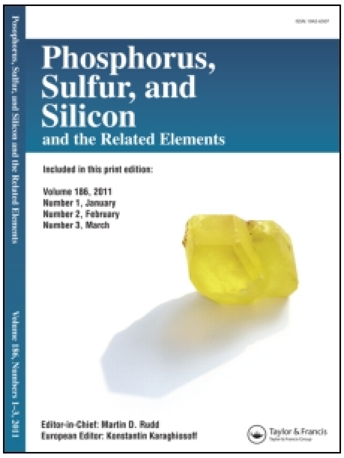

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PHOSPHORUS-NITROGEN COMPOUNDS. PART 48[1]. THE REACTIONS OF *N,N*-DIMETHYLTOLUIDINES WITH PHOSPHORUS(V) CHLORIDES. FORMATION OF A NOVEL HETEROCYCLIC SYSTEM

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PHOSPHORUS-NITROGEN COMPOUNDS. PART 48.[1] THE REACTIONS OF *N,N*-DIMETHYLTOLUIDINES WITH PHOSPHORUS(V) CHLORIDES. FORMATION OF A NOVEL HETEROCYCLIC SYSTEM

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The reactions of phosphorus oxychloride, $P(O)Cl_3$, with the three *N,N*-dimethyltoluidines have been studied. *O*-toluidine gave after suitable work-up only a "nitrogen-substituted" derivative, $P(O)(NMeC_6H_4Me\text{-}2)(OEt)_2$, whilst the *m*-analogue gave both "nitrogen-substituted", $P(O)(NMeC_6H_4Me\text{-}3)(OEt)_2$, and "carbon-substituted" products, $P(O)(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_2(OEt)$, as well as two purely organic compounds, $CH_2(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_2$ and $CH(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_3$. With *N,N*-dimethyl-*p*-toluidine in addition to two acyclic 'nitrogen-substituted' products, $P(O)(NMeC_6H_4Me\text{-}4)(OEt)_2$ and $P(O)(NMeC_6H_4Me\text{-}4)_2(OEt)$, the chloro- and ethoxy-derivative of a novel eight-membered heterocyclic system, $P(O)X[(NMeC_6H_3Me\text{-}4)_2CH_2\text{-}2,2']$ (X = Cl or OEt), as well as two organic products, $CH_2(C_6H_3Me\text{-}5\text{-}NHMe\text{-}2)_2$ and $CH_2(C_6H_3Me\text{-}5\text{-}NMe_2\text{-}2)(C_6H_3Me\text{-}5\text{-}NHMe\text{-}2)$ were isolated. The reaction of thiophosphoryl chloride, $P(S)Cl_3$, with *N,N*-dimethyl-*p*-toluidine also gave a similar heterocycle, $P(S)Cl[(NMeC_6H_3Me\text{-}4)_2CH_2\text{-}2,2']$. The ^1H NMR spectra are discussed and related to the X-ray crystal structures.

In Part 43[2] we reported the behavior of *N,N*-dialkylanilines towards phosphorus(v) chlorides.

The anilines behaved in these reactions as neutral ambident nucleophiles. The products of these reactions with phosphoryl chloride (**1**), $P(O)Cl_3$, and thiophosphoryl chloride, $P(S)Cl_3$, (**2**) were predominantly "carbon-substituted" with only a minor incursion of "nitrogen-substitution". (For a definition of "carbon-" and "nitrogen-substitution" see ref. 3). Typical products were e.g., $P(O)(C_6H_4\text{-}NMe_2\text{-}4)_2R$ (R = Cl, OH or EtO), $P(O)(C_6H_4\text{-}NMe_2\text{-}4)_3$ and $(PhNMe)P(O)R_2$(R = OEt). In all of these "carbon-substituted" products the phosphorus-containing moiety is in a *para*-position relative to the amino-group. This exclusive formation of *para*-derivatives in "carbon-substitution" is similar to that observed in the reactions of cyanuric chloride with *N,N*-dialkylanilines.[3] In general, in the reactions of activated benzene nuclei with electrophilic reagents when *para*-substitution is observed, blocking of this position enables, at least in some cases, *ortho*-substitution to come into its own. Examples of this are found in the work of Bell and Ramsden,[4] and of Dubois and his coworkers[5] on the bromination of anilines, toluidines, and xylidines. Bromination of the *para*-position is preferred and only when this is blocked by a methyl group does bromination of the *ortho*-position occur in substantial amounts. When the

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reaction of cyanuric chloride with *N,N*-diethyl-*p*-toluidine was studied however only 'nitrogen-substitution' was observed.[3] By contrast, the same electrophile yielded with *N,N*-diethyl-2-naphthylamine as only 'carbon-substituted' product a small quantity of a derivative with the triazine moiety in the 1-position, i.e., *ortho* to the amino group. Similar observations have been made in other ambident nucleophilic reactions, for instance, in the studies of the alkylation of 2-naphthoxides by Zagorevsky[6] and Kornblum and his coworkers.[7] What "carbon-substitution" occurred, took place at the 1-position. Whilst the naphthylamine system is obviously somewhat different from the aniline system, the much greater relative tendency for 'carbon-substitution' in the former compared to the latter is noteworthy.

