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N-Phosphorylated amides and thioamides

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ABSTRACT. **The first systematic review is presented on carboxylic and thiocarboxylic acid amides containing a four-coordinated phosphorus atom on the nitrogen atom. The synthesis, structure and certain chemical properties of this compound class have been examined together with their prototropic and phosphorylotropic tautomerism, their dual reactivity, and the structure and properties of some of their metallic and organic derivatives. Particular attention has been paid to the practical application of these compounds.**

The bibliography contains 223 references.

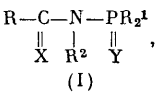
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I. Introduction

Carboxylic acid amides have been studied thoroughly and are widely used in industry, agriculture, and in various fields of science and technology.[1] Thioamides, however, have become a focus of attention only in the last decade in view of recently discovered practical applications, their diverse reactivity, and their potential value in organic synthesis.[2–5] *N*-Functionalised (including *N*-acylated) amides and thioamides, such as phthalimide, succinimide, and a large number of derivatives, have also proved to be very effective reagents in organic synthesis. Phosphorylated analogues of these polyfunctionalised compounds have also received much attention during the last two decades as a result of the discovery of a broad spectrum of properties of practical value.

The chemistry of *N*-phosphorylated amides and thioamides of type (I) has developed in three stages. After the initial



(I)

R = Alk, Ar; R^1 = Alk, Ar, AlkO, ArO, AlkS, ArS, Alk_2N, Ar_2N, etc.,

R^2 = H, Alk, Ar; X, Y = O, or S,

syntheses at the beginning of the 20th century,[6–8] there was a gap of some fifty years during which there was practically no research in this field. Then, during the fifties, A V Kirsanov's "phosphazo reaction" provided a new and simple methodology for preparing this class of compound.[9] Finally, in the 'seventies, with the discovery of their pesticidal activity, *N*-phosphorylated amides again became a focus of renewed interest, specifically with regard to (I, X = Y = O), the *N*-thiophorylated analogues (I, X = O, Y = S), *N*-phosphorylated thioamides (I, X = S, Y = O), and *N*-thiophosphorylated thioamides (I, X = Y = S). In this period, the broad spectrum insecticide, acephate (*O,S*-dimethyl *N*-acetylthiophosphoromonoamidate), was discovered and became commercially available.

In recent years, certain organophosphorus compounds of general formula (I) have proved to be highly effective complexing agents, extractants, and anti-microbial and -tumour agents, etc. This has stimulated the search for simple, convenient, and industrially viable routes to this class of compound, as well as the study of their chemical properties and structure.

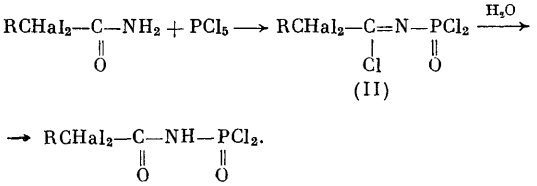
This is the first systematic review on the synthesis, structure and properties of *N*-phosphorylated amides and thioamides. Where possible, analyses have been made of the influence of the structure of these compounds on their reactivity and on other properties.

II. Methods of synthesis

1. Synthesis of *N*-phosphorylated amides

The first *N*-phosphorylated amides of type (I) were obtained by phosphorylation of α-halogeno- and α-nitrocarboxylic acid amides with phosphorus pentachloride.[6–8]

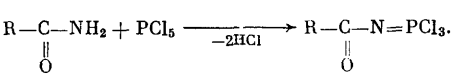
The authors suggested that reaction proceeds via *N*-phosphoryliminochlorides (II) which were converted to the corresponding amides (I, R = Hal, H, NO_2) on exposure to moist air.



(II)

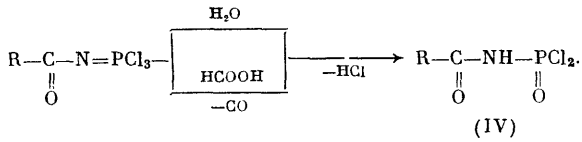
(Ia)

In 1954, A V Kirsanov renewed the study of the reaction between carboxylic acid amides and phosphorus pentachloride, and discovered that a trichlorophosphazo compound (III) was formed initially, rather than an *N*-phosphoryliminochloride.[9]



(III)

The above process was called the "phosphazo reaction". The resulting phosphazo compounds (III) are very hygroscopic and readily converted to the corresponding phosphoryl dichlorides (IV) in the presence of hydroxylic reagents.[10–13]



(IV)

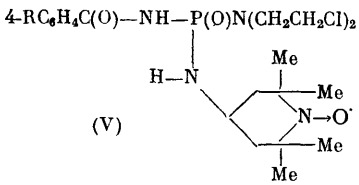
The acylaminophosphoryl dichlorides (IV) can be simply converted to the corresponding diesters on treatment with alkali metal alkoxides or alcohols.[14–20]

$$\underset{\text{(IV)}}{RC(O)NHP(O)Cl_2} \xrightarrow{2R^1OH \text{ or } 2R^1ONa} RC(O)NHP(O)(OR^1)_2.$$

In a similar way, the dichloride (IV) is readily converted into dithioesters,[14,19] bis(ethylenimides),[21] diamides[14,19] and hydrazides[22] of general formula (I).

$$RC(O)NHP(O)Cl_2 + 2HR^1 \rightarrow RC(O)NHP(O)R_2^1,$$
$$R^1 = SR^2,\ NHR^2,\ NHNHR^2,\ \overbrace{NCH_2CH_2}.$$

Sequential treatment of aroylaminophosphoryl dichlorides with bis(2-chloroethyl)amine in the presence of triethylamine, followed by 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl, affords the corresponding phosphoric acid triamides (V) which possess antitumour activity.[23] The intermediate monoamide need not be isolated.



(V)

R = H, F, Me.

Diarylphosphinic acid *N*-arolyamides (VI) may be prepared from arylmagnesium bromides. These amides resist hydrolysis.[24]

$$\underset{\text{(VI)}}{ArC(O)-NH-P(O)Ar_2}.$$

The ultimate stage in preparing *N*-acylphosphoromonoamidates need not involve the conventional displacement of halide. Thus, trialkoxy- or triaryloxy-*N*-acylphosphazenes (VII), obtained by treatment of the corresponding trichlorophosphazo compounds with alcohols and phenols, respectively, are converted to *N*-acylphosphoromonoamidates by action of water, aqueous ethanol, or dry hydrogen chloride.[14,17,20,25,26]

$$RC(O)N=PCl_3 + 3R^1OH \longrightarrow \underset{\text{(VII)}}{RC(O)N=P(OR^1)_3} \xrightarrow{H_2O(HCl)} \longrightarrow$$

$$\longrightarrow \underset{O}{\overset{\|}{RC}}-NH-\underset{O}{\overset{\|}{P}}(OR^1)_2.$$

It should be pointed out that triaryloxy-*N*-acylphosphazenes (VII, R^1 = aryl) are very easily hydrolysed. In fact, very high yields of diaryl *N*-acylphosphoromonoamidates are obtained simply by exposing these phosphazenes to moist air, water or 96% ethanol.[26–28]

In another route, *N*-acylphosphoromonoamidates are obtained from trichlorophosphazenes via partial replacement of chlorine atoms, followed by hydrolysis, alcoholysis or acidolysis of the resulting monochloro- or dichlorophosphazenes, (VIII) and (IX).[14,17,26]

$$RC(O)-N=PCl_3 + 2R^1OH + 2B \longrightarrow \underset{\text{(VIII)}}{RC(O)-N=P(OR^1)_2Cl} \xrightarrow{H_2O} \text{(I)},$$

$$\underset{\text{(IX)}}{ArC(O)-N=P(OC_6H_5)Cl_2} \begin{cases} \xrightarrow{ROH} ArC(O)-NH-P(O)(OC_6H_5)OR \\ \xrightarrow{HCOOH} ArC(O)-NH-P(O)(OC_6H_5)Cl. \end{cases}$$

In a similar way, *N*-phosphorylated thioamides of general structure (XI) are prepared from the corresponding phosphazenes (X) (having alkyl, alkoxy, amino or other functionality on phosphorus together with one or two chlorine atoms) on treatment with hydrogen suphide in trifluoroacetic acid.[29,30]

$$\underset{\text{(X)}}{RC(O)-N=PR_n^1Cl_{3-n}} + H_2S \rightarrow \underset{\text{(XI)}}{RC(O)-NH-P(S)R_n^1Cl_{2-n}}$$
$$R^1 = Alk,\ AlkO,\ NR_2,\ NHR;\ n = 1, 2.$$

P-Aryl-substituted *N*-phosphorylated amides, (XII) and (XIII), are obtained by hydrolysis or acidolysis of the corresponding aryl- or diaryl-chloro(*N*-acyl)phosphazenes.[25,31]

$$RC(O)N=P(C_6H_5)_2Cl \xrightarrow{HCOOH \text{ (or } H_2O)} \underset{\text{(XII)}}{RC(O)-NH-P(O)(C_6H_5)_2},$$

$$RC(O)N=P(C_6H_5)Cl_2 \xrightarrow{HCOOH \text{ (or } H_2O)}$$

$$\longrightarrow \underset{\text{(XIII)}}{RC(O)-NH-P(O)(C_6H_5)Cl} \xrightarrow{H_2O \text{ in } (CH_3)_2CO} RC(O)-NH-P(O)(C_6H_5)OH.$$

The monochlorinated amides (XIII) are readily converted to the corresponding *N*-acyl(phenyl)phosphonamidic acids by vigorous hydrolysis with aqueous acetone.[31]

Acylaminophosphoryl diamides and dihydrazides have been conveniently prepared by hydrolysis or acidolysis of the corresponding triamino- or dihydroazido-phosphazenes, obtained from *N*-acyltrichlorophosphazenes.[22,32]

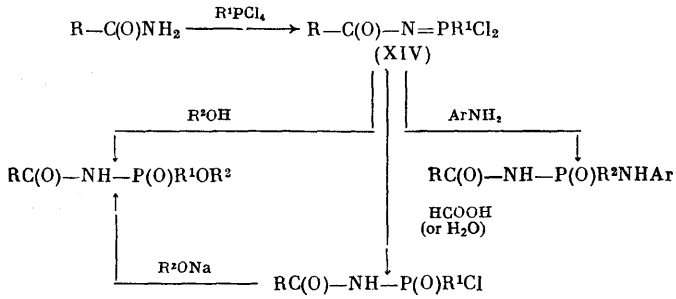
$$ArC(O)-N=P(NHAr^1)_3 \xrightarrow{H_2O \text{ (or } RCOOH)} ArC(O)-NH-$$
$$-P(O)(NHAr^1)_2,$$

$$RC(O)-N=P(OC_6H_5)(NHNHR)_2 \xrightarrow{OH^-} RC(O)-NH-$$
$$-P(O)(NHNHR)_2.$$

Structurally varied *N*-phosphorylated amides may be obtained by phosphorylation of carboxamides with halogenophosphoranes, e.g. phenyl-,[33] methyl-[34] and trichloromethyltetrachlorophosphorane,[35] in place of phosphorus pentachloride. Reactions

with these tetrachlorophosphoranes do not proceed as readily as reaction with PCl_5. The initially formed alkyl- or aryl-(dichloro)phosphazenes (XIV) may be easily converted to the corresponding *N*-phosphorylated amides by treatment with water, acid, alcohols or amines, as shown in Scheme 1.

