Intramolecular Catalysis of Aminolysis of Phosphorus Heterocycles Incorporating an α-Aminoamide Moiety. III. Synthesis of 2-Oxo or 2-Thioxo 1,3-disulfonyl-1,3,2-diazaphospholidines and Reactions with Amines and Alcohols.

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A series of 2-oxo or 2-thioxo 1,3-disulfonyl-1,3,2-diazaphospholidines **4** was prepared by condensation of phosphonyl dichlorides **2** with bis-*N*,*N*'-sulfonylethylenediamines **1** in pyridine. Complete aminolysis or alcoholysis of heterocycles **4** took place with regeneration of sulfonyldiamines **1**. These reactions are very sensitive to steric hindrance, and hydrolysis is generally favoured over aminolysis. The results are discussed in terms of mechanisms of phosphorylation.

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Aminolysis of the 2,4-dioxo or 4-oxo-2 thioxo-1,3,2-diazaphospholidines **A**, (incorporating an α-aminoamide moiety), is a key step in a scheme of repetitive and controlled peptide synthesis using unprotected α-amino-acids [1]. In aqueous solution, however, *hydrolysis* takes place, irrespective of substituents R and Y [1,2]. The study of the catalysis of aminolysis of **A**, intramolecularly by introducing a catalytic group into the R group was therefore suggested [1]. Recently this has been undertaken [3] postulating a scheme of intramolecular nucleophilic catalysis, by conversion of the heterocycle **A** into a new, selectively aminolysed one, **B**.

No phosphorus heterocycle **B** meeting this property has been described until now. We therefore undertook a preliminary study in order to find at least one such heterocycle **B**. To do so, we began with heterocycles $\mathbf{B_1}$ (Figure 1) built up with a β-aminoamide moiety [3,4], expecting that the selectivity of aminolysis versus hydrolysis would result from a change in the mechanism of phosphorylation, which is operative with **A**. In fact compounds $\mathbf{B_1}$ are even less susceptible to aminolysis by attack (cleavage a) on phosphorus than heterocycles **A**, and in one case (R^2 = Me) attack (cleavage b) of amines on the carbonyl was observed.

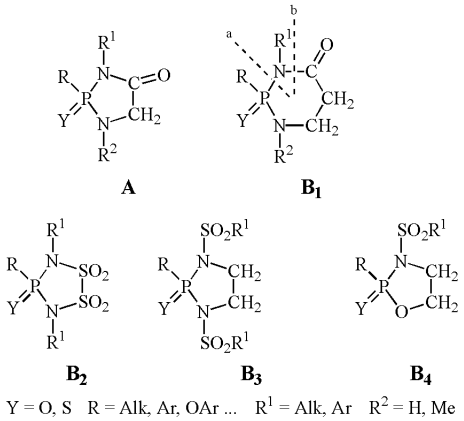

Figure 1. Heterocycles considered.

To prevent such a cleavage b, our choice was directed from the carboxamide to the sulfonamide group, which is not easily disrupted [5]. Furthermore, since a pseudorotation ψ associated with deprotonation of the primary zwitterionic intermediate **X**, formed by attack on the phosphorus of a nucleophile, is possible when a symmetrical moiety is incorporated in the heterocycle (made clear in the discussion, Figure 6) we considered disulfonamide heterocycles. Due to unavailability the endocyclic $\mathbf{B_2}$ [6] were rejected, and we selected exocyclic ones, *i.e.* $\mathbf{B}_3$ (Figure 1) instead. To the best of our knowledge these heterocycles have only been described with trivalent phosphorus [7]. In this paper, we report on their direct access and study their reactions with nucleophiles, particularly amines (the goal of this study) and alcohols.

Results.

Synthesis of $\mathbf{B}_3$ Heterocycles (consecutively numbered **4**).

The condensation of bis-*N*,*N*'-sulfonylethylenediamines **1a**, (R^1 = Ph) [8], **1b** (R^1 = Me) [9] with phosphonyl dichlorides **2a-e** is very sluggish, making vigorous experimental conditions necessary. In pyridine, dichlorides **2** are

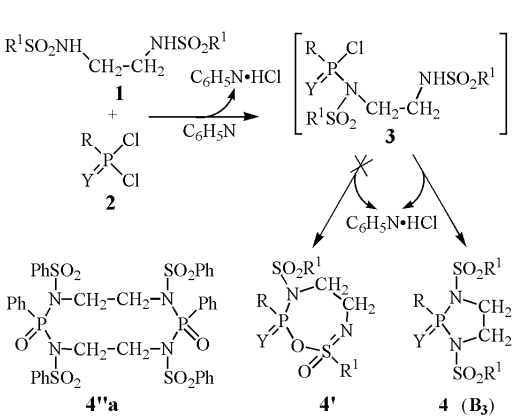

Figure 2. Synthesis of heterocycles **4**.

stable [10] and activated by nucleophilic catalysis. In fact at ~ 100 °C the reaction (Figure 2) is completed in a few days or hours depending on the reactivity of the dichlorides **2**: Me > Ph > NMe_2 > PhO. Intermediate **3** is not detected by ^{31}P NMR [11]. The condensation is also effective with phosphorus oxychloride. In this latter case, no subsequent reaction with **1a** of heterocycle **4d** is observed, probably because of complete precipitation in the reaction mixture.