As we had observed a similar preference for "carbon-substituted" products in the reactions of *N,N*-dialkylanilines with the phosphorus(v) halides (**1** and **2**), we decided to investigate the reactions of these electrophiles with the *N,N*-dimethyltoluidines. One mole of the halide (**1**) was heated with two of *N,N*-dimethyl-*o*-toluidine for 9 hours at 130°C. On working-up the reaction mixture after sodium ethoxide treatment,[2] only one product a "nitrogen-substituted" one was observed, diethyl *N*-methyl-*N*-(*o*-tolyl)phosphoramidate, $P(O)(NMeC_6H_4Me\text{-}2)(OEt)_2$ in a 40% yield. The reaction therefore mirrors the one of cyanuric chloride with *N,N*-diethyl-*o*-toluidine. The *ortho*-methyl group has reduced the back-conjugation of the lone-pair of electrons on the nitrogen atom thus leading to reduced reactivity at carbon and increased reactivity at nitrogen.

A similar reaction and work-up procedure with *N,N*-dimethyl-*m*-toluidine yielded a much wider spectrum of products. In addition to a small yield of an amidate, $P(O)(NMeC_6H_4Me\text{-}3)(OEt)_2$, analogous to that with the *ortho*-isomer, a larger yield of a 'carbon-derivative', bis(2-methyl-4-dimethylaminophenyl)ethyl-phosphinate, $P(O)(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_2(OEt)$ was isolated. Two purely organic products bis(2-methyl-4-dimethylaminophenyl)methane, $CH_2(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_2$, and tris(2-methyl-4-dimethylaminophenyl)methane, $CH(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_3$, were also observed. As in the reaction of *N,N*-diethyl-*m*-toluidine with cyanuric chloride "carbon-substitution" to "nitrogen-substitution" has remained at about the same ratio in the present system. A slightly greater preponderance of 'carbon-substitution' was observed with cyanuric chloride (see Table I) which contrasts with the results reported here. This may be due to the greater steric hindrance with the phosphorus compound. It is worth noting the vastly greater preference for "carbon-substitution" of phosphoryl chloride (**1**) compared with that of cyanuric chloride (Table I). Noteworthy is also the occurrence, as in the aniline reaction with the same halide, of diphenyl- and triphenyl-methane derivatives.

Of the reactions of the three isomeric *N,N*-dimethyl-toluidines with phosphoryl chloride, the one with the *para*-isomer gives the greatest variety of products. As in the reaction of *N,N*-diethyl-*p*-toluidine with cyanuric chloride "carbon-substitution" is not observed and "nitrogen-substitution" prevails. Two of these were readily explainable, *viz.*, diethyl *N*-methyl-*N*-(*p*-tolyl)phosphoramidate, $P(O)(NMeC_6H_4\text{-}Me\text{-}4)(OEt)_2$ and ethyl bis[*N*-methyl-*N*-(*p*-tolyl)-phosphorodiamidate, $P(O)(NMeC_6H_4\text{-}4)_2(OEt)$. The other two were unexpected and represent the chloro- and ethoxy-derivatives of a novel heterocyclic system. The structures were deduced from ^1H NMR spectroscopy and mass spectrometry. For the chloro-compound an X-ray analysis has been carried out. The fact that some chloro-derivative remains in

TABLE I

The reaction of phosphorus oxychloride with substituted anilines at 130°C for 9 hours, molar ratio 1 : 2 compared with that of cyanuric chloride at 90°C for 8 hours molar ratio 1 : 2

Amine	Relative number of bonds formed at different reaction sites in products		Total yield (%) of products
	C-substituted	N-substituted	
Me_2NPh	85–90	10–15	31*
	0	100	92†
Et_2NPh	97–99	1–3	27*
	30	70	96†
$Me_2NC_6H_4Me$-2	0	100	41*
$Et_2NC_6H_4Me$-2	0	100	39†
$Me_2NC_6H_4Me$-3	85	15	25*
$Et_2NC_6H_4Me$-3	55	45	75†
$Me_2NC_6H_4Me$-4	0	100	29*
$Et_2NC_6H_4Me$-4	0	100	78†

* With respect to phosphoryl chloride.
† With respect to cyanuric chloride.

spite of the solvolytic procedure (the same compound can be obtained by a non-solvolytic work-up, even without rigorous exclusion of moisture) suggests that the phosphorus-chlorine bound is fairly unreactive. Some spectroscopic properties and the structure will be discussed below.