Scheme 1



Methods of preparing *N*-phosphorylated amides via the phosphazo reaction are fairly straightforward and afford the desired product in high yield. However, such routes are not generally applicable. For example, the interaction of aliphatic carboxylic acid amides with PCl_5 proceeds to give both phosphazo compounds and chlorinated amides.[9] As a consequence, this method is not suitable for preparing simple *N*-phosphorylated *N*-acylamides unsubstituted in the acyl fragment, e.g. the pesticide acephate.

As an alternative to the phosphazo reaction the Staudinger reaction, based on trialkyl phosphites and acyl azides, can be applied to the preparation of *N*-acylphosphazenes. The resulting *N*-acyliminophosphates are converted to the desired *N*-phosphorylated amides on treatment with dry hydrogen chloride.[36,37]

$$(RO)_3P + R^1C(O)N_3 \longrightarrow (RO)_3P{=}NC(O)R^1 \xrightarrow[-RCl]{HCl} (I).$$

The synthesis of *N*-phosphorylated amides may also be achieved by another route: acylation of *N*-arylphosphazenes with acetyl chloride. Kabachnik and Gilyarov[39] showed that the trialkyl *N*-phenyliminophosphates formed by the Staudinger reaction are converted to *N*-acetyl-*N*-phenylphosphoromonoamidates on treatment with acetyl chloride. This is one of only a few methods reported in the literature for the preparation of *N*-phosphorylated amides having a tertiary nitrogen atom.

$$(RO)_3P + C_6H_5N_3 \xrightarrow[-N_2]{} (RO)_3P{=}N{-}C_6H_5 \xrightarrow{CH_3C(O)Cl} \longrightarrow (RO)_2P(O){-}N(C_6H_5){-}C(O){-}CH_3 + RCl.$$

A number of routes to *N*-phosphorylated amides are based on the functionalisation of phosphorus(V) acid derivatives in which the phosphorus atom is bonded to an unsaturated nitrogen-containing group. Thus, *N*-phosphorylated iminochlorides (XV, X = Cl), which are isomeric with *P*-chloro-*N*-acylphosphazenes, undergo hydrolysis and alcoholysis to give the corresponding *N*-phosphorylated amides. The latter are also obtained by hydrolysis of *N*-phosphorylated iminoesters (XVI).[16,17,28,39]

$$R{-}C(X){=}N{-}P(O)(OR^1)_2 \xrightarrow{H_2O\ (ROH)} (I),$$

(XV), (XVI)

X = Cl (XV), OR^2 (XVI).

There is also an unusual route to *N*-phosphorylated amides based on the interaction of aryl *N*-(diaryloxyphosphinyl)thioimidates with 25% H_2O_2 in acetic acid or with concentrated nitric acid.[40]

$$Ar{-}C(S{-}Ar^1){=}N{-}P(O)(OAr^2)_2 \xrightarrow{H_2O,\ [O]} Ar{-}C(O){-}NH{-}P(O)(OAr^2)_2.$$

The authors gave no details on this reaction.

A variety of *N*-phosphorylated amides with a functionalised acyl chain can be prepared by reaction of *N*-phosphorylisocyanates with compounds having a labile hydrogen atom. Thus *N*-phosphorylated amides are obtained in 36–61% yield by interaction of isocyanates (XVII) with acetic or propionic acid in the presence of a catalytic amount of sulphuric acid. Evidently, the reaction proceeds via an unstable anhydride (XVIII) which undergoes decarboxylation.[41]

$$(RO)_2P(O) - N = C = O + R^1COOH \xrightarrow{H_2SO_4\ (cat.)}$$

(XVIII)

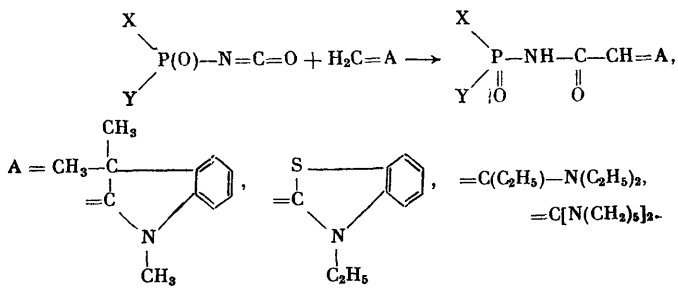
$$\longrightarrow [(RO)_2P(O){-}NH{-}C(O)OC(O)R^1] \xrightarrow[-CO_2]{} (RO)_2P(O){-}NH{-}C(O)R^1,$$

(XVIII)

R=CH_3, C_2H_5; R^1=C_2H_5.

Benzoic acid, however, does not participate in this reaction.

In another route based on phosphorylisocyanates, nitrogen-containing methylenic compounds add to the latter to give *N*-phosphorylated derivatives of α,β-unsaturated carboxylic acid amides.[42]



The above-described routes to *N*-phosphorylated and *N*-thiophosphorylated amides are essentially based on the intermediate formation and subsequent conversion of compounds with an unsaturated phosphorus atom, such as phosphazo compounds. Since there are limitations in the choice of the acyl group and the

Table 1. Synthesis of phosphorylated amides and thioamides by alkylation of amides and thioamides.

Anylamide	Acylating agent	Reaction conditions	Product	Yield %	Reference
		Acylation of phosphoramides			
$(RO)_2P(S)NHNa$	$ClC(O)C_6H_5$	Benzene, 20 °C	$(RO)_2P(S)NHC(O)C_6H_5$	50	[30]
$(RNH)_3P=S$	$ClC(O)CCl_3$	Benzene, 20 °C, Et_3N, 10 h	$RNHP(S)[NRC(O)CCl_3]_2$	Not given	[43]
$(RO)_2P(O)NH_2$	$ClC(O)R^1$	Without solvent, 30 °C, $PhNEt_2$, 3 h	$(RO)_2P(O)NHC(O)R^1$	64–72	[45]
$(EtO)_2P(O)NHR$	$[CF_3C(O)]_2O$	Pyridine, 20 °C	$(EtO)_2P(O)NRC(O)CF_3$	95	[50]
$(RY)(R^1S)P(O)NHR^2$	$ClC(O)R^3$	Benzene, Methylene chloride, chloroform, THF, 0–60 °C, 2–24 h	$(RY)(R^1S)P(O)NR^2C(O)R^3$	Not given	[47]
$R_2P(S)NHNa$	$ClC(O)R$	THF, 70 °C, 3–5 h	**$R_2P(S)NHC(O)R$**	8–87	[51]
$(iso\text{-}PrO)_2P(S)NH_2$	$ClC(O)C_6H_5$	Acetone, 20 °C, KOH, dibenzo-18-crown-6, 15 min	**$(iso\text{-}Pro)_2P(S)NHC(O)C_6H_5$**	36	[52]
$(R^1O)_2P(X)NH_2$	$ClC(O)R$	Acetone, 20 °C, KOH, crown ether	$(R^1O)_2P(X)NHC(O)R$	50–65	[53]
$R(ClCH_2CHFO)P(S)NH_2$	$[CH_3C(O)]_2O$	concd. H_2SO_4 (catalyst), 20–55 °C, 15 h	$R(ClCH_2CHFO)P(S)-NHC(O)CH_3$	Not given	[57]
$(RO)_2P(S)NH_2$	$[CH_3C(O)]_2O$	Methylene chloride, H_3PO_4, heat, 3 h	$(RO)_2P(S)NHC(O)CH_3$	98	[58]
$(RO)_2P(S)NH_2$	$R^1CH=C=O$	H_3PO_4 (catalyst) in MeCOOH, 20 °C, 3 h	$(RO)_2P(S)NHC(O)CH_2R^1$	86	[59]
$(RX)(R^1S)P(Y)NHR^2$	$CH_3C(O)OC(O)H$	THF, N_2, BuI	$(RX)(R^1S)P(Y)NR^2C(O)H$	88	[55]
$(RO)_2P(S)NH_2$	$ClC(O)C_6H_5$	Benzene, NaOH	$(RO)_2P(S)NHC(O)C_6H_5$	15	[30]
$(C_2H_5O)_2P(S)NH_2$	$ClC(O)C_6H_5$	Benzene, C_5H_5H	$(C_2H_5O)_2P(S)NHC(O)C_6H_5$	25	[30]
		Phosphorylation of acylamides			
$RC(X)NHNa$	**$ClP(S)R_2^1$**	THF, 70 °C, 3–5 h	$RC(X)NHP(S)R_2^1$	46–89	[51]
$C_6H_5C(O)NHNa$	**$ClP(S)(OR)_2$**	Benzene, heat, 3 h	$C_6H_5C(O)NHP(S)(OR)_2$	20–60	[30]
$CH_3C(S)NH_2$	**$ClP(S)(OPr\text{-}iso)_2$**	Acetonitrile, *t*-BuOK, 20 °C, 15 min	$CH_3C(S)NHP(S)(OPr\text{-}iso)_2$	15	[52]
$RC(O)NH_2$	$ClP(S)(OR)_2$	NaH in THF, heat, 16 h	$RC(O)NHP(S)(OR)_2$	19	[54]
$RC(O)NH_2$	$ClP(S)(OR)_2$	1 : 5 DMSO/Benzene, KOH, 5–25 °C	$RC(O)NHP(S)(OR)_2$	45	[54]
$CH_3C(O)NH_2$	1. $[(C_2H_5O)_2P]_2O$ 2. RI	1. 20 °C, 10 days 2. 20–80 °C, ⩽ 6 h	$CH_3C(O)NHP(O)(R)(OC_2H_5)$	Not given	[36]

substitution of the phosphoryl residue, the method has certain, and sometimes obvious, limitations. For this reason, there has been interest in the direct phosphorylation of amides and thioamides with phosphorus acid chlorides and in the acylation of phosphorus(V) acid amides with acyl or thioacyl halides:

$$\left.\begin{array}{l} RC(X)NH_2 + ClP(Y)R_2^1 \\ R_2^1P(Y)NH_2 + ClC(X)R \end{array}\right\} \xrightarrow[-HCl]{} R{-}\underset{\underset{X}{\|}}{C}{-}\underset{\underset{H}{|}}{N}{-}\underset{\underset{Y}{\|}}{PR_2^1}.$$