The separation of heterocycles **4**, (Table 1), from the pyridinium hydrochloride formed, is realized by aqueous extraction with the exception of P-Methyl derivatives **4f** and **4g** which are very sensitive to hydrolysis. In these two cases, addition of excess anhydrous potassium carbonate allows conversion of the partly soluble, in pyridine, pyridinium hydrochloride into the completely insoluble potassium chloride. With **4g** it also appeared necessary to add activated molecular sieves to prevent hydrolysis. Simple filtration then allows the easy separation of heterocycles **4f** or **4g** after concentration to near dryness of their pyridine solutions.

The IR spectra of the products do not show an NH absorption, establishing the cyclisation. The ^1H NMR spectra display complex multiplicity for the methylene protons, characteristic of an A_2B_2X or AA'BB'X patterns, thus firmly excluding the seven ring form **4'** [12] (one methylene is not coupled with phosphorus), a fact confirmed by analysis the of ^{13}C NMR spectra (only one type of methylene). Elemental analyses are correct. All these data are in accordance with structures **4** and **4''** (dimer). The fact is that the mass spectrum (chemical ionisation using ammonia) of the triphenyl derivative **4a** shows a feeble peak twice as high as expected, first attributed to **4''a**. However cryoscopic measurement in DMSO shows the mass of monomer **4a**. Therefore the higher observed value in the mass spectrum is attributed to a sandwich aggregate of two heterocycles **4a** with one proton [13].

Table 1

Heterocycles **4** prepared

No	R	Y	R^1	Mp°C (recrystallisation solvent)	Yield %	$\delta^{31}P$	(Solvent)
a	Ph	O	Ph	184-185 (MeOH)	89	+ 15	$CDCl_3$
b	PhO	O	Ph	174-175 (MeCN)	30	-4.2	CD_3SOCD_3
c	Me_2N	O	Ph	170 (iPrOH)	43	+ 7.3	$CDCl_3$
d	Cl	O	Ph	250-252 (MeCN)	58	-2.8	CD_3SOCD_3
e	Ph	S	Ph	161-162 (AcOEt)	48	+66.4	$CDCl_3$
f	Me	O	Ph	200-202 (AcOEt-Et_2O)	47	+28.3	$CDCl_3$
g	Me	O	Me	188-191 (MeCN)	39	+28.8	CD_3SOCD_3
h	Ph	O	Me	248-250 (MeCN)	60	+15.9	CD_3SOCD_3

Reactivity of the Heterocycles **4**.

In the presence of excess amines, successive substitution of the two sulfonamide leaving groups leads to the phosphonicdiamides **6** and regeneration of the bissulfonylethylenediamine (Figure 3). This reaction is very clean compared to the direct synthesis of **6** from **2**.

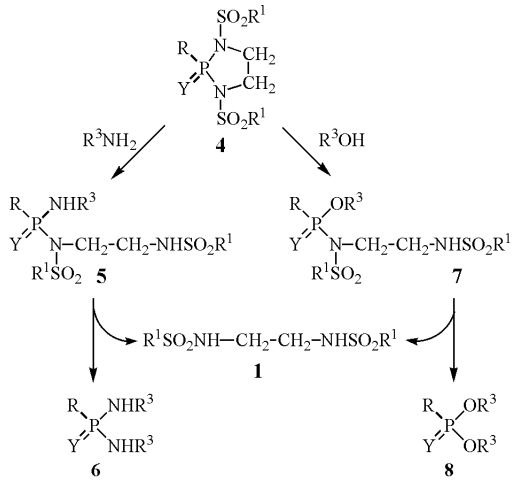

Figure 3. Reactivity of heterocycles **4** with amines and alcohols.

Intermediate **5** can not be detected by ^{31}P NMR. In contrast, with alcohols such an intermediate **7** is indeed observed before the formation of diesters **8**. Irrespective of the nucleophiles, a decrease in reaction rate is observed with R (Me > PhO > Ph > NMe_2), R^1 (Me > Ph) and R^3 substituents (Me > $PhCH_2$) showing that the major effect is steric hindrance. Accordingly, with the smallest nucleophile, water, hydrolysis is selective when reacting with the more congested heterocycle **4a** (Figure 4).