Two diphenylmethane derivatives were also isolated in small yield: bis(2-methylamino-4-methylphenyl)methane, $CH_2(C_6H_3NHMe\text{-}2\text{-}Me\text{-}5)_2$ and (2-dimethylamino-4-methylphenyl)-(2-methylamino-4-methylphenyl)methane, $CH_2(C_6H_3NMe_2\text{-}2\text{-}Me\text{-}5)(C_6H_3NHMe\text{-}2\text{-}Me\text{-}5)$. It is noteworthy that diphenyl- and triphenyl-methane derivatives were observed in the reactions of phosphoryl chloride (**1**) with *N*,*N*-dimethyl-aniline, and *m*- and *p*-toluidines but not with *o*-toluidine, possibly because in the last one, due to the *ortho*-effect, the ring is not activated towards electrophilic attack. A diphenylmethane derivative has also been reported by Bourneuf.[8]

In view of the unexpected heterocycle formation in the reaction of phosphoryl chloride (**1**) with *N*,*N*-dimethyl-*p*-toluidine, the same amine was allowed to react with thiophosphoryl chloride (**2**); the reaction was worked up using a sodium ethoxide treatment. The sole product isolated was the chloro-thiophosphoryl analogue of the previous heterocycle. The fact that it was not, at least in part, converted to an ethoxy-derivative shows a considerable inertness of the phosphorus-chlorine bond towards nucleophilic attack.

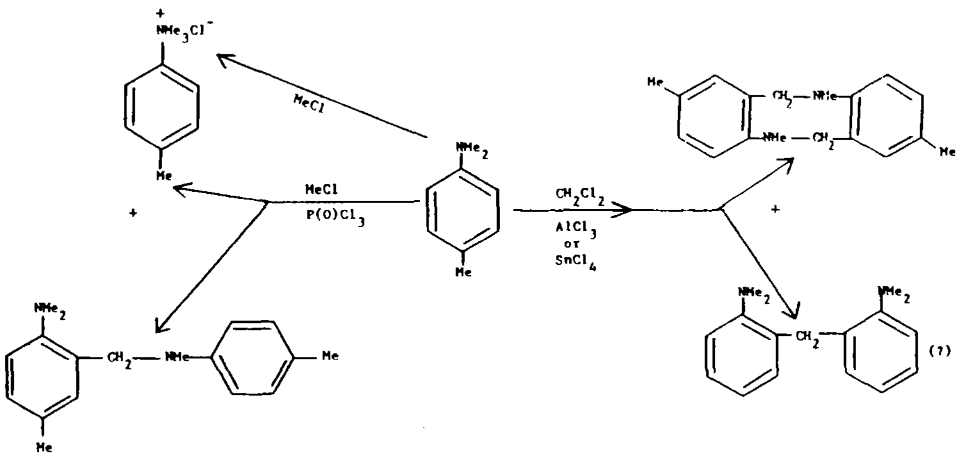
The reactions of the halides (**1** and **2**) with the secondary amine *N*-methyl-*p*-toluidine were also studied. As phosphoryl halides are more sensitive to inadvertent hydrolysis than thiophosphoryl halides, the reaction mixture of the former was worked up only after sodium ethoxide treatment, whilst that of the latter received either the same or a non-solvolytic treatment. From the phosphoryl chloride (**1**) reaction, diethyl *N*-methyl-*N*-(*p*-tolyl)phosphoroamidate, $P(O)(NMeC_6H_4Me\text{-}4)(OEt)_2$, ethyl bis[*N*-methyl-*N*-(*p*-tolyl)]-phosphorodiamidate, $P(O)(NMeC_6H_4Me\text{-}$

$4)_2(OEt)$, bis[*N*-methyl-*N*-(*p*-tolyl)]-*N*-(*p*-tolyl)phosphoramide, $P(O)(NMeC_6H_4Me\text{-}4)_2(NHC_6H_4Me\text{-}4)$, and tris[*N*-methyl-*N*-(*p*-tolyl)]phosphoramide, $P(O)(NMeC_6H_4Me\text{-}4)_3$ were isolated. Noteworthy is again that a small yield of a dealkylated product was observed. The analogous reaction with thiophosphoryl chloride was, because of its lower reactivity, carried out at higher temperature. Bis[*N*-methyl-*N*-(*p*-tolyl)]-phosphorodiamidothioic chloride, $P(S)(NMeC_6H_4Me\text{-}4)_2Cl$, or its ethoxy-derivative, $P(S)(NMeC_6H_4Me\text{-}4)_2(OEt)$, (depending on the work-up procedure) were isolated together with tris[*N*-methyl-*N*-(*p*-tolyl)]-phosphorotriamidothionate, $P(S)(NMeC_6H_4Me\text{-}4)_3$.