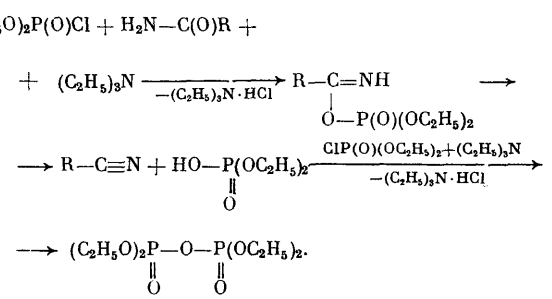
Most success has been achieved by applying the second of these routes. Thus, a whole range of methods is available for preparing (I) based on the interaction of phosphorus(V) and thiophosphorus(V) acid amides with acyl halides. Such reactions have been carried out both in the presence of base (to 'fix' hydrogen chloride)[43–45] and in the absence of base.[46–49] Tertiary *N*-phosphorylated amides have also been prepared by acylation of *N,N*-disubstituted phosphoramidates with acyl halides in the presence of pyridine.[50] These routes are quite suitable for the preparation of oxygen-containing *N*-phosphorylated amides and provide the desired products in an acceptable yield (Table 1).

Various methods involving acylamine metallation have been adapted for the effective preparation of *N*-thiophosphorylated amides. However, the yield of the latter is within a wide range (8 to 87%), depending on the structure of the starting materials.[30,51,52] Only a moderate yield (36%) of *N*-thiophosphorylated amides is obtained by acylation of thiophosphorus(V) acid amides with acyl halides in acetone in the presence of KOH and crown ether,[52] while, in superbasic media (DMSO/KOH), the yield of desired product is 24%. The authors note that under these conditions it is possible to prepare *N*-phosphorylated and *N*-thiophosphorylated amides which cannot be obtained by direct acylation of phosphorus(V) acid amides.[53,54]

Carboxylic acid anhydrides are also effective as the acylating agent. Thus, treatment of phosphorus(V) acid amides with butyllithium at −78 °C, followed by acetic formic anhydride, affords an entire range of *N*-phosphorylated amides and thioamides possessing pesticidal activity.[55] Acylation of thiophosphorus(V) acid amides can also be achieved with acetic anhydride in the absence of catalyst or in the presence of catalytic amounts of sulphuric or phosphoric acid.[56–59] Ketenes may also be used as the acylating agent in acetic acid containing sulphuric acid as catalyst.[59]

It is less convenient to prepare *N*-phosphorylated and *N*-thiophosphorylated amides by phosphorylation of carboxylic acid amides with phosphorus(V) acid halides. Thus, attempts to synthesise *N*-phosphorylated amides by treatment of carboxylic acid amides with dialkyl phosphorochloridates in the presence of triethylamine were unsuccessful. Under these conditions phosphorylation afforded the corresponding tetraalkyl pyrophosphates and nitriles, rather than the desired (I),[45] as shown in Scheme 2.

Scheme 2

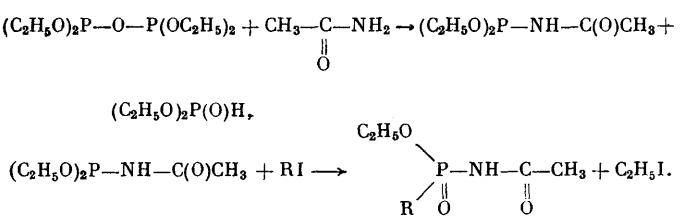


Tetraalkyl pyrophosphates and phenyl isocyanide were obtained by using formanilide.[45] Similar results were obtained on the interaction of amides with phosphono- and thiophosphono-chloridates.[60]

However, if the above phosphorylation is carried out on *N*-metallated acylamines rather than acylamines themselves, the desired displacement takes place in one step. Thus, *N*-sodio derivatives are phosphorylated with thiophosphorochloridates in 46–89% yield[51] (see Table 1). However, thiophosphorylation of amides in the presence of sodium hydride is not very effective (~18% yield), while in superbasic media (DMSO/KOH) the yield of *N*-phosphorylated amides can be increased to 45%.[54]

Phosphorus acid anhydrides are, evidently, also suitable for the phosphorylation of acylamines. Thus, *N*-phosphorylated acetamides may be prepared by using tetraethyl pyrophosphite as phosphorylating agent: the initially formed diethyl *N*-acetylphosphoromonoamidite then undergoes Arbuzov reaction with alkyl iodides to give the corresponding *N*-acetylphosphonamidates,[37] as shown in Scheme 3.

Scheme 3



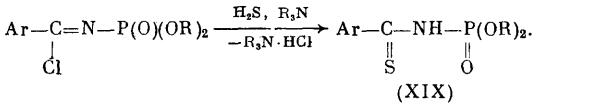
However, this route is more of theoretical than preparative interest, partly because the phosphorylating agent is not readily available and partly because it is difficult to separate the desired product for the diethyl phosphite formed as by-product.

2. Synthesis of *N*-phosphorylated thioamides

Although *N*-phosphorylated amides and thioamides are structurally similar, it is not always possible to adapt methods developed for the preparation of *N*-phosphorylated amides to the preparation of thioamide analogues. In recent years, a rather specific route has been developed for the synthesis of sulphur-containing *N*-phosphorylated acylamines. It is based on the addition of thio- and dithio-phosphorus acids to compounds containing a carbon-nitrogen multiple bond. The analogous addition of organophosphorus acids has not yet been reported. This highlights the necessity to distinguish the synthesis of *N*-phosphorylated and *N*-thiophosphorylated amides from that of *N*-phosphorylated and *N*-thiophosphorylated thioamides.

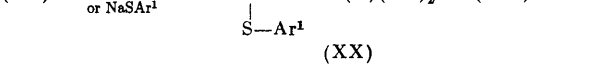
Attempts to adapt the phosphazo reaction to the preparation of thioamide derivatives, largely undertaken by Kirsanov, et al. in 1960,[61] met with failure. Thus, it was shown that the interaction of thiobenzamide with PCl_5 under the conditions of the phosphazo reaction leads to a complex mixture of products (HCl, PCl_3, $PSCl_3$, nitriles, thiadiazoles, and other unidentified compounds), rather than to the desired *N*-thioacylphosphazenes.[61]

However, cleavage of *N*-dialkoxyphosphoryl- and *N*-diaryloxyphosphoryl-iminochlorides with H_2S proceeds quite readily to give the corresponding *N*-phosphorylated thioamides (XIX). This is analogous to the hydrolysis of iminochlorides (XV).

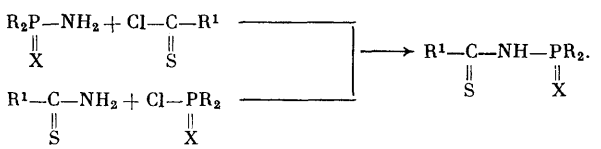


The above reaction can be achieved by using a tertiary amine as base, and leads to a high yield of desired product (70–98%).[61]

N-Phosphorylated thioamides (XIX) may also be obtained in 60–90% by treatment of (XV, R = aryl) either with thiophenols (in the presence of tertiary amine) or with sodium arylmercaptides, followed by hydrolysis of the resulting thioiminoesters (XX) in aqueous alcoholic media containing a base.[40]



For the preparation of *N*-phosphorylated thioamides and *N*-thiophosphorylated thioamides from readily available starting materials, more attention has been focussed on acylation or phosphorylation routes with acid chlorides (see earlier and in Tables 1 and 2), according to the following scheme:



The first of these methods, however, has no preparative value since thiocarboxylic acid chlorides are not readily available and, in many instances, are extremely unstable. The second route, based on the reaction of thioamides with phosphorus(V) acid chlorides is more effective.

In 1967 the synthesis was reported of *N*-(diphenylthiophosphinyl)thioacetamide by interaction of diphenylthiophosphinyl chloride with thioacetamide, as well as by action of methyllithium on diphenylthiophosphinyl isothiocyanate.[62] However, in each instance, acetonitrile and a diphenyldithiophosphinate were formed instead of the anticipated *N*-thiophosphinylthioamide (I, R = Me, R^1 = Ph, X = Y = S). Similar results were obtained for the interaction of diphenylthiophosphinyl chloride with the sodio-derivative of thiobenzamide.[63] However, the latter reaction with dimethyl- and dibenzyl-thiophosphinyl chloride does afford the desired *N*-thiophosphinylthioamide (I, R = Ph, R^1 = Me, $PhCH_2$, R^2 = H, X = Y = S) in 60–67% yield[51,63] (see Table 2).

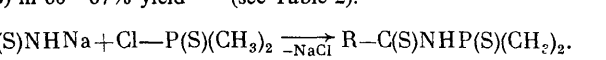


Table 2. Phosphorylation of thioamides.

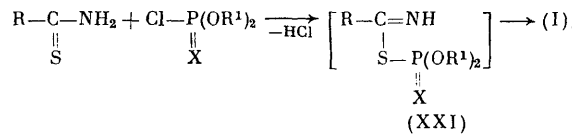
Thioamide	Phosphorylating agent	Reaction conditions	Product	Yield, %	Reference
RC(S)NHNa	$(CH_3)_2P(S)Cl$	THF, heat	$RC(S)NHP(S)(CH_3)_2$	60–67	[51, 63]
$CH_3C(S)NH_2$	$(iso\text{-}PrO)_2P(S)Cl$	*t*-BuOK in anhydrous MeCN	$CH_3C(S)NHP(S)(OPr\text{-}iso)_2$	15	[64]
$C_6H_5C(S)NH_2$	$(iso\text{-}PrO)_2P(S)Cl$	NaH, THF, heat, 15 h	$C_6H_5C(S)NHP(S)(OPr\text{-}iso)_2$	4	[65]
$RC(S)NH_2$	$(R^1O)_2P(S)Cl$	THF, $R_4N^+Cl^-$ (R = Et, Bu)	$RC(S)NHP(S)(OR^1)_2$	37–45	[53, 54, 66]
$RC(S)NH_2$	$(R^1O)_2P(S)Cl$	Dibenzo-18-crown-6, KOH, MeCN	$RC(S)NHP(S)(OR^1)_2$	51–66	[53, 54, 66, 67]
$RC(X)NH_2$	$(R^1O)_2P(Y)Cl$	DMSO, KOH	$RC(X)NHP(Y)(OR^1)_2$	65–80	[53, 54, 66]

The *N*-thiophosphorylthioamide (I, R = Me, R^1 = OPr-*i*, R^2 = H, X = Y = S) was obtained in 15% yield by treatment of diisopropyl dithiophosphorochloridate with the potassium salt of thioacetamide, prepared by treatment of the latter with potassium *tert*-butoxide.[64] The same reaction with thiobenzamide in the presence of sodium hydride gave only a small amount of desired product.[65] Phosphorylation of thioamides with phosphoryl chlorides does not take place in the absence of base or with weak organic bases.