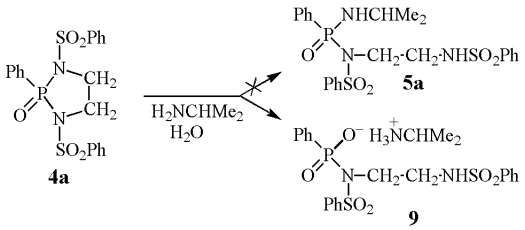

Figure 4. One case of competition between hydrolysis and aminolysis.

The reaction of chloride **4d** with dimethylamine is of interest because two possibilities exist for conversion into the dimethylamino derivative **4c** (Figure 5): this can occur indirectly (path a), *via* the dimethylaminochloro compound **3c** which eventually would cyclise, or directly (path b) without opening of the cyclic structure. Careful examination by ^{31}P NMR shows no intermediate peak corresponding to **3c**. As the same observation (see above) is made in the coupling reaction between dimethylaminodichloride **2c** and bissulfonamide **1a**, it cannot be excluded that **3c** is effectively formed but not detected when starting from **4d**.

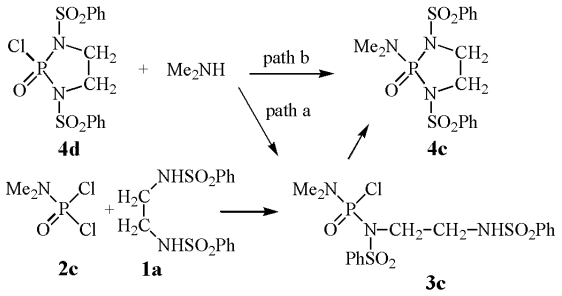

Figure 5. Syntheses of the dimethylamino derivative **4c**.

Discussion.

Usually aminolysis of activated phosphoryl derivatives is difficult [14], compared to that of carbonyl analogs. This study presents a notable exception. In a search for an explanation, the two stages of the overall diaminolysis have to be considered.

The first is easily understandable on the basis of the addition-elimination mechanism known to be operative in the case of other five-membered phosphorus heterocycles [14]. After addition of amines to the heterocycle **4**, the zwitterionic primary intermediate **X** formed, may lead to elimination of the first sulfonamide group in two ways (Figure 6): i) by direct collapse (path a) due to its good leaving ability (pKa ~ 10 [15] against ~ 11 for the ammonium); ii) indirectly (path b) by pseudorotation (ψ) associated with the deprotonation, with formation of a new, anionic, intermediate **Y**. This is stabilized by the equatorial position of the amino group, and of the apical position of the R substituent when the latter is electron-attracting, as is chlorine. This process results in the interconversion of the axial/equatorial position of each sulfonamide (distinguished by a star). The interconversion does not change the energy of the cyclic structure due to the symmetry of the bissulfonylethylenediamino group.

In the particular case of chloroheterocycle **4d** (R = Cl), path b should be favoured because chlorine is a much better leaving group than sulfonamide. It could have been discarded by the formation of **3c**. As this latter compound cannot be detected (see above) it is actually in fact not possible to distinguish whether i) or ii) is operative [16]. In contrast, with the phosphonyl heterocycles (R = Alk, Ar), the formation of anion **Y** should be more difficult because of lower stability when the R substituent is axial, thus favouring path a (Figure 6). In other words pseudorotation associated with path b would not then be a requisite condition for aminolysis [17].

The second stage is at first glance surprising because the electrophilicity of phosphorus in **5** is reduced by the introduction of the amino group. However, as no accumulation of **5** is observed, the intervention of the different, elimination-addition (EA), mechanism with formation of a metaphosphonimidate intermediate **Z**, (Figure 6) favoured by the good sulfonamide leaving group could be invoked.

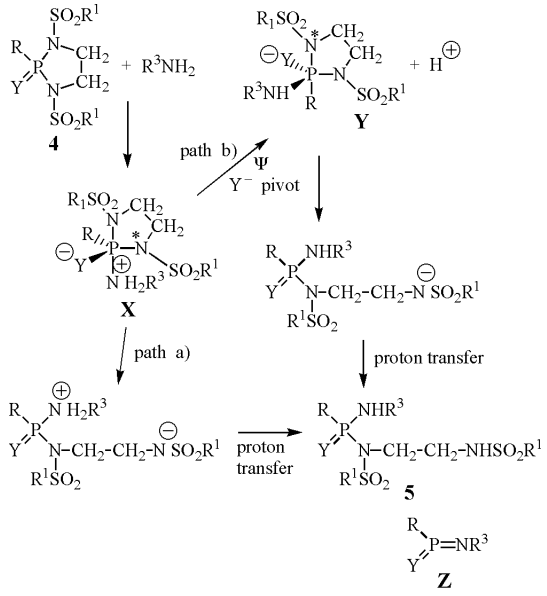

Figure 6 : Possible pathways of the first aminolysis of heterocycles **4**.