The two new heterocyclic chloro-derivatives were treated with nucleophilic reagents. Both the phosphoryl and the thiophosphoryl derivatives were rather inert, the latter more so than the former. From the former a methoxy- and an ethoxy-derivative were prepared with sodium alkoxide treatment. The same reactions with the thiophosphoryl heterocycle gave only recovered starting material. Both compounds appeared to be inert under our reaction conditions towards dimethylamine and *p*-toluidine. Drastic acid hydrolysis yielded from both compounds the same base bis(2-methylamino-4-methylphenyl)methane, $CH_2(C_6H_3NHMe\text{-}2\text{-}Me\text{-}5)_2$, together with starting material.

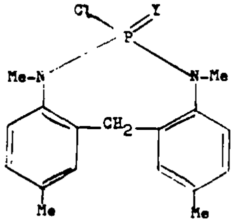
Some reactions were carried out to ascertain possible reaction mechanism for the formation of the diamino-precursor for the heterocycles. The reaction of *N*,*N*-dimethylaniline with methylene chloride in the presence of aluminium chloride gave bis(*p*-dimethylaminophenyl)methane and tris(*p*-dimethylaminophenyl)methane, whilst the same starting amine with methyl chloride yielded with or without phosphoryl chloride catalyst only the anticipated quaternary compound, $PhNMe_3{}^+Cl^-$. *N*,*N*-dimethyl-*p*-toluidine with methyl chloride gave the analogous quaternary compound, whilst in the presence of phosphoryl chloride catalysts in addition some 3-[*N*-methylene-*N*-methyl(*p*-toluidine)]-*N*,*N*-dimethyl-*p*-toluidine, $MeC_6H_3(NMe_2)(CH_2NMeC_6H_4Me)$ was isolated. The amine with methylene chloride in the presence of aluminium or stannic chloride gave 3,4-cyclo-bis-(3-methyleno-4-*N*-methyltoluene), $MeC_6H_3\overline{(CH_2)(NMeCH_2)(N}Me)C_6H_3Me$ together with a trace of a compound tentatively assigned the structure bis(2-dimethylamino-4-methylphenyl)methane, $CH_2(C_6H_3NMe_2\text{-}2\text{-}Me\text{-}5)_2$. The last two diamine-derivatives are also the product of the reaction between *N*-methyl-*p*-toluidine and formaldehyde under acid conditions.[9] It is clear that none of the above reactions provide a likely mechanistic model for the formation of the heterocycle. Scheme I

The ^1H NMR spectra of the new heterocycles give us some insight into their structures. These spectra differ significantly from their acyclic analogues. Most of the details for compound (**3**) have been published previously.[18] The site exchange of the two non-equivalent $N—CH_3$ groups is slow in the NMR time scale, with an energy barrier of approximately 14.7 kcal/mole. The thiophosphoryl heterocycle (**4**) gave an ^1H NMR spectrum resembling closely that of its phosphoryl analogue (**3**). By contrast the ethoxy or methoxy derivative of the latter at room temperature in $CDCl_3$ is markedly different. The methylene group is a somewhat broadened singlet and only one $N—CH_3$ (a sharp doublet) is observed. If however 1,2-dichlorobenzene is used instead of $CDCl_3$ as solvent the spectrum reverts to the same pattern as in the phosphoryl chloride derivative, i.e., an AB quartet for the methylene protons and two broad peaks for the $N—CH_3$ groups.



SCHEME 1

The structures as determined by X-ray crystallography of the two chlorine containing heterocycles (3, Y = O[10]; 4, Y = S)[11] are similar and will be discussed together. They confirm the eight-membered heterocycle and several other interesting features.