Recently, *N*-phosphorylated thioamides and *N*-thiophosphorylated thioamides were prepared under phase transfer catalysis or in superbasic medium by treatment of thioamides with phosphoryl and thiophosphoryl chlorides (see Table 2). The yield of desired product is 37–45% in 50% KOH containing a quaternary ammonium salt as phase transfer catalyst.[53,54,66] The yield can be increased to 62–66% if solid KOH/crown ether is used in place of the above 2-phase procedure with a quaternary ammonium salt and aqueous base, under which conditions undesired hydrolysis of the phosphoryl chloride takes place to some extent.[53,54,66,67]

In spite of the undoubted advantages of phase transfer catalysis for the phosphorylation of thioamides, the method is not applicable to the reaction of thioacetamide with dialkyl phosphorochloridates or to the reaction of thiobenzamide with dimethyl phosphorochloridate.[64–66] However, these reactions are possible in superbasic media, e.g. solid KOH in dimethyl sulphoxide.[53,54,66] The method can be used for the preparation of all four types of compound (I) with any organic substituent at the (thio)carbonyl or (thio)phosphoryl centre (see Table 2).

By analogy with the reaction of secondary N-sodiothioamides with acyl chlorides, which involve initial formation of *S*-acylthioimidates,[68] it has been proposed that the above phosphorylations proceed with the initial formation of an *S*-phosphorylthioimidate (XXI), which subsequently isomerises to give (I) by 1,3-*S*→*N*-(thio)phosphoryl group migration:



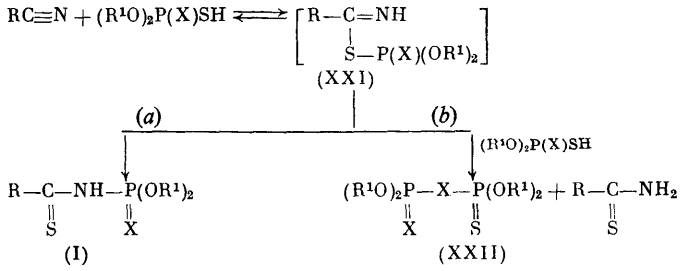
(XXI)

Apparently, the formation of intermediate (XXI) is dependent on a number of factors, which to a large extent compensate one for the other. Thus, in strongly basic media, deprotonation of acylamines is relatively facile, but, on the other hand, strong solvation of the phosphorus atom, bearing an effective positive charge, hinders the S_N2 displacement at phosphorus. It would also appear that the inductive effects of substituents at the carbon atom of the (thio)carbonyl group and at phosphorus on the rate of substitution are in the opposite sense: on the one hand the effect is to increase the acceptor properties of R, thereby facilitating *N*-deprotonation, and on the other hand to decrease the nucleophilic properties of the conjugate amide anion. Thus, structure-reactivity relationships involving phosphoryl chlorides are difficult to interpret. In this context, it is necessary to consider the effect of all the groups linked to phosphorus, both on the phosphorylation step and on the isomerisation of the intermediate (XXI) to give (I). The latter process also involves an S_N2 displacement at phosphorus, again subject to the juxtaposition of various intermolecular and intramolecular forces. Thus, the reaction in question is subject to a fine balance of various factors (electronic, steric, catalytic, medium effects), so that it is critical to select the appropriate method for each particular case.

N-Phosphorylated and *N*-thiophosphorylated thioamides may also be prepared by the reaction of monothio- and dithio-phosphorus(V) acids with nitriles.[69–74] This reaction proceeds via addition of the thiophosphorus(V) acid to the cyano group with the initial formation of the corresponding *S*-phosphorylthioimidate (XXI). The latter isomerizes to the corresponding *N*-(thio)phosphorylated thioamides (I, X = S, Y = O; see route (a) of Scheme 4) via 1,3-*S*→*N*-migration of the (thio)phosphoryl group. It should be

pointed out that the *S*-phosphorylthioimidates (XXI), being excellent phosphorylating agents in themselves, also undergo cleavage of the P–S bond by the starting thiophosphoric acid, with the result that carboxylic acid thioamides and (tri)thiopyrophosphates (XXII) are formed as by-products in a concurrent step of the reaction, i.e. path (b).

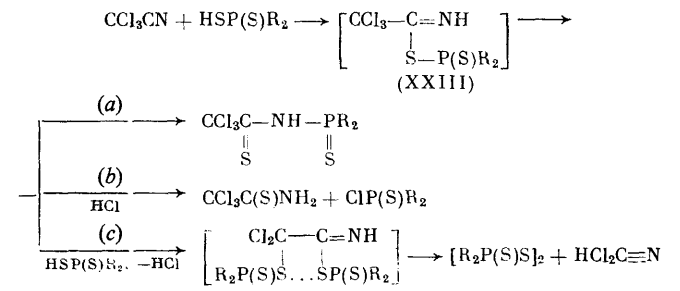
Scheme 4



The yield of phosphoramides (I) depends on the nature of the nitrile, the structure of the thiophosphoric acid, the proportion of the reactants, the reaction conditions, and the presence of impurities. The highest conversion of dithiophosphoric acids to thioamides (I) was achieved with aromatic nitriles.[71,75–78] Aliphatic nitriles either do not react at all or are converted to the corresponding *N*-thiophosphorylated thioamides only in small yield. In this instance, pathway (b) (Scheme 4) is the predominant step.[75] The method is not suitable for preparing *N*-diphenylthiophosphinyl-thioamides since diphenylthiophosphinic acid reacts with nitriles only by pathway (b).[72,79,80]

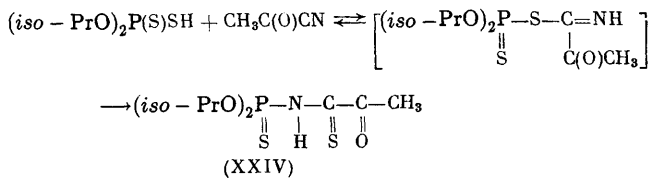
O,O-Dialkyl hydrogen thiophosphates are noticeably less reactive towards nitriles,[65,69,70,74] being converted to *N*-phosphorylated thioamides (I) only in 2.5–12% yield.[65] In no instance has it been possible to isolate the intermediate thioimidates (XXI) by reaction of (di)thiophosphoric acids with nitriles, although there is one publication in which the authors incorrectly assigned an *S*-dithio-phosphorylthioimidate structure to what, in fact, were *N*-thio-phosphorylated thioamides.[72] Only in the reaction with chloroacetonitrile has it been possible to detect the intermediate formation of *S*-dithiophosphorylthioimidates (XXIII) by ^{31}P NMR spectroscopy; in this instance, the intermediates undergo a number of transformations over the course of several hours.[81,82]

Scheme 5

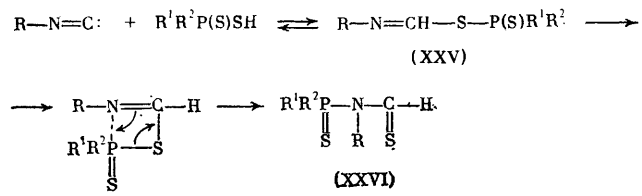


As shown in Scheme 5, only one of the ensuing reactions of (XIII), path (a), leads, via isomerisation, to *N*-thiophosphorylated thioamides, which were isolated in low yield. Decomposition with hydrogen chloride is also an energetically favourable reaction of (XIII), i.e. path (b) and in a third option, the intermediate may react with the starting dithiophosphorus(V) acid, i.e. path (c). This is a redox step which results in the formation of dichloroacetonitrile and a bis(dialkylthiophosphoryl) disulphide.

The reaction of dithiophosphorus(V) acids with benzoyl and acetyl cyanide is equally complex.[83,84] In the reaction with acetyl cyanide, it is only possible to isolate an *N*-thiophosphorylthioamide (XXIV) by treatment with *O,O*-diisopropyl hydrogen dithiophosphate. However, the yield of (XXIV) was only 12%.[71,84]



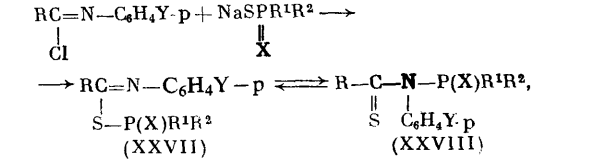
N-Thiophosphorylated thioformamides are readily formed by interaction of dithiophosphorus(V) acids with isonitriles, the method being similar to the reaction with nitriles. Thus, treatment of dithiophosphoric acids with 2,6-dimethyl- and 2,6-diethyl-phenyl isocyanide affords α-adducts (XXV),[84] which isomerise into the corresponding *N*-thiophosphorylthioformamide (XXVI).[71,86]



where R = C_6H_{11}, C_6H_5, 4-$CH_3C_6H_4$, 2,5-$(CH_3)_2C_6H_3$, 2,6-$(CH_3)_2C_6H_3$, 2,6-$(C_2H_5)_2$. C_6H_3; R^1,R^2 = AlkO

It has been established that the rearrangement of (XXV) to (XXVI) is a first-order reaction.[85] By substituting *O,O*-dimethyl dithiophosphate for *O,O*-diethyl dithiophosphate, the rate of the rearrangement is increased. Reaction is clearly slower with acidic dithiophosphonates (as opposed to dithiophosphates), and derivatives of diphenyldithiophosphinic acid do not rearrange at all.[85–87] Isomerisation is enhanced as the nucleophilicity of the nitrogen atom increases.[79,80] Formamides of type (XXVI) were not formed by reaction of isonitriles with dialkyl phosphoric[88] and monothiophosphoric acids or with monothiophosphonic acids.[89]

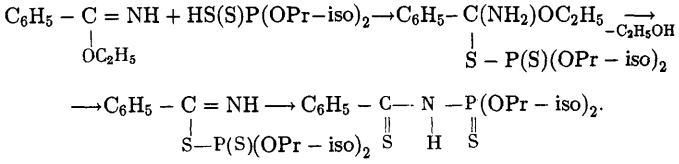
Tertiary *N*-phosphorylated thioamides and *N*-thiophosphorylated thioamides (XXVIII) may be prepared by reaction of iminochlorides with monothio- and dithiophosphorus(V) acids.[87,90] With acid derivatives having an O–P–S residue, reaction proceeds by attack of the sulphur atom.



