mmol) and of MeOH (0.09 g, 2.8 mmol, 9 equiv.) showed after 4 days *ca.* 70% conversion of **4d** (δ_P 9.7) into the product **8d**; δ_P 11.5; δ_H 2.44 (3 H, d, ^{3}J 13.6, PONH*Me*), 2.62 (3 H, d, ^{3}J 4.8, s with irr. at 8.36, CONH*Me*), 2.86 (3 H, d, ^{3}J 7.4, PONMeCO), 3.58 (3 H, d, ^{3}J 11.59, OMe) and 8.36 (1 H, q, ^{3}J 4.7, CON*H*Me); δ_C 23.8 (d, ^{2}J 3.46, $PONHCH_3$), 26.23 ($CONHCH_3$), 30.37 ($PONCH_3CO$), 52.28 (OCH_3), 164.18 (CO amide) and 168.21 (d, ^{2}J 8.9, CO imide).

When the reaction was not stopped at 70–80% conversion or performed in MeOH alone (terminated in less than 3 h) only **9d** δ_P +13.6 (see later) was detected. The reaction mixture was then concentrated to dryness, taken up with AcOEt. The insoluble material was filtered and dried and identified as **10**: mp 210–213 °C (lit.,[30] 215–217 °C).

Dimethylamino derivative 8e. After 1.5 days in methanolic solution at 60 °C, the phospholidine **4e** was recovered (^{31}P, ^{1}H NMR) quantitatively, after evaporation of the solvent.

Amino derivative 8f. 4f (1.15 g, 6.5 mmol) was dissolved in MeOH (*ca.* 30 g). After 1 h (reaction complete, a single signal δ_P +12.2) the solvent was removed and the product was crystallized from 20 g of propan-2-ol leaving the product **4f** (0.45 g), mp 117–118 °C (sharp). Further product (0.3 g, total yield 56%), was obtained by concentrating the mother liquors (Found: C, 28.9; H, 5.9; N, 19.9. $C_5H_{12}N_3O_4P$ requires C, 28.7; H, 5.8; N, 19.9%); ν_{max}(KBr)/cm^{-1} 3358, 3301, 3216 (NH + NH_2) and 1664 (broad, 2 CO); δ_H(CD_3SOCD_3) 2.64 (3 H, d, ^{3}J 4.7, s with irr. at 8.38, CONHMe), 2.92 (3 H, d, ^{3}J 7.56, PONMe), 3.57 (3 H, d, ^{3}J 11.88, OMe), 4.94 (2 H, d, ^{2}J 6.2, NH_2), 8.38 (1 H, q, ^{3}J 4.8, NH); δ_H($CDCl_3$) 2.87 (d, ^{3}J 5.11, CONH*Me*), 3.2 (d, ^{3}J 7.7, PONMe), 3.91 (s, NH_2), 3.7 (d, ^{3}J 11.24, OMe) and 7.24 (br s, CONH); δ_P(CD_3SOCD_3) +11.06; δ_C(CD_3SOCD_3) 25.04 ($NHCH_3$), 30.56 (m, $PONCH_3$), 52 (m, OCH_3), 164.12 (amide CO) and 167.69 (d, ^{2}J 7.2, imide CO); δ_C($CDCl_3$) 26.05 ($NHCH_3$), 32.35 (d, ^{2}J 3.1, $PONCH_3$), 53.26 (d, ^{2}J 5.6, OCH_3), 162.2 (amide CO) and 166.2 (d, ^{2}J 5.1, imide CO). In a methanolic (20 equiv.) CD_3SOCD_3 solution the reaction was over after *ca.* 20 min, $t_{\frac{1}{2}}$ *ca.* 10 min.

Second step of methanolysis of monomethyl esters 8 in neutral conditions

With 8a. 8a (0.23 g) in MeOH was heated at 60 °C until complete disappearance (3 days) of the signal of **8a**. ^{31}P NMR showed signals δ +2.57 (15%), 1.55 (4%), 1.32 (19%), −4.57 [50% after 2 days up to 60%, undecoupled: q, *J* 11.7 presumably PhOPO(OMe)OH], −4.88 (11%). After cooling to room temperature, the resultant insoluble material was identified as *N*,*N'*-dimethyloxamide **10** (0.03 g, 32%), mp 212–213 °C (lit.,[30] 215–217 °C). The filtrate was concentrated to dryness, taken up in $CDCl_3$, filtered (from more **10**) and analysed by ^{1}H NMR ($CDCl_3$) δ *ca.* 8 (acidic protons), *ca.* 3.6 (d, *J* *ca.* 12, POOMe groups) and practically no PONMe (d)

‡ **11a**: *p*-methoxyanilinium phenyl methylcarbamoylcarbonyl(methyl)-aminophosphonate.

§ **12**: 1,3-dimethyl-2,4,5-trioxo-1,3,2-diaza-λ^5-phospholidin-2-olate *p*-methoxyanilinium.

¶ Monoesters **8**: methyl methylcarbamoylcarbonyl(methyl)amino-phosphonate esters.

groups were observed. The solution was then diluted with *ca.* 10 g of $CHCl_3$ and extracted with 3 × 10 g of water. After removal of the chloroform a very small residue (0.01 g) was obtained, major products being more soluble in water. ^1H NMR analysis proved that no phenol was released.

When the methanolic solution of **8a** was left at room temperature, no reaction was detected after 3 days and after 23 days **8a** was still present (*ca.* 80% of the phosphorus content).