(3, Y = O)
(4, Y = S)

Both nitrogen atoms are almost trigonal planar [the nitrogen atoms deviate by only 0.014 and 0.089 Å (3, Y = O) and 0.06 and 0.09 Å (4, Y = S) respectively, from the plane of the three atoms bonded to them], but their trigonal planes are twisted with respect to the phenyl rings to which they are attached by 58.6 and 64.5° (3, Y = O) and 62° and 68° (4, Y = S) respectively, thus strongly reducing or eliminating any possibility of nitrogen lone-pair delocalisation into the aromatic rings. The N-$C_{(phenyl)}$ bond-lengths are 1.433 (9) and 1.455 (8) Å (3, Y = O), and 1.435 (4) and 1.443 Å (4, Y = S) respectively. In $Cl_2P(O)NPhP(S)Cl_2$[12] the N—C bond-length is 1.473 (7) Å and the angle between the P—N—P plane and the phenyl group is 88°, whilst in *trans*-$[PhP(S)NPh]_2$[13] the relevant C—N distance is 1.418 (3) Å and the angle only 8°. These results are in excellent agreement with recent work.[14] In *trans*-$[PhP(S)NC_6H_4$-*o*-$Me]_2$, N—C has a value of 1.440 (3) Å, angle 74°, whilst in *trans*-$[PhP(S)NC_6H_4$-*o*-$OMe]_2$ N—C is 1.423 (4) Å, angle 9.4°. Thus near coplanarity and some p_π-p_π conjugation give rise to short N—C bonds, whilst large dihedral angles between the phenyl group and the trigonal plane surrounding the nitrogen atom give longer N—C bonds.

The P—N bonds 1.637 (6) and 1.650 (6) Å (**3**, Y = O) and 1.634 (5) and 1.636 (4) Å (**4**, Y = S) respectively are in the general range of phosphazane bonds[15] and some back-donation from nitrogen to phosphorus is likely.

The two N—CH_3 groups are in each compound in different environments, as indeed is observed by ^1H NMR spectroscopy in solution. Both molecules (**3** and **4**) have a boat-shape. The rear of the phosphorus atom (opposite the P—Cl bond) is in both cases and especially in the thiophosphoryl case, shielded by the close approach of the methylene group. This might well account for the considerable inertness (especially of **4**) towards nucleophilic attack. Only strong and sterically undemanding nucleophiles (e.g., methoxide and ethoxide ions) seem to react with the less hindered phosphoryl chloride derivative (**3**), and even these fail with the thiophosphoryl analogue (**4**). In view of the previously observed deshielding effects of the P═O[16] and P═S groups[17] in ^1H NMR spectroscopy, it is tempting to assign to the deshielded proton the position nearer to the P═O or P═S group.

Thus chemical and ^1H NMR spectroscopic observations can be well reconciled with the structural information provided by X-ray crystallography. The ^1H NMR spectrum and X-ray crystallographic investigation of compound (**3**) have been briefly reported.[18]

EXPERIMENTAL

The purification of the reagents, the general reaction and working-up procedures, have been previously described.[2]

(1) *Reaction of N,N-Dimethyl-o-toluidine with phosphoryl chloride.* Sodium ethoxide treatment and chromatography on silica gel[2] gave on elution with a solvent varying from benzene-ethyl acetate (1 : 1) to pure ethyl acetate *diethyl-N-methyl-N-(o-tolyl)-phosphoramidate*, $\mathrm{P(O)(NMeC_6H_4Me\text{-}2)(OEt)_2}$, m.p. − 14°C (41% yield). (Found: C, 56.1; H, 8.0; N, 5.6; P, 11.8; M^+, 257. $C_{12}H_{20}O_3NP$ requires C, 56.0; H, 7.8; N, 5.45; P, 12.0%; M, 257).

(2) *Reaction of N,N-Dimethyl-m-toluidine with phosphoryl chloride.* Using the same procedure as in (1), the products were eluted in the following order: bis(2-methyl-4-dimethylaminophenyl)-methane, $\mathrm{CH_2(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_2}$, m.p. 83–84°C (4.3°% yield). (Found: C, 80.7, H, 9.2; N, 9.8%, M^+, 282. $C_{19}H_{26}N_2$ requires C, 80.8, H, 9.3; N, 9.9%; M 282). Tris(2-methyl-4-dimethylaminophenyl)methane, $\mathrm{CH(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_3}$, m.p. 189–191°C (4.4% yield). (Found: C, 81.2; H, 9.1; N, 9.8%; M^+ 415. $C_{28}H_{37}N_3$ requires C, 80.9; H, 9.0; N, 10.1%; M, 415). Diethyl *N*-methyl-*N*-(*m*-tolyl)phosphoroamidate, $\mathrm{P(O)(NMeC_6H_4Me\text{-}3)(OEt)_2}$, m.p. −9°C (6.5% yield). (Found: C, 56.0; H, 7.8; N, 5.6; P, 11.95%; M^+, 256. $C_{12}H_{19}O_3NP$ requires C, 56.2; H, 7.5; N, 5.5; P, 12.8%, M, 256). Bis(2-methyl-4-dimethylaminophenyl)-ethylphosphinate, $\mathrm{P(O)(C_6H_3Me\text{-}2\text{-}NMe_2\text{-}4)_2(OEt)}$, m.p. −2°C (18.5% yield). (Found: C, 66.5; H, 8.1; N, 7.6; P, 8.8%; M^+, 360. $C_{20}H_{29}O_2N_2P$ requires C, 66.65; H, 8.1; N, 7.8; P, 8.6%; M, 360).