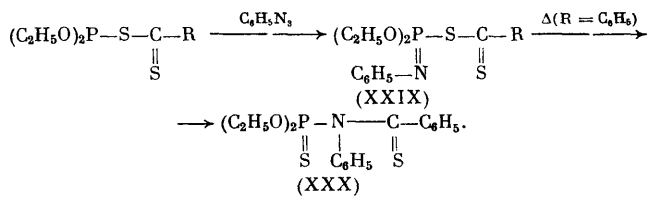
where R = C_6H_5, R^1 = R^2 = AlkO, X = O, S, Y = H, Br, CH_3, CH_3O, NO_2.

In certain instances, the thioamides (XXVIII) are formed as an equilibrated mixture with their thioimidate form (XXVII).

A low yield (3–5%) of *N*-thiophosphorylated thioamides has also been recorded by interaction of dithiophosphoric acids with iminoesters.[71,82,91,92]



Recently, tertiary *N*-thiophosphorylated thioamides, e.g. (XXX), have been obtained from *O,O*-dialkyl S-thioaroyl thiophosphorimidates (XXIX), which undergo imide-amide rearrangement by S→N-migration of the thiocarbonyl group within the S–P–N residue.[93] The rearrangement also takes place on distillation of the product obtained by Staudinger reaction of *O,O*-dialkyl S-thioacyl monothiophosphites with phenyl azide.



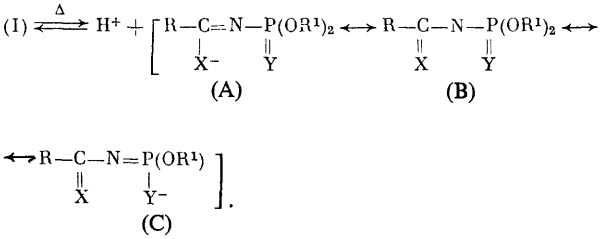
A similar rearrangement, involving migration of a trifluoroacetyl group within the O–P–N residue, has been observed with *O*-acylphosphazo compounds.[94]

III. The structure of *N*-phosphorylated amides and thioamides

Each of the four types of *N*-phosphorylated amide (I) contain three potentially reactive centres—a carbonyl (or thiocarbonyl) group, a phosphoryl (or thiophosphoryl group), and a secondary >N–H group with a labile hydrogen atom. Each of these groups migrates fairly easily, thereby facilitating proto-, acylo- and phosphoro-tropic processes.[36,51,87,95–97] The question of deprotonation and hydrogen migration to the basic centres X, Y and N in (I) has already been addressed quite thoroughly in the literature.[36,37,51,95–97]

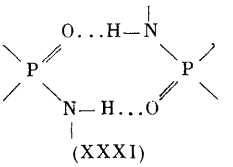
Amides (I) are moderately strong acids. From potentiometric data, it has been calculated that the acid dissociation constants, pK_a, in water[36,96] or aqueous alcoholic media[36,51,95–99] are in the range 4.16–10.7, depending on the nature of the substituent in the acyl and phosphoryl residue.

Numerous and diverse IR-spectroscopic studies on (I) have been carried out, primarily to analyse prototropic shifts and determine the character of hydrogen bonding in these compounds. It has been shown that under normal conditions in solution and in concentrated media, they exist exclusively in the amide form;[36,37,95,97–104] dissociation of the amide hydrogen may only take place at fairly high temperature in solution or on melting. The electronic structure of the resulting anion may be represented by three canonical forms:



On varying the conditions (in solution, in the melt, or on heating), the contribution of each structure may change. The corresponding shifts in the electron density of the anion can be detected in the IR spectrum of the compounds.[104] At the same time, ^1H and ^{31}P NMR spectroscopy indicates the extent of intramolecular hydrogen bonding of the type P=S(O)...H–N and C=O(S)...H–N.[105]

The structures of compounds (I) are dependent to a large extent on the nature of the hydrogen bonding in the various associated amide forms. In *N*-phosphorylated amides, hydrogen bonding of the type C=O...H–N[98,101] or P=O...H–N[36] may be evident. However, in *N*-phosphorylated thioamides, the thioacyl group does not participate in hydrogen bonding; in such compounds, the molecules are associated in the form of cyclic hydrogen-bonded dimers of type (XXXI).



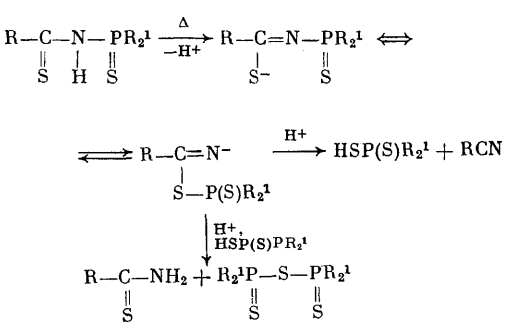
The IR spectra of *N*-thiophosphorylated thioamides indicate that the character of the hydrogen bonding depends on the nature of the acyl group. Derivatives of thioacetamide (I, R = Me, R^1 = OPr-*i*, R^2 = H, X = Y = S) are stabilised in the solid state by intermolecular hydrogen bonding of the type C=S...H–N, which is easily disrupted on dissolving the compounds in carbon tetrachloride. Thiobenzamide analogues (I, R = Ph, R^1 = OPr-*i*, R^2 = H, X = Y = S), however, are characterised by hydrogen bonding of the type P=S...H–N, which is also disrupted on dissolution.[104] Carbonyl analogues of these compounds are associated by intermolecular hydrogen bonding involving the carbonyl oxygen;[104] however, in the solid phase and in solution one cannot exclude the possibility of hydrogen bonding with the thiophosphoryl group. Hydrogen bonding in *N*-phosphorylated thioamides (I, X = S, Y = O) can be simply represented by the dimeric structure (XXXI), the thiocarbonyl group being unassociated. It has been shown[104] that the majority of compounds of type (I) exist in solution or in the melt as an equilibrated mixture of associates each having a distinct electronic structure.

IR- and ^1H or ^{31}P NMR-spectroscopic studies of *N*-(diisopropoxythiophosphoryl)thioacetamide at high temperature (80–170 °C).[104] have provided evidence on the chemical processes which take place under these conditions (Scheme 6).

Table 3. Bond lengths for compounds of general formula $R-\underset{\underset{X}{\|}}{C}-\underset{\underset{R^2}{|}}{N}-\underset{\underset{Y}{\|}}{PR_2^1}$

Compound	R	R^1	R^2	X	Y	Bond lengths, Å							Reference
						C=X	C–N	N–H	P=Y	N–P	N...Y	H...Y	
(I, *a*)	C_6H_5	CH_2CH_2N	H	O	O	1.211	1.376	0.71	1.475	1.671	2.84	2.14	[108]
(I, *b*)	m-IC_6H_4	CH_2CH_2N	H	O	O	1.226	1.364		1.428	1.661	2.78	1.81	[109]
(I, *c*)	p-FC_6H_4	CH_2CH_2N	H	O	O	1.219	1.375	0.79	1.473	1.664	2.84	2.06	[110]
(I, *d*)	p-$CH_3OC_6H_4$	CH_2CH_2N	H	O	O	1.215	1.385	0.98	1.482	1.664	2.89	1.91	[111]
(I, *e*)	$CH_2=CHCH_2OC_6H_4$	CH_2CH_2N	H	O	O	1.220	1.378		1.468	1.678	2.84	1.91	[112]
(I, *f*)	CH_3	OPr-iso	H	S	S	1.643	1.345	0.80	1.905	1.684	3.346	2.55	[64]
(I, *g*)	C_6H_5	OPr-iso	H	O	O	1.185	1.386	0.76	1.443	1.649	2.79	2.07	[113, 114]
(I, *h*)	C_6H_5	OPr-iso	H	O	S	1.218	1.356	0.97	1.903	1.688	2.913	2.21	[52, 116]
(I, *i*)	C_6H_5	OPr-iso	H	S	S	1.635	1.354	0.99	1.912	1.686	3.613	2.72	[115, 116]
(I, *j*)	C_6H_5	OPr-iso	K	S	S	1.703	1.312		1.940	1.620	–	–	[113]
(I, *k*)	C_6H_5	OPr-iso	Hg	S	S	1.733	1.286		1.980	1.610	–	–	[117, 118]
(I, *l*)	C_6H_5	OPr-iso	Pb	S	O	1.740	1.268		1.492	1.634	–	–	[117, 119]
(I, *m*)	C_6H_5	OPr-iso	H	S	O	1.646	1.360	0.92	1.457	1.672	–	–	[119]
(I, *n*)	C_6H_5	OC_2H_5	H	S	O	1.633	1.359	0.82	1.456	1.667	–	–	[116]

Scheme 6

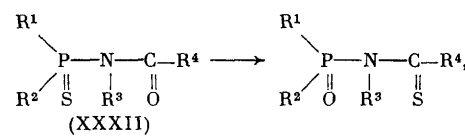


This has been supported by independent studies.[87,97]

The identification of nitriles, thioamides, dithiophosphates and trithiopyrophosphates among the products formed by thermolysis of *N*-thiophosphorylated thioamides provides unequivocal support for the above pathway (Scheme 6), which incorporates a protolytic dissociation and an amidothiophosphate-imidoyldithiophosphate rearrangement. These represent clear examples of 1,3-(N→S)-thiophosphoryl migration in secondary *N*-phosphorylated amides (see Ref. 87 and references cited therein).

Thiophosphoryl group migration in tertiary *N*-thiophosphorylated thioamides also takes place readily. In certain instances, such thioamides exist at room temperature as a tautomeric mixture, in which the proportion of the two forms may reach 1 : 1.[82,87,90] It has been shown that the position of the amide-imide equilibrium depends on several factors and to a large extent on the nature of the substituent on the tertiary nitrogen atom†.