Accordingly, on the contrary, with **7**, for the second alcoholysis, such a mechanism cannot intervene (SN_2P only being operative, as in β position of phosphorus the hydrogen necessary for the EA mechanism is not available) and accumulation is actually observed.

Conclusion.

As expected, sulfonylation is not observed but phosphorylation is observed in the reactions of nucleophiles with the heterocycles $\mathbf{B}_3$. Aminolysis takes place easily, a result without precedent for phosphorus heterocycles [14]. However in aqueous conditions hydrolysis prevails. As in all the reactions so far studied steric hindrance plays a major role. It could be expected that, with less congested heterocycles, aminolysis could be selective even in the presence of water. Thus, in the next publication in this series, heterocycles $\mathbf{B}_4$ (Figure 1) incorporating a β-*N*-sulfonylaminoalcohol moiety, which replaces one bulky sulfonamide group of $\mathbf{B}_3$ with an oxygen, [18] will be studied.

From the practical point of view of a clean synthesis of diamides **6** this study shows that heterocycles **4** are more appropriate than dichlorides **2**. Byproducts **1a** or **1b** are easily eliminated by simple filtration in the appropriate solvent (diethylether or water) used for the solubilization of diamides **6**.

EXPERIMENTAL

Melting points were determined in capillaries using Dr Tottoli's apparatus and are uncorrected. The infrared spectra (IR) were recorded on a Perkin-Elmer Model 1600, with calcium fluoride (CaF_2) or sodium chloride (NaCl) windows (nujol mulls for solids,

films for liquids). A Bruker AC 80 Nuclear Magnetic Resonance spectrophotometer was used to obtain the ^{31}P, ^{1}H and ^{13}C (J modulated) NMR spectra, with lock on internal or external (capillaries of d_6-benzene or deuterium oxide) deuterium and a Perkin Elmer Hitachi R24 Model for the 60 MHz ^{1}H NMR spectra. All reactions were monitored using ^{31}P NMR. Analytical thin layer chromatography was performed on silica gel plates 60 F254 (Merk) with a 2:1 v/v chloroform/acetonitrile mixture and U.V. detection. Mass spectra (chemical ionisation with ammonia) were obtained with a Nermag R10-10C apparatus. Elemental analyses were carried out on a Carlo Erba Model G 1106 by the "Service interuniversitaire de microanalyse" in Toulouse, France.

I. Synthesis of Starting Bissulfonamides **1a** and **1b**.

N,*N*'-Bisphenylsulfonylethylenediamine (**1a**).

To ethylene diamine (20.05 ml, 0.3 mole), benzene sulfochloride (12.76 ml, 0.1 mole) was added dropwise for 20 minutes under magnetic stirring and ice cooling (exothermic reaction). The reaction mixture was stirred at room temperature for an additional hour. Water (100 ml) was then added, and the product precipitated immediately. After filtration, rinsing with water (3 x 50 ml) and drying 11.41 g (67% yield) mp 160-163° were obtained. After recrystallization from dimethyl formamide/methanol (DMF/MeOH) the product melted at 167-168° (lit [8] 165-168°). Chromatography: rf = 0.8; IR: ν NH 3320, 3270 cm^{-1}; ^{1}H (DMSO-d6): δ 7.65 (m, 12H, 2 C_6H_5 + 2 NH), 2.79 (s, 4H, 2 CH_2); ^{13}C (DMSO-d6): δ 140.1 (2 Cquat.), 132.4 (2 Cpara), 129.2 (4 C meta or ortho), 126.3 (4 C ortho or meta), 42.1 (2 *C*H_2). The product is slighty soluble in chloroform and completely insoluble in water and diethylether.

N,*N*' -Bis Methylsulfonylethylenediamine (**1b**).

In a first step ethylenediamine was bissilylated in acetonitrile (in toluene the reaction is very slow), at 50°, in the presence of a catalytic amount of ammoniun sulfate and of 1.4 equivalents of hexamethyldisilane until the release of ammonia nearly ceased (2-3 days). After concentration to dryness and kugelrohr separation (105°/12mm) a 65% yield was obtained. IR: ν NH 3372; ^{1}H ($CDCl_3$): δ 2.57 (s, 4H, 2 CH_2), -0.06 (s, 18H, 2 $Si(CH_3)_3$); ^{13}C ($CDCl_3$) : δ 45.56 (2 *C*H_2), 0 (18 *C*H_3).