(3) *Reaction of N,N-Dimethyl-p-toluidine with Phosphoryl Chloride.* Using the same procedure as in (1), but commencing elution with toluene, the products appeared in the following order: *N,N*-dimethyl-*p*-toluidine (41%), *N*-methyl-*p*-toluidine (9%), (2-dimethylamino-4-methylphenyl) (2-methylamino-4-methylphenyl)methane, $\mathrm{CH_2(C_6H_3NMe_2\text{-}2\text{-}Me\text{-}5)(C_6H_3NHMe\text{-}2\text{-}Me\text{-}5)}$, m.p. 66–67°C (2% yield). (Found: C, 80.5; H, 8.8; N, 11.0%, M^+ 268. $C_{18}H_{24}N_2$ requires C, 80.6; H, 9.0; N, 10.4%; M 268). Bis(2-methylamino-4-methylphenyl)methane, $\mathrm{CH_2(C_6H_3NHMe\text{-}2\text{-}Me\text{-}5)_2}$, m.p. 85–86°C (0.5% yield). (Found: 80.1; H, 8.5; N, 11.4%; M^+, 254. $C_{17}H_{22}N_2$ requires C, 80.2; H, 8.7; N, 11.1%; M, 254). Bis(*N*-methyl-*N*-(4-methylphenyl)2,2′-methylene phosphorodiamidic chloride, $\mathrm{P(O)Cl[(NMeC_6H_3Me\text{-}4)_2CH_2\text{-}2,2']}$ recrystallised from ethyl acetate, m.p. 170–171°C (10.6% yield). (Found: C, 66.1; H, 6.2; N, 8.2; P, 9.4; Cl, 10.5%; M^+, 334. $C_{17}H_{20}ON_2PCl$ requires C, 61.0; H, 6.0; N, 8.4; P, 9.3; Cl, 10.6%; M, 334). A mixture of two ester phosphoramides (purified as shown below) and ethyl bis[*N*-methyl-*N*-(4-methylphenyl)]2,2′-methylene phosphoramidate, $\mathrm{P(O)(OEt)[(NMeC_6H_3Me\text{-}4)_2CH_2\text{-}2,2']}$; m.p. 116–117°C (10% yield). (Found: C, 66.3; H, 7.3; N, 8.2; P, 9.2%; M^+, 344. $C_{19}H_{25}O_2N_2P$ requires C, 66.0; H, 7.3; N, 8.15; P, 9.0%; M, 344). The above mixture of the two ester phosphoramidates was chromatographed on alumina,

eluent light petroleum-ethyl acetate (5 : 3) diethyl *N*-methyl-*N*-(*p*-tolyl)-phosphoramidate, $\mathrm{P(O)(NMeC_6H_4Me{-}4)(OEt)_2}$ was collected in the earlier fractions, m.p. − 7°C (4.5% yield). (Found: C, 55.9; H, 7.9; N, 5.6; P, 12.2%, M^+, 257. $\mathrm{C_{12}H_{20}O_3NP}$ requires C, 56.0; H, 7.8; N, 5.45; P, 12.0%; *M*, 257). From the later fractions impure mono ester was obtained (in the case of the 36 h reaction pure mono ester was isolated). The oil was triturated with light petroleum (b.p. 40–60°C), cooled, and on warming to room temperature two layers appeared. The light petroleum layer was decanted. The residue was repeatedly treated in the same manner until it solidified. It was recrystallised from ethyl acetate. Ethyl bis(*N*-methyl-*N*-(4-methylphenyl)phosphoramidate, $\mathrm{P(O)(NMeC_6H_4Me{-}4)_2(OEt)}$ m.p. − 5°C (4% yield). (Found: C, 65.1; H, 7.4; N, 8.2; P, 9.5%, M^+, 332. $\mathrm{C_{18}H_{25}O_2N_2P}$ requires C, 65.05; H, 7.6; N, 8.4; P, 9.3; *M*, 332). In another reaction (36 h) there were isolated 19.5% of the phosphorodiamide chloride, 16.8% of its ethoxy derivative, 2% of the diethyl phosphoramidate and 14.3% of the ethyl phosphorodiamidate. In another reaction (9 h) without sodium ethoxide treatment, only the phosphorodiamidic chloride was isolated (19.3%), comparable to the total yield of this heterocycle as two derivatives in ethoxide treatment.