Recently, it has been shown that tertiary *N*-thiophosphorylated amides readily undergo isomerisation wherein the oxygen atom of the carbonyl group and the sulphur atom of the thiophosphoryl group are transposed.[106,135]



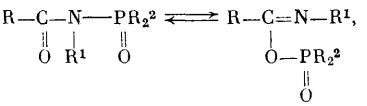
(XXXII)

R^1, R^2=CH_3O, C_6H_5; R^3=H, CH_3, C_6H_5; R^4=CH_3, C_6H_5, iso-BuO

For compounds (XXXII; R^3 = Me or Ph), the isomerisation proceeds even at 40 °C. However, (XXXII); R^3 = H) failed to isomerise. The rate of rearrangement decreases as follows: (XXXII; R^1 = R^2 = MeO) > (XXXII; R^1 = MeO, R^2 = Ph) > (XXXII; R^1 = R^2 = Ph). Benzoylamides (R^4 = Ph) rearrange significantly more readily than acetamide derivatives (R^4 = Me).

† The factors responsible for phosphorylotropic processes in compounds of type (I) have been analysed in more detail in earlier reviews.[82,87] Of necessity, the present review only touches on more recent data in this area.

With oxy-analogues (I, X = Y = O), N→O-phosphoryl migration has been detected under the conditions of electron impact mass spectrometry.[107]



$R = CH_3$, C_6H_5; $R^1 = H$, CH_3; $R^2 = CH_3O$, C_2H_5O, C_2H_5.

Data obtained from X-ray structural analyses of amides (I) and certain of their metallated derivatives (Table 3) confirm the amido(thio)phosphate structure for these compounds. There was no evidence to support any isomeric structure. From these structural analyses of compounds (I), it is quite clear that the *N*-benzoyl derivative (Ia), its analogues (Ib–e), and compounds (If–i) (studied by ourselves) are associated by intermolecular hydrogen bonding. Compounds (Ig) and (Im) are associated by hydrogen bonding of the type N–H...O=P; in compound (Im) the molecules are linked in the form of a centrosymmetrical dimer, while in the oxygen analogue (Ig) the dimer is associated with other molecules in the crystal lattice. In the *N*-thiophosphorylated thioamide (Ii), hydrogen bonding forces the molecules into uniformly extended spiral chains. The molecules of compound (Ih) also exist as a uniform chain linked by hydrogen bonding of the type N–H...O=C.

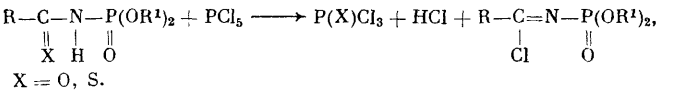
The P=S and P=O bond lengths in compounds (I) are as would be anticipated.[120] The nitrogen atom is planar tricoordinated, the P–N bond length being shorter than the norm (1.77 Å) indicative of partial double bond character. All the compounds in the Table contain the atomic grouping, PNHC(Y)C, the planarity of which provides evidence for π-delocalisation of the double bond, O=C=N, as is found in peptides. This is supported by the bond lengths for compounds (Ig) and (Ih).

In the thioamide anion (Ij), the P=S and C=S bond lengths are longer than in the neutral molecule (Ii), while the P–N and N–C bond length are shorter. This confirms that the negative charge is delocalised in the fragment XCNPY.[113] In the mercury and lead complexes (Ik, Il), the C=S and P=S(O) bond lengths are even greater, approximating to single bonds, while the P–N and N–C bonds are even shorter.[117–119]

IV. Chemical properties

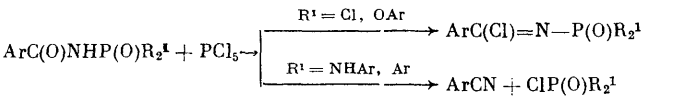
N-(Thio)phosphorylated amides and thioamides participate in a variety of chemical reactions by involvement of one or more of their potentially reactive centres: the labile hydrogen (in secondary amides), the nucleophilic atoms of oxygen or sulphur, and the electrophilic atoms of phosphorus and carbon of the P=X- and C=Y-groups. However, in their reactivity, compounds (I) are markedly different, depending on the nature of atoms X and Y and their bonding, and on the nature of the substituents at the (thio)carbonyl and (thio)phosphoryl centres.

N-Phosphorylated amides (I, X = Y = O) are relatively inert and only a limited number of their reactions have been studied. The replacement of chlorine atoms at the phosphorus centre has been discussed in section II.1. *N*-Acyl- and *N*-thioacyl-phosphoromonoamidates, obtained by alcoholysis of the corresponding dichlorides, react with PCl_5 to give the corresponding *N*-phosphorylated iminochlorides[39,61] which are valuable synthons for the preparation of other derivatives of I.[12,13,17,34,121]

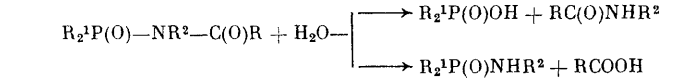


X = O, S.

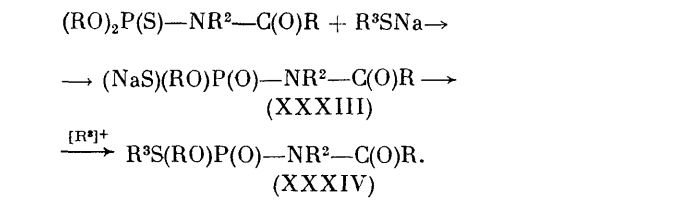
The reaction of PCl_5 with arylcarboxylic acid *N*-phosphinylamides depends on the nature of the substituents in the phosphinyl group: dichloro- and diaryloxy-phosphinyl derivatives are also converted into iminochlorides, whereas bis(arylamino)- and diaryl-phosphinyl derivatives are cleaved to give the corresponding phosphorus(V) acid chloride and aryl cyanide.[15,24]



As *N*-phosphorylated amides (I, X = Y = O) are weakly acidic, they are readily converted to the corresponding salts on treatment with alkali metal hydroxide or alkoxide;[20,122,123] depending on the conditions, hydrolysis of *N*-phosphorylated amides may take place[124] either by cleavage of the P–N[38,56] or C–N[42] bond.

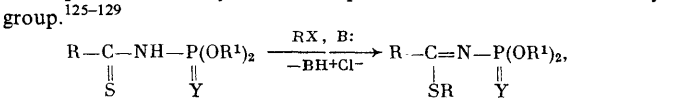


Treatment of tertiary *N*-thiophosphorylated amides with sodium alkylmercaptides effects isomerisation of the thiophosphoryl groups to give the corresponding sodium thiolophosphoramidates (XXXIII) which are readily converted to diesters (XXXIV) with alkyl halide. The products are analogues of acephate.[46]



Attempts to alkylate *N*-phosphorylated amides with alkyl halides in the presence of triethylamine were without success, even on prolonged heating of the reactants,[125] Evidently, the nucleophilicity of the OPNCO group is insufficient for nucleophilic substitution under these conditions.

Amides (I), where either or both of the oxygen atoms (X,Y) are replaced by sulphur, are considerably more reactive. The alkylation of *N*-phosphorylated thioamides (I, X = S, Y = O) and *N*-thiophosphorylated thioamides (I, X = Y = S) with alkyl halides takes place exclusively at the sulphur atom of the thiocarbonyl group.[125–129]



Y = O, S; R = Alk, CH_2COOH, $CH_2COOH \cdot N(C_2H_5)_3$, $CH_2C(O)OCH_3$, CH_2CN.

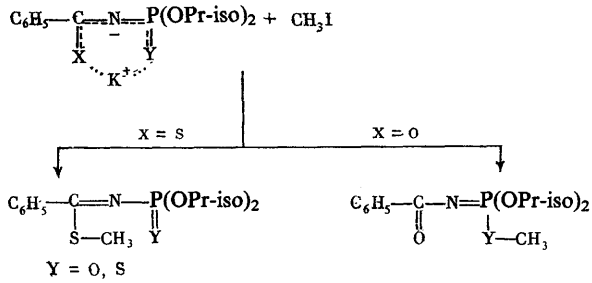
Complete regioselectivity was observed on alkylation with monochloroacetic acid, -acetic acid ester, -acetonitrile, and -acetic acid triethylammonium salt.[126]

On methylation of (I, X = O, Y = S) with diazomethane, S-methylation of the thiophosphoryl group was preferred over N-methylation by a factor of 9:1.[128] However, on alkylation of dimethylthiophosphinic N-thiobenzoylamide with diazomethane, the sulphur atom of the thiocarbonyl group is marginally more reactive than the sulphur atom of the thiophosphinyl group (by a factor of 6:5).[51]

$$C_6H_5C(S)NHP(S)(CH_3)_2 \xrightarrow{CH_2N_2} C_6H_5C(SCH_3)=N-P(S)(CH_3)_2 + C_6H_5C(S)-N=P(SCH_3)(CH_3)_2.$$

With the *N*-potassio derivatives of (I), the regioselectivity of alkylation is higher[124] (see Scheme 7). Thus. methylation of *N*-phosphorylated and *N*-thiophosphorylated *N*-potassiothioamides takes place exclusively at the thiocarbonyl group, irrespective of the nature of the Y atom (O or S); in contrast, with *N*-phosphorylated and *N*-thiophosphorylated amides, reaction takes place only at the phosphoryl (or thiophosphoryl) centre. The yield of alkylated product is always high (73–86%).[129]

Scheme 7



These studies verify that the regioselectivity of alkylation of (I) is dependent on the nature of the nucleophilic centres present and on the reaction conditions. The sulphur atom of the thiocarbonyl group possesses the highest nucleophilicity and polarisability. Suitably activated thiophosphoryl and phosphoryl groups may also be alkylated, but the carbonyl oxygen is effectively inert under these conditions. Alkylation of the XCNPY function can be promoted by increasing the basicity of the medium: by choosing a stronger base (or superbase), by the addition of crown ethers, or by conducting the reaction under phase transfer catalysis conditions. The nature of the alkylated product depends also on the type of amide: *N*-thiocarbonyl derivatives afford imino(thio)phosphates, whereas *N*-acyl derivatives yield phosphazo compounds (see Scheme 7). The nitrogen atom is relatively inert, presumably for steric reasons