In the second step the silylated derivative just prepared (moisture sensitive) was heated overnight at 60° with 3.3 equivalents of methane sulfonylfluoride in anhydrous toluene. Product **1b**, which had quantitatively precipitated, was separated from the supernatant and recrystallized from 95% ethanol with a 70% yield; mp 105-109° (lit [9] 109-110°); ^{1}H (DMSO-d_6): δ 7.07 (s, 2H, 2 NH) , 3.05 (s, 4H, 2 CH_2), 2.91 (s, 6H, 2 CH_3). The product is highly soluble in water and completely insoluble in diethylether.

II. Synthesis of the Heterocycles **4** (Table 1).

1,3-Diphenylsulfonyl-2-oxo-2-phenyl-1,3,2-diazaphospholidine (**4a**).

Illustrative Procedure.

A solution in dry pyridine (10 ml) of the bissulfonamide **1a** (1.03 g, 3 mmoles) and phenyl phosphonic dichloride **2a** (0.47 ml, 3.3 moles) was heated at 100° with exclusion of moisture. The ^{31}P NMR spectra showed the single signals of **2a** and **4a** before completion of the reaction (2 days). The solution was concentrated to dryness and the residue dissolved in a mixture of water and chloroform (10 ml each). The organic layer was dried with sodium sulfate (Na_2SO_4), concentrated and the product crystallized. Chromatography : rf = 0.55; IR: NH bands not observed, ν SO_2 1356, 1172, PO 1259 cm^{-1} ; ^{1}H ($CDCl_3$): δ 7.65 - 7.4 (m, 15H, 3 C_6H_5) ; 3.5 (m, 4H, 2 CH_2) ; ^{13}C ($CDCl_3$): δ 137.09 (2 C *para* $PhSO_2$), 133.53 (d, J = 2.92 Hz, C *para* PhPO), 132.53 (d, J = 12.07 Hz, 2 C *meta* PhPO), 129.34 (4 C *meta* $PhSO_2$), 129.11 (d, J = 170.53 Hz, C *ipso* PhPO), 128.91 (d, J = 16.48 Hz, 2 C *ortho* PhPO), 128.03 (4 C *ortho* $PhSO_2$), 44.08 (d, J = 5.35 Hz, 2 CH_2); mass spectrum, relative intensity: 925, 3 % (2M + H), 480, 100 % (M + NH_4), 463, 78 % (M + H); cryoscopy in DMSO: calcd.: 462, found: 424.

Anal. Calcd. for $C_{20}H_{19}N_2O_5PS_2$ (462.47): C, 51.94; H, 4.14; N, 6.06; P, 6.7; S, 13.86. Found: C, 51.84; H, 4.08; N, 6.03; P, 6.53; S, 13.56.

1,3-Diphenylsulfonyl-2-oxo-2-phenyl -1,3,2-diazaphospholidine (**4b**).

The reaction was completed after three days (15% of reaction after one day, by ^{31}P NMR). Chromatography: rf = 0.62; IR: ν SO_2 1360 cm^{-1}; ^{1}H 60 MHz (DMSO-d_6): δ 7.9 - 7.5 (m, 15H, 3 C_6H_5), 3.45 (m, 4H, 2 CH_2).

Anal. Calcd. for $C_{20}H_{19}N_2O_6PS_2$ (478.47): C, 50.21 ; H, 4.00 ; N, 5.85. Found: C, 50.11; H, 3.88; N, 5.78.

1,3-Diphenylsulfonyl-2-oxo-2-dimethylamino-1,3,2-diazaphospholidine (**4c**).

The reaction was completed after 3 days (60 % of reaction after one day). Chromatography: rf = 0.57; IR: NH bands not obsrved, ν SO_2 1358, 1171 cm^{-1}; ^{1}H ($CDCl_3$): δ 8 - 7.6 (2 m, 10H, 2 C_6H_5), 3.6 - 3.2 (2 m, 4H, 2 CH_2), 2.81 (d, J = 11.97 Hz, 6H, 2 CH_3); ^{13}C ($CDCl_3$): δ 137.49 (2 C *para*), 129.32 (4 C *meta* or *ortho*), 128.02 (4 C ortho or *meta*), 42.39 (d, J = 8.85, 2 *C*H_2), 36.3 (d, J = 5.23 Hz, 2*C* H_3).

Anal. Calcd. for $C_{16}H_{20}N_3O_5PS_2$ (429.44): C, 44.75 ; H, 4.69 ; N, 9.78. Found: C, 44.95; H, 4.68; N, 9.63.