With 8d. The reaction mixture obtained previously after completion was concentrated to dryness and taken up with AcOEt. The insoluble material was filtered and identified as **10** by ^1H NMR; $\delta_H(CD_3SOCD_3)$ 2.67 (3 H, d, ^3J 4.93, Me) and 8.61 (1 H, s, NH). The filtrate was concentrated to dryness, dissolved in $CDCl_3$ and analysed by ^{31}P NMR; δ_P +13.6; δ_H 2.46 (3 H, dd, $^3J_{NHMe}$ 5.4, NHMe, $^3J_{PNMe}$ 12.05, NH*Me*) and 3.59 (3 H, d, ^3J 11.07, 2 OMe).

With 8e. Not available, as **8e** was not formed in neutral media.

With 8f. A solution of **8f** (0.07 g) in 0.3 g MeOH was kept at room temperature until complete disappearance (6 days; $t_{\frac{1}{2}}$ 2 days) of the monoester. Two signals were observed by ^{31}P NMR; δ_P +20.8 (8%) and +14.2 (92%). As with **8d**, *N*,*N*′-dimethyloxamide **10** was separated and the residue of the filtrate was analysed by NMR after dissolution in $CDCl_3$, δ_P +15.2 (lit.,[31] +15.2); δ_H 3.70 (d, ^3J 11.5, OMe).

Second step of methanolysis of monoesters 8 in basic media

With 8a. A solution of **8a** (0.15 g, 0.52 mmol) in MeOH (1.15 g) containing NEt_3 (0.01 g, 0.01 mmol) was kept at room temperature until complete disappearance (24 h) of both the starting monoester (in less than 0.5 h) and a transitory product referred to as **8g** (in 2 h) δ_P 2.56 being observed to the extent of 24% after 0.5 h. The reaction mixture was concentrated to dryness and the oily residue with a strong smell of phenol readily dissolved in $CDCl_3$. The ^1H NMR spectrum showed an equimolar mixture of **9d**, phenol and **13**. The solution was then diluted with $CHCl_3$ (*ca.* 15 g) and repeatedly extracted with 10 g of water. ^1H NMR analysis of the residues of both the organic layer (in $CDCl_3$) and the combined aqueous extracts (in D_2O) showed respectively phenol and a 1:1 mixture of **13** and **9d**. After two crystallizations from AcOEt, pure **13** was obtained, mp 80–82 °C (lit.,[32] 85 °C); ν_{max}(Nujol)/cm^{-1} 3351 (NH), 1748 (CO ester) and 1693 (CO); $\delta_H(CDCl_3)$ 2.90 (3 H, d, ^3J 5.16, NMe), 3.86 (3 H, s, OMe) and 7.2 (1 H, s, NH); δ_C 27.13 (NCH_3), 53.13 (OCH_3), 157.26 (CO amide) and 161.02 (CO ester). **9d**: δ_H and δ_P as above (second step methanolysis of **8d** in neutral conditions); $\delta_C(CDCl_3)$ 26.23 ($NHCH_3$) and 32.68 (d, ^2J 5.44, 2 OCH_3).

With 4e. (*i*) A $CDCl_3$ solution of **4e** (0.1 g, 0.49 mmol), MeOH (0.07 g, 2.18 mmol, 4.4 equiv.) and NEt_3 (0.05 g, 0.5 mmol, 1 equiv.) was kept until complete disappearance of both the starting **4e** (2.5 days) and a transitory product **8e**, δ_P 11 [6 days, maximum (38%) after 7 h]. Two signals were finally observed (no change after 3 weeks): δ +20.7 (40%) and +2.9 (60%) which begun to appear after 7 h (14%). The solvent was removed and the oily residue easily dissolved in $CDCl_3$. The ^1H NMR spectrum showed the ethyl signal attributed to the salt **11c**. After diluting with $CHCl_3$ and one extraction of **11c** (very soluble) with water, the ^{31}P NMR spectrum showed the single signal of **9e** δ +20.3.

(*ii*) **4e** (0.38 g, 1.85 mmol) was easily dissolved in 1.5 mol dm^{-3} MeONa (1.70 g) in methanol. At the completion of the reaction (a single signal δ +21.4 in less than 1 h) the solvent was removed. The IR spectrum of the residue showed the intense carbonyl absorption of **13** at 1734 cm^{-1}. After addition of water (10 g), then neutralization with citric acid, extraction with 3 × 10 g of CH_2Cl_2, drying (Na_2SO_4), filtering and concentration to dryness, the product **9e** (0.18 g, 82%) was obtained, mp 38–40 °C (Et_2O) (Found: C, 31.0; H, 8.8; N, 18.1. $C_4H_{13}N_2O_2P$ requires C, 31.6; H, 8.6; N, 18.4%); ν_{max}(film)/cm^{-1} 3240, 3420 (NH), 2940 (CH) and 1216vs (PO); $\delta_H(CD_3SOCD_3)$ 2.36 (3 H, dd, $^3J_{NHMe}$ 5.62, $^3J_{PNHMe}$ 12.18, NHMe), 2.56 (6 H, d, ^3J 9.90, NMe_3), 3.46 (3 H, d, ^3J 10.86, OCH_3) and 4.3 (1 H, s, NH); $\delta_P(CDCl_3)$ +20.3; $\delta_C(CDCl_3)$ 26.92 ($NHCH_3$), 36.67 [d, ^2J 3.77, $N(CH_3)_2$] and 51.86 (d, ^2J 5.04, OCH_3).

With 8f. 8f (0.14 g, 0.67 mmol) was dissolved in a solution of NEt_3 (0.97 g, 14.4 equiv.) in MeOH (0.97 g). The reaction was over in *ca.* 20 min. As above (in neutral conditions) after concentration to dryness, work up with AcOEt, both **10** and **9f** were isolated and characterized by ^1H and ^{31}P NMR spectroscopy.

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