The high nucleophilicity of the thiocarbonyl group in *N*-phosphorylated and *N*-thiophosphorylated thioamides is the salient factor determining their reactivity. In the absence of catalyst, these thioamides add to compounds with a carbon-nitrogen multiple bond. Thus, interaction with *N*-acetyltrichloroacetaldimine under mild conditions leads, exothermically, to adducts (XXXV) in >90% yield. The reaction takes place over several hours.[130]

$$(RO)_2P(X)-NH-C(S)-R^1 + CCl_3CH=N-C(O)-CH_3 \longrightarrow (RO)_2P(X)-N=C(R^1)-S-CH(CCl_3)-NH-C(O)-CH_3$$

X=O, S. (XXXV)

In a similar way, the thiocarbonyl sulphur of *N*-thiophosphorylated thioamides reacts with cyclohexyl isocyanide to give S-iminoformyl derivatives:[131]

$$XC_6H_4-C(S)-NH-P(S)(OR)_2 + \text{cyclo-}C_6H_{11}N=C: \rightarrow (RO)_2P(S)-N=C(C_6H_4X)-S-CH=N-C_6H_{11}\text{-cyclo}$$

Evidently, reactions of thioamides (I) may proceed via an initial isomerisation into an imidoyl thio- or dithiophosphate. Thus, *N*-thiophosphorylated thioformamides (XXVI) interact with aromatic amines by nucleophilic attack at the methine carbon of the intermediate anil (XXXVI) to give the corresponding formamidine salts of dithiophosphoric acid O,O-diesters (XXXVII).

$$H-C(S)-N(Ar)-P(S)(OR)_2 \rightleftharpoons Ar-N=CH-S-P(S)(OR)_2 \xrightarrow{ArNH_2} [Ar-N=CH-NHAr]\cdot[HSP(S)(OR)_2]$$

(XXVI) (XXXVI) (XXXVII)

The latter compounds were also prepared independently from a mixture of the appropriate dithiophosphoric acid and anil.[71,86] Acidic cleavage of tertiary *N*-thiophosphorylated thioamides by protic reagents such as water or monothiophosphoric, acetic, thioacetic, and trifluoroacetic acid is thought to proceed in a similar way.[132] It is proposed that this reaction, which takes place even at room temperature, involves an intermediate imidoyl dithiophosphate formed via amide-imidoyl tautomerism. The protic reagent then reacts to give the corresponding thioamide and anhydride (XXXVIII).[132]

$$R-C(S)-N(R^1)-P(X)(OR^2)_2 \rightleftharpoons R-C(S-P(X)(OR^2)_2)=N-R^1 \xrightarrow{HA} R-C(S)NHR^1 + A-P(X)(OR^2)_2$$

(XXXVIII)

A=OH, XP(S)(OR³)₂, OC(O)CH₃, XC(S)CH₃, OC(O)CF₃.

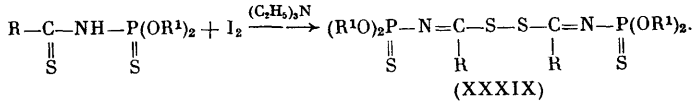
A number of redox reactions of *N*-thiophosphorylated amides and thioamides have also been studied. The outcome depends on the nature of the reagent. Thus, mercuric oxide effects replacement of the thioacyl sulphur atom by oxygen, thereby converting *N*-phosphorylated thioamides to the corresponding amide.[61]

$$ArC(S)NHP(O)(OR)_2 + HgO \rightarrow ArC(O)NHP(O)(OR)_2 + HgS.$$

Nitrogen oxides, iodine in ethanolic KOH, and hydrogen peroxide react with *N*-thiophosphorylated thioamides by sequential replacement of the two sulphur atoms by oxygen.[133] The phosphoryl sulphur is replaced initially, followed by the thiocarbonyl sulphur:

$$R-C(S)-NH-P(S)(OR^1)_2 \xrightarrow{[O]} R-C(S)-NH-P(O)(OR^1)_2 \xrightarrow{[O]} R-C(O)-NH-P(O)(OR^1)_2.$$

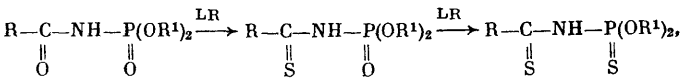
The oxidation of *N*-thiophosphorylated thioamides with iodine in carbon tetrachloride takes a completely different course in the presence of triethylamine:[133,134]



(XXXIX)

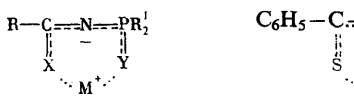
The disulphide (XXXIX) is also formed in small amounts by interaction of *N*-thiophosphorylated thioamides with lead oxide.[119]

There is also the possibility of sequential replacement of the oxygen atoms by sulphur, i.e. the conversion of *N*-phosphorylated amides to *N*-thiophosphorylated thioamides.[133] Lawesson's reagent (2,4-*bis*(*p*-methoxyphenyl)-1,2,3,4-dithiadiphosphetane 2,4-disulphide) is very effective for this purpose.[70]

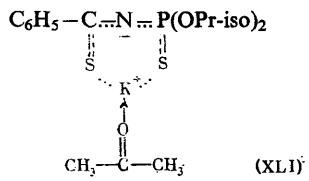


where LR = Lawesson's reagent.

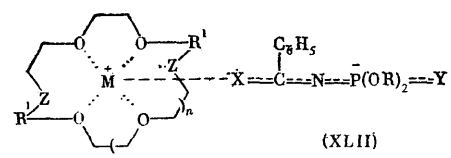
Recently, several publications have appeared (mainly from our own research) on the synthesis and properties of metallic salts of (I),[54,67,97,113,117–119,136,137] Alkali metal salts are formed from (I) by treatment of the amides and thioamides with alkali metal hydroxide or alkoxide. These salts can also be obtained by phosphorylation of amides and thioamides with (thio)phosphorochloridates under phase transfer catalysis conditions in the presence of base and a crown ether.[104,113] Salts of type (XL), their solvate complexes (XLI), and crown ether complexes (XLII) may all be prepared by these routes.



(XL)



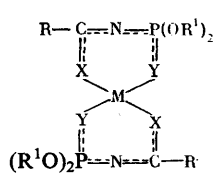
(XLI)



(XLII)

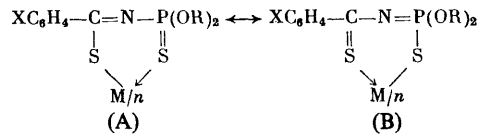
X, Y = O, S; Z = O, NH; n = 0, 1; M = Na, K; R = Alk; R^1 = $-(CH_2)_2-$ o-C_6H_4

Both Na^+ and K^+ complexes of type (XL) (X and Y = O or S) have been prepared.[113,117] Amides (I) also form 1:2 complexes (XLIII) with divalent metal cations.[51,66,97,118,119,136,137]



(XLIII)

These complexes are obtainable from both metal salts (M = Co^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+}, Pb^{2+}, Pd^{2+}, Hg^{2+}, etc.) and metal oxides (M = Hg, Pb). IR-, NMR-, and EPR-spectroscopic studies of [XLIII, M = Ni(II), Cu(II), Hg(II)] have shown that complexes exist as an equilibrated mixture of two isomeric forms, structure (A) predominating.[97,136]



(A) (B)

Spectrophotometric and potentiometric determinations of the stability of these complexes indicate that those with sulphur ligands are more stable. In complexes of the type ML_2, electron-accepting substituents (X) in the benzene ring of the thioacyl fragment tend to destabilise, and electron-donating substituents stabilise the structure. X-Ray analyses have also been performed on the mercury and lead complexes of *N*-phosphorylated thioamides (XLIII),[118,119] the bond lengths [for compounds (Ik) and (Il)] being given in Table 3.

V. Practical applications

As was mentioned earlier, of all the compounds of type (I), most attention has been given to O,S-dimethyl *N*-acetylthiophosphoromonoamidate which is a highly effective insecticide with low toxicity and a broad spectrum of activity. The compound is known under its commercial name, acephate, which is marketed by many companies throughout the world.[138] It is primarily a contact insecticide with limited systemic activity, being degraded in plants relatively quickly to give non-toxic products. In the soil, it is effective, on average, over 15 days, and it is completely deactivated within a year. According to the French company Chevron, which markets acephate under the name of Orthene, its protective action lasts from 7–10 days.[139]

The toxicity of the compound is relatively low: LD_{50} 945 mg/kg (orally in rats); 361 mg/kg (orally in mice); 2000 mg/kg (s.c. in rabbits).[49,139]

Two reviews on the chemistry and biological properties of acephate have been published[140,141] (the data therein being excluded from the present review). More recent information on the compound is given below. There have been dissertations on a whole range of problems associated with the use of acephate in the battle against pests and crop disease. The compound is very active against ticks and plant lice,[142–148] ants,[149,150] tobacco and maize infestations,[151,152] the larvae of ticks,[153] and termites.[154,155] There are also data on the use of acephate as an antiviral agent in plants,[156] and as a compound which affects the growth and quality of certain floral cultures.[157]

In a number of formulations containing acephate and a second active ingredient, synergism has been observed with a number of compounds: 2,2-dimethyl-1,3-benzodioxol-4-yl methylcarbamate, metoxil or carbaryl; peremetrin, O,O-dimethyl S-[α-(ethoxycarbonyl)benzyl] dithiophosphate, S-(3-phenyl-2(1*H*)-pyrazinon-5-yl) O,O-diethyl thiophosphate (in 1:4 proportion), ethoprophos (in 1:3 to 5:1 proportion), basudin (in 1:4 to 4:1 proportion), and 0.2–4% epoxidised linseed oil.[157–179] These combinations have been used successfully to combat various plant infestations, house flies, mosquitoes, etc.