The product was also obtained (89 % yield) by reacting the chloro derivative **4d** with 1.1 equivalents of dimethylammonium chloride in pyridine at 65°. The ^{1}H NMR spectra of the reaction mixture showed no intermediate signals of aminolysis and the progresive conversion of the chloride **4d** into the product, terminated after two weeks.

1,3-Diphenylsulfonyl-2-oxo-2-chloro-1,3,2-diazaphospholidine (**4d**).

The reaction was completed in less than 2 days. After concentration to a few ml the suspension was diluted with ethanol, the product filtered off, rinsed with ethanol, dried and recrystallized. Chromatography: rf = 0.65; IR: NH bands not observed, ν SO_2 1375, 1185, PO 1290 cm^{-1}; ^{1}H (DMSO-d_6): δ 7.9 - 7.6 (2 mf, 4H + 6H, 2 C_6H_5), 3.29 (d, J = 8.15 Hz, 2 CH_2); ^{13}C (DMSO-d_6): δ 137.56 (2 C quat.), 133.68 (2 C *para*), 129.21 (4 C *meta* or *ortho*), 127.38 (4 C *ortho* or *meta*), 129.21(4 C *meta* or *ortho*), 42.18 (d, J = 9.26, 2 *C*H_2).

Anal. Calcd. for $C_{14}H_{14}ClN_2O_5PS_2$ (420.88): C, 39.95; H, 3.35; Cl, 8.42; N, 6.66. Found: C, 40.24; H, 3.18; Cl, 8.52; N, 6.51.

1,3-Diphenylsulfonyl-2-thioxo-2-phenyl-1,3,2-diazaphospholidine (**4e**).

The reaction was completed after three days. Chromatography: rf = 0.7; IR: NH bands not observed, ν SO_2 1360, 1170 cm^{-1}.

1,3-Diphenylsulfonyl-2-oxo-2-methyl-1,3,2-diazaphospholidine (**4f**).

The reaction was completed after two days (66 % of reaction after one day). After completion, only one extraction was performed, at ~ 10°, with brine. IR: NH bands not observed, ν SO_2 1359, 1175, PO 1249 cm^{-1}; ^1H ($CDCl_3$): δ 8 - 7.5 (2 m, 4H + 6H, 2 C_6H_5), 3.6 - 3.17 (2 m, 4H, 2 CH_2), 2.41 (d, J = 17.53 Hz, 3H, CH_3); ^{13}C ($CDCl_3$): δ 137.37 (2 C quat.), 134.09 (2 C *para*), 129.4 (4 C *meta* or *ortho*), 128.20 (4 C *ortho* or *meta*), 43.63 (d, J = 5.23 Hz, 2 *C*H_2), 19.56 (d, J = 119.58 Hz, *C*H_3); mass spectrum, relative intensity: 418, 100 % (M + NH_4), 401, 5 % (M + H).

Anal. Calcd. for $C_{15}H_{17}N_2O_5PS_2$ (400.40): C, 44.99; H, 4.28; N, 6.99. Found: C, 44.04; H, 4.07; N, 6.93.

1,3-Dimethylsulfonyl-2-oxo-2-methyl-1,3,2-diazaphospholidine (**4g**).

The reaction was completed after ~ 10 hours. For the separation activated 4 Å molecular sieves and anhydrous potassium carbonate (respectively 7.5 and 5.3 g for 7.5 mmoles of dissulfonamide **1b**) were added and left under vigorous stirring for 3 hours. The insolubles were filtered off, the filtrate concentrated to dryness, and the product crystallized at ~ 15°. Without addition of molecular sieves complete hydrolysis took place. IR: NH bands not observed, ν SO_2 1356, 1157, PO 1238 cm^{-1}; ^1H (DMSO-d_6): δ 3.76 (m, 4H, 2 CH_2), 3.27 (s, 6H, 2 CH_3SO_2), 2.03 (d, J = 17.46 Hz, 3H, CH_3PO); ^{13}C (DMSO-d_6): δ 43.06 (d, J = 5.08Hz, 2 *C*H_2), 40.3 (2 CH_3SO_2), 17.64 (d, J = 118.34 Hz, *C*H_3PO); mass spectrum, relative intensity: 294, 100 % (M + NH_4); cryoscopy in DMSO: calcd.: 276, found: 214.

Anal. Calcd. for $C_5H_{13}N_2O_5PS_2$ (276.26): C, 21.74 ; H, 4.74 ; N, 10.14. Found: C, 21.65; H, 4.69; N, 10.14.

1,3-Dimethylsulfonyl-2-oxo-2-phenyl-1,3,2-diazaphospholidine (**4h**).