(4) *Reaction of N,N-Dimethyl-p-toluidine with Thiophosphoryl Chloride.* Using the same procedure as in (1) with toluene yielded only one compound, bis(*N*-methyl-*N*-(4-methylphenyl)]-2,2′-methylenephosphorodiamidothioic chloride, $\mathrm{P(S)Cl[(NMeC_6H_3Me{-}4)_2CH_2{-}2,2']}$, m.p. 209–210°C (30% yield). (Found: C, 58.1; H, 5.7; N, 7.95; P, 8.9; S, 9.1; Cl, 10.2%; M^+, 350. $\mathrm{C_{17}H_{20}N_2PSCl}$ requires C, 58.2; H, 6.3; N, 8.0; P, 8.8; S, 9.1; Cl, 10.1%; *M*, 350).

(5) *Reaction of N-Methyl-p-toluidine with Phosphoryl Chloride.* Phosphoryl chloride (1 mole) was heated with *N*-methyl-*p*-toluidine (6 mole) for 2.5 h at 50°C. Sodium ethoxide treatment and chromatography using ethyl acetate as eluent gave a mixture of the two ester phosphoramidates (which were separated as in (3). Diester (58.3% yield), monoester (2.5% yield). The same reaction but for 9 h at 130°C yielded the monoester (41.8% yield). Bis[*N*-methyl-*N*-(*p*-tolyl](*N*-*p*-tolyl) phosphorotriamide, $\mathrm{P(O)(NMeC_6H_4Me{-}4)_2(NHC_6H_4Me{-}4)}$, m.p. 160–161 (1.8% yield). (Found: C, 70.1; H, 7.3; N, 10.8; P, 7.7%; M^+, 393. $\mathrm{C_{23}H_{28}ON_3P}$ requires C, 70.2; H, 7.2; N, 10.7; P, 7.9%; *M*, 393). Tris[*N*-methyl-*N*-(*p*-tolyl)]phosphorotriamide, $\mathrm{P(O)(NMeC_6H_4Me{-}4)_3}$, m.p. 126–127°C (43% yield). (Found: C, 70.7; H, 7.5; N, 10.3; P, 7.8%; M^+, 407. $\mathrm{C_{24}H_{30}ON_3P}$ requires C, 70.9; H, 7.4; N, 10.35; P, 7.6%; *M*, 407).

(6) *Reaction of N-Methyl-p-toluidine with Thiophosphoryl Chloride.* Thiophosphoryl chloride (1 mole) and *N*-methyl-*p*-toluidine (6 mole) were heated for 6 h at 130°C. Sodium ethoxide treatment and chromatography (toluene as eluent) gave ethyl bis[*N*-methyl-*N*-(*p*-tolyl)]phosphorodiamidothionate, $\mathrm{P(S)(NMeC_6H_4Me{-}4)_2(OEt)}$, m.p. −6°C (86% yield). (Found: C, 61.9; H, 7.2; N, 8.1; P, 9.1; S, 9.3%; M^+, 348. $\mathrm{C_{18}H_{25}ON_2PS}$ requires C, 62.0; H, 7.2; N, 8.0; P, 8.9; S, 9.2%; *M*, 348). Tris[*N*-methyl-*N*-(*p*-tolyl)]phosphorotriamido-thionate, $\mathrm{P(S)(NMeC_6H_4Me{-}4)_3}$, m.p. 87–88°C (7% yield). (Found: C, 68.0; H, 7.1; N, 9.8; P, 7.4; S, 7.5%; M^+, 423. $\mathrm{C_{24}H_{30}N_3PS}$ requires C, 68.1; H, 7.1; N, 9.0; P, 7.3; S, 7.6%; *M*, 423). The same reaction without sodium ethoxide treatment gave bis[(*N*-methyl-*N*-(*p*-tolyl)]phosphorodiamidothioic chloride, $\mathrm{P(S)(NMeC_6H_4Me{-}4)_2Cl}$, m.p. −5°C (90.5% yield). (Found: C, 56.6; H, 5.75; N, 8.35; P, 9.3; S, 9.5; Cl, 10.3%; M^+, 338. $\mathrm{C_{16}H_{20}N_2PSCl}$ requires C, 56.7; H, 5.95; N, 8.3; P, 9.1; S, 9.5; Cl, 10.5%; *M*, 338, and the phosphorotriamido-thionate, (7% yield).