As acephate is used extensively in agriculture, much attention has focussed on methods of detecting traces of this compound and one of its more toxic metabolites, O,S-dimethyl thiophosphoro-

monoamidate (monitor), in the surrounding soil,[180–182] in various organisms,[183] in biological samples,[184] in pesticidal formulations and commercial products,[185] in water, in food products, and in various agricultural products.[186–191]

A vast amount of research has been devoted to preparing analogues of acephate and diversely functionalised derivatives. The following *N*-acylaminophosphoryl derivatives, $(R^1Y)(R^2S)P(O)-NR^3-C(O)R^4$, have been reported: compounds where R^1 and R^2 = C_1-C_6-alkyl, alkenyl, alkynyl, R^3 = H or C_1-C_{18}-alkyl, R^4 = H, C_1-C_{18}-alkyl, C_3-C_8-cycloalkyl, C_2-C_{18}-alkenyl, C_3-C_{18}-alkynyl, Y = O,S;[48,49,192] compounds of type $(R^1S)(R^2O)P(O)NR^3-C(O)R^4$, where R^1 = Me, Et, $CH_2=CHCH_2$, $HC\equiv CCH_2$, R^2 = Me, Et, R^3 = H, Me, R^4 = H, alkyl, halogenalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylthioalkyl, alkenyl, $(CH_2)_nPh$ (*n* = 1,2), $CH=CMe_2$, $CH=CHPh$, CH_2YPh (Y = O,S);[49,193] compounds of type $(R^1O)_2P(S)-NH-C(O)R$, where R^1 = C_1-C_3-alkyl, R = aliphatic residue with 0–4 halogen atoms, C_6-C_{12}-aryl with 0–2 halogen atoms;[58] compounds of type $(R^1O)_2P(S)-NH-C(O)CH_2R^2$, where R^1 = C_1-C_3-alkyl, R^2 = H, aliphatic residue.[59]

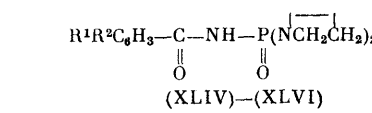
It has been shown that *N*-phosphorylated and *N*-thiophosphorylated halogenocarboxamides possess high herbicidal,[194] fungicidal,[194–197] and antimicrobial[198] activity; furthermore, acetylphosphates and -thionophosphates with halogenalkoxy groups on phosphorus also display the same pesticidal properties as amides (I).[56,57]

Patents have been deposited on pesticidal acephate salts and analogues thereof: $M^{2+}[(R^1O)(R^2S)P(O)-N=C(O^-)R]_2$, where M = Ca, Ba; R^1, R^2 = C_1-C_6-alkyl, R = C_1-C_{18}-alkyl;[122] $MS(R^1O)P(O)-NR_2-C(O)R$, where M = Na, K, NH_4, R^1 = C_1-C_6-alkyl, alkenyl or alkynyl, R^2 = H, C_1-C_6-alkyl, R = H, alkyl, phenyl, aralkyl or alkylaryl which may contain fluorine, chlorine, bromine, or a C_1-C_4-alkylthio group.[199]

It is reported that S-sodio derivatives may be used as starting materials for the preparation of acephate analogues, obtained by alkylation with alkyl halides or alkyl sulphonates[123] (see also Section IV and Ref. 46).

Numerous structure-activity studies have been carried out on acephate derivatives with pesticidal activity (see Ref. 49 and references cited therein). It has been found that it is the environment immediately surrounding the phosphorus atom which largely determines the biological activity of *N*-phosphorylated amides and thioamides. Thus, alkoxy and alkylthio groups on phosphorus impart pesticidal activity to amides (I). However, compounds with ethylenimino groups on phosphorus have another important practical use: as effective antiviral agents.[108–112] Bis(ethylenimino)-phosphoryl derivatives of substituted benzamides are the most active in this respect.[200]

In pharmacological studies of amides (I), most research has been devoted to evaluating the activity of *N*-bis(ethylenimino)phosphoryl-benzamide derivatives, notably benzoTEF (XLIV), fluorobenzoTEF (XLV), and diiodobenzoTEF (XLVI).[108–112]



(XLIV)–(XLVI)

(XLIV): $R^1=R^2=H$; (XLV): $R^1=H$, $R^2=4$-F;

(XLVI): $R^1=R^2=2,5$-I.

Clinically, benzoTEF has proved to be highly effective in the treatment of ovarian and lung cancer, and has also proved to be beneficial in the treatment of breast and stomach cancer, and other malignant diseases.[201] Fluorobenzoyl analogues of this drug have an even broader spectrum of therapeutic activity, having, for example, antiblastic properties.[202] Other analogues of benzoTEF have been synthesised and their toxicity (on s.c. and i.v. administration) measured. These data have shown that *n*-[bis(ethylenimino)-phosphoryl]-arylamines and-acylamines[21,203–209] generally possess lower toxicity than tris(ethylenimino)phosphate (TEF), which, having a relatively high LD_{100} value (30 mg/kg),[200] is widely used medicinally.

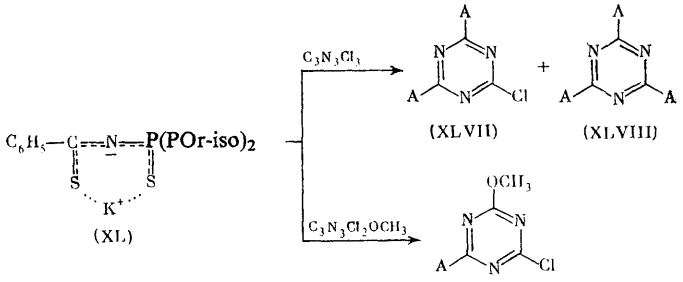
In view of the broad application of these compounds medicinally, there have been several reports in the literature on methods of identifying and assaying the drugs quantitatively in pharmacological preparations and in organisms.[210–214]

In recent years, other pharmacological uses of phosphorylated amides (I) have been studied. Their antiviral activity, for example, has been a topic of our researches.[67,215] Notably, it has been shown that acephate, *N*-thiophosphorylated thioamides (I, R = Me, R^1 = OPr-*i*, R^2 = H, X = Y = S), and the thiobenzamide analogue protect animals (white mice) exposed to influenzal pneumonia. The oxygen analogues (I, R = Ph, R^1 = OMe, R^2 = H, X = Y = O) do not possess antiviral properties, but the water-soluble N-sodio derivatives in certain instances do display an effective antiviral action.[67] A comparison of the antiviral activity of thioacetamide with that of the *N*-phosphorylated analogue has shown that there is little pharmacological difference between the two, but the phosphoryl derivative is less toxic.

Metallo-derivatives (XL) and (XLIII),[216] as well as crown ether complexes (XLII),[215] also possess antiviral activity. It has been found that the antiviral properties of these salts depends little on the nature of the organic substituents; it is the metal itself which largely determines their activity. A comparison of the antiviral properties of crown ethers and derivatives of type (XLII)[215] has shown that, whereas activity in the crown ethers is completely absent, the amide complexes (XLII), on the other hand, possess high activity. Effectively, it is the phosphorus-containing residue which is responsible for the biological activity, while the crown ether serves as lipophilic handle thereby facilitating penetration of the active agent across the cell membrane, i.e. enhances the rate of assimilation of the virucide in cells.[215]

In the search for new types of biologically active compound, a variety of functionalised *N*-phosphorylated amides and thioamides have been synthesised and tested. *N*-Substituted amides, obtained by alkylation with chloroacetic acid (see Section II[126,216,217]), are noticeably inferior to *N*-unsubstituted derivatives in their insecticidal and acaricidal properties. Triazine derivatives have also been prepared by treatment of *N*-potassio-*N*-thiophosphorylated thioamides with cyanuric chloride and its methoxy derivative. The former reacts by replacement of two or three chlorine atoms to give, for example, (XLVII) and (XLVIII), while the methoxy-analogue reacts by displacement of only one chlorine to give (XLIX). Compounds (XLVII) and (XLVIII) possess high fungicidal,

herbicidal and insecticidal activities, the former being 2.5 times as active as carbophos against sugar-beet lice.[218]



A = (iso-PrO)$_2$P(S)–N=C(C$_6$H$_5$)S– . (XLIX)

Among the metallo derivatives (XLIII), complexes with Cu(II), Ni(II), Co(II), Zn(II), Hg(II), Pb(II) and Ag(I) have also been found to possess insecticidal, fungicidal and antiviral properties.[54,216,218]

The synthesis of *N*-metallo derivatives of (I) broadens the potential value of these compounds. Thus, *N*-thiophosphorylated thioamides may be used as highly effective extractants, notably for the separation of copper from iron, zinc, lead, nickel, cobalt and other elements.[54,97,136,137] *N*-(Diisopropoxythiophosphoryl)benzamide, on the other hand, has been used in a liquid ion-exchange electrode for the determination of mercury in the presence of a variety of metal ions: Cu(II), Ni(II), Co(II), Zn(II), Cd(II), Pb(II), Mn(II), Fe(III), Cr(III), Be(III), Al(III), and Ag(I).[219]

In collaboration with others, we have also found new uses for amides (I) and their metallo derivatives (XL). Thus, amides (I) have been found to inhibit the corrosion of steel in concentrated solutions of mineral and carboxylic acids. In this respect, compounds with a P=S or C=S group are more effective than analogues with a P=O or C=O bond. These compounds offer 70–99.5% protection of steel in acids at varying concentration, and can also be used in galvanic systems.[220]

Potassium and sodium salts (XL) possess excellent sorption properties. In this instance, replacement of an oxygen atom in *N*-phosphorylated amides by an atom of sulphur leads (other things being equal) to an increase in chromatographic polarity constants relative to all standard sorbates; the potassium salts are more effective than sodium salts in this respect. The energy of activation of the absorbed molecules was found to be dependent on the nature of the organic substituents in the sorbent which determines their selectivity.[221]

Finally, it should be noted that macrocyclic complexes of structure (XLII) possess liquid crystal properties. On melting, compounds (XLII) are transformed into homogeneous smectic droplets (spherolites). On cooling with exposure to a narrow beam of light from a microscope, the droplets are seen to develop thread-like off-shoots. Smectic phases with structured layers are formed in these complexes. Compounds (XLII) are clearly of interest because they are mesomorphogenic in nature, and form an electrically conducting meso-phase. By contrast with crown ether complexes (XLII), alkali metal salt complexes (XL) do not display liquid crystal properties.[113,222,223]

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From the data presented in this review, it is clear to us that studies on the chemistry of phosphorylated amides have proved valuable and should continue to be so. In particular, the practical applications of *N*-phosphorylated amides and thioamides may even be extended to other fields. Even though polyfunctionalised amidophosphates are relatively accessible and display a broad spectrum of reactivity, they have been rarely employed as intermediates in organic synthesis. There are few reactions involving functionalisation of the XCNPY system, especially where the (thio)phosphoryl centre participates. The participation of the nitrogen atom of secondary amides in chemical reactions is an intriguing question. We await quantitative structure-reactivity data on the reactions of (I) which involve functionalisation and tautomerism. Evidently, many new developments will emerge from further studies on the complexation of (I), their extracting properties, and their use as analytical reagents for the determination and separation of heavy metal ion in biological samples, in sewage, and in industrial effluent. It is difficult to foresee what other important and interesting questions will be raised in connection with the chemistry and use of (I) and derivatives thereof.

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