The reaction was completed in less than a week, at 80° (78 % of reaction after three days). IR: NH bands not observed, ν SO_2 1357, 1156, PO 1238 cm^{-1}; ^1H (DMSO-d_6): δ 7.9 - 7.6 (m, 5H, C_6H_5), 4 -3.9 (m, 4H, 2 CH_2), 3.17 (s, 6H, 2 CH_3); ^{13}C (DMSO-d_6): δ 133.1 (C *para*), 132.06 (d, J = 12.18 Hz, 2 C *meta*), 129.51 (d, J = 169.54 Hz, C *ipso*), 128.47 (d, J = 16.1 Hz, 2 C *ortho*), 44.3 (d, J = 5.28 Hz, 2 CH_2), 40.22 (2 *C*H_3); mass spectrum, relative intensity: 356, 100 % (M + NH_4), 339 1 % (M + H).

Anal. Calcd. for $C_{10}H_{15}N_2O_5PS_2$ (338.33) : C, 35.5 ; H, 4.47 ; N, 8.28. Found : C, 35.83 ; H, 4.36 ; N, 8.34.

III. Aminolysis of Heterocycles **4**.

Phenylphosphonic Dibenzylamide (**6a**).

Illustrative Procedure.

A solution of the heterocycle **4a** (104 mg, 0.22 mmole) and benzylamine (0.22 g, 2.05 mmoles, 9.3 equivalents) in anhydrous acetonitrile (1.2 g) was heated at 70°, with exclusion of moisture, until complete disappearance (one week) in the ^{31}P NMR spectrum of the signal of **4a**. Two products δ + 20 (80 %, **6a**) and + 10 (20 %, salt related to **9**) were then observed. After concentration to dryness, the residue was triturated in a 10 % solution of citric acid (a few ml) and the insoluble material, free of the salt**,** was filtered, dried and dissolved in boiling methanol (a few ml). After standing overnight at room temperature the crystaline dissulfonamide **1a** (mp 168-170°) was isolated by filtration (80 mg, quantitative yield). The filtrate was concentrated to dryness and **6a** was crystallized from ethylacetate (0.5g): 30 mg (40% yield) mp 95-97° (lit [6] mp 100-101°). ^{31}P NMR ($CDCl_3$): + 21.27; ^1H ($CDCl_3$): δ 7.8 - 7.5 (m, 5H, C_6H_5PO), 7.24 (s, 10H, 2 $CH_2C_6H_5$), 4.2 (dd, J ~ 9 and 6 Hz, 4H, 2 CH_2).

Phenyl Phosphonic Acid bis-*N*-Phenylsulfonylethylenediamide, Isopropylammonium Salt (**9**).

To a solution of heterocycle **4a** (157 mg, 0.34 mmole) in acetonitrile (0.3 g) were added first isopropylamine (0.3 g, 5.07 mmoles, 15 equivalents), then isopropanol (0.3 g, 15 equivalents) and finally after two weeks, under stirring (emulsion), 0.4 g of water. The ^{31}P NMR spectra showed 10 % and 100 % of conversion into the salt **9** respectively before and 4 days after addition of water. After concentration to dryness the residue was recrystallized from acetonitrile yielding 160 mg (87 %) of the product, mp 180-182°. IR: ν NH 3370, NH_2^+ 2620, 2580, SO_2 1325, 1160, PO 1190 cm^{-1}; ^1H (DMSO-d_6): δ 7.7 - 7.45 (m, 18H, 3 C_6H_5 + NH_2^+ + NH), 3.3 - 2.85 (2 mf, 5H, 2 CH_2 + CH), 1.15 (d, J ~ 8 Hz, 6H, 2 CH_3); ^{13}C (DMSO-d_6): δ positive values: 3 C quat: δ 142.98, 141.20, 139.83 (d, J = 172.77 Hz, C *ipso*); 2 CH_2: 46.27, 43.86; negative values: ten CH signals (expected: eleven), CH: 43.66, CH_3: 21.15.

Anal. Calcd for $C_{23}H_{30}N_3O_6PS_2$ (539.6): C, 51.20; H, 560; N, 7.70. Found: C, 50.80; H, 5.59; N, 7.73.

Methylphosphonic Methylamide (**6g**).