(7) *Preparation of Ethoxy (Methoxy) Derivative of Phosphoryl Chloride Heterocycle.* The phosphoryl chloride heterocycle (2 g.) was added to a freshly prepared sodium ethoxide (methoxide) solution in ethanol (methanol). A milky solution was obtained, which was treated as for the sodium ethoxide treatment outlined earlier.[2] Chromatography and elution with ethyl acetate gave the ethoxy (methoxy) derivative in about 80% yield. Ethoxy-compound m.p. 116–117°C. (Found: 66.2; H, 7.3; N, 8.2; P, 9.2; M^+, 334. $\mathrm{C_{19}H_{25}O_2N_2P}$ requires C, 66.0; H, 7.3; N, 8.15; P, 9.0%; *M*, 334). Methoxy-compound m.p. 109–110°C. (Found: C, 65.0; H, 7.3; N, 8.05; P, 8.8%; M^+, 330. $\mathrm{C_{18}H_{23}O_2N_2P}$ requires C, 65.45; H, 7.0; N, 8.5; P, 9.4%; *M*, 330). The thiophosphoryl-derivative was recovered under similar conditions.

(8) *Hydrolysis of the Phosphoryl and Thiophosphoryl Chloride Heterocycles.* The heterocycle (2 g.) was dissolved in absolute ethanol (50 ml), 2N $\mathrm{H_2SO_4}$ (50 ml) were added and the whole heated in a sealed tube at 150°C (100 h). On cooling and opening the tube, water (50 ml) was added to the mixture and this was made alkaline (litmus paper) with 6 N NaOH. The brown solution was heated on a water bath (3 h), then cooled and extracted with ether. The ether layer was dried ($\mathrm{Na_2SO_4}$) and on evaporation of the solvent a brown oily substance remained. T.l.c. showed two spots. Chromatography on a silica gel column eluent toluene: ethyl acetate (10 : 1) gave starting material (the phosphoryl derivative eluted after the diamine, the thiophosphoryl derivative before the diamine), and bis(2-methylamino-4-methylphenyl)methane, $\mathrm{CH_2(C_6H_3NHMe{-}2{-}Me{-}5)_2}$, m.p. 85–86°C.

(9) *Reaction of the above Diamine with Phosphoryl Chloride.* Phosphoryl chloride (0.61 g., 0.004 mole) was added to the diamine (1.02 g, 0.004 mole). After 9 h at room temperature the reaction was worked up

and chromatographed as in (8) to give starting material and heterocycle (65% yield). The same reaction as above, but in the presence of triethylamine (0.008 mole) increased the yield to 85%.

(10) *Friedel Crafts and Related Reactions.* (a) *N*,*N*-Dimethyl-aniline and methyl chloride (with or without catalytic amounts of phosphoryl chloride) gave only trimethylphenyl ammonium chloride. (b) The same amine and methylene chloride in the presence of aluminium chloride gave bis(*p*-dimethylaminophenyl)-methane, m.p. 85–86°C, (8%) and tris(*p*-dimethylaminophenyl)methane, m.p. 175–177°C (4.5%). (c) *N*,*N*-Dimethyl-*p*-toluidine and methyl chloride gave only the quaternary compound. The same reagents in the presence of catalytic amounts of phosphoryl chloride gave 3-[*N*-methyleno-*N*-methyl(*p*-toluidine)]-*N*,*N*-dimethyl-*p*-toluidine, m.p. 68°, lit[9], 64°C, *N*,*N*-dimethyl-*p*-toluidine and methylene chloride in the presence of catalytic amounts of aluminium or stannic chloride gave 3,4-cyclo-bis(3-methyleno-4-methyl toluene), m.p. 149, lit.[9], 149°C, (3.5%) and a trace of a compound which on mass spectrometric evidence was a bis(dimethylamino-methylphenyl)methane. In the absence of catalysts only the cyclic compound (2%) was observed.

^{1}H NMR spectra were obtained on a Varian Associates Model A 60 spectrometer equipped with a 60 Mc/s. radiofrequency source at the School of Pharmacy, University of London. The 100 Mc/s. ^{1}H NMR spectra were recorded on a Varian HA 100 machine in the Chemistry Department of Imperial College.

Mass spectra were obtained from the A.E.I. M.S.9 mass spectrometer at the School of Pharmacy, University of London and University College, London.

Melting points were determined on a Reichert-Kofler microheating stage fitted with a polarising microscope. The apparatus was adapted to measure low temperature melting points.

Microanalyses were carried out by Dr. A. Bernhardt, Mülheim, Ruhr, Germany, and Drs. A. Weiler and P. B. Strauss, Oxford, England.

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