Similarly with heterocycle **4g** in the presence of a large excess of methylamine in a mixture of chloroform, dimethylformamide, pyridine (2.7:1:0.3) a complete reaction took place in less than a day. The solution was concentrated to dryness and the residue triturated in deuterochloroform leaving an insoluble material. ^1H NMR analysis of the residue dissolved in DMSO-d_6 and of the filtrate showed, respectively, diamide **1b** and a mixture of **1b** and **6g** (major product). ^1H-NMR (DMSO-d_6): δ 2.32 (dd J = 12.01 and 4.5 Hz, 6H, 2 NCH_3), 1.23 (d, J = 15.19 Hz, 3H, CH_3). After addition of D_2O the product is nearly exclusively extracted. ^{31}P (D_2O): δ + 39.5; ^{13}C (D_2O): 27.89 (2 *NC*H_3), 13.72 (d, J = 112.31 Hz, *C*CH_3).

The same diamide **6g** was also obtained from heterocycle **4f** in less than a week in the presence of a large excess (25 equivalents) in chloroform. After concentration to dryness a quantitative yield of a mixture of dissulfonamide **1a** and phosphodiamide **6g** was obtained. After trituration in deuterochloroform the ethylene diamide **1a** was isolated by filtration with a 55 % yield. ^1H NMR analysis of the filtrate showed the characteristic signals of **6g** with those of **1a** (~ 0.5 equivalents).

A first control experiment using methane phosphonic dichloride reacted with two equivalent of dry methylammonium chloride and four equivalents of triethylamine in dichloromethane showed traces of the product [*cf*. ref. 10]. A second experiment with slow addition of the dichloride to a cold (0°) solution in pyridine of excess methylamine showed a rather selective reaction, the expected product **6g** accounting for 60 % of the total phosphorus content. The pure product was separated by tetrahydrofuran (THF) extraction of the residue obtained after concentration to dryness of the reaction mixture with two equivalents of sodium hydroxide.

IV. Alcoholysis of Heterocycles **4**.

Dimethylphenylphosphonate (**8a**).

Illustrative Procedure.

A solution of the heterocycle **4a** (1.38 g, 3 mmoles) in methanol (20 ml) containing DBU (a few drops) was kept at room temperature for 3 weeks. The ^{31}P NMR spectrum showed

two signals δ + 21.6 (80 % **8a**) and + 14 (20 %, salt). The solution was concentrated to dryness, the residue diluted with chloroform (~ 40 ml) filtered from some dissulfonamide **1a** (identified by its mp). After extraction with a solution a 10 % citric acid solution (3 x 20 ml), drying (Na_2SO_4), and concentration to dryness 0.4 g (72 % yield) of **8a** was obtained as an oil, pure by NMR. ^{31}P NMR ($CDCl_3$): δ + 21.1 (lit [19] : + 20.5); ^1H NMR ($CDCl_3$): 7.9 - 7.3 (m, 5H, C_6H_5), 3.65 (d, J = 11.11 Hz, 6H, 2 CH_3). The salts were eliminated by extractions, and the rest of the dissulfonamide by filtration with Na_2SO_4.

In the presence of pyridine and an excess of methylate/ methanol the salt δ + 14 is the major product: 20 % after 2 days, 80 % after 3 weeks.

In the absence of base, the heterocycle **4a** is quantitatively recovered (^{31}P) after two weeks.

Dimethylmethylphosphonate (**8f**).

Similarly starting with the heterocycle **4f** in the presence of a large excess of methanol and pyridine the diester **8f** was quantitatively formed in less than 12 hours. The ^{31}P NMR spectra after 10 minutes, 1 hour and 45 minutes, and 12 hours showed respectively 34, 76 and 100 % of the product δ 34.1, 36, 0, and 0 % of **4f** and 29, 24 and 0 % of the intermediate **7f** δ + 33.5. After separation the product **8f** was obtained as an oil: ^1H ($CDCl_3$): δ 3.68 (d, J = 11.18 Hz, 6H, 2 OCH_3), 1.43 (d, J = 17.49 Hz, CCH_3); ^{31}P ($CDCl_3$): δ + 33.28 (lit [17]: neat, δ + 32).

The same product was also isolated from the heterocycle **4g** after reaction in a mixture of dimethyl formamide/pyridine/ methanol (excess). The ^{31}P NMR spectra after 30 minutes and one day showed respectively 31 and 100 % of the product δ 34.8, S1 and 0 % of the heterocycle δ 34.4 and 18 and 0% of the intermediate δ 31.4.

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[10] See *inter alia*: M. Mulliez, *Phosphorus Sulfur*, **9**, 209 (1980) and references cited (in note 15). In the presence of tertiary amines like triethylamine or *N*-methylmorpholine, decomposition of **2** occurs rapidly.

[11] Note that such an easy cyclisation is required in the postulated scheme of nucleophilic catalysis [3].

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[13] The same phenomenon has been observed with $\mathbf{B}_1$ heterocycles (ref. 4). Note that **4a** has a sharp melting point, establishing the presence of one single form of the compound.

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